Prospective Study of Symptoms of Ovarian Cancer in Postmenopausal Women

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Declaration

I, Penny Louise Allen, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Penny Louise Allen

Abstract

Background

Research has identified key symptoms of ovarian cancer, although there are gaps in the knowledge about the pattern of symptom onset, severity and frequency. Previous studies are limited by use of non-validated questionnaires, recall bias and under-reporting bias in medical records.

Aim

The aim of the research was to prospectively identify type, severity, frequency and duration of symptoms that precede ovarian cancer diagnosis in postmenopausal women.

Methods

Questionnaire development methods described by the European Organisation for Research and Treatment of Cancer were utilised to develop a validated ovarian cancer symptoms questionnaire (OCSq). Interviews with 21 gynaecological oncology clinicians/nurses and 25 women with ovarian cancer guided development of the OCSq. The OCSq was piloted among 1,339 women and posted to 100,000.

Results

A total of 829 women completed a pilot OCSq and baseline analysis of the finalised OCSq included 51,007. Symptoms were ubiquitous, with 89% of women reporting any symptoms, 55-56% symptoms at level 2-3 severity and 42-49% at ≥12 days frequency and <12 months duration. Abdominal/pelvic pain, increased abdominal size/bloating or feeling full at ≥12 days and <12 months was reported by 11-16%. There were 263 women who had an abnormal ovarian cancer screening result in the pilot and two women were diagnosed with ovarian cancer. No symptoms were consistently associated with abnormal results when severity, frequency and duration criteria were added to analyses. Multivariate analyses found age, pelvic pressure, tiredness/fatigue, pelvic bloating/fullness, shortness of breath, leg ache/pain and abdominal pressure independently predicted abnormal ovarian cancer screening results at various levels of analysis. However, odds

ratios were low and confidence limits were wide. Symptom reporting was strongly correlated with previous awareness of the possibility of an ovarian lesion and depression screening status.

Conclusion

The research is currently ongoing with follow-up analyses planned to commence in late 2010. Preliminary findings indicate that there is currently insufficient evidence to justify symptoms awareness campaigns based upon the results of previous retrospective research, and that such campaigns risk overwhelming primary care services with 'worried-well' women, increasing psychological morbidity, service costs, unnecessary investigations and potentially harmful surgery.

Acknowledgements

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Abbreviations

A&E	Accident and emergency department
BCC	Basal cell carcinoma
BMI	Body mass index
CI	Confidence interval
CT	Computerised tomography
DoH	Department of Health
DVT	Deep vein thrombosis
EORTC	European Organisation for Research and Treatment of Cancer
GCF	Gynecological Cancer Foundation
GHQ	General Health Questionnaire
GI	Gastrointestinal
GP	General practitioner
HRT	Hormone replacement therapy
ICC	Intra-class correlation coefficient
IQR	Inter-quartile range
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NPV	Negative predictive value
MDN	Median
OCP	Oral contraceptive pill
OCSq	Ovarian cancer symptoms questionnaire
OCEDS	Ovarian Cancer Early Detection Study

OR	Odds ratio
PPV	Positive predictive value
REC	Research Ethics Committee
RMI	Risk of malignancy index
ROC	Risk of ovarian cancer
OCSq	Ovarian cancer symptoms questionnaire
QoL	Quality of Life
SD	Standard deviation
TVS	Transvaginal ultrasound scan
UK	United Kingdom
UKCTOCS	United Kingdom Collaborative Trial of Ovarian Cancer Screening
US	United States
UTI	Urinary tract infection

Chapter One – Background and Study Design

1.0 Introduction

Each year in the UK approximately 6,600 women are diagnosed with ovarian cancer and 4,300 women die of the disease.[1] Five-year survival is approximately 38%,[2] although only 16% among women diagnosed with stage III ovarian cancer.[3] While ten-year survival rates have remained relatively static, these are expected to improve once data become available for the past decade.[2] Low survival rates are a result of a continuation of the trend for a majority of women to be diagnosed with advanced stage disease.[3] Progress has been slow in identifying new biomarkers and treatments resulting in a significant mortality impact. Attempts to detect the disease earlier through better understanding of the symptoms of ovarian cancer have advanced rapidly over the past nine years. However, there are concerns that this knowledge is based upon largely retrospective research. Many questions remain, including issues of the ways in which the diagnosis of ovarian cancer itself, and interactions with clinical teams, shape symptom reporting. There are also concerns that the symptoms of ovarian cancer are ubiquitous among postmenopausal women, therefore awareness campaigns may have the perverse effect of increasing morbidity and mortality among those most at risk of the disease.

1.1 Brief overview of ovarian cancer symptoms research

Despite very early evidence to the contrary, ovarian cancer was regarded as a 'silent killer' throughout much of the 20th century.[4] From the late 1970s onwards a small number of studies began to challenge this perception. In 1979 Ranney & Ahmad[5] published a US study which found 'most women' with ovarian cancer experience symptoms. This was soon followed by UK-based research which described abdominal distension, abnormal vaginal bleeding and change in bowel habit as important symptoms of ovarian cancer, alongside the clinical sign of abdominal mass.[6] A steady trickle of symptoms studies were published throughout the 1980s and 1990s, including questionnaire studies,[7] studies

describing symptoms which prompt women to seek medical attention,[8-9] and medical records reviews describing symptoms by stage of diagnosis.[10-12]

In 2000 Goff *et al*.[13] published findings from their survey of symptoms among 1,725 women with ovarian cancer. This research found 89% of women with stage I or II ovarian cancer reported symptoms, firmly refuting the historical perception of ovarian cancer as a silent disease in the early stages. This paper pushed forward the research agenda, and was quickly followed by a plethora of other large studies, including several case-control studies utilising questionnaire methods, and reviews of medical or insurance records. This volume of literature consistently identified increased abdominal size, bloating, abdominal or pelvic pain, urinary frequency or urgency, change in appetite or feeling full, fatigue, change in bowel habit and gastrointestinal symptoms, such as indigestion, as symptoms of ovarian cancer.[14-22]

In 2007 the Goff group published an ovarian cancer symptoms index.[23] The index included: pelvic or abdominal pain, increased abdominal size or bloating and difficulty eating or feeling full, when experienced more than 12 days per month and for less than 12 months. Since this paper was published research has focussed on identifying and validating symptoms indices which could be used prospectively to identify women who may benefit from CA125 testing or ultrasound.[24-26]

While the existing literature has contributed significantly to knowledge of the spectrum of symptoms associated with ovarian cancer, there is a paucity of research explicating symptom severity, frequency and patterns of onset. There is also a dearth of information about ovarian cancer symptom complexes in women living outside the US.

1.2 From ‘silent killer’ to ‘symptom index’, a condensed history of ovarian cancer patient advocacy

It is not clear why ovarian cancer was historically perceived as a disease with few or very subtle symptoms. Social scientists who have critiqued biomedicine more generally have suggested that, as the influence of biomedicine increased, there

was shift in focus, away from 'subjective' symptoms reported by patients, towards 'objective' signs of illness.[27-29] No theorists to-date have specifically explored these issues in relation to ovarian cancer, although perhaps it could be suggested that increasing recognition of ovarian cancer as a symptomatic disease is a result of patient empowerment movements over the last two decades.

In January 2007 patient advocacy groups in the US succeeded in their efforts to have ovarian cancer symptoms awareness campaigns signed into law ('Johanna's Law'). This law set aside $16.5 million to educate health professionals and women about the signs and symptoms of ovarian cancer. Later in the same year the US Gynecologic Cancer Foundation (GCF) released a symptoms 'consensus statement' which was endorsed by the American Cancer Society and the Society of Gynecologic Oncologists.[30] This stated, 'women with bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, or a frequent or urgent need to urinate, for more than a few weeks should see their doctor, preferably a gynecologist. Prompt medical evaluation may lead to detection at the earliest possible stage of ovarian cancer'.

In their endorsement of the US consensus statement, the American Cancer Society and the US Society of Gynecologic Oncologists acknowledged, 'proof that earlier recognition of symptoms improves outcomes does not yet exist'. However they also suggested, 'there is little to be lost and much to be potentially gained by increasing awareness of ovarian cancer symptoms'.[30]

After publication of the US consensus statement, the UK charity Ovarian Cancer Action embarked upon a symptoms awareness campaign to improve referrals and conversion rates of ovarian cancer, and help GPs' monitor women who present with symptoms associated with ovarian cancer. The campaign included a symptom diary (available online and listing the same symptoms as the GCF consensus statement) which the group encouraged GPs to give to women to fill-in for one month.[31] The diary advised that if bloating/increased abdominal size, pelvic/abdominal pain, difficulty eating/feeling full quickly, or frequent/urgent urination are experienced more than 12 times during four weeks then ovarian cancer should be considered as part of the differential diagnosis.

The UK Department of Health has responded to concerns raised by ovarian cancer patient advocacy groups about the sometimes lengthy time span from first presentation in primary care to diagnosis. In April 2008 a meeting attended by clinicians, researchers, policy-makers and ovarian cancer support group representatives was held in London to discuss symptoms of ovarian cancer. Members of the group worked together after the initial meeting to produce a UK consensus statement and a key messages document for health professionals.[32-33] The UK consensus statement noted that cancer charities, scientists and doctors agreed that three symptoms (persistent pelvic and abdominal pain, increased abdominal size/persistent bloating, but not bloating that comes and goes, and difficulty eating/feeling full quickly) are more frequent in women with ovarian cancer.[32]

1.3 Risks and benefits of ovarian cancer symptoms awareness efforts

Ovarian cancer advocacy groups have argued that increasing women's and clinicians' awareness of the early warning signs of the disease may lead to earlier stage diagnosis, although there is no evidence to substantiate this at the current time. There are benefits to patient empowerment, including encouraging women to assert themselves in their interactions with health professionals if they do not feel that their concerns are being taken seriously. This may lead to prompt referrals and shorter diagnostic timelines. The knowledge that they have acted upon their awareness of symptoms, and achieved a prompt diagnosis, may also confer psychological benefits to women diagnosed with ovarian cancer.

Clinicians have approached ovarian cancer symptoms awareness with caution, asserting that current evidence is insufficient to warrant large-scale education campaigns. They have argued that raising women's awareness of the symptoms of ovarian cancer could result in unnecessary and expensive investigations, anxiety and distress.

There are also concerns that earlier diagnosis may not necessarily reduce the stage of disease. Thus women will have to live longer with the psychological, social,

quality of life and financial repercussions of a cancer diagnosis, without the benefit of improved survival. Encouraging women to consult their GPs based upon as yet unproven symptom indices also runs the risk of swamping primary care with the worried-well. Inevitably, this would result in escalating health care costs without necessarily improving the health of the target population. Indeed, additional investigations are likely to identify more harmless or benign conditions than would have been otherwise diagnosed. This may result in increased unnecessary surgery which has the potential for serious complications.

1.4 Justification for the research

Prospective research into the symptoms of ovarian cancer is needed as current screening methodologies have yet to demonstrate efficacy in the general population of women. Previous studies have identified symptom complexes with sensitivities approximating CA125 screening for the detection of ovarian cancer.[23-24] However, these are limited by poor design, the use of non-validated questionnaires, selection bias and retrospective data collection. To-date no research has prospectively collected symptoms data in non-clinical populations, then correlated symptoms with the development of ovarian cancer on follow-up. With the exception of a recent PhD study,[34] only one questionnaire study of ovarian cancer diagnosis has been conducted in the UK.[35] However, symptoms findings from this research have not been published.

The research presented in this thesis attempts to address these deficiencies by developing an ovarian cancer symptoms questionnaire according to rigorous methodology, then using the questionnaire in a large prospective study recruiting women from 13 regions throughout the UK.

1.5 Study aims

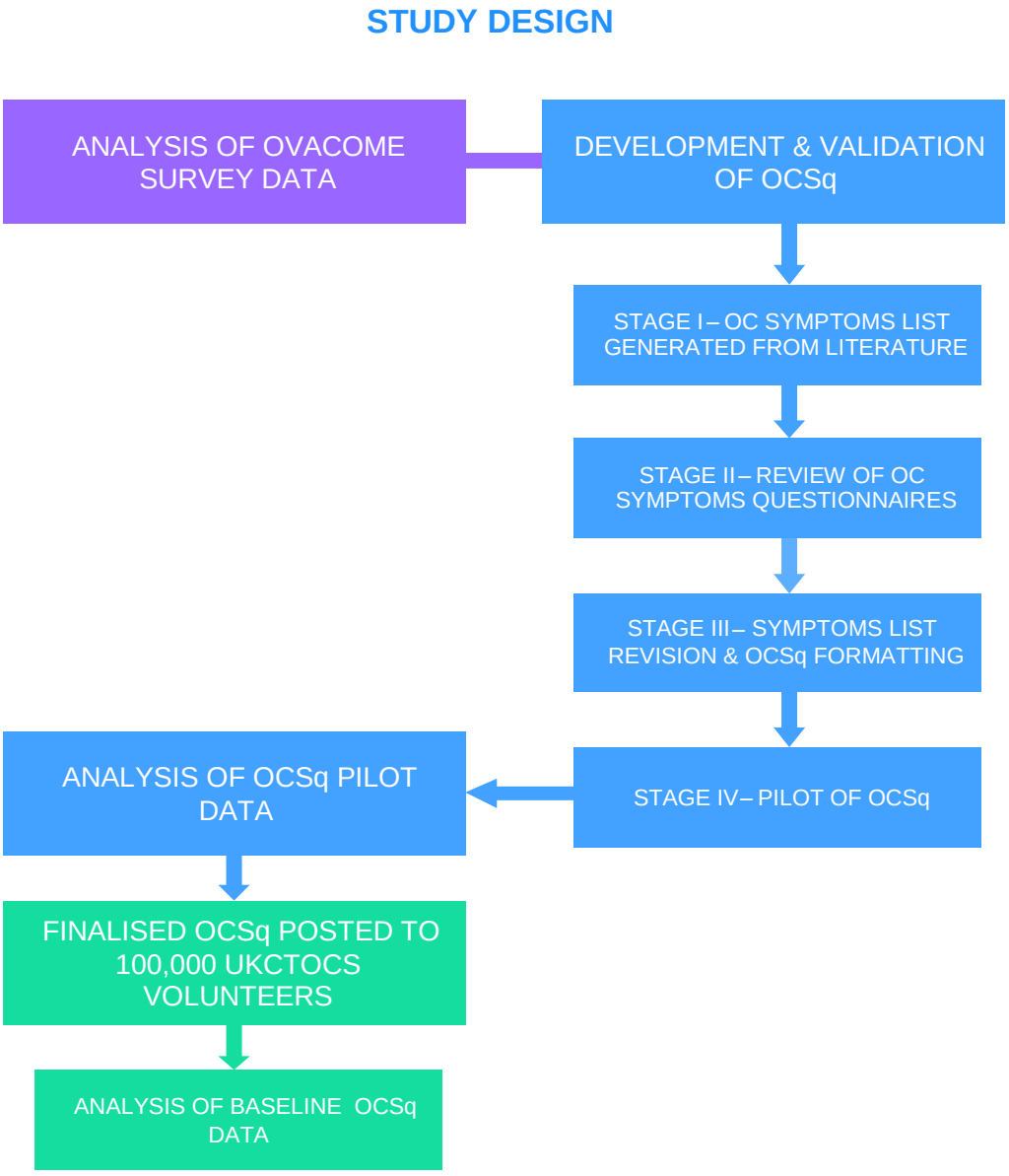
- To prospectively identify type, severity, frequency and duration of symptoms that precede ovarian cancer diagnosis in a pilot study using a cohort of apparently healthy volunteers participating in a screening trial (UKCTOCS)

- To set up a prospective study to assess performance characteristics (sensitivity, specificity and positive predictive value) of a variety of symptoms and symptom complexes for diagnosis of ovarian cancer

1.6 Study design

The research described in this thesis comprised three components: 1) analysis of symptoms data from the Ovacome survey; 2) development of an ovarian cancer symptoms questionnaire (OCSq) including analysis of pilot data; and 3) analysis of baseline data from the OCSq study among 100,000 women (Figure 1.1).

Figure 1.1 *Study design*



1.7 Ethical approval

Ethical approval for the research was granted by the Joint UCL/UCLH Committees on the Ethics of Human Research (Committee A) on 7 March 2007 (REC reference number 06/Q0505/103). A substantial amendment consisting of the finalised OCSq and associated documentation was submitted to the Joint UCL/UCLH Committees on the Ethics of Human Research (Committee A) on 17 November 2008. The Sub-Committee of the REC provided favourable ethical opinion of the amendment on 2 December 2008.

1.8 Overview of UKCTOCS

The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) is a randomised controlled trial designed to provide data for clinicians and health authorities to make an informed decision about the introduction of population screening for ovarian cancer.

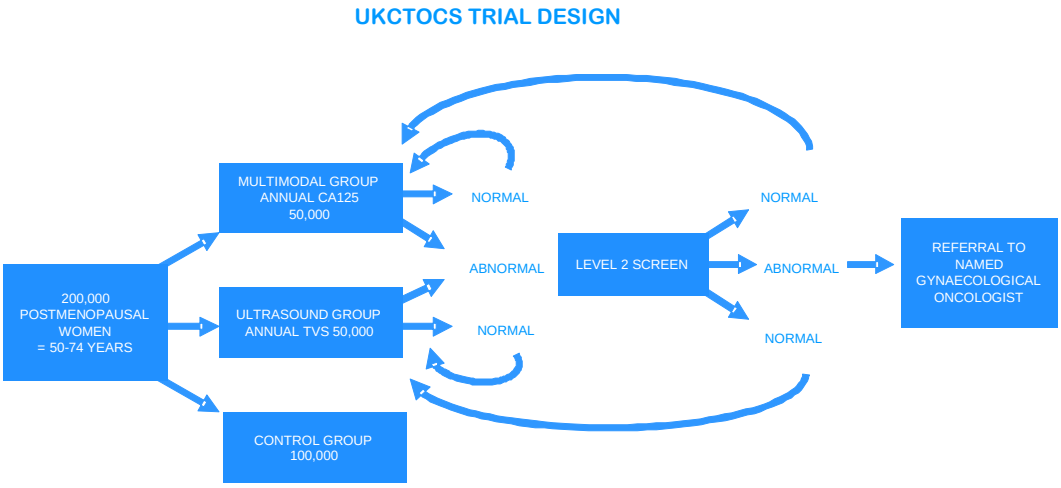
Figure 1.2 summarises the trial design. The study has several objectives. Firstly, it aims to establish the impact of screening for ovarian cancer on mortality. Secondly, the study set out to determine the physical and psychological morbidity of ovarian cancer screening. Other trial objectives include an assessment of cost and resource implications of screening and resulting clinical interventions, assessment of the feasibility of population screening as reflected by volunteer compliance, comparison of the performance of multimodal screening (CA125 and ultrasound) versus transvaginal ultrasound screening alone and, finally, to establish a serum bank for future biomarker studies.

Inclusion criteria were women aged 50-74 years and postmenopausal status (defined as amenorrhoea for 12 or more months). Exclusion criteria were previous bilateral oophorectomy, active non-ovarian malignancy, previous ovarian malignancy, increased risk of ovarian cancer due to familial predisposition and participation in other ovarian cancer screening trials.

Invitations to participate in UKCTOCS were posted to women in 27 Primary Care Trusts. These women were identified from Primary Care Trust records, with invitation letters being sent between April 2001 and September 2005. The invitation letters were written in English and were not translated into other languages. A total of 205,090 women (74% of those sent appointments) attended for recruitment and 202,638 were randomised to one of the three study arms (multimodal, ultrasound or control) using a 1:1:2 ratio.[36] The trial was designed to screen volunteers for seven years, although this was recently extended by two years due to a healthy volunteer effect. UKCTOCS operates in 13 regional centres within NHS secondary care trusts in England, Wales and Northern Ireland (Belfast, Liverpool, Llandudno, Cardiff, Bristol, Portsmouth, Royal Free London, St. Bartholomew's London, Notttingham, Derby, Manchester, Middlesbrough and

Gateshead). The trial coordinating centre is based within the Gynaecological Cancer Research Centre, Institute for Women's Health, University College London.

Figure 1.2. *UKCTOCS trial design*



1.8.1 UKCTOCS data collection

All UKCTOCS volunteers completed a baseline questionnaire at initial recruitment. This elicited information on demographic, lifestyle and reproductive variables. Approximately 3.5 and 7 years after recruitment volunteers are asked to complete a follow-up questionnaire which collects information on education level, co-morbidities and pelvic surgery.

The psycho-social impact of ovarian cancer screening is assessed by a battery of questionnaires. At recruitment to UKCTOCS women completed the General Health Questionnaire (GHQ12), the Speilberger Trait Anxiety Inventory (STAIT) and a Sexual Activity Questionnaire (SAQ). Volunteers who have an abnormality detected at any point during the trial are invited to complete follow-up GHQ, STAIT, SAQ questionnaires, and a tool to measure acceptability of screening. Women who have surgery for a pelvic mass are invited to complete these questionnaires six weeks and six months post-surgery. Women diagnosed with ovarian cancer are also asked to complete the FACT-O tool, which measures the psycho-social impact of ovarian cancer diagnosis. In addition to these event-based assessments, anxiety associated with screening is being measured on an annual

basis in a cohort of 1,532 randomly selected women. These women are posted the GHQ, STAIT, SAQ and screening acceptability questionnaire after each annual screen.

Cancer registrations and deaths are notified to the trial through a flagging system with the NHS Information Centre for Health and Social Care in England and Wales and with the Central Services Agency and Cancer Registry in Northern Ireland. Hospital notes are obtained for volunteers who undergo surgery for pelvic masses and a final diagnosis including primary site, stage and grade of any cancer is made by an independent outcomes committee.

UKCTOCS questionnaires are electronically scanned using computerised intelligent character reading and optical mark reading software (Teleform Elite version 8.1.1, Cardiff Software Inc, Vista, CA, USA). Information not recognised by the data-capture software is verified manually by data entry staff at the coordinating centre. All questionnaire, screening and diagnosis data is logged onto a custom-built SQL database which is hosted at the research coordinating centre.

1.8.2 Summary of screening in the multimodal arm

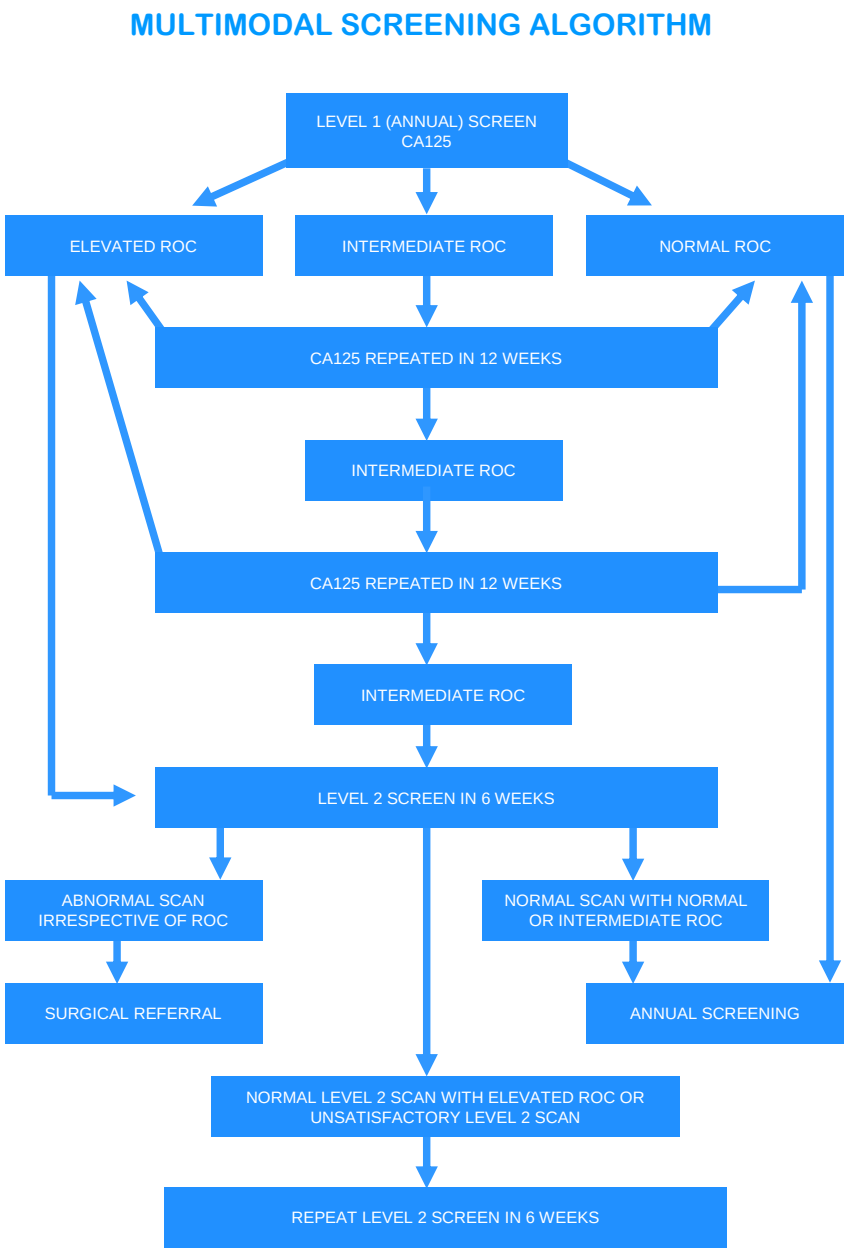
1.8.2.1 Annual (Level 1) screening

Volunteers in the multimodal arm have annual venepuncture for serum CA125 testing and calculation of Risk of Ovarian Cancer (ROC) (Figure 1.3). The ROC algorithm determines the probability of ovarian cancer based on absolute concentration and serial change with time of the tumour marker serum CA125, in addition to age-specific incidence of ovarian cancer. ROC scores are calculated automatically by the UKCTOCS trial management system. Women who have a normal ROC (<1 in 1,000 risk of ovarian cancer) are returned to annual screening, with their next screening appointment in 12 months. Women who have an intermediate ROC (1 in 2000 to 1 in 500 risk) are recalled for repeat CA125 in 12 weeks. Women with an elevated ROC (>1 in 500) are recalled for a Level 2 screen in 6-8 weeks.

1.8.2.2 Repeat (Level 2) screening

Women recalled for Level 2 screening undergo venepuncture for repeat CA125 and transvaginal ultrasound. Women who have a normal ROC and normal ultrasound result are referred back to annual screening. Those with an abnormal scan result are referred to a named gynaecological oncologist for evaluation with regard to the need for surgery, irrespective of the ROC. Women with an elevated ROC and normal or unsatisfactory scan result (one or both ovaries and iliac vessels not visualised) are recalled for repeat Level 2 in six weeks, although earlier scans are arranged if there is a high index of suspicion of malignancy. If the ROC remains elevated at repeat Level 2 women are referred to the named gynaecological oncologist for clinical decision.

Figure 1.3. *UKCTOCS multimodal arm screening algorithm*



1.8.3 Summary of screening in the ultrasound arm

1.8.3.1 Annual (Level 1) screening

Women in the ultrasound group are sent annual appointments for a transvaginal scan. If transvaginal ultrasound is not acceptable to the volunteer, or is not possible for other reasons, transabdominal scan may be attempted after bladder filling. The ultrasonographer assesses ovarian morphology and calculates the

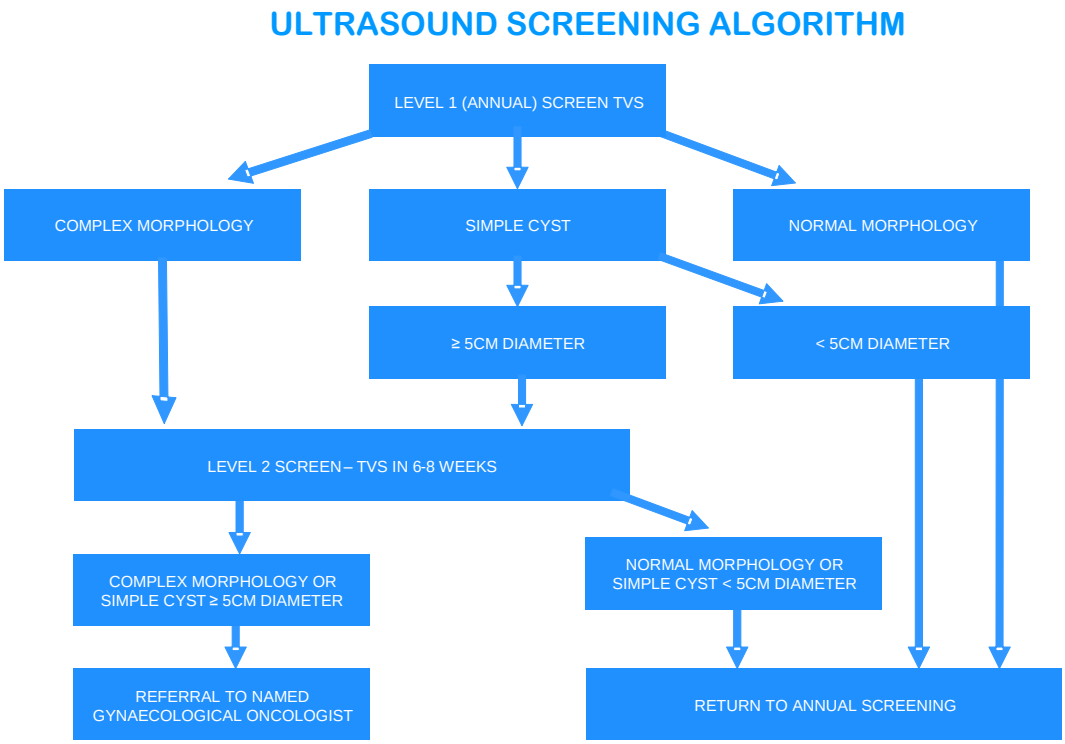
volume of each ovary using the formula for an ovoid (d1 x d2 x d3 x 0·532). Ultrasounds are classified as unsatisfactory, normal or abnormal. The following findings are classified as normal: 1) ovaries not visualised but a good view of the iliac vessels was obtained, 2) both ovaries have normal morphology, or 3) a single simple cyst which measures less than 5cm in diameter. Women with normal findings are sent another annual appointment in approximately 12 months.

Any of the following findings are categorised as abnormal: 1) more than one simple cyst, 2) more than one inclusion cyst in one ovary, 3) complex adnexal mass (having solid areas, papillations, septae or irregular outline), 4) a simple cyst measuring over 5cms in diameter, or 5) ascites (defined as a vertical pool measurement ≥ 10 mm). Women with abnormal ultrasound results are recalled for a Level 2 ultrasound in 6-8 weeks and those with highly suspicious findings are recalled earlier (Figure 1.4).

1.8.3.2 Repeat (Level 2) screening

Based on the same criteria used to assess annual scans, results of Level 2 screens are categorised as unsatisfactory, normal or abnormal. Women with normal results are referred back to annual screening, unsatisfactory results are recalled for a repeat Level 2 in 6-8 weeks and those with abnormal scans are referred for clinical assessment with a gynaecological oncologist.

Figure 1.4. *UKCTOCS ultrasound arm screening algorithm*



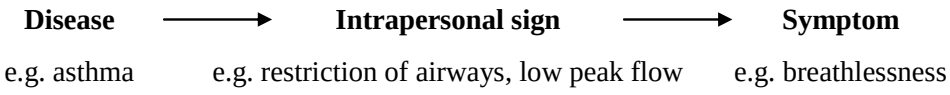
1.9 Definition of a symptom and theoretical framework

The term 'symptom' is used in medical contexts to describe subjective bodily experiences which may be interpreted as evidence of underlying disease. Theorists working in the fields of psychology, anthropology and sociology have proposed broader definitions of a symptom. For example, Pennebaker defines a symptom as, 'a perception, feeling, or even belief about the state of our body. The sensation is often - but not always - based on physiological activity. Above all, a physical symptom or sensation represents information about internal state.' (Pennebaker,[37] p.1)

While symptoms can occur as a result of normal bodily processes or environmental factors, the term 'symptom' will be used in this thesis to describe bodily feelings or experiences which are consciously perceived by individuals and which arise from internal physiological changes which may be related to ovarian disease processes.

A ‘common sense’ model of symptom perception provides a theoretical framework for this definition. This model has two basic assumptions. Firstly, it assumes that measurable and verifiable bodily signs of illness are reflected in symptom perceptions. Secondly, it is assumed that there is a ‘lawful correspondence’ between an underlying physiological state, signs of this physiological state and the experience of symptoms. In her critique of the common sense symptom model, St. Claire[38] provides a useful diagram to illustrate how it functions (Figure 1.5).

Figure 1.5 *Common sense symptom perception model*

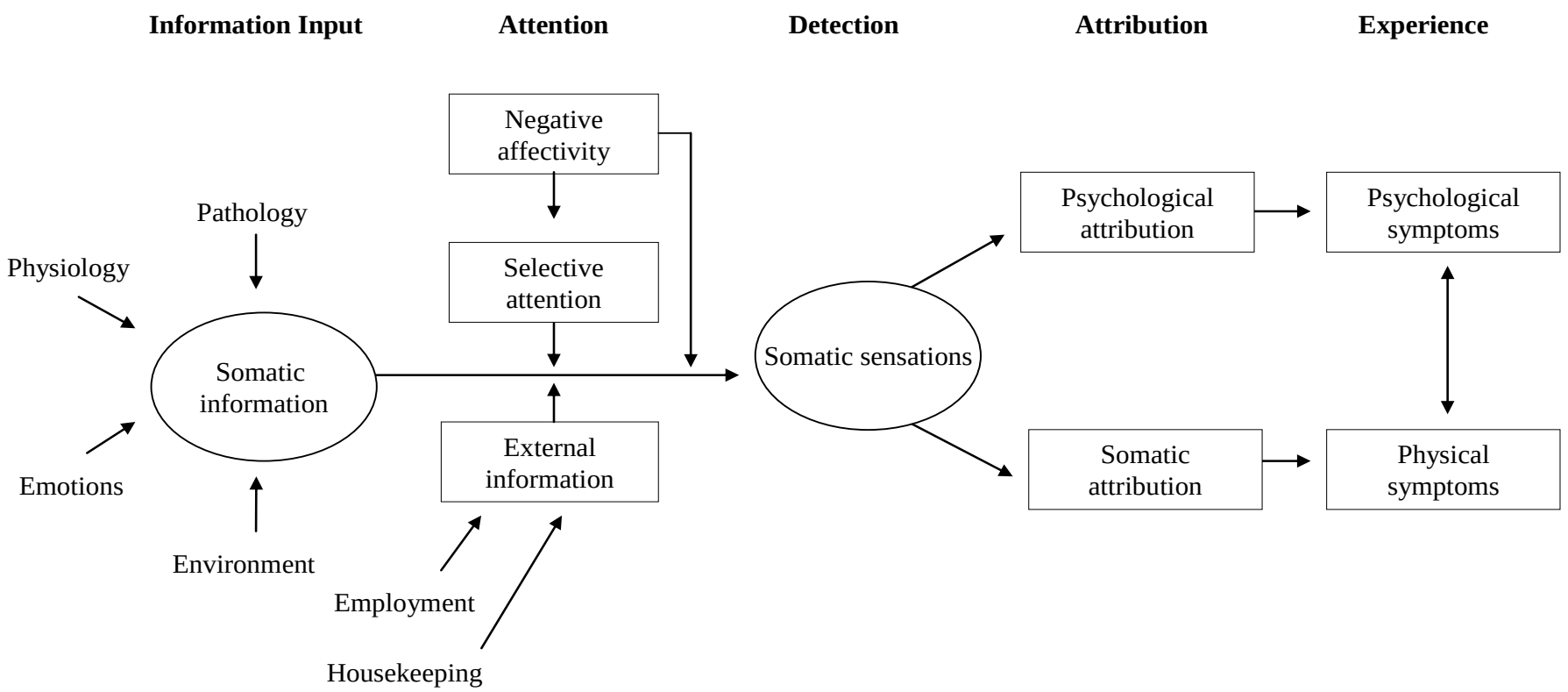


Source: St. Claire[38]

Psycho-social theorists have critiqued the common sense symptom model for failing to take into account psychological, cultural and social factors involved in symptom perception. They argue that there is no simple and direct correspondence between physiological changes and symptom perception. For example, Kolk *et al.*[39] propose that perception of physiological changes is mediated by limited attention capacity. Under this model, an individual’s attention to bodily changes, and the detection and interpretation of symptoms, is shaped by complex internal factors, such as mood states and personality, and external stimuli such as family relationships and work (Figure 1.6).

One questionnaire-based study of ovarian cancer symptoms investigated psychological factors associated with symptom reporting by asking participants to complete depression and anxiety measures.[23] However, quantitative methods are generally not appropriate for the exploration of nuanced social, cultural and psychological influences on symptom perception and reporting. Thus, a common sense symptom perception model provides the theoretical framework for the quantitative research described in this thesis.

Figure 1.6. *Psychological symptom perception model*



Source: Kolk et al.[39]

1.10 Thesis chapter plan

This thesis begins with a description of ovarian cancer trends in **Chapter Two,** then continues with a review of previous research into the symptoms of ovarian cancer. **Chapter Three** describes analysis of symptoms data from the 2006 Ovacome patient survey. **Chapter Four** provides an overview of questionnaire development theory and describes the findings of a review of ovarian cancer symptoms questionnaires used in previous studies. This chapter also details each stage of development of the OCSq. **Chapter Five** describes findings from analysis of symptoms data obtained from the questionnaire pilot. The final results chapter, **Chapter Six**, details findings from analyses of baseline data from the OCSq study involving 100,000 women. **Chapter Seven** provides an overarching discussion of the research findings and a summary of future plans.

Chapter Two – Literature Review

2.0 Introduction

This chapter begins with an overview of ovarian cancer trends and diagnosis. These sections describe the problem of increasing ovarian cancer incidence rates over the past 30 years, with limited progress in improving survival rates. The diagnostic pathway is described and time spans in the care trajectory are discussed, including the problem of sometimes lengthy time periods between the onset of symptoms and eventual diagnosis. The second part of the chapter critically reviews the literature on symptoms of ovarian cancer in order to understand what is already known on this topic, to identify gaps in knowledge and to explore the limitations of published research. The findings of this critique provide a rationale for the research described in subsequent chapters of this thesis.

2.1 Ovarian cancer trends, investigations and diagnosis

2.1.1 Incidence

Based on the latest available data from 2005, the UK has an age-standardised ovarian cancer incidence rate of 16.9 per 100,000.[40] This makes it one of the highest rates in Europe, with only Lithuania, Denmark, the Czech Republic, Estonia, Ireland and Latvia having higher incidence of the disease. Table 2.1 lists the number of new cases of ovarian cancer and the age-standardised rate for regions of the UK for 2001 to 2005. As can be seen in the table, Northern Ireland has the highest incidence of ovarian cancer at 19.1 per 100,000, while Scotland has the lowest at 14.0 per 100,000.

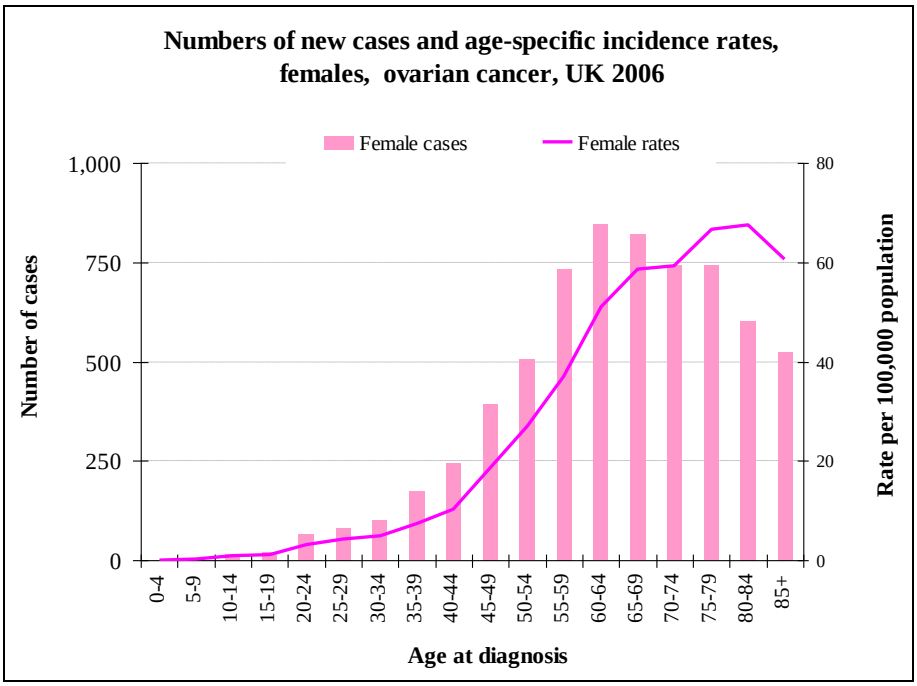
Table 2.1. *New cases and age-standardised incidence of ovarian cancer*

Cases	England	Wales	Scotland	N.Ireland	UK
Females	5,528	380	500	188	6,596
Age-standardised rate	17.1	18.6	14.0	19.1	16.9

Source: CRUK ovarian cancer incidence statistics 2006[40]

Ovarian cancer incidence rates increase with age, tripling from approximately 10 per 100,000 in women aged 40-44 years to approximately 37 per 100,000 in women aged 55-59 years (Figure 2.1).[40] Incidence peaks at around 68 per 100,000 in women aged 80-84 years, then begins to decline.

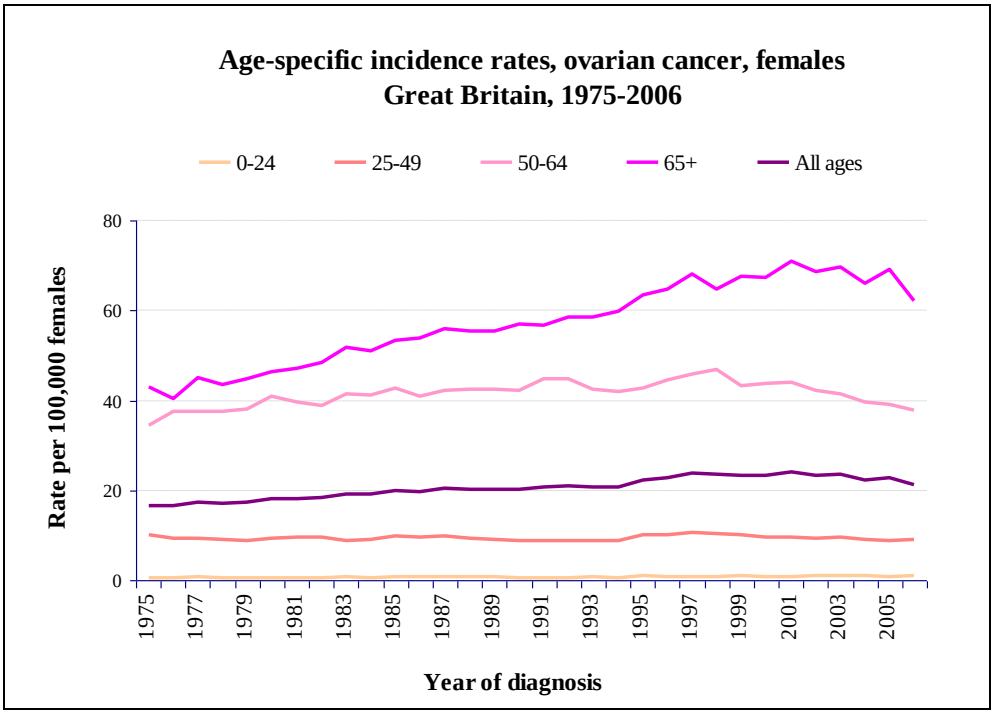
Figure 2.1. *Age-specific incidence rates for ovarian cancer in UK*



Source: CRUK ovarian cancer incidence statistics[40]

Over the past 30 years incidence of ovarian cancer in the UK has increased, from approximately 15 per 100,000 in 1975 to a peak of 19.3 per 100,000 in 2001, although incidence has been falling in recent years.[1] This trend is explained by large increases in the incidence rate among women aged over 65 years but not other age groups (Figure 2.2). It has been hypothesised that this may be due to the widespread use of oral contraceptives, which have a protective effect for ovarian cancer. This trend may also have arisen from increased longevity and improved diagnosis and disease reporting.

Figure 2.2. *Age-specific incidence rates for ovarian cancer, UK 1975-2006*



Source: CRUK ovarian cancer incidence statistics[41]

2.1.2 Diagnosis

In the UK, Department of Health Guidance provides a framework for the diagnosis of cancer. In 2000 *The NHS Cancer Plan* was published. This document stated, 'the ultimate goal is that no one should wait longer than one month from an urgent referral for suspected cancer to the beginning of treatment except for a good clinical reason or through patient choice' (Department of Health,[42] p.6). The directive established a number of targets relating to referral and treatment waiting times, including implementation by 2005 of maximum two week waits for urgent GP referrals for suspected cancer. *Referral Guidelines for Suspected Cancer*, also published in 2000, described suspicious pelvic masses detected on ultrasound, postmenopausal bleeding and post-coital bleeding as criteria for urgent referrals.[43] The National Centre for Health and Clinical Excellence (NICE) issued similar guidance in 2005, advising that abdominal palpation should be carried out on any woman presenting with unexplained abdominal or urinary symptoms.[44] As in the earlier guidance, the document advised that women with unexplained pelvic

masses detected on examination, persistent inter-menstrual bleeding or unexplained postmenopausal bleeding should be urgently referred. However, the document noted that women with ovarian cancer may present 'with vague, non-specific abdominal symptoms … bloating, constipation, abdominal or back pain, urinary symptoms' (NICE,[44] p.26).

Despite implementation of various guidelines for suspected cancer referrals, a 2006 study found 39% of women diagnosed with ovarian cancer are not urgently referred.[45] Reasons for this are unclear, although recent research suggests that symptoms included in earlier criteria for urgent referrals may not have the highest positive predictive values for identifying ovarian cancer.[23 46-47] This situation may improve following new Department of Health guidance for health professionals, which described persistent pelvic/abdominal pain, increased abdominal size and difficulty eating/feeling full as key symptoms of ovarian cancer.[33]

Women with suspected ovarian cancer are referred to specialist gynaecological cancer teams based in Cancer Units or regional Cancer Centres.[43] Cancer Units are located within district hospitals and are responsible for providing diagnostic procedures for all suspected gynaecological cancers. Where ovarian cancer is strongly suspected, women are immediately referred to the specialist gynaecological oncology team at the nearest regional Cancer Centre. Members of these multi-professional teams have a special interest in gynaecological cancer and are responsible for the diagnosis, treatment and management of all women with ovarian cancer.

Work-up at specialist gynaecological cancer centres includes family history assessment, abdominal and pelvic examination, assessment of CA125 and other tumour markers, transvaginal ultrasound and other cross-sectional imaging. These investigations may identify a mass as highly suspicious of ovarian cancer, although a definitive diagnosis is not made until confirmed by histopathology from samples obtained during surgery.

2.1.3 Presenting symptoms

Since the early 1990s several studies have reported that symptoms of increased abdominal size or bloating, abdominal or pelvic discomfort, loss of appetite or

early satiety, fatigue, indigestion, urinary symptoms and change in bowel habit are common among women with ovarian cancer, including women with early stage disease.[10-11 13 15-16 19 22 48-51] However, women and clinicians often attribute these symptoms to menopause, ageing, stress, existing conditions or changes in lifestyle or diet.[8 13 46 51] This mistaken attribution delays women seeking medical advice, and once they visit their doctor, may delay prompt referral to a specialist. By the time women are seen in specialist gynaecological oncology clinics, many have symptoms of advanced disease including increased abdominal size, abdominal or pelvic pain, abdominal mass and ascites. A detailed discussion of pre-diagnostic symptomatology continues in the second part of this chapter.

2.1.4 Key investigations

Transvaginal (TVS) or transabdominal ultrasounds are provided by specialist gynaecological cancer teams. Ultrasounds assess the morphological features of adnexal masses, the presence of neovascularisation and resistance to flow using colour and pulsed Doppler. Morphological characteristics associated with ovarian cancer include large cyst volume, presence of papillary projections and cyst complexities such as solid areas, loculations, wall structures, septal thickness and echogenicity of fluid.[52] In addition to ultrasound, specialist centres may offer computerised tomography, magnetic resonance imaging and radio-nucleotide imaging.[53]

While ultrasounds are useful for characterisation of adnexal masses, they are difficult to interpret and ultrasound alone is not specific enough to provide a diagnosis of malignancy. To overcome this lack of specificity, various scoring systems to predict ovarian cancer have been proposed. Among these is the commonly used system developed by Sassone *et al.*[54] which adds individual scores for four ultrasound characteristics (inner wall structure, wall characteristics, septa and echogenicity) to give an overall risk of malignancy. For example, the inner wall structure is assessed as either: smooth = 1 point, irregularities ≤3mm = 2 points, papillarities >3mm = 3 points, or mostly solid = 4 points. A total score of ≥9 indicates a positive finding under the system.

CA125 is a tumour biomarker that is elevated in ovarian cancer. CA125 blood tests are routinely used in clinical investigations to diagnose ovarian cancer and post-treatment disease recurrence. A cut-off value of 35 U/mL is widely accepted for healthy postmenopausal women.[55] Levels of ≥35 U/mL are found in approximately 83% of patients with ovarian cancer and approximately 90% with advanced disease.[56] However, it has poor sensitivity for detection of early stage ovarian cancer as only 50-60% of patients with stage I have CA125 levels ≥35 U/mL.[57-58] CA125 also has a lack of specificity as it is raised in a number of other conditions, including diverticulitis and cirrhosis, benign gynaecological disease such as endometriosis, and also in breast, pancreatic, bladder, liver and lung cancers.[59]

A number of other ovarian cancer serum biomarkers have been investigated in recent years, including HE4, mesothelin, M-CSF, osteopontin, kallikreins and soluble EGF.[60] Some of these novel biomarkers have shown promising early results, although further research is needed to determine their specificity and sensitivity in large populations of women. At the present time, CA125 and ultrasound remain the clinical modalities of choice for the detection of ovarian cancer.

2.1.4.1 Risk of malignancy index

Researchers have sought to overcome the limitations of CA125 and ultrasound investigations alone by developing scoring systems to predict ovarian cancer. It is now almost 20 years since Jacobs *et al.*[61] first described their risk of malignancy index (RMI). This study found three variables: 1) menopausal status, 2) ultrasound score and 3) serum CA125, to be independently associated with the likelihood of malignancy. The risk of malignancy index was defined as: RMI = *U* x *M* x serum CA125. Where *U* = ultrasound score and *M* = 1 if premenopausal and *M* = 3 if postmenopausal. Ultrasound reports were scored one point each for the presence of multilocular cyst, evidence of solid areas, evidence of metastases, presence of ascites and bilateral lesions. The study found an RMI score of 200 had a sensitivity of 85% and specificity of 97% for predicting malignancy. Moreover, the combination of these three criteria provided a greater level of distinction

between benign and malignant masses than by any of the individual criterion alone. This research was innovative in the way it combined CA125, ultrasound data and menopausal status data to determine an overall risk score. Since the initial study of 143 participants diagnosed at a single hospital research site, the RMI has been validated by numerous independent researchers. RMI scores of >200 have been reported to have sensitivities ranging from 71-90%, with specificities from 77-92% and positive predictive values ranging from 75-96%.[62-67] Furthermore, a recent systematic review of ovarian cancer prediction models recommended the RMI as the scoring system of choice for preoperative assessment of adnexal masses.[68]

The RMI is simple to use in clinical practice and is a useful tool for triaging patients with adnexal masses to either: 1) standard surveillance, 2) repeat testing or 3) immediate referral. The scoring system also helps clinicians to identify patients who should be urgently referred to specialist gynaecological oncology surgeons. The usefulness of the tool is reflected in the recommendation by the Royal College of Obstetricians and Gynaecologists for clinicians to use the RMI for triaging postmenopausal women as at either: 1) low, 2) moderate or 3) high risk of malignancy.[69]

2.1.5 Time spans in the care trajectory

Researchers investigating the cancer care trajectory often divide the diagnostic pathway into two stages. The first of these is the patient or self-care phase and the second is the health care provider phase, which is composed of a primary care and secondary care component. A focus of much of the research in this field is the identification of delays, whether these are related to delays in patients presenting to their GP, delays in primary care referrals to secondary care, or delays in investigations and treatment.

The term ‘delay’ is problematic as it carries negative connotations of blame. It ignores the often complex reasons why patients do not readily attend their GP surgery after the onset of symptoms, and why GPs do not refer women to secondary care earlier. The term also fails to take into account unavoidable lapses of time required for diagnostic procedures to be carried out and appropriate

referrals made. Unfortunately, the semantic complexities of the term are often overlooked in the literature, where it is applied arbitrarily to both quantified durations of time in the care trajectory and to preventable delays. For these reasons, I will endeavour to avoid using the term delay in the following discussion, although its ubiquity within the literature makes it difficult to avoid entirely.

2.1.5.1 Total duration of time from symptom onset to diagnosis

Papers that report the duration of time between symptom onset and diagnosis suggest that women experience symptoms for a median of 2-4 months before being diagnosed with ovarian cancer.[12 14-15 20 48 70-72] However, there is variation within the literature, with two month durations reported by medical records studies,[20 71-72] compared to 4-12 months in patient surveys and qualitative studies.[5 46]

There is also variation between studies which used similar methods. A US qualitative study described average symptom durations of 3-12 weeks,[70] while a UK qualitative study reported a median duration of 12 months.[46] This difference may be explained by the fact that the US study interviewed family members and women with ovarian cancer together, while women were interviewed on a one-to-one basis in the UK study. Perhaps the women in the US study did have symptoms for much longer but were reluctant to discuss them with their family members for a number of reasons. Another possible explanation may be recall bias in the US study, although this is difficult to estimate as the authors do not provide information on the time interval between diagnosis and interview. Alternately, as 60% of the women in the UK study were interviewed prior to diagnosis, perhaps they were particularly anxious about their impending surgery and had enhanced recollection of the timing of symptom onset.

Similar differences may be observed in the findings of two studies conducted by the same group in the eastern states of America. The first study found a median duration of four months between symptom onset and diagnosis for women with invasive ovarian cancer,[15] while the second found a median duration of 12 months for women with early stage invasive cancer.[16] This disparity may be due to

differences in the stage distribution of women included in each study, although this is unclear as the authors do not report stage information for the first study.

2.1.5.2 Duration of time from symptom recognition to GP visit

A 1970s study of the medical records of 250 women with ovarian tumours reported an average interval of 13 months between symptom onset and women seeking medical advice.[5] Unfortunately, due to the age of this paper, I was only able to obtain the abstract. Therefore I was unable to ascertain how the methods may have influenced this finding. However, other research has found comparatively shorter intervals between symptom onset and medical consultations. Goff *et al.*[13] found women experienced symptoms for a median of 2-3 months before seeking medical advice. Questionnaire studies conducted in Australia,[73] and in Iowa in the US reported medians of four weeks between symptom onset and medical consultations,[8] as did a Swedish medical records study,[72] although a recent Japanese study found a slightly longer median duration of 5.5 weeks.[74]

A pertinent issue in relation to these relatively short time spans is that the fact that the medians conceal a wide range of durations. For example, 25% of women in Thulesius *et al.*[72] delayed seeking medical care for nine weeks or longer and 23% in Smith and Anderson[8] delayed for three months or longer. Webb *et al.*[73] similarly found 29% of women with borderline tumours, 19% with early and 13% with advanced disease delayed consulting their doctor for three months or more.

As these studies utilised survey and medical records reviews in countries as diverse as Sweden, the US and Australia, variations in patient delays are unlikely to be the result country-specific variables. This indicates that 13-29% of women later diagnosed with ovarian cancer wait approximately three months after the onset of symptoms before seeking medical care. The reasons for this delay are often complex. These are discussed in the second section of this chapter under the sub-heading ‘symptom perception and interpretation’.

2.1.5.3 Duration of time from GP visit to diagnosis

Research indicates that women wait an average of 2-8 weeks between initially consulting their doctor and receiving a diagnosis of ovarian cancer. However, the Goff *et al.*[13] survey of recipients of an ovarian cancer patient support group newsletter found 26% waited longer than six months before receiving a correct diagnosis.

A UK study of general practice records by Kirwan *et al.*[14] found 60% of women with ovarian cancer were referred to a secondary care gynaecological oncologist within two weeks of their first GP visit and 73% were referred within one month. However, by the time patients were seen in secondary care, a median of 95 days had elapsed since symptom onset. Similarly, a postal survey of 306 women with ovarian cancer, conducted by a patient support and advocacy group in the UK (Ovacome), reported an average clinical delay of 11.5 weeks.[35] While the findings of the US and UK advocacy group surveys are likely to be limited by self-selection bias and recall bias, the research by Kirwan *et al.*[14] collected data from existing primary care records and included all women with ovarian cancer identified through a regional audit. It is pertinent to consider that the findings of Kirwan *et al.*[14] may not be representative of the rest of the UK. However, this study, qualitative research by Bankhead *et al.*[46] and the Ovacome survey, all established that delays in diagnosis are a problem in the UK.

With the exception of two studies,[13 15] longer delays in diagnosis have been described among women with advanced disease compared to women with borderline or early stage ovarian cancer. Flam *et al.*[9] and Webb *et al.*[73] described delays of three months or more occurring in approximately double the number of women with advanced disease, compared to women with early stage tumours. Another study found patients with stage I tumours waited a mean of 35 days from first consultation to operation, while patients with stage III tumours waited 64 days.[48] These findings may stem from difficulties identifying the cause of disease due to the systemic nature of symptoms in advanced ovarian cancer. The divergent finding of longer delays among women with early stage tumours in Vine *et al.*[15] is unlikely to be due to selection bias related to better survival among

women with early stage disease, as the study excluded women who were diagnosed for longer than six months. However, the difference may be explained by country-specific factors.

Research has also found that many women endure convoluted and erroneous referral pathways before eventually receiving a diagnosis of ovarian cancer. A large study of the health insurance records of women with ovarian cancer in California reported that abdominal imaging (rather than pelvic) and gastrointestinal investigations were the most common diagnostic procedures in women 4-36 months prior to diagnosis.[21] Goff *et al.*[13] found 30% of women initially received a wrong diagnosis, while the Ovacome study reported that it took an average of three clinical appointments to achieve a correct referral to a specialist gynaecological oncologist.[35] The most common misdiagnoses reported by women in the Goff *et al.*[13] research were irritable bowel syndrome (15%), stress (12%), being told nothing was wrong (13%), gastritis (9%), depression (6%) and constipation (6%). Medical records and qualitative research reported similar misdiagnoses in addition to menopause, indigestion, thyroid disease, cholecystitis, diverticulitis and depression.[50 75-77]

Incorrect initial diagnoses are not necessarily due to clinician errors. It is likely that the often subtle and non-specific nature of ovarian cancer symptoms, or their similarity to symptoms of more common gastrointestinal diseases or pre-existing conditions, also plays a role in misdiagnosis. Poor communication between patients and health professionals has also been identified as a factor which contributes to delays.[13 50 75] Nearly one-fifth of the women in the Goff *et al.*[13] study described unhelpful clinician attitude as a factor which contributed to a delayed diagnosis, while women in a small qualitative study by Fitch *et al.*[75] described clinicians treating them in an insensitive manner or not listening to their intuitive concerns. However, these two studies are likely to have an element of self-selection bias. As described previously, the Goff questionnaire was posted to women who received an ovarian cancer patient support newsletter, while Fitch *et al.*[75] recruited a convenience sample. Women who had lengthy delays or particularly poor care may have had greater motivation to participate in these studies compared to women who experienced minimal delays. Another possible

explanation may be after-the-event wisdom, where a relationship between symptoms and a diagnosis of ovarian cancer seems obvious on retrospect.

Bankhead[78] also found that the number of symptoms reported to GPs, patient personality and frequency of previous consultations influence referrals to secondary care. Administrative and referral errors, problems with ordering tests and lack of follow-up after initial investigations also result in health system delays.[50 77 79]

Delays in diagnosis are a cause for concern as studies involving patients with other types of cancers have found an association between delays and advanced stage at diagnosis.[80-81] A review of time spans in the diagnosis of breast cancer reported that delays of three months are associated with 12% lower five-year survival.[82] Among ovarian cancer patients, two studies have reported an association between delay in diagnosis and advanced stage,[5 13] and one of these studies also found an association between patient delays and reduced survival.[5] However, other research has not found an association between delays in diagnosis and stage or survival.[8 14 51 72-73]

2.1.6 Pathology

2.1.6.1 Histology

More than two-thirds of malignant ovarian tumours arise from the ovarian surface epithelium.[83] These are grouped into sub-types based upon the World Health Organisation's histomorphologic classification of tumours (Jaffe 2003 in Soslow[84]). The main histological sub-types of ovarian cancer described by this system are serous, mucinous, endometrioid, clear cell, transitional cell, and squamous ovarian neoplasms. These sub-types are described as benign, borderline or malignant depending on the cytologic and architectural features of the tumour.

Serous carcinomas are the most common sub-type of ovarian cancer in Western industrialised countries.[83] Research indicates that they comprise approximately 80-85% of ovarian carcinomas, followed by clear cell carcinomas (13%) and endometrioid tumours (9%).[85] Only 3% are mucinous, while transitional and squamous ovarian carcinomas are rare at less than 1%.

In recent years it has been increasingly accepted that ovarian cancer does not constitute a single disease entity, but rather a heterogeneous group of distinct diseases. Each histological sub-type has its own risk factors, underlying molecular events, behaviour, natural history and treatment-response.[86-87] While stage distribution is more commonly reported, six symptoms studies have described tumour class distribution among women in their research.[6 10 15 20 25 48] However, comparison of symptoms findings according to histological classification is difficult due to changes in tumour classification over the last 20 years.

2.1.6.2 Stage

Ovarian cancer is staged during laparotomy. Full staging is defined by the EORTC as including infracolic omentectomy, sampling of iliac and para-aortic lymph nodes, biopsies of the right hemidiaphragm, samples of the right and left paracolic gutter, pelvic sidewalls, ovarian fossa, bladder peritoneum and cul-de-sac, in addition to sampling of all suspicious areas and peritoneal washings.[88] Stage is then determined according to guidance issued by the International Federation of Gynecology and Obstetrics[89] (FIGO) (Table 2.2).

Table 2.2. *FIGO ovarian cancer stage*

Stage I	**Tumour confined to one or both ovaries**
IA	Tumour limited to one ovary; no tumour on ovarian surface; capsule intact; no malignant cells in ascites or peritoneal washings.
IB	As above with tumour involving both ovaries.
IC	Tumour limited to one or both ovaries with any of the following: capsule ruptured, tumour on ovarian surface, malignant cells in ascites or peritoneal washings.
Stage II	**Tumour involving one or both ovaries with pelvic extension**
IIA	Extension and/or implants in uterus and/or fallopian tubes; negative washings. No malignant cells in ascites or peritoneal washings.
IIB	Extension to other pelvic organs. No malignant cells in ascites or peritoneal washings.
IIC	Tumour staged 2A or 2B with malignant cells in ascites or peritoneal washings.
Stage III	**Tumour involving one or both ovaries with microscopically confirmed peritoneal metastasis outside of the pelvis and/or regional lymph node metastases**
IIIA	Microscopic peritoneal metastases beyond the pelvis.
IIIB	Macroscopic peritoneal metastases beyond pelvis, none exceeding 2cm in diameter.
IIIC	Peritoneal metastases beyond pelvis greater than 2cm in diameter and/or regional lymph node metastasis.
Stage IV	**Distant metastases**

Source: FIGO[89]

More than two-thirds of serous carcinomas are diagnosed as stage III or IV, compared to approximately 25% of clear cell and endometrioid tumours.[83 86] Stage I serous tumours are uncommon and account for less than 10% of serous carcinomas. By contrast, 63% of clear cell, 48% of endometrioid and 71% of mucinous tumours are diagnosed as stage I disease.[86 90]

2.1.7 Treatment

The primary treatment approach for ovarian cancer is maximum cytoreductive surgery with full staging. The objective of surgery is to reduce residual tumour volume to <1cm in diameter.[91] Laparoscopy is the preferred approach in women with suspected early stage tumours while laparotomy is usually conducted in women with advanced disease.[92] Patients typically have bilateral salpingo-oophorectomy with tumour debulking, hysterectomy, infracolic omentectomy and node sampling during surgery. Surgery is usually followed by six cycles of platinum (carboplatin or cisplatin) and paclitaxel-based chemotherapy as recommended by NICE guidelines.[93]

A recent meta-analysis concluded that intraperitoneal administration of platinum and taxane-based chemotherapy has survival advantages over systemic administration.[94] However, both routes of administration yield impressive results, almost doubling survival by adding a median of three years to an expected median survival of 2.5 years with no treatment.

Patients diagnosed with well differentiated stage Ia or Ib disease who have undergone removal of the tumour and optimal staging have low risk of recurrence. Research has found that it is safe to withhold adjuvant chemotherapy from these patients and that it does not improve disease-free survival.[88 95] Unfortunately, risk of recurrence is high in patients diseased with stage Ic or more advanced disease. Approximately 70% of women with stage III disease will experience recurrence within a median of two years.[96] For these women, cytoreductive surgery may be repeated and second-line treatment initiated. Patients who have no macroscopic residual tumour after secondary debulking surgery have been found to have significantly longer post-recurrence survival compared to patients left with macroscopic residual tumour.[97]

2.1.8 Prognosis

A number of pathological, clinical and patient variables have been described as prognostic factors in ovarian cancer. Stage at diagnosis has been found to be the strongest predictor of outcome, with a powerful inverse relationship between stage and survival.[98-99] (Table 2.3 in survival section[53])

Volume of residual disease after initial and secondary cytoreductive surgery has also been found to be an important prognostic factor. Bristow *et al.*[97] describe a 'less is more' relationship between residual disease and survival outcome. Patients with microscopic residual disease up to 1cm have been found to have the longest progression-free and overall survival.[100-103] This association has been demonstrated both in women undergoing primary cytoreductive surgery and in those who have secondary surgery for recurrence.[97]

Other clinical factors associated with better prognosis include patients being operated on by experienced gynaecological oncology surgeons rather than general surgeons, the absence of ascites, complete staging, absence of surface capsule involvement and management of treatment within a multidisciplinary team.[100 104-106]

Several studies have investigated CA125 serum levels as a prognostic variable. This research has reported mixed findings. One study reported pre-operative CA125 levels of <65 U/mL are associated with longer survival in patients with early stage disease,[107] while another study reported CA125 levels of ≤30 U/mL are most important for survival.[108] Low pre-operative CA125 has also been found to be an important predictor of progression-free survival in patients with advanced stage disease.[109] Other research suggests that lower CA125 level at the end of primary therapy is more important as a predictor of overall, and progression-free, survival than preoperative CA125 level.[110-111]

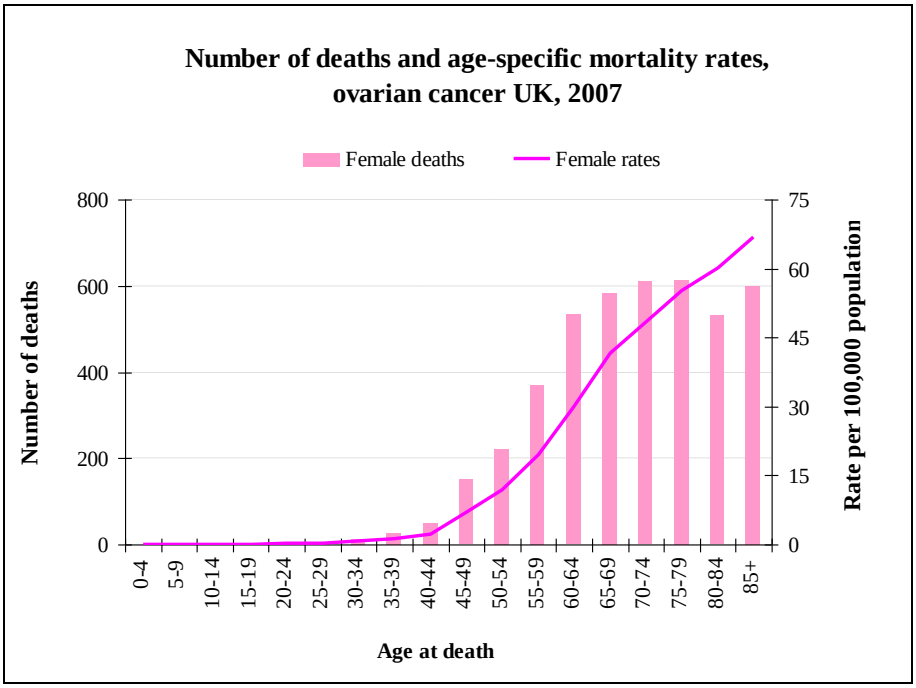
Symptom severity at presentation has been identified as an unfavourable prognostic factor, independent of stage.[72 98] DiSilvestro *et al.*[98] reported that a one stage increase in symptom severity (e.g. systemic rather than localised) increased the hazard of death by 2.28, even after controlling for stage.

Advanced age at diagnosis, poor performance status and malnourishment have also been identified as factors associated with poor prognosis.[99 112-116] Chan *et al.*[112] reported that overall survival was significantly better in younger women, even after stratification by stage and result of cytoreductive surgery. The same study also reported that women with poor performance status had a 90% increased risk of cancer-specific death relative to healthier patients.

2.1.9 Mortality

In contrast to dramatic improvements in survival trends for breast cancer over the last two decades, mortality rates for women with ovarian cancer have only slightly decreased. In the UK, approximately 4,300 women die per annum as a result of ovarian cancer.[117] Ovarian cancer mortality rates follow the same trend as incidence, increasing from approximately 12 per 100,000 in women aged 50-54 years to approximately 55 per 100,000 in women aged 75-79 years and peaking at approximately 67 per 100,000 in women over 85 years (Figure 2.3).[118]

Figure 2.3. *Age-specific mortality rates for ovarian cancer in UK*



Source: CRUK ovarian cancer mortality statistics[118]

2.1.10 Survival

Stage of disease at diagnosis is considered the most important determinant of survival for women with ovarian cancer. Cancer Registry statistics from one region of the UK for the period 1992-1996 show 73% five-year relative survival rates for women diagnosed with stage I compared to 16% for stage III disease.[119] Wider research indicates more dramatic survival differences based on stage at diagnosis (Table 2.3).[53]

Table 2.3. *Median and five-year survival for FIGO stage*

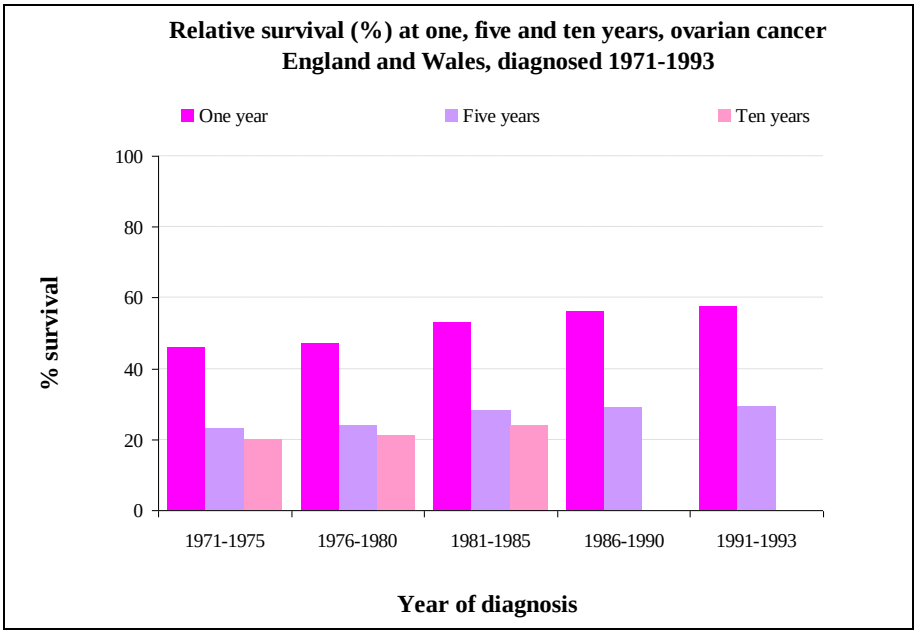
Sub-stage	Median survival (months)	Five-year survival (%)
IA	96+	92.1 ± 0.9
IB	96+	84.9 ± 3.4
IC	96+	82.4 ± 2.0
IIA	85+	67.0 ± 4.3
IIB	92.3	56.4 ± 3.6
IIC	86.1	51.4 ± 4.5
IIIA	41.1	39.3 ± 2.8
IIIB	26.4	25.5 ± 2.6
IIIC	20.7	17.1 ± 1.4
IV	14.7	11.6 ± 0.9

Source: Byrom & Davies[53]

Statistics for England for the period 1991-1993 reveal the importance of age as a determinant of survival. Among women aged 15-39 years, five-year survival is relatively high at 69%, however this figure is halved for women aged 50-59 years (34%).[3] Five year survival drops to 25% in women aged 60-69 years and to 18% for women aged 70-79 years at diagnosis.

One-year survival rates for ovarian cancer increased from approximately 46% to 58% during the period 1971-1993.[3] Over the same period there was a modest improvement in five-year survival from 23% to 29% (Figure 2.4). This trend has continued with recent statistics indicating 66% one-year survival for the period 1996-1999.[2] Five-year survival rates have improved largely as a result of treatment advances which have added three years to the expected median survival of 2.5 years in ovarian cancer patients.[94] Ten-year survival rates have remained low as there has been little change in stage at presentation, although these are expected to improve to 33% by 2013.[2]

Figure 2.4. *One, five and ten year ovarian cancer survival, England and Wales*



Source: CRUK ovarian cancer survival statistics[3]

2.2 Symptoms of ovarian cancer

2.2.1 Introduction

Ovarian cancer has been historically perceived as a 'silent killer', with medical textbooks published throughout the 20th century typically describing the disease as asymptomatic until the advanced stages. However, as far back as 1936 there was evidence to suggest one-third of patients experience pain for more than six months before being diagnosed with ovarian cancer (Lynch 1936 in Smith[4]).

This literature review provides an overview of ovarian cancer symptoms research published over the past 30 years. As described in Chapter One, the term 'symptom' will be used throughout this and all chapters to refer to bodily feelings or experiences which are consciously perceived by individuals and which may be interpreted as evidence of underlying ovarian lesions.

2.2.2 Prevalence of symptoms

A systematic review of ovarian cancer symptoms studies by Bankhead *et al.*[120] found the proportion of asymptomatic patients ranges from 5-26%. Questionnaire and medical records research published after this study reported similar findings.[51] [121-122]

2.2.3 Types of symptoms associated with ovarian cancer

The systematic review by Bankhead *et al.*[120] included 21 papers on symptoms of ovarian cancer. A meta-analysis was conducted to identify the most frequently reported types of symptoms. This included quantitative papers where symptoms were elicited directly from participants and studies utilising medical records data. The analysis found abdominal pain or discomfort, abdominal bloating and abdominal swelling were the most common symptoms in the literature. Other symptoms frequently described in the literature included fatigue, urinary symptoms, early satiety, weight gain or loss and gastrointestinal symptoms such as indigestion, constipation or diarrhoea, while gynaecological symptoms such as abnormal vaginal bleeding or pain during intercourse are less commonly reported. Questionnaire and medical records research published after the review reported analogous findings.[13 47 51 71 121 122]

There is considerable variation in the ways in which authors have chosen to report symptoms. Some studies combined abdominal and pelvic pain,[12 15-16 123] while others considered these distinct symptoms.[7 13 18 124] Abdominal pain only, and not pelvic pain, is reported by another group of studies,[8 14 19 22 51] while two papers combined abdominal and back pain together.[11 17] All of these studies found abdominal or pelvic pain, or abdominal and lower back pain, were among the most frequently reported symptoms by women with ovarian cancer. However, none of the authors explained how their research participants understood the terms abdominal and pelvic. It is likely that women participating in questionnaire research had variable levels of understanding in relation to the term pelvic, yet no paper discusses this possibility. Indeed, wider research has found poor understanding of anatomy among the general public, with only 40% of participants in a recent study being able to locate the ovaries on a diagram.[125] This

emphasises the need to clearly define anatomical terms, or use diagrams clearly labelling the parts of the body these terms refer to.

Studies which combine abdominal and pelvic pain symptoms into one questionnaire item may be also be criticised for failing to distinguish between these different parts of the body. Both Vine *et al.*[15-16] studies combined a number of different abdominal and pelvic symptoms into one item 'pelvic or abdominal discomfort such as heaviness, fullness, pressure or pain'. This is problematic as sensations of fullness and heaviness are very different to pain.

Similarly, Olson *et al.*[17] asked participants about 'unusual abdominal or lower back pain'. This terminology would have reduced the specificity of the data due to the high prevalence of chronic lower back pain in the general population.[126] The shortcomings of these studies emphasise the need to ask research participants about specific symptoms, or if symptoms are combined, to have very robust reasons for doing so.

The symptoms abdominal swelling (also referred to as increased abdominal size) and abdominal bloating are sometimes combined as one symptom in the literature,[51 77 127] although several studies report information on one or the other, but not both. Goff *et al.*[13] differentiated between bloating and increased abdominal size, finding increased abdominal size was the most common symptom (reported by 61%) followed by abdominal bloating (57%). Another study by the same group reported a reversal of these rankings, with bloating being more common than increased abdominal size among the 44 women with malignant tumours.[18]

Similarly to the way in which they combined pain symptoms, Olson *et al.*[17] grouped together 'bloating, fullness and pressure in the abdomen or pelvis'. The authors found this was reported by 71% of the 168 women with ovarian cancer in their study, making it the most common symptom. Paulsen *et al.*[20] reported 'distended or tense abdomen' was the second most common symptom, with 44% of women with invasive tumours and 32% with borderline tumours having this symptom in their medical records. However, the authors do not define the term 'tense'. They explain that free-text symptoms were first extracted from medical

records, then grouped into 10 symptom categories. However, no information is given on the types of free text symptoms that formed the category 'distended or tense abdomen', or any of the other symptoms in their study, including the rather obscure symptom 'pain outside the abdominal cavity'.

Bankhead[78] investigated women's understandings of the terms bloating and abdominal distension in her qualitative research. This research was the first to elucidate this information, finding that persistent abdominal distension but not transient bloating was associated with ovarian cancer.[46 78] This study emphasises the value of in-depth interviews in exploratory research. The findings clarified how women in the UK undergoing investigations for ovarian masses understand symptoms terms. Apparently healthy women in the general population may have different interpretations of these symptoms compared to women in the study, who were undergoing clinical investigations. Nevertheless, this research confirmed the need to specifically ask women about both increased abdominal size and bloating in my own research, rather than combining these symptoms into one item.

A number of qualitative, questionnaire and medical records-based studies have identified fatigue as one of the three most common symptoms of ovarian cancer.[7-8 13 17-18 20 124 127] Urinary frequency or urgency is also commonly reported,[8 17-18 22 47 50 123-124] as are gastrointestinal symptoms such as nausea, indigestion or heartburn and changes in bowel habit.[6 14 20 22] Abnormal vaginal bleeding has been described as a less common symptom of ovarian cancer.[9 12 120 124] However, recent research has found a large odds ratio for the symptom in the medical notes of cases compared to controls,[47] and it was one of four symptoms included in a recent ovarian cancer symptoms index.[25] Abnormal vaginal bleeding has also been found to be a symptom which is most likely to prompt women to seek medical advice.[8 51]

2.2.4 Symptom complexes and indices

Six studies investigated the prevalence of different combinations of symptoms, or symptom complexes, in women with ovarian cancer, although one of these is a PhD study where the findings have yet to be published. The first of these studies was conducted by Smith & Anderson[8], who reported on combinations of

symptoms in 83 women with ovarian cancer. The authors found 72% of women had symptom combinations consisting of two symptoms. A double symptom complex of abdominal swelling and fatigue identified 24% of women, while abdominal swelling and urinary symptoms, or abdominal swelling and abdominal pain, identified 18%. A triple symptom complex consisting of abdominal swelling, abdominal pain and fatigue identified 29% of women.

Three case-control studies have investigated symptom complexes. Vine *et al.*[16] investigated symptom complexes in a study of 267 women with ovarian cancer and 287 population-based controls. The authors calculated the number of women in each group who had combinations of three symptoms. The ten most common combinations included bloating or feeling of fullness, distended or hard abdomen, pelvic or abdominal discomfort, fatigue, gas/nausea/indigestion, and weight gain/loss. Women with ovarian cancer were significantly more likely to report each of the top ten three symptom combinations compared to controls (26-39% vs. 2%).

Goff *et al.*[18] found the combination of three symptoms (bloating, increased abdominal size and urinary urgency) gave the highest odds ratio (9.4) of any symptom complex. This was reported by 43% of women who were later diagnosed with ovarian cancer compared to 8% of women attending primary care.

Lurie *et al*.[25] investigated symptom complexes in a population-based study conducted in Hawaii. Combinations of symptoms were investigated among 432 women with ovarian cancer compared to 491 controls, and the sensitivity and specificity of different complexes was assessed. The study found a four symptom index that included abdominal pain, distended and hard abdomen, abdominal mass and abnormal vaginal bleeding had the best predictive ability, with a sensitivity of 74% and specificity of 77%. However, the findings of this study are limited by possible recall bias as there was a median interval of 8.9 months between diagnosis and participation in the research.

Despite Vine *et al.*[16] and Lurie *et al.*[25] conducting research at a population level, 22% of women with ovarian cancer in the latter study declined participation, indicating that selection bias may have been introduced into the study. Goff *et*

al.[18] only reported the number of women with a pelvic mass who completed their survey, but not the number who refused. The authors contend that it was not possible to calculate the response rate in controls due to repeat primary care visits. While the prospective method of this study may have reduced recall bias, the researchers did not even attempt to estimate the effect of selection bias on the results.

A later study by the Goff group developed an ovarian cancer symptom index by assessing symptoms in 149 women later diagnosed with ovarian cancer compared to 255 women participating in an ovarian cancer screening study and 233 women attending pelvic ultrasound appointments.[23] Symptoms included in the exploratory model were those with large odds ratios between the groups. Confirmatory analyses identified pelvic/abdominal pain, increased abdominal size/bloating and feeling full/difficulty eating, when present for less than 12 months and experienced more than 12 days per month, as having the greatest sensitivity for detecting ovarian cancer. However, feeling full/difficulty eating was not significant in exploratory analyses. This combination of symptoms had a sensitivity of 56.7% for identifying women with early stage ovarian cancer and 79.5% for advanced disease. In women over 50 years of age, the symptom index had a sensitivity of 66.7% and specificity of 90%. The authors note that these levels of sensitivity and specificity are similar to CA125 and have the advantage of minimal cost.

While the Goff *et al.*[23] results are impressive, the study had several methodological weaknesses which are not addressed by the authors. Chief among these was the decision to include symptoms data from 55 women with ovarian cancer who participated in their 2004 study. These women represent over a third of the total 149 ovarian cancer cases. While other participants were randomly assigned to either exploratory or confirmatory analyses, all 55 ovarian cancer cases from the earlier study were allocated to the exploratory group. The authors state that these women filled in the same questionnaire as the rest of the women in the research. However, this is not the case, as my own review of their questionnaires (detailed in Chapter Four) found the earlier study presented participants with a 20 item symptom checklist, and the latter study used a 23 item

checklist. The authors fail to address how potential bias arising from the original study's recruitment or data collection methods may have affected the results of the symptom index. The study is also limited by the recruitment of women who had heightened awareness of ovarian cancer (either through their participation in a familial ovarian cancer screening study, current pelvic ultrasound investigations or impending surgery for a pelvic mass) with no comparative population-based group. This may have resulted in over-reporting bias in each group.

Shortly after publication of the Goff symptom index the United States Gynecologic Cancer Foundation (GCF) released their Ovarian Cancer Symptoms Consensus Statement.[30] This statement is based upon symptom index yet it includes urinary urgency/frequency. The decision to include urinary symptoms was possibly based upon the findings of the earlier Goff group study which identified a three symptom complex that included urinary urgency, or other research which has found urinary urgency or frequency to be a common symptom among women with early stage ovarian cancer.[11 15 49 51 73]

A recent study by the Goff group investigated the stability of the six item symptom index over time.[26] Volunteers in an ovarian cancer screening trial completed the symptom index at two time periods, approximately 100 days apart. This research found the symptom index was negative at both points in time for 86% of women and positive at both time points for 2%. The authors suggest that high correlation between symptom index results for the two time periods provides evidence of the reliability of the index as a clinical tool. However, it may also be argued that it is premature to test the reliability of the index given that its validity has not yet been established in populations of women living outside the state of Washington on the west coast of America.

2.2.5 Number of symptoms, onset, frequency and severity

Symptoms associated with ovarian cancer are also frequently reported by healthy women and women with benign gynaecological disease. However, research indicates women with ovarian cancer are more likely to report multiple, recently onset symptoms, which are more frequent and persistent compared to healthy women, or women with benign disease.

Qualitative and questionnaire research has found women with ovarian cancer report an average of 3-8 symptoms during the time leading up to their diagnosis. Case-control studies have found population-based controls report fewer symptoms.[7 16-18 25 51 77] Lurie *et al.*[25] found controls participating in an annual government health survey reported a mean of 2.6 symptoms compared to 3.6 among women with ovarian cancer, while an earlier study in New York with population-based controls identified through random-digit dialling found a median 1.3 symptoms in this group compared to 3.0 among in women with ovarian cancer.[17] A case-control study with commensurate methodology conducted in North Carolina found women with ovarian cancer reported a median of 5-6 symptoms compared to just one symptom among controls.[16]

While all of these studies found women with ovarian cancer reported significantly more symptoms compared to controls, the findings are limited by retrospective research designs and possible selection bias. Recall bias is an inherent problem in retrospective designs and is likely to have changed the way women with ovarian cancer in these studies remembered symptoms. Following diagnosis women may have thought a lot more carefully about possible symptoms of their disease and may have recalled symptoms that healthy women would not recall. Selection bias is a possibility as other research has demonstrated that individuals who participate in research tend to have better health than the general population.[128] This 'healthy volunteer effect' may have resulted in the recruitment of particularly healthy controls not representative of women in the general population.

Research suggests controls recruited through primary care clinics report a greater number of symptoms compared to population controls, but still significantly fewer than women with ovarian cancer. Goff *et al.*[18] argue that a primary care control group is necessary to detect differences in the symptoms reported by women attending for care due to other conditions and women likely to have ovarian cancer. The study found controls attending primary care reported a median of four symptoms compared to eight among women with ovarian cancer. A shortcoming of the study which may explain this finding is the fact that controls were 10 years younger than cases. Wider research has shown the number of symptoms reported by individuals increases with age.[37] Perhaps the greater number of symptoms

among the cases simply reflects their advanced age compared to controls, rather than an association with ovarian cancer.

Questionnaire-based research suggests women diagnosed with ovarian cancer have more recent onset of symptoms compared to population-based controls and women with other conditions.[16-18] As their earlier research suggested some women with ovarian cancer are initially misdiagnosed with IBS,[13] Goff *et al.*[18] investigated the onset of symptoms in women with ovarian cancer compared to IBS. They found that women with ovarian cancer experienced symptoms for a median of six months or less, while women with IBS and primary care controls had symptoms for a median of 12 to 24 months.

An association has also been described between recent onset of symptoms and advanced stage disease.[12 15-17 20] Vine *et al.*[15] found women diagnosed with borderline tumours had symptoms for six months compared to four months in women with invasive tumours. Similarly, Eltabbakh *et al.*[12] reported women with borderline disease had symptoms for eight months compared to 3.4 months in women with invasive tumours. These differences are most likely due to the rapid progression of invasive cancers in comparison to borderline tumours which are slow growing, indolent and have a good prognosis. In addition, there may have been some form of selection bias as women with invasive tumours who experienced symptoms for lengthy periods may have died before researchers had an opportunity to interview them. Recall bias may also have contributed to these findings in the questionnaire studies as women were interviewed after surgery.[15 17]

Evidence from three studies suggests that symptoms are more frequent and persistent in women with ovarian cancer compared to controls. Goff *et al.*[18] found women with ovarian cancer typically reported symptoms occurring on a daily basis, whereas controls experienced symptoms 2-3 times per month. The findings of Olson *et al.*[17] concur as they reported women with ovarian cancer are more likely to report 'constant' bloating, fullness and pressure in the abdomen, while controls experienced these symptoms intermittently.

The symptom index published by Goff *et al.*[23] in 2007 confirmed the importance of symptom duration and frequency as predictive factors for ovarian cancer. The

six symptom index with the greatest sensitivity specified that symptoms must have onset within the past 12 months and have a frequency of greater than 12 days per month. However, these findings must be interpreted with caution as no other research group has described specific symptom frequencies associated with ovarian cancer. Also, frequency is largely irrelevant for increased abdominal size as this should be relatively constant.

The questionnaires used by the Goff group for their 2004 and 2007 studies asked women to report symptom frequency over the past month on a seven-point Likert scale. Women were asked to tick the number of days they experienced symptoms, either: 1 day, 1-2 days, 3-6 days, 7-12 days, 13-19 days or more than 20 days. Questionnaire design theorists have argued that Likert scales consisting of 7-10 points are most reliable.[129-130] However, other research has cast doubt on whether an individual, particularly if they older or unwell, can accurately recall minor symptoms experienced during the past month. Thus, the quality of the Goff *et al*.[23] symptom frequency data is questionable. For example, it would be difficult to remember whether a symptom was experienced five days or seven days over the past month. The authors did not validate their questionnaires so the reliability is unknown. Perhaps a shorter time frame (e.g. one week), or fewer Likert scale categories, would collect more accurate data.

Only two published studies, both by the Goff group,[18 23] investigated symptom severity, although this has also been assessed in a recent PhD study.[34] The Goff studies asked women to rank the severity of symptoms on a five point Likert scale where 1 equalled minimal and 5 equalled severe. The first study found that a greater proportion of women with malignant masses ranked symptoms as 4 or higher compared to IBS patients and women attending primary care for other reasons. Among women later diagnosed with malignant ovarian cancer, 36% experienced pelvic pain ranked 4 or higher on severity, compared to 9% of IBS patients and 10% of primary care patients.[18] This pattern was also observed for abdominal pain, bloating, increased abdominal size, urinary symptoms, constipation and fatigue. These findings clearly merit further investigation to determine whether they are replicated in ovarian cancer patients living in other countries. However, the later Goff group study reported divergent results, finding that the addition of severity to a symptom index did not change odds ratios in exploratory analyses.[23] Therefore the final symptom index only included duration and frequency.

It is important to note that symptom frequency and severity are not necessarily independent variables. A woman who experiences frequent abdominal pain may be more likely to report it as having a higher severity than a woman who experiences a similar intensity of pain infrequently. Similarly, a single episode of abnormal vaginal bleeding may be considered more serious than daily bouts of indigestion. Prospective assessment of symptom severity and frequency is crucial as wider research has demonstrated an association between symptom severity and symptom reporting,[131-132] and a tendency for patients to retrospectively 'recompose' frequently experienced symptoms into a single episode,[133] which may alter the perception of severity at different time periods.

2.2.6 Symptoms reported by studies of medical and insurance records

One of the earliest medical records studies of ovarian cancer symptoms was conducted by Kennedy & Gordon[6] and included 97 patients diagnosed at a UK hospital. This research identified abdominal pain, abdominal distension, abdominal mass, postmenopausal bleeding and altered bowel habit as the most common presenting symptoms of ovarian cancer.

Since the late 1990s a number of other medical records studies have been conducted in the UK,[14 34 47] the US,[21 49-50 121-122] Norway,[20] Sweden,[11] Switzerland,[134] Japan,[135] Greece,[136] Israel[137] and Australia.[19] Many of these reviewed hospital and primary care records, although two of the UK studies investigated symptoms in general practice records only,[14 47] while the third utilised questionnaires in addition to GP records.[34]

Medical and insurance records research has consistently identified abdominal or pelvic pain, increased abdominal size, bloating, urinary symptoms, gastrointestinal symptoms, fatigue, abnormal vaginal bleeding, palpable abdominal mass and change in weight as symptoms most frequently recorded in the medical notes of women with ovarian cancer. However, the proportion of women with these symptoms varies considerably from study to study. For example, the proportion of women with abdominal or pelvic pain recorded in their medical notes ranges from 33-80% in the literature,[6 135] while increased abdominal size or bloating is recorded in 13-59% of women's medical notes.[10 50]

It is unclear why 59% of women in the Wikborn *et al.*[10] study in Sweden had abdominal swelling in their medical records yet only 13% in a Minnesota study by Yawn *et al.*[50]. Perhaps this difference stems from women in the US study being more willing to consult their doctor earlier, before swelling often related to the presence of ascites had become a significant symptom, compared to women in Sweden. A UK study also found fewer women had abdominal swelling in their hospital notes compared to the Swedish study. The difference between the 59% with abdominal swelling in Wikborn *et al.*[10] and 21% in Kennedy & Gordon[6] is probably explained by the different methods used. The Swedish study also collected data from referring doctors and clinics while the UK study collected data

only from secondary care records. This demonstrates how medical records research using single-source patient notes can underestimate symptom prevalence.

Some of the most recent records-based research included large numbers of women with ovarian cancer. For example, Ryerson *et al.*[121] investigated symptoms in the medical insurance records of 3,250 women aged 65 years and older with ovarian cancer and Wynn *et al.*[122] compared symptoms in the insurance records of 920 women with ovarian cancer and 2,760 matched controls for the 270-31 days before diagnosis. Ryerson *et al.*[121] found abdominal pain was the most common symptom (43%), followed by abdominal or pelvic swelling (43%), constipation, diarrhoea or other digestive disorders (18%), ascites (17%), urinary symptoms (13%), malaise or fatigue (12%) and menopausal disorders (12%). Hamilton *et al.*[47] also reported that abdominal pain was the most common symptom (53%), followed by abdominal distension (36%). Somewhat paradoxically to Ryerson *et al.*[121] who found early satiety recorded in the notes of only 2% of women with cancer, 21% of the women with ovarian cancer in the Hamilton *et al.*[47] study had loss of appetite in their GP notes.

Absence of recall bias is an advantage of medical records research. However, these study designs are prone to misclassification bias. This may occur due to missed diagnoses, or cases being diagnosed shortly after the research. Another source of bias is under-reporting of symptoms. This can be observed by comparing symptom prevalences reported in medical records and questionnaire studies. For example, Hamilton *et al.*[47] found abdominal distension in 36% of GP records, while Bankhead *et al.*[46] found 86% of women with ovarian cancer reported the symptom in a pre-surgery questionnaire, although it must be noted that these differences may also stem from the progressive nature of ovarian cancer symptoms. Wider research corroborates these findings. One study found the proportion of cervical cancer patients who reported symptoms on a questionnaire was seven times that recorded in medical notes.[138] While another study among hysterectomy patients found only fair (k = 0.29) agreement between medical records and patient-reported pre-surgery pain.[139] Questionnaires have also been found to elicit up to twice the number of symptoms found in medical records (Young 1972 in Harlow & Linet[140]). This is often due to time limited medical

consultations, patient personality, physician communication skills, clinical interests and a propensity for clinicians to focus upon a single symptom.[141] Normative social interactions explain the tendency for patients to present a single 'current' symptom and for physicians to 'interrupt' presentation of adjacent symptoms.[142] Under-reporting can also arise when women forget to disclose symptoms during consultations, or when they are too embarrassed to discuss certain symptoms. Researchers investigating symptoms in primary care populations more generally have argued that symptoms studies should not rely exclusively on medical records for these reasons.

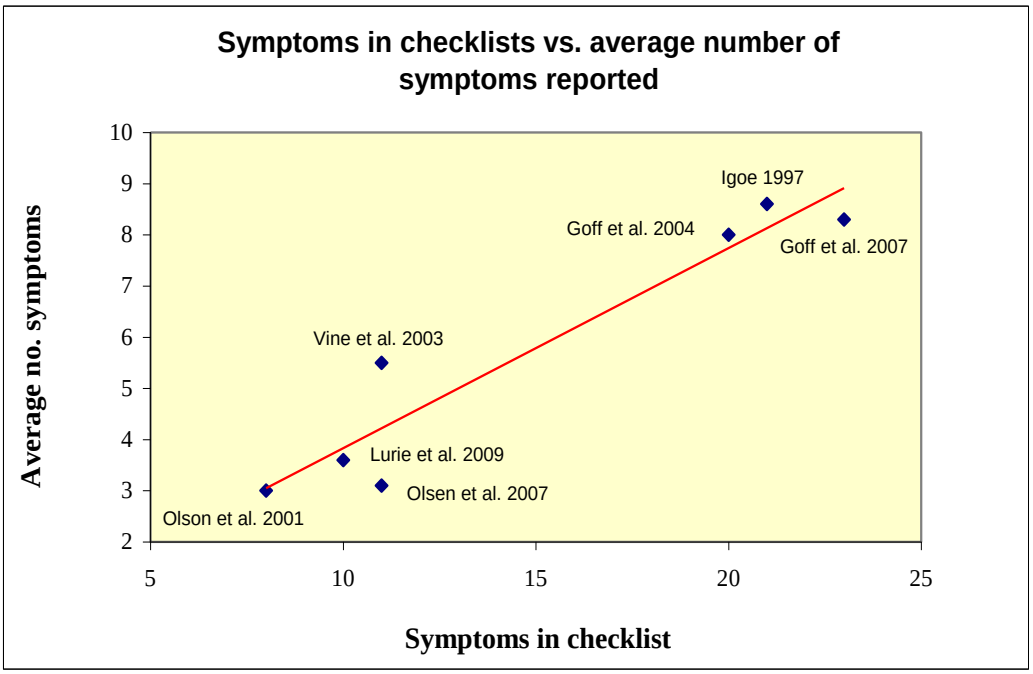
2.2.7 Symptoms reported by questionnaire studies

While not as common as reviews of medical records, questionnaires have been widely utilised in ovarian cancer symptoms research. These studies typically report 90-95% of women experience symptoms leading up to diagnosis.[7 9 13 15-16 18 123] While questionnaire studies have reported a wider spectrum of symptoms compared to medical records research, the most commonly described symptoms are equivalent. Abdominal or pelvic pain, increased abdominal size, fatigue, gastrointestinal symptoms such as indigestion, urinary frequency/urgency and bowel symptoms are the most common symptoms reported by retrospective and prospective surveys.[7 13 15-18 22 25 51 73] Unfortunately, the largest questionnaire study conducted in the UK (by Ovacome) did not publish detailed findings on symptoms, although the group did present a poster on diagnosis experiences,[35] and they also provided symptoms data for the analyses described in Chapter Three.

The average number of symptoms reported by women varies considerably. However, this may be explained differences in the number of symptoms included in checklists. As can be seen in Figure 2.5, the average number of symptoms reported appears to correlate with the number of symptoms in questionnaires. This graph includes seven papers which described the average number of symptoms reported by women and also the number of symptoms in the questionnaire (or provided to me directly when I requested this information, as detailed in Chapter Four).

Studies which used the longest symptom checklists, such as those by Goff *et al.*[23] (23 items) and Igoe[7] (21 items), also reported the highest median number of symptoms (8.3 and 8.6 respectively). Alternately, studies which presented women with shorter checklists, such as Olson *et al.*[17] (8 items) and Olsen *et al.*[51] (11 items), found the lowest average number of symptoms (3.0 and 3.1 respectively). Olson *et al.*[17] and Igoe[7] state that their symptom checklists were constructed from reviews of relevant literature, yet it is unclear why Olson *et al.*[17] used a questionnaire with approximately half the number of symptoms used by Igoe[7].

Figure 2.5. *Number of symptoms in checklists and number of symptoms reported*



The correlation between the number of symptoms included in questionnaires and the number of symptoms reported by women is probably due to a stimulus-response or memory-cueing effect, where respondents have enhanced recall if they specifically asked about a symptom.[129] An acquiescent effect, described by Kroenke[141] as 'over-endorsement bias', is also likely. This refers to the tendency of respondents to positively endorse a symptom when asked about it. These findings underscore the need for researchers to use validated questionnaires in order to avoid over or under-reporting bias. The validation process should result

in the omission of superfluous items while ensuring the overall comprehensiveness of the symptom checklist.

Only three studies described the use of a validated questionnaire. Igoe[7] used a questionnaire that had undergone face and content validation, and reliability testing, while Koldjeski *et al.*[70] reported use of a symptoms checklist which had undergone congruent validation. Rather disappointingly, these authors did not publish findings from their validation analyses, so the validity and reliability of their tools is unknown. Portenoy *et al.*[143] used an independently validated questionnaire, although this was a generic pain measure not specifically developed for ovarian cancer.

Poorly defined inclusion and exclusion criteria are another limitation of some questionnaire studies. This results in selection bias and the recruitment of study populations not representative of the wider population of women with ovarian cancer. The recruitment of non-random samples is potentially a large source of bias in three studies. Igoe[7] recruited women through the internet and snowball sampling, while the Goff *et al.*[13] and Bayne & Gilbert[35] mailed surveys to members of ovarian cancer support groups. The women who participated in these studies are likely to have been better educated, more affluent, younger and healthier than the general population of women with ovarian cancer.

2.2.7.1 Retrospective questionnaire studies

Most questionnaire studies have been conducted after women have been diagnosed with ovarian cancer. This is a source of considerable bias as experimental research has found participants over-report symptoms associated with a disease when informed of a positive diagnosis.[144] While it would be unethical to test this theory in relation to ovarian cancer, this may be one possible explanation for the larger median number of symptoms reported by cases compared to controls in retrospective questionnaires.

Given poor survival rates in ovarian cancer, the potential for selection bias is a pertinent concern in retrospective studies. Selection bias probably plays a much larger role in the Goff *et al.*[13] study, where nearly half the respondents completed a questionnaire more than two years after diagnosis, compared to Smith & Anderson's[8] research which reported an average interval of 10 weeks.

Lengthy time intervals between diagnosis and participation result in recall bias. This is a source of concern as wider research has demonstrated both exponential memory decay over time,[129 145-147] and a tendency for respondents to overestimate symptoms in retrospect.[148-151] The types of symptoms reported are also likely to change over time. Minor, transient symptoms will often be remembered in the short-term. However, only those symptoms with particular salience, or those which had personal implications (such as prompting medical consultations) are likely to be remembered after 30 days.[129] Poor recollection of symptom onset can also occur due to the propensity for individuals to remember salient events but forget the date of their occurrence. This can lead to 'telescoping' where respondents misplace symptoms in time.[129 133]

Only one study described a strict exclusion criterion of not interviewing women who had been diagnosed with ovarian cancer for longer than six months.[15] Other studies appear to have had more flexible recruitment criteria, including Vine *et al.*[16] who reported a median time from diagnosis to interview of 4.6 months but a range of up to 22 months, and Olson *et al.*[17] who reported a mean interval of 4.7 months but more than a quarter of the participants were interviewed nine months after diagnosis.

While most authors report the time delay between diagnosis and interview, some studies do not report this information while others fail to provide sufficient detail. For example, Chan *et al.*[22] and Webb *et al.*[73] state that 'newly diagnosed' patients were interviewed, yet the authors do not define the term 'newly diagnosed', or provide information on potential exclusions due to long delays between diagnosis and women being invited to participate in the research.

Although it is rarely discussed in the literature, it is also possible that some questionnaire studies were biased by differential recall bias between cases and controls with benign disease. One paper that did consider this possibility noted that the interval between diagnosis and interview was slightly longer for women with borderline disease than for women with early or late stage disease.[73] The study found larger proportions of women with borderline disease were asymptomatic, which may reflect poorer symptom recall among this group.

2.2.7.2 Prospective questionnaire studies

The only way to avoid recall bias in questionnaire studies is to conduct the research prospectively, yet just three questionnaire studies, two by the Goff group in the US,[18 23] and the as yet unpublished PhD research by Anita Lim in the UK,[34] asked women to complete symptoms checklists prior to surgery for a suspected ovarian mass. An earlier Swedish study described women being asked specific questions about symptoms prior to hospital admission.[9] However, it is unlikely that this took the form of a symptoms questionnaire.

Goff *et al.*[18] argue their prospective design excluded the possibility of differential symptom reporting due to recall bias. However, they do not discuss how pre-surgery anxiety may have led to over-reporting of symptoms in women with ovarian cancer compared to controls attending primary care. The more recent Goff study interviewed three groups: women who were scheduled to have surgery for pelvic masses, women presenting for pelvic ultrasound and high-risk women who were enrolled in the Ovarian Cancer Early Detection Study (OCEDS).[23] The authors found high odds ratios between the three groups for the symptoms pelvic/abdominal pain, increased abdominal size/bloating, and difficulty eating/feeling full. It is important to note that women who were about to have surgery for an ovarian mass were probably more likely to have heightened awareness of symptoms compared to women who had several normal screens in the OCEDS study. This limitation of the study indicates the need for further, genuinely prospective questionnaire-based research to confirm whether the six symptoms have similar sensitivity for predicting ovarian cancer when women are

asked about these symptoms prior to being informed of the possibility of malignancy.

2.2.8 Qualitative studies of ovarian cancer symptoms

A small number of studies have utilised qualitative methodological frameworks to investigate symptoms of ovarian cancer. Of the five published papers, the study by Ferrell *et al.*[127] was the largest, including 21,896 letters, cards and emails sent to an ovarian cancer support group newsletter. This large volume of data is unusual, and many theorists would argue unnecessary, for a qualitative study. The researchers identified 677 comments pertaining to symptoms and analyses revealed bloating or abdominal swelling, fatigue, abdominal/pelvic pain and urinary frequency as the most commonly experienced symptoms.

Fitch *et al.*[75] explored experiences of being diagnosed with ovarian cancer in a group of 18 women. Thirteen stated that they experienced changes in their bodies prior to diagnosis, including bloating, weight gain around the middle of the body, indigestion, bowel changes, abdominal pain, fatigue and urinary problems. Koldjeski *et al*.[70] investigated symptoms of ovarian cancer using qualitative interviews in addition to a symptoms checklist. The study unusually interviewed 19 women with ovarian cancer together with their family members. This may have resulted in under-reporting of symptoms which women were reluctant to discuss in front of their children, such as pain during sexual intercourse. However, the findings were very similar to other studies, with the most frequently reported symptoms being bloating, abdominal pain, indigestion, fatigue, abdominal mass or lumps and urinary problems.

A fourth study, by Evans *et al.*[77] did not set out to specifically describe symptoms of ovarian cancer but did ask women about symptoms as part of an investigation into delays in diagnosis. Thirty-eight of the 43 women interviewed reported experiencing symptoms prior to diagnosis. The most common symptoms were abdominal distension or bloating, reported by 27 women, abdominal pain, reported by 26 women and urinary frequency/urgency which was reported by 10 women.

Each of these studies was conducted after women were diagnosed with ovarian cancer. In one study the mean length of time between diagnosis and participation in the research was 4.5 years. As stated earlier, long durations of time between diagnosis and interviews increase the likelihood of recall and selection bias. One recent qualitative study sought to avoid this bias by interviewing women prior to definitive diagnosis.[46] The study included 44 women with malignant tumours and found persistent abdominal distension (but not fluctuating bloating), postmenopausal bleeding, loss of appetite, early satiety and progressive symptoms were associated with ovarian cancer. Unfortunately, the researcher was unable to interview 49% of the participants (61 out of 124) prior to surgery, so the findings of this study are also limited by recall bias.

2.2.9 Symptoms by histology and stage

Several studies have reported that the prevalence of symptoms increases with stage of ovarian cancer.[13 15-16 19-20 51 73] Three studies observed a trend of increasing proportions of symptomatic women by stage, but did not detect statistically significant differences.[12 22 49] However, this may be due to smaller study populations. For example, the Chan *et al.*[22] study included 43 women with early stage ovarian cancer and 37 with late stage, while the Eltabbakh *et al.*[12] study included 22 women with borderline ovarian tumours and 50 with malignant disease.

Research has also found women diagnosed with benign ovarian tumours report fewer symptoms compared to women with invasive disease. Goff *et al.*[18] reported an average of four symptoms among women with benign tumours compared to eight in women with malignant tumours. Olsen *et al.*[51] also found women with benign tumours reported fewer symptoms. However, differences between the groups were not as dramatic. Women with benign disease reported an average of 2.2 symptoms compared to 2.8 in women with borderline tumours and 3.6 in women with advanced invasive tumours.

These studies also suggest women with benign tumours report key symptoms of ovarian cancer less frequently than women with malignant tumours. Goff *et al.*[18] found women with malignant tumours were significantly more likely than those

with benign tumours to report bloating (70% vs. 49%), increased abdominal size (64% vs. 45%), urinary symptoms (55% vs. 31%) and constipation (50% vs. 21%). The study also identified a high odds ratio between the benign and malignant groups for difficulty eating. The retrospective case-control study by Olsen *et al.*[51] included 151 women with benign tumours and 244 women with invasive ovarian cancer and found similar results. Approximately double the number of women with advanced ovarian cancer, compared to those with benign masses, reported abdominal swelling (60% vs. 31%), bowel symptoms (32% vs. 14%) and gas, nausea or indigestion (44% vs. 24%), compared to women with benign tumours, and differences were even more striking for weight loss (14% vs. 2%) and malaise (22% vs. 5%).

Women with borderline ovarian cancer have been found to report similar types of symptoms to those with invasive disease, although the prevalence of specific symptoms is often lower. Vine *et al.*[15] found those with borderline tumours were significantly less likely to report bowel irregularity and pelvic discomfort compared to women with invasive tumours. A review of the medical records of 486 women diagnosed with invasive ovarian cancer and 137 with borderline ovarian tumours in Norway confirmed these findings, as smaller proportions of women with borderline disease reported abdominal pain (34% vs. 53%), bowel irregularity (10% vs. 26%) and persisting fatigue or weight loss (7% vs. 26%).[20] However, another large study conducted in Australia involving 146 women with borderline tumours and 665 women with malignant tumours found women with borderline disease were more likely to report gynaecological symptoms, abdominal swelling and an abdominal mass.[73] These findings require further investigation in prospective research to determine whether they reflect real differences in the types of symptoms experienced by women due to the differing natural history of borderline and invasive cancers, or whether they are due to recall or reporting bias associated with women's awareness of the degree of malignancy.

There is also evidence that the type of symptoms reported by women with ovarian cancer vary according to stage. In their meta-analysis, Bankhead *et al.*[120] found gynaecological symptoms and symptoms of pelvic mass were more frequently

reported by women with early stage disease. Several other studies have also described an association between urinary symptoms and early disease, while systemic symptoms, such as malaise, fatigue and weight loss are associated with advanced ovarian cancer.[9 11 16 20 73]

2.2.10 Symptom perception and interpretation

Psycho-social research into symptom perception, interpretation and communication has found that these are influenced by a number of complex and inter-related variables, including an individual's gender, cultural and socio-economic background, social group, personality, life experiences, health knowledge, previous illness experiences and health beliefs.[152-158] Research among other groups of cancer patients has also confirmed that a person's symptom perception and health-seeking behaviours are fundamentally shaped by their existing knowledge of the warning signs of cancer and their fears of the disease.

A small number of studies have explored symptom interpretation among women with ovarian cancer. Unfortunately, only one of these studies, by Bankhead[46 78] included prospective interviews. It is therefore difficult to disentangle recollections of symptom perception and interpretation from the effects of knowledge of an ovarian cancer diagnosis.

Qualitative and quantitative studies have identified symptoms not being recognised as precursors of cancer as a primary reason for women not visiting their doctor sooner after symptom onset.[8 13 51 75 77 127] This research has also found symptoms being mild, intermittent or being misattributed stress, menopause or previous benign conditions such as pelvic inflammatory disease or IBS, are also common reasons for delay. For example, Smith & Andersen[8] reported that 47% of women in their study initially regarded their symptoms as 'not serious' due to mistaken attribution of symptoms to normal body changes (such as ageing or menopause), lifestyle, diet, weight changes and emotional or work-related stress. After women recognise bodily changes as symptoms of something potentially serious, fear of cancer may lead them to further delay seeking medical care.[8 51 78] However, the role of fear is unclear as one study found 2% of women delayed due to fear,[51] while another found fear was a factor in the delay of 23%.[8] Hope that

symptoms would resolve, not wanting to bother GPs and care obligations to family members are also factors which delay women seeking medical advice.[78]

Other research has suggested that the main symptom which prompts women to seek medical advice is not necessarily the symptom of the longest duration.[9] Abdominal or pelvic pain, increased abdominal size, abnormal vaginal bleeding or discharge, back pain and gastrointestinal symptoms such as heartburn have been described as symptoms most likely to prompt women with ovarian cancer to seek medical advice.[8-9 51 73 123] Olsen *et al.*[51] also reported that chest or respiratory pain, abnormal bleeding followed by abdominal pain were the symptoms most likely to prompt women to seek medical care within one week of onset.

2.2.11 Depression as a symptom of ovarian cancer

There is limited data on depression as a symptom of ovarian cancer. Two qualitative studies reported depression as symptom of ovarian cancer among a small number of women prior to diagnosis.[7 127] One of these studies utilised the same *CONVERSATIONS!* patient support group newsletter data as Goff *et al.*[13] The authors found diagnostic delay was associated with patients being labelled as suffering from stress or depression.[127]

The recent Goff group study asked participants to complete a depression scale and an instrument to measure positive and negative affect.[23] The research found depression was significantly more common among women with ovarian cancer compared to controls. However, the authors may be criticised for failing to properly scrutinise this finding. It is likely that the higher prevalence of depression among women with ovarian cancer was associated with their impending surgery and perhaps an awareness of the possibility of malignancy, yet the authors fail to discuss this explanation. While the association between depression and ovarian cancer may be spurious, these findings warrant further investigation in other populations, particularly as depression screening measures can be easily integrated into existing questionnaires.

2.3 Summary

In this review I have presented data on ovarian cancer trends and described time spans in the care trajectory. This data reveals increasing ovarian cancer incidence rates up until recent years, yet minimal improvements in five-year survival. UK research suggests that it is not uncommon for women to wait 3-4 months before receiving a diagnosis of ovarian cancer, and one study described a total interval of 12 months from symptom onset to diagnosis.[46] While there is no conclusive evidence that delays lead to poorer survival outcomes, this seems counter intuitive considering evidence from research into other types of malignancies.

Over the last quarter of a century numerous international groups have investigated symptoms of ovarian cancer with the hope that furthering knowledge in this area may lead to earlier detection of the disease and improvements in survival. While this research has succeeded in identifying symptoms associated with ovarian cancer, there is still a great deal to learn about the exact pattern of symptom onset, severity and frequency, particularly among women outside the US.

I have discussed the methodological weaknesses of previous studies and demonstrated the correlation between the number of symptoms included in questionnaires and the median number of symptoms reported by women. I also described the inconsistent and non-validated ways in which researchers have combined groups of symptoms originating in different parts of the body, such as abdominal pain and back pain, or grouped together different types of bodily sensations into one questionnaire item, such as abdominal heaviness, fullness, pressure and pain. These methodological weaknesses emphasise the importance of researchers using validated symptoms tools. Yet I found only descriptions of limited attempts at validation, and no published evidence of the results of these analyses in the literature. This urgently needs to be addressed as the use of non-validated tools casts doubt on the quality of published survey data. These findings underscore the need for new research using a rigorously developed and thoroughly validated symptoms questionnaire.

Four previous studies, two of which were conducted in the UK, have collected symptoms data directly from women prior to definitive diagnosis. However, in all

of these studies, women were already undergoing clinical investigations for suspected malignancy. This raises questions about the ways in which an enhanced awareness of the possibility of ovarian cancer may have biased the results.

A particular issue of concern associated with ovarian cancer symptom indices is the very limited evidence surrounding their use. The Goff *et al.*[23] symptom index was developed among women living in one state on the west coast of America. There is currently no evidence that the symptom index would yield equivalent sensitivity or specificity in other populations of women. Moreover, the Goff symptom index did not include urinary frequency/urgency, yet this has been added to the GCF symptom index and the Ovarian Cancer Action symptoms diary in the UK. Only two other studies have developed and evaluated the sensitivity and specificity of symptom indices, although the results of one study are not yet published,[34] and the other study was conducted retrospectively.[25] The symptom index developed by Lurie *et al.*[25] did not include difficulty eating/feeling full but did include vaginal bleeding. This reveals the need for further research to identify particular combinations of symptoms which may have superior sensitivity and specificity for detecting ovarian cancer among women in other parts of the world.

In the review I described findings on delays in diagnosis among ovarian cancer patients in the UK from the Ovacome survey. I noted that symptoms data from this survey had not been published, despite it being the largest symptoms study conducted in the UK to-date. This is an obvious gap in the literature as questionnaire studies from several countries have been published, but not yet in the UK. In the next chapter I describe analysis of symptoms data from the Ovacome survey in order to establish whether UK-based questionnaire respondents report similar types of symptoms compared to women in other countries.

Chapter Three – Analysis of Ovacome Survey Data

3.0 Introduction

Questionnaire-based studies of ovarian cancer symptoms have mainly been conducted in the US, although a small number of studies have been carried out in Sweden, Hong Kong, Australia and the UK. The survey conducted by Goff *et al*.[13] in the US and Canada is the largest study of ovarian cancer symptoms to utilise questionnaire methods. Two UK questionnaire studies have been conducted, although one of these is a recent PhD study where the findings have not yet been published.[34] The first UK questionnaire study was conducted by the Ovacome patient support and advocacy group in 2006. Results of the research were presented as a poster at the International Gynaecological Cancer Society conference in 2007,[35] although detailed symptoms findings have not been published.

This chapter describes a symptom-focused analysis of data collected from women aged 50 years and over who participated in Ovacome survey. This age group was selected as the literature review in Chapter Two demonstrated that ovarian cancer incidence in the UK is highest among women aged 50 to 84 years. Furthermore, I was interested in analysing symptoms data collected from a population of women with an equivalent age range to the UKCTOCS cohort. As described in the literature review, Ovacome only published survey findings relating to women's diagnostic and treatment experiences. Before embarking upon my own data collection, I considered it vitally important to investigate symptoms reported by women in the Ovacome survey. Up to the present time the survey is still the largest European questionnaire-based study of ovarian cancer symptoms.

3.1 Aims

- To determine prevalence of symptoms among survey respondents aged 50 years or older at the time of diagnosis
- To identify types of symptoms experienced by these women
- To describe the symptom-diagnosis pathway

3.2 Methods

3.2.1 Setting

Ovacome is a UK-based ovarian cancer patient advocacy and support group. The Director of Ovacome, also a member of the project consensus group, suggested the possibility of Ovacome sharing anonymised symptoms data from their 2006 Patient Survey. The Ovacome Board of Directors approved the proposal and the anonymised data were received on 5 November 2007.

3.2.2 Sample

The Ovacome 2006 Patient Survey was promoted through the group's newsletter and website. Ovacome members were posted the survey and the website had a downloadable version which women could print out. Non-members were not excluded from the research. It is likely that many participants were recruited through snowball sampling via the website and patient networks. Information on non-response of Ovacome members, and the number of women recruited through the website or other means was not provided by Ovacome.

A total of 306 completed Patient Surveys were received by Ovacome. Survey data from women aged 49 years or younger at the time of diagnosis was excluded for the research described in this chapter. This gave a final data set consisting of 188 respondents.

3.2.3 Data collection

The Ovacome Patient Survey collected information on age, date of diagnosis, type of ovarian cancer, symptoms, diagnosis experiences, quality of care and treatment. Data provided by Ovacome for the research described in this chapter consisted of the demographic, symptoms and diagnosis sections of the questionnaire.

The symptoms section asked the following questions:

- Did you have *any* signs or symptoms of your disease before diagnosis? Yes/No
- What was the date of your *first* symptom? Month/Year
- What was this symptom?
- Did you have any *other* symptoms? Yes/No (Please state what they were)
- Did you go and visit your GP or visit A&E at this point?
- Details of visits – date, where (GP, A&E, etc.), what were symptoms, treatments given, tests done, specialist referral, what was diagnosed?

3.2.4 Data considerations

Free text data for 'other' symptoms was manually recoded into numeric variables to enable calculation of frequencies. It was not possible to investigate urinary frequency and urinary urgency as separate 'first' symptoms as the data set provided already combined these into one variable.

As the survey only asked women for the year of diagnosis, and not the month, it was not possible to accurately calculate duration of time between symptom onset and diagnosis, or initial medical visit for symptoms and date of diagnosis. For the calculation of number of appointments to diagnosis, visits to health professionals for reasons not likely to be related to ovarian cancer were excluded. For example, appointments for high cholesterol were not included.

3.2.5 Data analysis

Data were imported into SPSS version 12.0.1 (SPSS Inc., Chicago, USA) and variables were recoded where necessary. The data were scrutinised by running frequencies, descriptives and explore functions.

Symptoms reported by respondents

The prevalence of 'first' and 'other' symptoms were investigated separately, then these variables were combined to calculate the overall prevalence of each symptom. 'First' symptoms were the first symptoms women remembered experiencing which they attributed to their later ovarian cancer diagnosis while 'other' symptoms were any subsequent symptoms which they also attributed to their diagnosis. Combined 'first' and 'other' symptoms were investigated in women with early compared to advanced stage ovarian cancer.

Symptom complexes

Combinations of symptoms were investigated to identify complexes with the highest prevalence. These included various combinations of: abdominal or pelvic discomfort/pain, increased abdominal size, bloating, tiredness/fatigue, change in bowel habit, abnormal vaginal bleeding, urinary frequency/urgency, backache/pain, change in appetite or difficulty eating, abdominal mass/lump, heartburn or indigestion, nausea, weight change, UTIs and abnormal vaginal discharge.

Women were classified as positive for a symptom complex if they reported at least one of the symptoms in the complex. Symptom complexes derived from the data were compared to symptom indices proposed by Goff *et al.*[23] and Lurie *et al.*[25] (described in Chapter Two).

Women were considered positive on the Goff index if they reported abdominal/pelvic pain, feeling full quickly, bloating or increased abdominal size. The Goff symptom index includes frequency (>12 days during the past month) and duration (<12 months since onset), however, the Ovacome survey did not collect this frequency information and duration data were inaccurate due to the survey not eliciting information on both the month and year of symptom onset and

diagnosis. Women were therefore classified as Goff index positive on the basis of symptom prevalence only.

Women who reported either abdominal pain, increased abdominal size or hard abdomen, abdominal mass/lumps or abnormal vaginal bleeding were classified as positive on the Lurie symptom index.

The number of women who were positive on symptom complexes derived from the data was compared to the number of women who were positive on the Goff and Lurie indices. Symptom complexes were then investigated according to stage at diagnosis.

Duration of time from symptom onset to seeking medical advice

Time spans from symptom onset to medical consultations were explored according to number of symptoms, stage at diagnosis and symptom type.

Duration of time from seeking medical advice to diagnosis

Stage of ovarian cancer at diagnosis was investigated according to the duration of time between initial consultation for symptoms and diagnosis. The median number of appointments required for a correct diagnosis to be made was explored according to stage. Symptoms which prompted women to consult a doctor were compared in those who were diagnosed within three appointments and those who required more than three appointments to receive a correct diagnosis.

Statistical analysis

Non-parametric data were investigating using Mann-Whitney *U* and Kruskal-Wallis statistics with post-hoc tests. Categorical variables were compared using the Chi-square statistic, and Fisher's exact test where appropriate, and odds ratios were calculated. As few symptoms were found to be significantly associated with ovarian cancer on univariate analyses, multivariate analyses were not conducted. Differences were accepted as significant at $p < 0.05$ for all tests.

3.3 Results

Median age was 63.0 years (range 51-86, IQR 59-68) and median age at diagnosis was 58.0 years (range 50-82, IQR 53-63). The median length of time between diagnosis and participation in the survey was 4.0 years (range 0-19, IQR 2-6). The survey instrument did not collect any other demographic data.

As can be seen in Table 3.1, 57.9% of women were diagnosed with stage III/IV disease, in keeping with expected stage distribution. Women diagnosed with stage III were older than other women (stage I *Mdn* 54.0 years, stage II *Mdn* 56.5, stage III *Mdn* 59.5 and stage IV *Mdn* 57.0, $H(3) = 9.3$, $p = 0.03$), with post-hoc tests test revealing a significant trend of advanced stage with increasing age ($J = 6021$, $z = 2.51$, $r = 0.77$).

Table 3.1. *Stage at diagnosis*

Stage	**n**	**%**
Stage I	38	20.2
Stage II	28	14.9
Stage III	86	45.7
Stage IV	23	12.2
Don't know	7	3.7
Missing	6	3.2
Total	*188*	*100.0*

Serous cancer was the most common tumour type (21.3%) among those who knew the type of ovarian cancer they were diagnosed with, although 113 (60.1%) women did not know this information (Table 3.2). Twelve women (6.4%) ticked the 'other' box (1 adenocarcinoma, 1 granulosa cell, 1 mixed mullerian, 1 sarcoma, 1 fallopian tumour, 7 women did not specify type).

Table 3.2. *Type of ovarian cancer reported by women*

Type	n	%
Don't know	113	60.1
Serous	40	21.3
Other	12	6.4
Clear cell	8	4.3
Missing	7	3.7
Mucinous	4	2.1
Borderline	3	1.6
Endometrial	1	0.5
Total	*188*	*100.0*

3.3.1 Symptoms reported by respondents

A total of 169 (89.9%) women reported that they had signs or symptoms prior to diagnosis. Surprisingly, there was no difference in the proportion of symptomatic women among those with advanced disease (stage III/IV) compared to early disease (stage I/II) (89.0% *vs*. 92.4%, *ns*). Among women who experienced symptoms, a median of 3.0 symptoms was reported (range 1-12, IQR 1-4). There was no difference in the number of symptoms experienced by women with different stages of disease. There was also no difference in the number of symptoms according to age.

The most common 'first' symptom was abdominal/pelvic pain (30.3%), followed by increased abdominal size (26.6%), bloating (22.9%) and tiredness/fatigue (19.7%) (Table 3.3). Many women reported simultaneous first symptoms, for example: abdominal/pelvic pain, bloating and fatigue.

Table 3.3. *'First' symptoms reported by women*

Symptom	n=188	%
Abdominal discomfort/pain	57	30.3
Increased abdominal size	50	26.6
Bloating	43	22.9
Tiredness, fatigue or lack of energy	37	19.7
Urinary frequency or urgency	27	14.4
Abnormal vaginal bleeding	27	14.4
Change in bowel habit	24	12.8
Change in weight	14	7.4
Back ache or pain	11	5.9
UTI	11	5.9

Ninety (47.9%) women reported experiencing 'other' symptoms. The most common 'other' symptoms were increased abdominal size (12.2%), bloating (10.6%), urinary frequency/urgency (9.6%) and abdominal/pelvic pain (9.6%) (Table 3.4).

Table 3.4. *'Other' symptoms reported by women*

Symptom	n=188	%
Increased abdominal size	23	12.2
Bloating	20	10.6
Urinary frequency	18	9.6
Abdominal or pelvic discomfort/pain	18	9.6
Tiredness, fatigue or lack of energy	14	7.4
Change in bowel habit	14	7.4
Abnormal vaginal bleeding	9	4.8
Heartburn or indigestion	8	4.3
Change in weight	6	3.2
Back ache or pain	4	2.1

Table 3.5 lists the 10 most common symptoms overall (calculated by combining data for 'first' and 'other' symptoms). Abdominal/pelvic pain was the most common symptom overall (34.6%), followed by increased abdominal size (31.9%), bloating (25.5%) and tiredness/fatigue (21.3%). Change in appetite or difficulty eating was not among the ten most common symptoms. Seven women (3.7%) reported either a decrease or increase in their appetite, but just one woman reported 'difficulty in getting food down' (in addition to multiple other symptoms).

Table 3.5. *Most common 'first' and 'other' symptoms combined*

Symptom	n=188	%
Abdominal or pelvic discomfort/pain	65	34.6
Increased abdominal size	60	31.9
Bloating	48	25.5
Tiredness, fatigue or lack of energy	40	21.3
Urinary frequency or urgency	35	18.6
Abnormal vaginal bleeding	32	17.0
Change in bowel habit	29	15.4
Change in weight	16	8.5
Heartburn or indigestion	15	8.0
Back ache or pain	12	6.4

Symptoms were compared in the 66 women with stage I/II ovarian cancer and the 109 with stage III/IV. Apart from abnormal vaginal bleeding and change in bowel habit (Table 3.6), there were no associations between symptoms and stage of disease. Women with stage I/II were more likely to report abnormal vaginal bleeding (OR 4.30 95% CI 1.87-9.93), while change in bowel habit was more common among women with advanced disease.

Table 3.6. *Symptoms in women with early vs. advanced disease*

Symptom	n	Stage I/II n (%)	Stage III/IV n (%)	OR (95% CI)	p-value
Abnormal vaginal bleeding	175	20 (30.3)	10 (9.2)	4.30 (1.87-9.93)	<0.0001
Change in bowel habit	175	5 (7.6)	21 (19.3)	0.34 (0.12-0.96)	0.035

3.3.2 Symptom complexes

A total of 139 (73.9%) women reported either abdominal/pelvic pain, increased abdominal size/bloating or abnormal vaginal bleeding (Complex 3A), making this the most prevalent three-symptom complex. The second most prevalent three-symptom complex identified 135 (71.8%) women and was comprised of abdominal/pelvic pain, increased abdominal size/bloating or change in bowel habit (Complex 3B). The third most prevalent symptom complex identified 132 (70.2%) women and included abdominal/pelvic pain, increased abdominal size/bloating or tiredness/fatigue.

A four-symptom complex consisting of abdominal/pelvic pain, increased abdominal size/bloating, abnormal vaginal bleeding or urinary frequency/urgency (Complex 4A) identified the largest number of women (n = 152, 80.9%), followed by abdominal/pelvic pain, increased abdominal size/bloating, abnormal vaginal bleeding or change in bowel habit (Complex 4B), which identified 148 (78.7%) women. The third ranking four-symptom complex comprised abdominal/pelvic pain, increased abdominal size/bloating, abnormal vaginal bleeding or tiredness/fatigue, which identified 142 (75.5%) women.

3.3.2.1 Goff and Lurie symptom indices

A total of 127 (67.6%) women were positive on the three-symptom Goff index (abdominal/pelvic pain, increased abdominal size/bloating or feeling full quickly/difficulty eating) and 126 (67.0%) women were positive on the four-symptom Lurie index (abdominal pain, increased abdominal size/hard abdomen, abdominal mass/lumps or abnormal vaginal bleeding). Fewer women were positive on the three-symptom Goff index compared to complex 3A (67.6% *vs*. 73.9%, $p < 0.0001$) and the four-symptom Lurie index compared to complex 4A (67.0% *vs*. 80.9%, $p < 0.0001$). This is due to the lower prevalence of feeling full/difficulty eating and abdominal mass/lumps compared to abnormal vaginal bleeding, change in bowel habit and tiredness/fatigue.

Symptom complexes by stage

Figure 3.1 shows the percentage of women from each stage who were identified by the most prevalent three-symptom complexes and the Goff index. As can be seen in the graph, complex 3A had superior performance for identifying women with stage I (78.9% *vs*. 65.8%, $p < 0.0001$) and II disease (82.1% *vs*. 67.9%, $p = 0.026$) compared to the Goff index. The three complexes and the Goff index had commensurate performance for identifying women with stage III, while complex 3B appeared most efficient at identifying women with stage IV disease.

Figure 3.1. *Three-symptom complexes by stage*

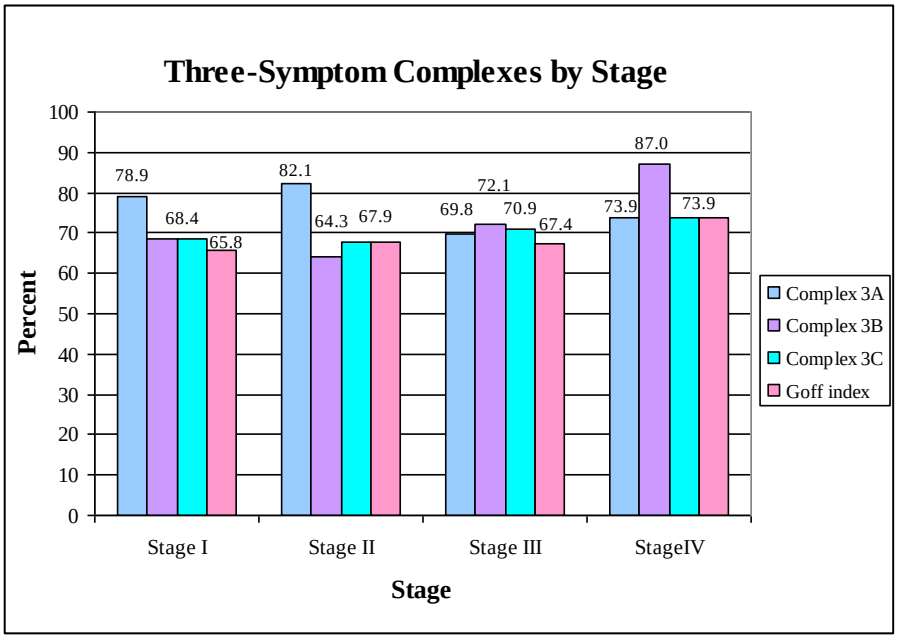
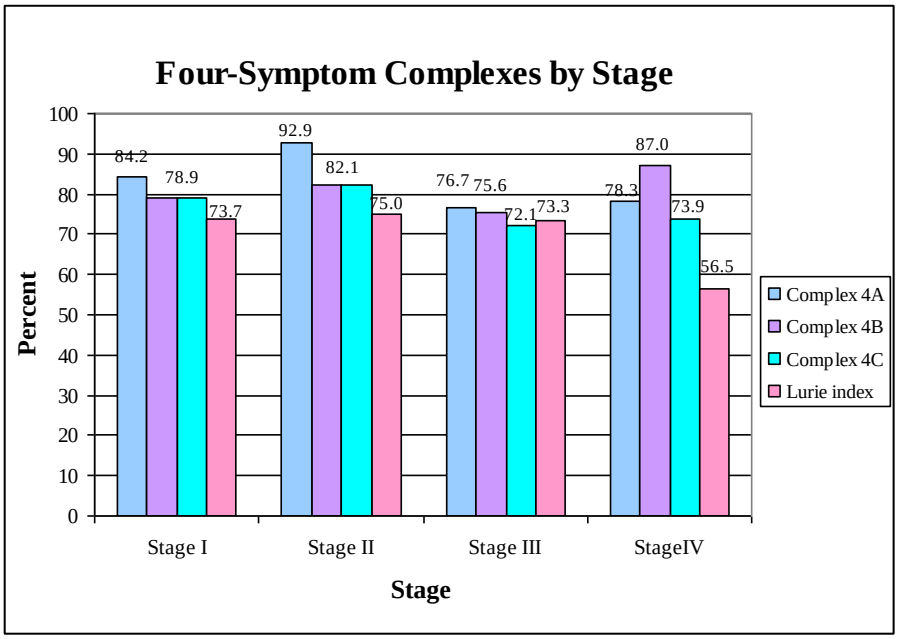


Figure 3.2 shows the percentage of women from each stage who were identified by the three most prevalent four-symptom complexes and the Lurie index. Complex 4A identified the largest percentage of women from stage I to stage III, while complex 4B identified the most women with stage IV. Complex 4B, which included abdominal/pelvic pain, increased abdominal size/bloating, abnormal vaginal bleeding or change in bowel habit, identified the most women (92.9% of stage II) out of any of the three or four-symptom complexes when investigated according to stage at diagnosis.

Figure 3.2. *Four-symptom complexes by stage*



3.3.3 Duration of time from symptom onset to seeking medical advice

A total of 161 women reported the month and year of symptom onset, and month and year they first visited a GP or other health care professional for advice relating to symptoms. The median duration of time between symptom onset and seeking medical advice was two months (range 1-77, IQR 1-4). As can be seen in Figure 3.3, 45.3% visited a health care professional within one month of symptom onset, 63.3% within two months and 73.9% within three months. Thirteen women (6.8%) did not seek medical advice for longer than one year.

Figure 3.3. *Months between symptom onset and seeking medical advice*

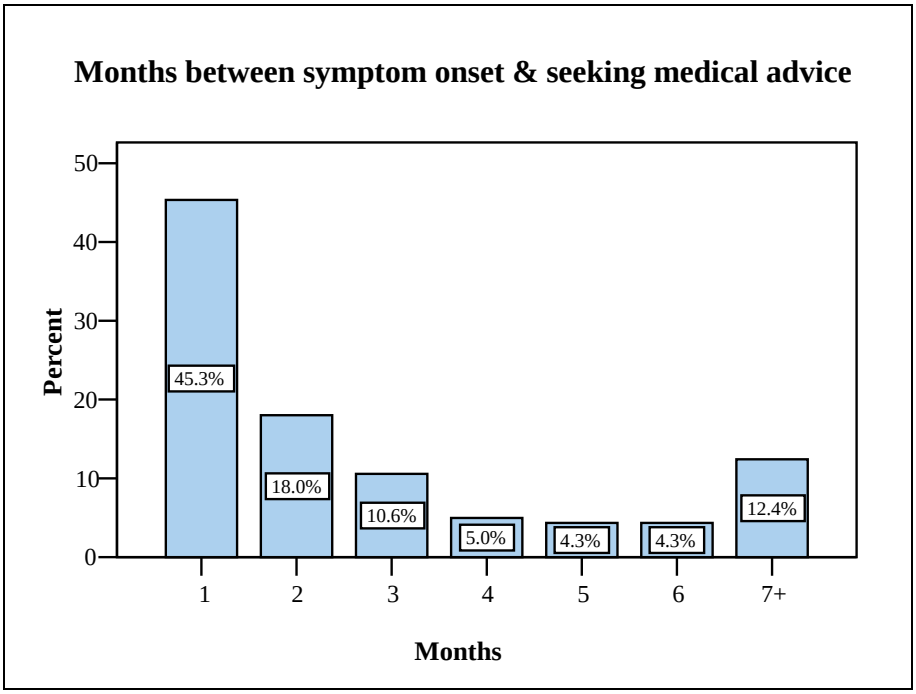


Table 3.7 lists the five women who did not seek medical care for longer than two years after symptom onset. All of these women experienced either increased abdominal size or bloating as a 'first' symptom. Respondent 1 first noticed an abdominal mass/lump, abdominal/pelvic pain and bloating. Respondent 2 noticed increased abdominal size and nausea. Respondent 3 noticed fatigue, bloating and abnormal vaginal bleeding as her 'first' symptoms. Respondent 4 noticed increased abdominal size, fatigue, bloating, change in weight and indigestion, while respondent 5 noticed increased abdominal size, abdominal/pelvic pain, bloating, change in bowel habit, UTI and change in weight. Three of these women received a diagnosis of suspected ovarian cancer at their first medical appointment, one within two appointments and another within four appointments.

Table 3.7. *Women who did not seek medical advice for two years or more*

No.	Age at diagnosis	Months to first appointment	Appointments to diagnosis	Tumour type	Stage
1	62	26	1	Don't know	II
2	56	26	4	Don't know	III
3	52	29	2	Borderline	I
4	54	77	1	Serous	II
5	63	77	1	Serous	III

There was no association between the number of symptoms women experienced and the number of months between symptom onset and seeking medical advice. There was also no association between stage at diagnosis and the number of months between symptom onset and medical consultation. Women diagnosed with stage I (range 1-29, IQR 1-3), stage II (range 1-77, IQR 1-5.5) and stage III (range 1-77, IQR 1-4.8) all experienced symptoms for a median of two months before consulting a doctor. Women with stage IV experienced symptoms for a median of one month (range 1-4, IQR 1-2) before seeking medical advice, however, this difference was not significant.

A total of 175 (93.1%) women visited a GP first for medical advice, 3% visited an unspecified hospital department, 2% an A&E department and 1% initially saw a practice nurse. There were 103 (54.8%) women who reported that one symptom initially led them to seek medical advice, 55 (29.3%) reported two symptoms and 24 (12.8%) reported three symptoms prompted them to consult their doctor.

While abdominal mass/lump and nausea or vomiting were less common symptoms overall, all of the women who reported these symptoms consulted their GP about them. Abdominal/pelvic pain (87.7%) was the next most common symptom which prompted women to consult their doctor, followed by heartburn or indigestion (80.0%) (Table 3.8). Surprisingly, only 65.6% of those with abnormal vaginal bleeding consulted their GP about the symptom.

Table 3.8. *Most common symptoms which prompted medical advice*

Symptom	No. with symptom (n =188)	No. symptom GP reported (n =188)	% of all women	% with symptom
Abdominal or pelvic discomfort/pain	65	57	34.6	87.7
Increased abdominal size	60	33	31.9	55.0
Bloating	48	30	25.5	62.5
Abnormal vaginal bleeding	32	21	17.0	65.6
Change in bowel habit	29	17	15.4	58.6
Tiredness or fatigue	40	14	21.3	35.0
Urinary frequency or urgency	35	14	18.6	40.0
Heartburn or indigestion	15	12	8.0	80.0
Abdominal mass or lump	11	11	5.9	100
Nausea or vomiting	9	9	4.8	100

With the exception of bloating, there were no associations between the type of symptom experienced and the length of time from symptom onset to seeking medical advice. Women who experienced bloating were more likely to wait longer than six months before seeking medical care (27.9% *vs*. 12.7%, $\chi^2(1) = 5.2$, $p = 0.02$).

Abnormal vaginal bleeding was the fourth most common symptom which prompted women to consult a doctor. While there was no significant association between abnormal vaginal bleeding and the length of time women waited until they consulted their doctor, six of the 32 women who experienced this symptom waited for more than six months after symptom onset before seeking medical advice.

3.3.4 Duration of time from initial medical consultation to diagnosis

Due to the design of the survey instrument, it was not possible to calculate the exact duration of time between initial GP visit for symptoms and the date of diagnosis. It was, however, possible to calculate the approximate number of years between women first seeking advice about symptoms and receiving a diagnosis of ovarian cancer.

Among the 174 women who wrote the year of first visit for symptoms and the year of diagnosis, 94.3% were diagnosed within one year and 98.3% within two years. There was no association between stage and the duration of time between first GP visit and diagnosis. Women diagnosed with early (range 1-2, IQR 1-1) and advanced disease (range 1-7, IQR 1-1) were diagnosed within a median of one year. However, this may have changed if it was possible to calculate the exact number of months between GP consultation and diagnosis.

Women attended a median of 3.5 appointments with health care professionals before receiving a diagnosis of ovarian cancer (range 1-11, IQR 1-4). There was no difference in the number of appointments according to age. Women diagnosed with stage I/II attended fewer appointments before they received a correct diagnosis compared to those with advanced disease (*Mdn* 2.0 *vs*. *Mdn* 3.0, U = 2161.0, p = 0.001, r = -0.26).

Women who reported that abnormal vaginal bleeding led them to consult their doctor were 4.75 (95% CI 1.37-16.48) times more likely to be diagnosed within three appointments (Table 3.9). All 11 women who reported abdominal mass or lump prompted them to seek medical advice received a diagnosis within three appointments. There were no other associations between symptoms women consulted their doctor about and the number of appointments required for a diagnosis to be made.

Table 3.9. *Symptoms associated with diagnosis within three appointments*

Symptom	n	≤ 3 appt. to diagnosis (%)	>3 appt. to diagnosis (%)	OR (95% CI)	p-value
Abnormal vaginal bleeding	174	25 (21.2)	3 (5.4)	4.75 (1.37-16.48)	0.008
Abdominal mass or lump	172	11 (9.4)	0	∞	0.017

Among the 173 women who provided details about the outcome of their initial medical consultation, 98 (56.6%) reported that they were not given a diagnosis or did not write information about the diagnosis, 23 (13.2%) were told they had a suspected ovarian mass, 16 (9.2%) were told they had IBS, 12 (6.9%) were diagnosed with a gynaecological condition not related to the ovaries, seven (4.0%) were diagnosed with a UTI and five (2.9%) with gastroenteritis. Three (1.7%) were told their symptoms were related to ageing or menopause, two (1.2%) were told they had gall stones, two (1.2%) were informed they needed to diet or exercise and another two (1.2%) were told they had diverticulitis. Other diagnoses, ranging from appendicitis to stress, were reported by only one woman each.

Forty-five (26.0%) women were referred to a gynaecological oncology consultant during their initial GP visit, 17 (9.8%) were referred for an ultrasound or CT scan, 13 (7.5%) were referred to another hospital department (e.g. gastroenterology or urology), 11 (6.4%) to a general surgeon and one woman was sent directly to A&E.

3.4 Discussion

The Ovacome patient survey was the first and largest study to-date to collect symptoms data directly from British women diagnosed with ovarian cancer. The survey parallels research by Goff *et al.*[13] who posted symptoms questionnaires to subscribers of the '*Conversations*' support group newsletter in the US and Canada.

Among Ovacome survey respondents aged 50 years or more at disease diagnosis included in these analyses, 90% experienced symptoms during the period leading up to their diagnosis. This is to be expected in a disease for which screening is currently not available and diagnosis is only possible if a woman presents to a doctor with symptoms. The finding is commensurate with several other questionnaire studies which reported approximately 90-95% of women experience symptoms prior to a diagnosis of ovarian cancer.[9 16-18 22 51 73] However, all but one of these studies found an increasing proportion of symptomatic women with more advanced disease. In contrast, in this data set there was no significant difference in the proportion of women with early stage disease who reported symptoms, compared to those with advanced disease. However, this may have arisen from selection bias, with symptomatic women across all stages more likely to take part in the survey than women who had no symptoms.

The lengthy period between diagnosis and participation in the research may also explain the absence of a difference in the proportion of symptomatic women across the stages. Research has found higher symptom levels increase the hazard of death in women with ovarian cancer.[98] Perhaps women with early stage disease with higher symptom levels had already died, and those with advanced disease who had low symptom levels survived, resulting in a balancing out of the proportion of symptomatic women across the stage categories.

Women reported a median of 3.0 symptoms during the period leading up to their diagnosis, while a median of three to 8.6 symptoms is reported in the literature.[7 17] The relatively low number of symptoms reported by Ovacome survey respondents most likely results from the open-question format of the questionnaire, which asked women to write down their 'first' and 'other' symptoms, but did not list symptoms which have previously been found to be associated with ovarian cancer. It is possible that women would have reported many more symptoms if they were presented with the 23 item list used by Goff *et al.*[23] especially as wider research has found open questions elicit comparatively few symptoms compared to checklists.[129 141 159-160] It is to be noted that the final endpoint of this research is to make it easier for doctors to diagnose ovarian cancer. The method currently adopted in consultations is open questions followed by a few directed questions

on specific symptoms. Using a checklist of a large number of symptoms for every consultation could prove difficult to implement.

The relatively low number of symptoms reported by Ovacome respondents also raises important questions about women's perception of symptoms and what they regard as precursors of cancer. Open questions rely on women having sufficient knowledge to spontaneously report symptoms of interest to the researcher and to remember these symptoms without the aid of memory cueing checklists, which can result in substantial under-reporting bias.[129 159] This is likely to have occurred in the Ovacome survey as the prevalence of bloating, abdominal/pelvic pain, fatigue and urinary symptoms were approximately half that reported by women in the Goff *et al.*[23] study. While a validated symptoms list in questionnaire-based research can correct this bias, it is itself associated with over-reporting bias.[129 141]

Despite using an open-question format, the types of symptoms reported by survey respondents were commensurate to those reported by women in other research. Several questionnaire studies and reviews of medical records have reported that abdominal/pelvic pain is the most common symptom of ovarian cancer.[6 12 14-16 19-20 22-23 50-51 73 121 135] This was also the most common symptom among survey respondents, with 35% reporting that they experienced the symptom leading up to their diagnosis.

Twenty-six percent of Ovacome respondents reported bloating, which is approximately half the number reported by Goff *et al.*[13] and Vine *et al.*[16], but equivalent to a Hong Kong study which used open-questions and a structured interview study conducted in Iran.[22 161] Perhaps this stems from differences in cultural interpretations of bloating, with US women being more attuned to the bodily sensation of bloating compared to women in other parts of the world. US women may also have a greater awareness of bloating as a symptom of benign conditions such as IBS or food intolerances.

The lack of awareness of bloating as a symptom of ovarian cancer among Ovacome survey respondents is evidenced by the finding that the symptom was associated with women waiting longer than six months before seeking medical care. Perhaps, once these women perceived the symptom, they interpreted it as a

normal physiological change associated with ageing or menopause, which research has found to be a reason for women not consulting their doctor earlier after symptom onset.[8 13 17 51]

Seven women reported that they experienced change in appetite, although only one reported feeling full quickly. This finding is at odds with some research which has described early satiety as a symptom predictive of ovarian cancer.[18 23 46-47 124] However, the low prevalence of the symptom among Ovacome women is not exceptional. Three other questionnaire studies did not describe feeling full as common symptom of ovarian cancer,[22 51 73] while a large medical records study found only 2% of women with ovarian cancer had early satiety recorded in their medical insurance notes.[121] However, it is conceivable that a greater number of Ovacome respondents may have reported appetite changes or feeling full if they were specifically asked about the symptom. Women in the Goff *et al.*[13] research were asked if they were 'unable to eat normally' during the period leading up to their diagnosis and 16% responded positively.

Given the median of four years between diagnosis and participation in the research, it is also probable that women forgot less salient symptoms such as feeling full. Other research has demonstrated exponential memory decay and has indicated that symptoms which are severe, unusual or characterised by rapid onset are more likely to be remembered.[131-132 147 159 162] Perhaps this may explain why few women reported the relatively subtle symptom of feeling full but many reported abdominal/pelvic pain and abnormal vaginal bleeding.

No associations were observed between age at diagnosis and the number or type of symptoms reported by women. Findings in the literature are equivocal, with two studies reporting age is negatively,[13 18] and one positively,[73] correlated with the number of symptoms reported. Previous studies have also found an association between age and stage of ovarian cancer,[15 19 73] although this was not observed among Ovacome respondents. The disparate findings in the present data may have arisen from analyses being restricted to those aged 50 years or over at diagnosis, while other studies included women as young as 18 years.

Two symptoms were associated with stage of disease at diagnosis. Women who reported abnormal vaginal bleeding were more likely to be diagnosed with early stage ovarian cancer. Vaginal bleeding in older women is always referred to a gynaecologist for investigation and is one of the symptoms requiring urgent referral for suspected cancer in the 2005 NICE guidance.[44] In addition, some slow growing cancers such as granulosa cell tumours secrete hormones which lead to bleeding and diagnosis in stage I. The finding corresponds to several previous studies,[11-12 19 47 49 73] including a meta-analysis which found gynaecological symptoms are more frequently reported among women with early stage ovarian cancer.[120] The association observed between change in bowel habit and advanced disease has also been widely reported.[15 20 22 51] It is often associated with delays in diagnosis due to referral to gastroenterological and surgical specialities. Despite being described in several studies, [9 16-17 49 73] no association was found between other non-gynaecological symptoms, such as urinary frequency/urgency or fatigue, and stage at diagnosis.

The Goff and Lurie symptom indices were used to interrogate the data to determine their sensitivity in this data set which had been collected without use of a checklist. Goff *et al.*[23] found their symptom index had a sensitivity of 67% for identifying women with ovarian cancer aged 50 years or over, while Lurie *et al.*[25] reported their index had a sensitivity of 74%. Among Ovacome survey respondents, the Goff index, modified to exclude symptom frequency and duration, maintained its sensitivity (68%). The four-symptom Lurie index had decreased sensitivity of 67% for women with ovarian cancer diagnosed over the age of 49. Complex 4A (abdominal/pelvic pain, increased abdominal size/bloating, abnormal vaginal bleeding and urinary frequency/urgency) had the highest sensitivity (81%) but it must be noted that the latter were not tested on an independent data set, which is usually associated with a fall in the estimated sensitivity.

The Goff and Lurie symptom indices seemed to have poor sensitivity for detecting early stage disease compared to the three and four-symptom complexes derived from the dataset. As stage at diagnosis is the most important determinant of survival in ovarian cancer,[53 99 119] this is a crucial factor in the evaluation of any

symptom index. This finding underscores the need for further research into symptom complexes among British with ovarian cancer, in a study that is not limited by recall bias. The wide publicity being mounted in response to the UK Department of Health 'Ovarian cancer - Key messages' document,[33] and the symptom diary being promoted by Ovarian Cancer Action,[31] adds urgency to this need as the latter does not include change in bowel habit. Abnormal vaginal bleeding is also not included but given that in postmenopausal women it is already part of the clinical guidance for urgent gynaecological cancer referral, omission of this symptom is of less concern for reducing delays in diagnosis. However, this symptom may need to be considered for inclusion in general ovarian cancer awareness campaigns aimed at postmenopausal women as abnormal bleeding did not always prompt women to seek medical advice.

The median duration of time between symptom onset and seeking medical advice was one month, which is similar to the findings of research conducted in the US, Hong Kong and Australia.[8 22 73] Unfortunately, due to the design of the survey instrument, it was not possible to calculate the number of weeks between these events. A concerning finding was that 26% of women reported three months or longer between symptom onset and medical consultation. This is substantially higher than the 8% who delayed longer than three months in another UK study.[14] This discrepancy may have arisen from the different methodological approaches. Kirwan *et al.*[14] study utilised primary care records and included all women diagnosed during a fixed period. The Ovacome research collected data directly from women and was perhaps biased by self-selection among those who experienced delays in diagnosis. Patients in the Kirwan *et al.*[14] study reported time of onset of symptoms to their GP with less recall bias and with no knowledge that they had ovarian cancer, unlike women in the Ovacome survey who reported symptoms a median of four years after diagnosis.

The Ovacome survey asked women to write the month and year of symptom onset, and the month and year of first seeking medical advice, but only the year of diagnosis. Unfortunately, this meant that it was not possible to calculate the number of months between symptom onset and diagnosis. This may have yielded

some interesting information, as another recent UK study reported a lengthy median duration 12 months between symptom onset and diagnosis.[46]

Abdominal mass/lump, nausea or vomiting and abdominal/pelvic pain were most likely to prompt women to seek medical advice, while only two-thirds of those with abnormal vaginal bleeding discussed the symptom with their GP. The reason for this is unknown, although it may be due to women interpreting abnormal bleeding as a symptom of menopause. Despite this, women who reported abnormal bleeding to their GP were most likely to receive a prompt diagnosis. Abdominal mass/lump was also associated with fewer appointments to diagnosis. Two studies have found abdominal mass/lump, abdominal/pelvic pain and abnormal vaginal bleeding to be important symptoms which prompt women to consult their doctor, although nausea or vomiting has not been described previously as a symptom most likely to lead women to seek medical care.[8 51]

No association was found between the duration of time between symptom onset and seeking medical advice, and stage of ovarian cancer at diagnosis. This finding is commensurate with two other studies,[8 51] although the largest study to investigate this found women who ignored symptoms were more likely to have advanced disease.[13] By contrast, Chan *et al.*[22] found women with advanced disease had shorter time intervals between symptom onset and seeking medical advice. The lack of an association among Ovacome women may have been the result of recall bias or selection bias due to the considerable length of time between diagnosis and participation in the research among some women.

Study strengths

Strengths of the Ovacome survey include the fact that it was the first UK study to collect ovarian cancer symptoms data directly from women with the disease. Ovacome is run by women living with ovarian cancer, which meant that the survey collected information important to women with the disease.

To-date, the Ovacome survey recruited the largest number of women with ovarian cancer of any UK study. This was achieved through the direct mailing of surveys to Ovacome members and encouraging them to direct other women with ovarian cancer to the Ovacome website where they could download the survey. This

method of snowball sampling, also used by Igoe[7], is a cost effective way of boosting recruitment.

Study limitations

Unfortunately, there were a number of problems with the design of the survey instrument, including not asking women to write down the month and year of their diagnosis and the use of open questions.

A disadvantage of the snowball sampling method used in the Ovacome survey is the inability of researchers to calculate response rates. It is likely that women with ovarian cancer who actually experienced symptoms, or had lengthy delays in diagnosis, responded more frequently than women who did not have these experiences. This self-selection bias may have inflated findings on symptom prevalence and the number of appointments required to make a diagnosis. A disproportionate number of survivors is also likely. These biases are shared with the Goff survey,[13] which used the same method of recruitment. In contrast, medical records research avoids this bias by systematically collecting data from all women diagnosed with ovarian cancer over a certain time period.

Women who participated in the survey may not have been representative of the wider population of British women with ovarian cancer due to the use of internet-based recruitment of women already aligned to the Ovacome group. These women are likely to have been younger, healthier and better educated than the general population of women living with ovarian cancer. Research has found a minority (22%) of the over-60s use the internet,[163] although this is likely to have increased considerably over recent years. The data set described in this chapter excluded women aged younger than 50 years at the time of diagnosis, yet the median age was still relatively low at 64 years. In order to participate, women required moderate to good English literacy skills as the survey was not translated into other languages. This would have resulted in the recruitment of women with higher education levels and less ethnic diversity, compared to the general population of women with ovarian cancer in the UK.

The findings of the research are also limited by recall bias. The four year interval between diagnosis and participation in the survey is considerably longer than the

average of 4.7 months reported by Olson *et al.*[17] However, half the women in Goff *et al.*[13] were recruited more than two years after diagnosis. No women were excluded from analyses due to lengthy time intervals between diagnosis and participation, as exclusion of women diagnosed for longer than three years would have reduced the data set by more than half. Recall bias was accepted as a significant and unavoidable limitation of the data. This emphasised the importance of collecting prospective data in my own research.

Women self-reported diagnosis of ovarian cancer in the Ovacome survey. This information was not confirmed by medical records or histopathology findings. The relatively long survival time among Ovacome survey respondents may have arisen from a disproportionate number of women diagnosed with less aggressive mucinous, endometrioid or borderline tumours. Unfortunately, poor knowledge of tumour subtype among women prevented exploration of this possibility. Another potential, although less likely, explanation is survey respondents did not correctly recall the year of their diagnosis.

Poor recall of the year of symptom onset may have been a factor among the five women who reported that they delayed consulting their doctor for 26 to 77 months after symptom onset. These women may have simply inaccurately recalled the year of symptom onset, or may have overestimated duration of symptoms, particularly if they felt their doctor had not listened to their concerns. These women were considered for exclusion from the data analysis. However, it is possible that women did experience symptoms for several years as a serum bank study found elevations in CA125 five years prior to clinical diagnosis,[56] while other research which modelled ovarian serous tumour progression estimated cancers originate, on average, nine years prior to clinical diagnosis.[164]

3.5 Summary

In this chapter I have presented findings from analyses of the Ovacome Patient Survey 2006. I found approximately one in four women experienced an interval of more than three months from symptom perception to presentation for medical care. Abdominal/pelvic pain, increased abdominal size, bloating, fatigue and

urinary frequency or urgency were the most commonly reported symptoms, while early satiety was rarely reported. Symptom complexes including abdominal/pelvic pain, increased abdominal size/bloating, abnormal vaginal bleeding and urinary frequency/urgency identified larger numbers of women compared to symptom indices described in the literature, and were particularly efficient for identifying women with early stage disease.

Analysis of the Ovacome data helped to identify symptoms for inclusion in the prospective research described in subsequent chapters of this thesis. As the survey was conducted among British women, similar symptom experiences are anticipated in the UKCTOCS cohort. Analyses were restricted by the design shortcomings of the Ovcacome survey instrument, although this highlighted the need to develop a robust ovarian cancer symptoms questionnaire for a prospective study. The next chapter describes development and validation of the questionnaire.

Chapter Four – Development of the Ovarian Cancer Symptoms Questionnaire (OCSq)

4.0 Introduction

This chapter describes development of the ovarian cancer symptoms questionnaire (OCSq) over a 28 month period from October 2006 to February 2009. The chapter begins with a discussion of the theoretical framework which underpins health questionnaire design and introduces the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire development methodology. Components of questionnaire validation are explored, followed by presentation of the research findings. These are divided into the four stages of the questionnaire's development.

Stage I - Generation of the ovarian cancer symptoms list, explains how a comprehensive list of ovarian cancer symptoms was identified from the literature. Stage II - Review of ovarian cancer symptoms questionnaires, describes findings from a review of existing questionnaires and the reasons why we had to develop our own questionnaire. Stage III - Revision of the symptoms list and formatting the provisional questionnaire, details the stepwise process of editing the symptoms list and drafting the questionnaire. Finally, Stage IV - Pilot of the provisional OCSq, details validation and reliability findings from the pilot of the draft questionnaire. The aims, methods and results of each stage are presented separately, followed by an overarching discussion and summary.

4.1 Theoretical frameworks for investigating symptoms

Symptoms studies may be broadly described as belonging to either the positivist biomedical model or the interpretivist tradition (although a minority of studies combine elements of both in mixed-methods frameworks). The biomedical model provides the theoretical foundation for bioscience and medicine. This framework bases knowledge on observable and measureable facts in the physical world. The paradigm maintains that disease is caused by specific, potentially identifiable,

biological agents or disease entities. These etiological explanations are paramount within the model, whereas subjective interpretations based on social, cultural or psychological factors are regarded as unreliable or irrelevant.[153-154 165] The biomedical model underpins well-known quantitative health surveys such as the Short Form 36 Health Status Questionnaire (SF-36) and the Health Survey for England. It also provides a framework for disease-specific measures, including ovarian cancer symptoms questionnaires.

Critics of biomedicine have argued that the primacy of observable facts has shifted the emphasis away from the symptom experiences of patients towards signs of illness. Aronowitz[27] suggests that prior to the dominance of biomedicine, symptoms were regarded as arising from, accompanying, or constituting a particular illness. As the influence of biomedicine increased, symptoms came to be reconsidered as subjective and arising from functions. Signs, meanwhile, were increasingly defined as perceptible and objective alterations of the body arising from altered physiological states.[27] Social scientists have argued that this transformation was accompanied by a change in focus, away from listening to patients' subjective symptoms, towards a search for signs of disease.[27-29] Patient advocacy groups may suggest this tendency is evident in the historical perception of ovarian cancer as a 'silent' disease and a research bias towards screening based on CA125 and ultrasound rather than symptoms indices.

Interpretivist and constructivist frameworks are alternatives to the biomedical model. Sociologists, anthropologists and psychologists commonly adopt these conceptual models in order to study symptoms. All interpretivist approaches emphasise human experience in the social world, rather than the physical world. Theorists working within these traditions view knowledge and truth as constructed rather than objective 'facts'.[166] Constructivists in particular are interested in the ways in which meaning, values, ideas and cultural concepts are socially constructed.[166-167] Researchers working within these paradigms typically investigate symptoms using qualitative methodologies such as ethnography, patient narratives or in-depth interviews. These methods are particularly useful for exploratory research into a particular phenomenon. For example, qualitative studies by Ferrell *et al.*[127], Fitch *et al.*[75], Koldjeski *et al.*[70] and Bankhead *et al.*[46]

played a vital role in elucidating symptoms of ovarian cancer and the ways in which women interpret and communicate bodily changes associated with the disease.

4.2 Health questionnaire design theory

The positivist biomedical paradigm provides a theoretical foundation for health questionnaires. This can be readily observed in the common aim to gather objective data on variables of interest, then, using statistical methods, to correlate with clinical diagnoses or health outcomes. However, it could also be argued that questionnaires go beyond the narrow limits of the biomedical model in the way they give credence to the subjective experiences of research participants. For example, a number of questionnaires have been developed to measure highly subjective phenomena such as pain and anxiety.

Foddy[129] notes that a stimulus-response model provides a conceptual framework which underpins the collection of 'objective' data in questionnaire research. This model refers to the theory that research participants will respond in comparable ways to a standardised stimulus (usually a single questionnaire item). Under this model, the researcher makes a number of implicit assumptions. Firstly, it is assumed that questions are understood in the same way by all respondents. It is also assumed that respondents will interpret questions in the way that the researcher intended them to be understood and that research participants will respond in the same way. Questionnaires typically utilise closed questions in order to fulfil this requirement for standardised responses. The standardised responses are then assumed to represent facts in the real world, rather than written interaction between the researcher and respondent. Perhaps the most important understanding required under the stimulus-response model is the assumption that standardised responses given by different respondents can be meaningfully compared with one another. All quantitative questionnaires and surveys operate under these assumptions, whether or not this is actually acknowledged by the researchers.

Questionnaires are typically informed by at least one other theoretical perspective in addition to the stimulus-response model. For example, Brooks[168] discusses the ways in which Lawton's (1972) behavioural model informed development of Katz's (1983) Instrumental Activities of Daily Living measure (IADL). Similarly, theories of well-being have informed the development of health-related quality of life measures (HRQoL). Fayers & Machin[169] describe how Calman's (1984) expectations model, which takes into account an individual's aims and goals in life, provided the conceptual basis for inclusion of personal values in the Patient Generated Index (PGI).

Symptoms questionnaires are usually informed by the stimulus-response model and the 'common sense symptom perception model' (described in Chapter One), both of which are grounded within the positivist biomedical paradigm. Under the common sense symptom perception model it is hypothesised that women with ovarian cancer are able to perceive symptoms of the disease. Furthermore, the severity, frequency and number of symptoms perceived by women should increase with advancing stage of ovarian cancer.

4.2.1 EORTC questionnaire development methodology

A number of questionnaire development textbooks and articles were consulted throughout the research period.[129-130 168-176] These outlined rigorous questionnaire development methods and described essential components of the validation process. Reading this literature identified the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group questionnaire development methodology as well established in producing valid and reliable tools for measuring cancer-related symptoms.[169-170] Furthermore, EORTC questionnaire development methodology fulfils six of the seven criteria described by Guyatt *et al.* (1986, in Brooks[168]) as a 'Rolls-Royce' model of questionnaire development. The one criterion not met is the requirement for questionnaires to contain Likert scales consisting of seven to 10 points. This number of categories is also described by Streiner & Norman[130] as ideal for good reliability of questionnaires. By contrast, EORTC questionnaire methods specify, 'items should preferably employ four-point Likert scales'.[177] Moreover, validation of four-point

Likert scales by the EORTC group among diverse cancer populations has proven good reliability.[178-183]

The EORTC approach to questionnaire development was also adopted on the basis of demonstrated success in producing a valid and reliable measure for assessing symptoms in ovarian cancer patients.[184-185] The EORTC ovarian cancer module (QLQ-OV28) was developed to assess treatment-related symptoms and quality of life. Unfortunately, the post-diagnosis focus of the questionnaire meant that the tool itself was inappropriate for our own research.

On the basis of this information, it was decided to use an EORTC questionnaire development methodology. Guidelines published by the EORTC Quality of Life Group informed the research described in this chapter.[177 186-187] However, some aspects of the methodology were not appropriate as the ovarian cancer symptoms questionnaire was not designed as a psychometric measure. The next section describes the principal components of questionnaire validation.

4.2.2 Questionnaire validation methods

Questionnaire development methods describe a number of different components of validation. Face, content and construct validation are requisite to demonstrate the acceptability and usefulness of any health questionnaire, while reliability analyses are essential to establish the consistency of a tool.

Face validation is the fundamental component of questionnaire validation. This assesses whether a questionnaire is readable, appears to be sensible and whether the items in a tool appear to measure the construct they claim to measure. Questionnaires should be visually appealing, with an uncluttered design. Clear instructions showing respondents how to complete items should always be included and the basic format should be readily understandable. Face validity is vitally important as it promotes acceptance of the questionnaire among research participants. It is only after a questionnaire has demonstrated face validity that other aspects of validity can be investigated.

Content validation assesses whether the items in a questionnaire are relevant and whether it is comprehensive enough to adequately investigate the subject it is designed to measure. Convergent validity, also referred to as construct or trait validity, refers to the consistency with which individual items in a questionnaire measure the same theoretical construct. While there is no single experiment to prove construct validity, a number of different internal consistency analyses may be undertaken to assess convergent validity.

Questionnaires which set out to measure a single construct, such as depression, should have high internal consistency. This is determined by assessing correlations between items in a questionnaire, and the extent to which they correlate with an overall score. Cronbach's alpha statistic, sometimes using a split-half method, is often utilised for this purpose. Factor analysis typically follows correlation analyses in the development of psychometric scales. This allows simplification of a large number of correlated variables based on underlying constructs or 'factors' in order to reduce the number of items in a scale.

Concurrent validity, also referred to criterion or discriminant validity, involves assessment of a questionnaire against an established 'gold standard' to determine whether the new questionnaire measures the same construct. In clinical trials, discriminant validity refers to the ability of a health measure to distinguish clinically significant outcomes in therapeutic responses among cases and controls.[168] For example, the EORTC core questionnaire (QLQ-C30) has been used to assess treatment-related quality of life outcomes in randomised controlled trials conducted in 35 countries.[188]

Test-retest reliability refers to the ability of a questionnaire to consistently capture equivalent information over time, other things being equal. Depending on the intended use of the questionnaire, reliability is determined either by different observers using the same tool to assess the same person (inter-observer reliability), or by a single observer using the questionnaire on different occasions (intra-observer reliability). For questionnaires completed by research participants, rather than the researcher, intra-observer reliability is assessed. Respondents are

asked to complete the same questionnaire within a time-frame when the outcome of interest is expected to be stable. The test-retest interval should not be too short or the respondent's memory will influence responses but it should also not be too long, or the phenomenon being measured may have changed. The intraclass correlation coefficient is commonly used to assess the reliability of health questionnaires. High reliability coefficients indicate that a measure has good stability. Questionnaires with low reliability should either be redesigned and re-validated or excluded from use.

4.3 Stage I - Generation of the ovarian cancer symptoms list

4.3.1 Aim

- To generate an exhaustive list of symptoms described as associated with ovarian cancer by previous research

4.3.2 Methods

4.3.2.1 Literature search

The literature search sought to identify journal papers and conference proceedings describing research into the symptoms of ovarian cancer. Three electronic databases were searched: Cinahl, Embase and PubMed. The search was limited to English language articles, papers referring to human subjects and to the period from 1980. Databases were searched using the terms listed in Table 4.1.

Table 4.1. *Database search terms*

Database	Search terms
Cinahl	#1 cancer* OR malignan* OR tumo?r* OR neoplasm* OR carcinoma* (AB) #2 #1 AND ovar* (AB) #2 AND symptom* (AB)
Embase	#1 cancer* OR malignan* OR tumo?r* OR neoplasm* OR carcinoma* (TI) #2 #1 AND ovar* (TI) #2 AND symptom* (TI)
Pubmed	#1 cancer* OR malignan* OR tumo?r* OR neoplasm* OR carcinoma* (TI) #2 #1 AND ovar* (TI) #2 AND symptom* (TI)

Search terms based on Bankhead et al.[120]

Reference lists of articles were read to identify other potentially relevant papers not retrieved through the literature search. Electronic searches were also conducted from the homepages of seven journals: Gynaecologic Oncology, International Journal of Gynaecological Cancer, European Journal of Gynaecological Oncology, British Journal of Obstetrics and Gynaecology, European Journal of Obstetrics and Gynaecology, Obstetrics and Gynaecology and Current Obstetrics and Gynecology. Saved literature searches were used to set up automatic email alerts from databases and journal homepages. Literature searches for the purpose of generating an ovarian cancer symptoms list concluded in January 2007.

4.3.2.2 Generation of the symptoms list

The titles of articles retrieved through literature searches were initially screened and the abstracts of potentially relevant papers were read to exclude those not directly related to the topic of ovarian cancer symptoms. The following inclusion and exclusion criteria were then applied to identify articles suitable for generation of the symptoms list.

Inclusion criteria

- Articles describing original research into the symptoms of ovarian cancer

Exclusion criteria

- Articles describing symptoms post-diagnosis
- News articles and commentaries
- Reviews of previous research
- Case reports
- Research exclusively based upon International Classification of Disease (ICD) codes or medical insurance codes for symptom descriptions

After applying these criteria the remaining papers were carefully read to extract all symptoms terms. The symptoms list was generated by typing each new term and reference source directly into an Excel spreadsheet whilst reading the article. All symptoms described as occurring during the period leading up to diagnosis were included. Similar symptom terms were separately listed, for example: abdominal bloating, bloated, abdominal bloating or pressure, bloatedness, bloating, etc.

4.3.3 Results

The literature search identified 157 potentially relevant papers in Cinahl, 58 in Embase, and 50 in Pubmed. After screening and additional searches, 45 journal papers, one conference poster and one conference abstract were read in full. A total of 37 articles fit the criteria for inclusion. One case report, by Goldberg *et al.*[189], was included as this provided additional information on a cohort of 52 patients. The paper by Portenoy *et al.*[143] was included as it described pain 'associated with disease onset' in addition to post-diagnosis pain symptoms.

At the conclusion of the stage I a list of 349 ovarian cancer symptoms were generated from the literature. These terms and reference sources are listed in appendix 1.

4.4 Stage II – Review of ovarian cancer symptoms questionnaires

4.4.1 Aims

- To critically review existing ovarian cancer symptoms questionnaires in order to identify design strengths and weaknesses
- To assess whether any existing questionnaire (or its sub-components) could be used in the prospective study

4.4.2 Methods

4.4.2.1 Questionnaire acquisition

Articles included in the generation of the symptoms list were categorised as either: 1) potentially utilising a symptoms questionnaire; 2) using qualitative methods; or 3) utilising medical or insurance records. Papers published after the symptoms list was compiled were categorised in the same way up until May 2008 when the draft OCSq was formatted. Authors of articles which appeared to use a questionnaire were contacted and a copy of their research tool was requested. Using the criteria below, each questionnaire was then critically appraised to assess face and content validity. This process was overseen by a lecturer experienced in the development of health questionnaires.

4.4.2.2 Questionnaire assessment criteria

- Does the questionnaire actually measure ovarian cancer symptoms?
- What is the length of the questionnaire? Is it too short or too long?
- How many symptoms are included?
- Symptoms question format – open or closed?
- Does the questionnaire include any symptoms not covered by the draft symptoms list?
- Is the layout visually appealing and user friendly?

- Is the wording readily comprehensible by persons of average literacy?
- How are symptoms measured? Individually or in combinations?
- Does the questionnaire assess symptom severity?
- Does the questionnaire assess symptom frequency?
- Does the questionnaire assess symptom duration?
- Does the questionnaire collect information on symptoms reported to GPs?
- What are the main strengths of the questionnaire?
- What are the main weaknesses of the questionnaire?
- Could the questionnaire, or a sub-component, be used for the planned research?

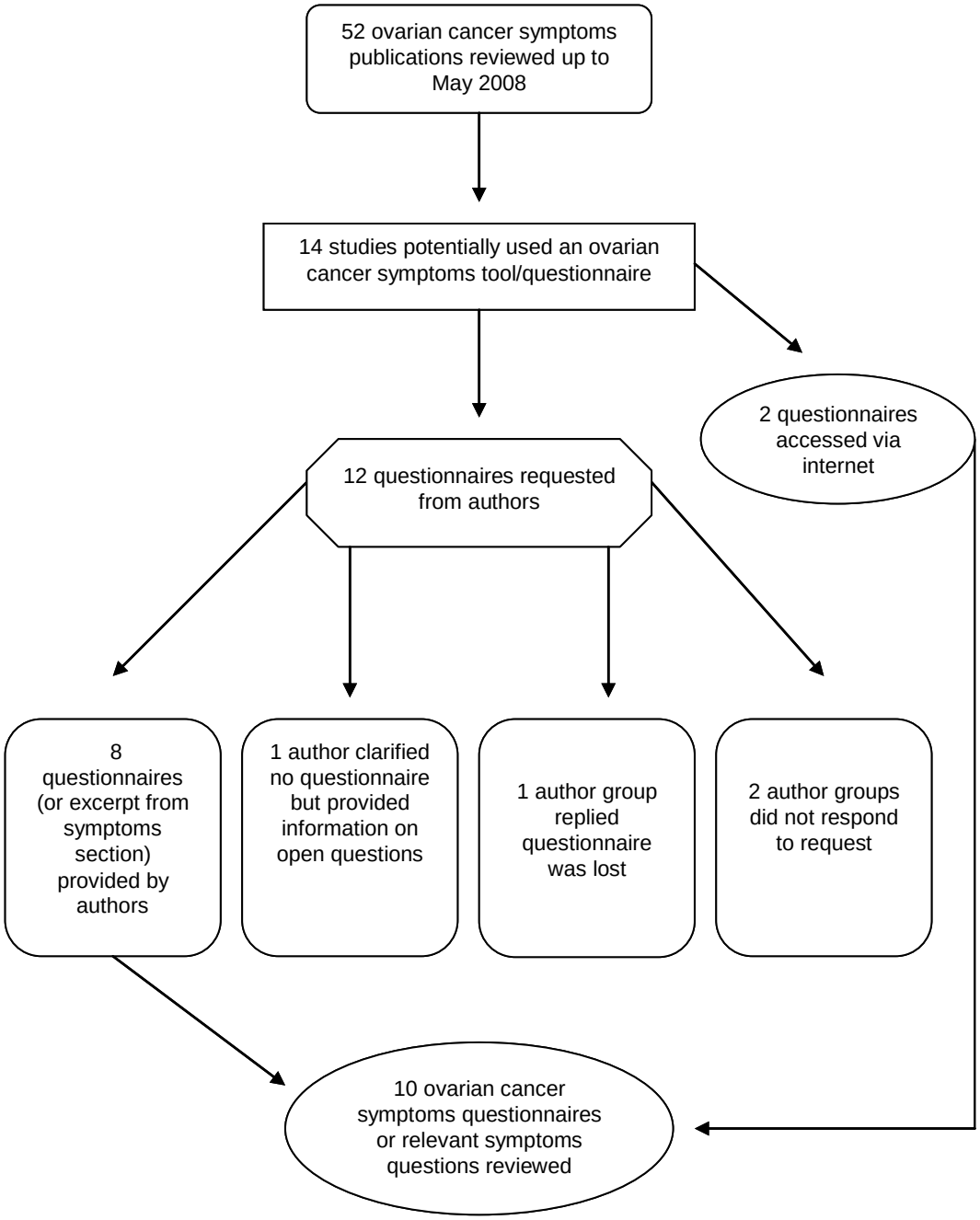
4.4.3 Results

4.4.3.1 Questionnaire acquisition

By May 2008, 52 ovarian cancer symptoms articles had been read in full. Thirteen of the 37 articles included in the generation of the symptoms list were identified as potentially utilising a questionnaire (appendix 1). One additional paper, published by Olsen *et al*.[51] in late 2007, also used a symptoms questionnaire and was included in the review. From a total of 14 articles, two questionnaires were accessed directly through internet searches. The remaining 12 authors were contacted, or contact was attempted, and a copy of their research tool was requested (Figure 4.1).

Two author groups did not respond to the request to provide a copy of their questionnaire and one group responded that the questionnaire had been lost. One author replied stating his study did not use a questionnaire but provided information on the open questions participants were asked. Eight author groups provided either their full questionnaire or an excerpt containing the symptoms questions. By the conclusion of this process a total of ten questionnaires, or relevant symptoms sections, were reviewed.

Figure 4.1. *Questionnaire acquisition process*



4.4.3.2 Questionnaire review findings

Table 4.2 provides a summary of the main findings of the questionnaire review and Table 4.3 describes the strengths and weaknesses of each questionnaire. As discussed in the literature review, two previously developed ovarian cancer symptoms questionnaires are described as having undergone a form of validation.[7] [70] However, these papers provided scant details of the validation process. Igoe[7]

stated that the questionnaire used in her research had undergone reliability testing in addition to face and content validation, yet the paper fails to fully explain these components of the research. A rather restricted validation is described by Koldjeski *et al.*[70], who state that their symptoms checklist had undergone congruent validity testing, although the authors do not provide any details. Good practice in questionnaire design includes sharing questionnaires, and validation findings, when requested by other researchers. Unfortunately, I was unable to obtain copies of the questionnaires developed by these authors, or full details of their validation methods and results. The authors either did not receive, or ignored, requests to provide these documents. The principal finding of the review was, therefore, the absence of a readily available ovarian cancer symptoms questionnaire which had been previously validated by another research group.

The secondary finding of the review was that no existing questionnaire was entirely suitable for our planned prospective research. As can be seen in Table 4.3, the 2007 Goff questionnaire was most compatible with our need for an instrument to collect information on a wide number of symptoms, to assess severity, frequency and duration of symptoms, and to measure reporting of symptoms to GPs. This questionnaire also had a visually appealing layout and was easily understandable. The main disadvantage of this questionnaire was the complexity of its Likert scales. It was noted that the range of six response categories for frequency, and seven for duration, may confuse respondents without necessarily improving validity or reliability. Given that the target population for the finalised questionnaire are women aged 50 to 80 years, it was thought that simplified Likert scales should be used. A further consideration in relation to the Goff questionnaire was the number of symptoms included. Their list of 23 symptoms appeared comprehensive, however it was noted that additional symptoms identified in stage I may need to be included in our own questionnaire.

Two questionnaires, by Bayne & Gilbert and the Webb group collected information about symptoms using open questions. All other questionnaires listed symptoms associated with ovarian cancer and asked respondents to indicate whether or not these were experienced during the period up to diagnosis or participation in the questionnaire. It was noted that open questions could result in

under-reporting of symptoms as women are not prompted to remember specific symptoms. Other limitations of open questions are the need to provide adequate space for women to write in all relevant information. Unfortunately, the Webb questionnaire provided only three short lines for women to write down symptoms. A further concern regarding open questions is the need to collect all relevant information. Without asking about specific symptoms, there is the possibility that respondents may report multiple irrelevant symptoms and overlook symptoms relevant to ovarian cancer. These issues led to the decision to include a list of specific symptoms in our own questionnaire.

The questionnaire by Olsen asked women about abdominal pain or pressure but did not include pelvic symptoms. Questionnaires developed by Olson and the Vine groups combined abdominal and pelvic symptoms together, while all the Goff questionnaires asked about pelvic and abdominal symptoms separately. In order to collect specific information about the area of the body where women experience pain symptoms, it was decided to adopt the Goff group's format and ask women about pelvic and abdominal symptoms separately.

The number of symptoms listed in questionnaires ranged from three to 23. This variability is largely explained by different approaches to the wording of individual items, although the comprehensiveness of different questionnaires is also a factor. For example, the Goff questionnaires only combined very similar symptoms, such as nausea and vomiting, but did not combine symptoms in different parts of the body. By contrast, the Vine questionnaires combined bloating with bowel symptoms such as diarrhoea, constipation and gas, while the Olson questionnaire combined back pain with abdominal or pelvic bloating symptoms. None of the authors explained the reasons why they decided to group certain symptoms together into single items.

Table 4.2. *Questionnaire review, summary of findings*

Authors	OC symptoms	Pages/symptom questions	Format	No. symptoms	Symptoms not in draft list	Layout	Wording	Individual or combinations of symptoms	Severity	Frequency	Duration	GP Reported
Bayne & Gilbert (2007)	Symptoms section in a larger questionnaire investigating diagnosis, treatment and care	15 pages, 4 symptom questions	Open questions	None	N/A	Appealing except matrix section: too little space, doubtful whether women could remember details of 10 GP visits, quality of information from matrix doubtful	Clear and easily comprehensible except for treatment names and jargon term NICE	N/A	No	No	Only asks year of first symptom onset then year of diagnosis. Not exact dates	Yes. Asks if women visited GP or other health care provider after onset of first symptom or if not what made them visit their GP/A&E. Detailed information about GP visits in matrix section but probably too confusing to yield quality information

Authors	OC symptoms	Pages/symptom questions	Format	No. symptoms	Symptoms not in draft list	Layout	Wording	Individual or combinations of symptoms	Severity	Frequency	Duration	GP Reported
Goff et al. (2000)	Questionnaire about symptoms and diagnosis	2 pages	Mainly closed-ended	18	No	Largely appealing although layout is a little cramped. Tick boxes and line to write 'other' symptom	Clear and easily comprehensible	Individual symptoms listed	No	No	Yes, asks how long it took a doctor to make a diagnosis. Asks how long symptoms experienced before surgery – n/a, 1 month, 2 months, 3-4 months, 5-6 months, 7-9 months, 10-12 months, over a year	Women asked when they first saw a doctor about symptoms but not which type of symptoms they consulted about

Authors	OC symptoms	Pages/symptom questions	Format	No. symptoms	Symptoms not in draft list	Layout	Wording	Individual or combinations of symptoms	Severity	Frequency	Duration	GP Reported
Goff et al. (2004)	Questionnaire about symptoms	Symptoms section – single matrix	Closed-ended	20	No	Appealing tick-box Likert scales	Clear and easily comprehensible	Individual symptoms listed	Yes, Likert scale from 0-no symptom, 1-minimal, to 5-severe	Yes, Likert scale for days per month symptom experienced - <1 day, 1-2 days, 3-6 days, 7-12 days, 13-19 days, ≥ 20 days	Yes, Likert scale for number of months symptom has persisted - <1 month, 1-2 months, 3-4 months, 5-6 months, 7-9 months, 10-12 months, > 12 months	Asked reason for clinic visit at time questionnaire was completed but no detailed information on separate symptoms reported to GP/other health care professionals

Authors	OC symptoms	Pages/symptom questions	Format	No. symptoms	Symptoms not in draft list	Layout	Wording	Individual or combinations of symptoms	Severity	Frequency	Duration	GP Reported
Goff et al. (2007)	Questionnaire about symptoms	5 pages	Closed-ended	23	No	Appealing tick-box Likert scales	Clear and easily comprehensible	Individual symptoms listed	Yes, Likert scale from 0-no symptom, 1-minimal, to 5-severe	Yes, Likert scale for days per month symptom experienced - <1 day, 1-2 days, 3-6 days, 7-12 days, 13-19 days, ≥ 20 days	Yes, Likert scale for number of months symptom has persisted - <1 month, 1-2 months, 3-4 months, 5-6 months, 7-9 months, 10-12 months, > 12 months	Separate tick boxes for 23 symptoms – asks women to tick all that prompted them to seek medical advice in the last year

Authors	OC symptoms	Pages/symptom questions	Format	No. symptoms	Symptoms not in draft list	Layout	Wording	Individual or combinations of symptoms	Severity	Frequency	Duration	GP Reported
Olsen et al. (2007)	Questionnaire about symptoms and diagnosis	Full questionnaire not provided, length unknown	Mainly closed-ended	11	No	Layout not known	Clear and easily comprehensible	Mainly individual symptoms (e.g. unexplained weight loss) Some combined symptoms (e.g. gas, nausea or indigestion; unexplained bleeding/discharge)	No	No	Yes, for each symptom, asks month/year of onset and month/year when a doctor was first visited about the symptom	For each symptom, asks whether a GP was consulted about the symptom and asks month/year when doctor was first visited about the symptom

Authors	OC symptoms	Pages/symptom questions	Format	No. symptoms	Symptoms not in draft list	Layout	Wording	Individual or combinations of symptoms	Severity	Frequency	Duration	GP Reported
Olson et al. (2001)	Symptoms section in a larger survey of risk factors for ovarian cancer	47 pages in total, 2 pages on symptoms	Closed-ended	11 items but 3 of these on medications related to symptoms	No	Slightly cramped and confusing	Some terms (e.g. intermittent) could be difficult to comprehend	Some individual symptoms (e.g. nausea) Some combined symptoms (e.g. unusual abdominal or lower back pain; unusual bloating, fullness & pressure in the abdomen and pelvis)	No	Yes, asks whether each symptom was constant or intermittent, asks how many times each symptom was experienced and if this was on a day, week or month basis	Yes, for each symptom asks how many months experienced	No

Authors	OC symptoms	Pages/symptom questions	Format	No. symptoms	Symptoms not in draft list	Layout	Wording	Individual or combinations of symptoms	Severity	Frequency	Duration	GP Reported
Portenoy et al. (1994)	Set of questionnaires reviewed but none specific to ovarian cancer so excluded from assessment	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Authors	OC symptoms	Pages/symptom questions	Format	No. symptoms	Symptoms not in draft list	Layout	Wording	Individual or combinations of symptoms	Severity	Frequency	Duration	GP Reported
Vine et al. (2001)	Symptoms section in larger epidemiological survey of reproductive health	56 pages in total, 1 page on symptoms	Closed	3	No	Visually appealing, good spacing in symptoms section but then not enough space before symptoms and question about first GP visit	Clear	Combination for two symptoms (pelvic or abdominal discomfort such as heaviness, fullness, pressure or pain; bowel irregularity such as diarrhoea, constipation, gas or bloating) One individual symptom (need to urinate more often than usual)	No	No	Yes, for each symptom asks how many months symptom experienced before diagnosis	Asks the primary reason for the visit to the doctor that led to diagnosis but does not specifically ask which symptom prompted visit to doctor

Authors	OC symptoms	Pages/symptom questions	Format	No. symptoms	Symptoms not in draft list	Layout	Wording	Individual or combinations of symptoms	Severity	Frequency	Duration	GP Reported
Vine et al. (2003)	Questionnaire about symptoms and diagnosis	6 pages in total, 3 pages on symptoms	Closed	11	No	Visually appealing at first glance, table format and horizontal shading, but on closer inspection it becomes confusing – coding in boxes and final column too messy	Clear	Some individual symptoms (e.g. fatigue) Some combined symptoms (e.g. gas, nausea or indigestion ; pelvic or abdominal discomfort such as heaviness, pressure or pain) Abdominal and pelvic symptoms asked together	No	No	Yes, asks month and year of onset of each symptom and asks how long each symptom lasted	Yes, asks if doctor seen for each symptom and asks the month and date a doctor was seen

Authors	OC symptoms	Pages/symptom questions	Format	No. symptoms	Symptoms not in draft list	Layout	Wording	Individual or combinations of symptoms	Severity	Frequency	Duration	GP Reported
Webb et al. (2004)	Symptoms section in larger epidemiological survey of ovarian cancer	Symptoms section – two pages	Mainly open questions	None	N/A	Very confusing, unclear which boxes require information, unclear what type of information is required in each box	Wording is clear but uses jargon word practitioner instead of doctor	N/A	No	No	No	Yes but confusing way of asking, asks respondent to code type of practitioner seen on multiple visits, asks for detailed information about each visit, questionable whether this information is reliable

Table 4.3. *Main strengths and weaknesses of questionnaires*

Authors	Strengths	Weaknesses	Appropriate for prospective research
Bayne & Gilbert (2007)	Generally clear wording Open questions allow women to describe symptoms using their own language	Too long Some sections (e.g. matrix) too complex to collect reliable data Open question format does not remind women of potentially important symptoms – leading to underreporting No accurate assessment of symptom duration Symptom severity and frequency not assessed	No
Goff et al. (2000)	Fairly comprehensive list of 18 symptoms of ovarian cancer Provides space for women to write an 'other' symptom not in the list Assesses symptom duration in months	Focus mainly on diagnostic procedures and processes rather than symptoms Symptom severity and frequency not assessed	No
Goff et al. (2004)	Comprehensive list of 20 symptoms of ovarian cancer Clear and concise Collects information on symptom severity, frequency and duration	Does not collect detailed information about reporting of symptoms to GPs/ other health professionals	No

Authors	Strengths	Weaknesses	Appropriate for prospective research
Goff et al. (2007)	Comprehensive list of 23 symptoms of ovarian cancer Good length overall, not too long Clear and appealing layout Includes section about symptoms which prompted women to seek medical attention in the last year Includes depression scale and measure of positive and negative affect	Questionable whether Likert scales with 6 to 7 categories (e.g. frequency and duration) on past events actually improve validity/reliability	Maybe – although would have to investigate possibility of reducing the number of response categories on the Likert scales and adding symptoms from the draft issues list
Olsen et al. (2007)	Collects comprehensive information about symptom reporting to GPs Asks month and year of symptom onset and month and year the symptom was first reported to a GP for all symptoms	Does not specifically ask about pelvic symptoms, only abdominal Symptom severity and frequency not assessed	No
Olson et al. (2001)	Collects comprehensive information on symptom frequency	Includes questions about medication use (e.g. were you taking laxatives to prevent constipation?) in with symptoms questions Does not ask any information about symptom reporting to GP/other health care professionals Layout is confusing	No

Authors	Strengths	Weaknesses	Appropriate for prospective research
Vine et al. (2001)	Clear and concise Uncluttered layout	Very long questionnaire but symptoms section too brief Combines different symptoms together (e.g. discomfort, heaviness, fullness, pressure or pain) Combines abdominal and pelvic discomfort/pain symptoms into one item Symptom severity and frequency not assessed	No
Vine et al. (2003)	Collects comprehensive information about symptom reporting to a GP/other health care professional For all symptoms - asks month and year of symptom onset and month and year the symptom was first reported to a GP/other health professional	Combines different symptoms together (e.g. abnormal bleeding and abnormal discharge) Combines abdominal and pelvic discomfort/pain symptoms into one item Symptom severity and frequency not assessed	No
Webb et al. (2004)	Open questions allow women to describe symptoms using their own language	Very confusing format Symptom severity, frequency and duration not assessed Respondents not likely to remember the detailed information they are asked to provide about GP visits	No

Another finding from the questionnaire review was the importance of an appealing and easy-to-understand layout. Questionnaires with good spacing and symmetry were much more inviting to complete than those which were cramped or cluttered with data coding instructions. It was noted that Likert scales are visually appealing and useful for capturing detailed information, although scales with more than five categories appeared overwhelming. The format of the Vine 2003 questionnaire (large table with headed columns and shaded rows) was most appealing at first glance. For our own questionnaire, it was decided to combine the layout of the Vine 2003 questionnaire with Likert scales similar to those used in the Goff 2007 questionnaire.

By the conclusion of stage II it was apparent that no existing questionnaire met the data collection or design specifications required for our prospective study of ovarian cancer symptoms. It was therefore decided to continue using EORTC questionnaire design methodology to develop our own questionnaire. The next stage describes the process of refining the ovarian cancer symptoms list and formatting a draft questionnaire.

4.5 Stage III – Revision of the symptoms list and formatting the provisional questionnaire

4.5.1 Aims

- To use feedback from health professionals and patients to check the comprehensiveness and appropriateness of the symptoms list
- To revise the list for brevity without deleting important symptoms
- To identify and solve potential problems in the administration of the OCSq

4.5.2 Methods

4.5.2.1 Preliminary revision of the symptoms list

The symptoms list generated from the literature was reviewed by a consultant gynaecological oncologist with extensive experience developing questionnaires according to EORTC guidelines. The purpose of this preliminary review was: 1) to remove very similar and duplicate terms in order to reduce the size of the list; 2) to remove medical terminology and replace with lay language where appropriate. This preliminary review took place on 25 January 2007.

4.5.2.2 First consensus group review of the symptoms list

A group of 12 clinicians, nurses, researchers and a patient peer group representative met on 30 January 2007 to revise the symptoms list. The group systematically discussed each symptom, debating its relevance, changing wording where they felt it could be improved and making suggestions for the final draft. The revised list of symptoms agreed by the consensus group was used for health professional interviews.

4.5.2.3 Interviews with health professionals

Interviews were conducted with surgeons and nurses with expertise in the management of ovarian cancer in patients presenting clinically, as well as those identified through UKCTOCS. Five regional gynaecological oncology departments out of 13 potential sites were purposively selected to maximise regional and socio-economic diversity. We sought to recruit one site each in Northern Ireland, Wales, the north of England, the south of England and London.

The UKCTOCS lead clinician and lead nurse in each site were contacted by email and provided with a description of the proposed research. The leads discussed the proposal with local staff before indicating whether or not the team, as a whole, was willing to participate. None of the sites refused to participate, although some requested additional information before agreeing to take part.

Interview dates and times were arranged through the lead nurse in each site. Verbal consent was provided by all health professionals prior to participation and

interviews were conducted face-to-face in consultation rooms, meeting rooms and office spaces. The only potentially identifiable information written on the symptom questionnaire was the interview location and the participant's professional role. No other personal information was recorded. Interviews lasted 21 to 50 minutes.

The symptom questionnaire completed by health professionals (appendix 2) required a relevance score to be given to each symptom. Respondents scored symptoms based on their knowledge and experience working with postmenopausal women diagnosed with ovarian cancer. The focus on postmenopausal women was due to the intention to use the finalised OCSq in the UKCTOCS cohort, where all volunteers are postmenopausal. A score of one on the Likert scale denoted a symptom as 'not at all' relevant, while four represented 'very much' relevant. Respondents were also asked to select up to 25 symptoms they would prioritise from the list of 82 for inclusion in a draft questionnaire. They were also asked to identify additional symptoms not already listed in the list, but which they considered to be important for a finalised questionnaire.

After completing the symptom questionnaire, health professionals were invited to participate in semi-structured tape-recorded interviews. The format of the interview followed EORTC questionnaire development guidelines. For each symptom that the participant scored 'not at all' or 'a little relevant', they were asked to describe the reasons behind their decision. Participants were also asked to provide information about additional symptoms they suggested for inclusion in the finalised questionnaire.

Data from the questionnaires was entered into SPSS version 12.0.1 (SPSS Inc., Chicago, USA). Following EORTC guidelines, mean relevance scores were calculated for each symptom by averaging scores on the Likert scale. The percentage of health professionals who prioritised each symptom was also calculated.

Tape-recorded interviews were transcribed verbatim. The transcripts were then read through while the interviews were played back to check for errors or omissions. Once the transcripts were quality-assured they were imported into

QSR-Nvivo version 7 (QSR International, Doncaster, Australia) for analysis. Transcripts were manually coded using quantitative content analysis techniques.[190-192] 'Free nodes' were created for each symptom that health professionals discussed. Transcripts were systematically analysed to ensure that all relevant text was coded. When data coding was complete the content of each node was read to check for accuracy. The validated nodes were then exported into a Word document for discussion during the second consensus meeting.

4.5.2.4 Second consensus group review of the symptoms list

A second consensus group meeting was held on 24 September 2007. Data from interviews with health professionals was presented to the group. The objective of the meeting was to delete low relevance items from the symptom list, in order to reduce patient burden when completing questionnaires and positively influence compliance.

While there were no strict decision rules for eliminating items, symptoms with a mean relevance score of 2.40 or lower, and which were prioritised by less than 10 percent of health professionals, were considered for deletion. The consensus group read coded interview data for low scoring symptoms before deciding whether to delete them. All additional issues mentioned by health professionals were considered for inclusion in the revised symptoms list.

4.5.2.5 Telephone interviews with ovarian cancer patients

Women who previously participated in UKCTOCS and were diagnosed with ovarian cancer were invited to participate in a telephone interview about the symptoms they experienced prior to diagnosis. Women were recruited from the same five regional centres that participated in the health professional interviews, plus one additional centre (Nottingham), to increase the number of potential participants.

Inclusion criteria

- Previously participated in UKCTOCS
- Confirmed diagnosis of ovarian cancer registered on the UKCTOCS database
- Diagnosed with ovarian cancer within the last three years
- For controls only - telephone or questionnaire notification of ovarian cancer diagnosis to the UKCTOCS coordinating centre (to avoid invitation of women who may have been upset or angry about their allocation to the control group and who no longer wished to be contacted)

Exclusion criteria

- Women who were having difficulties psychologically coping with their diagnosis
- Women unable to use a telephone (e.g. due to hearing impairments)
- Women with cognitive difficulties (e.g. dementia)
- Any woman who had made a complaint relating to their participation in UKCTOCS
- For screening group volunteers - those identified by their consultant as inappropriate for the research due to poor health

The lead consultant in each of the regional centres was faxed a list of potential telephone interview participants. Women identified by their consultant as inappropriate for the research were not contacted. As the consultants treating controls were unknown, this was only done for screening group women.

Women who met the inclusion criteria were sent a letter of invitation (appendix 3), study information sheet (appendix 4) and consent form (appendix 5). Women were requested to complete the consent form if they wished to participate and to also indicate their preferred interview date, time and telephone number, then return the consent forms in the stamped, return-addressed envelope provided.

Prior to interview, all participants provided written consent and for their interview to be audio-tape recorded.

The symptoms list revised during the second consensus group was formatted as a questionnaire for telephone interviews (appendix 6) and an interview guide was used (appendix 7). Participants were posted the questionnaire to help them follow the interview. Women were asked the extent to which they experienced each symptom during the 18 months leading up to their ovarian cancer diagnosis. The same Likert scale that was used for health professional interviews was used during telephone interviews. If the interviewee experienced the symptom they were probed about its occurrence (interview guide, appendix 7). Participants were also asked to identify up to 10 symptoms that caused them the most trouble during the 18 months leading up to their diagnosis, and if they experienced any additional symptoms not included in the list. Telephone interviews lasted from 30-75 minutes depending on the symptom experiences of the interviewee.

All quantitative questionnaire data were entered into SPSS version 12.0.1 (SPSS Inc., Chicago, USA) and mean relevance scores were calculated for symptoms in the same way as for health professional data. Frequencies were run to calculate the percentage of women who prioritised each item as a symptom that 'caused the most trouble'. Additional symptoms suggested by women were entered as a free text variable.

Telephone interviews were transcribed verbatim then transcripts were read through while the tape was played back to check for errors or omissions. After quality assurance, transcripts were imported into QSR Nvivo version 7 (QSR International, Doncaster, Australia) for content analysis. 'Free nodes' were created for all symptom issues then each interview was systematically coded. When all coding was complete the free nodes were read through to check for accuracy. The validated nodes were then exported into a Word document for discussion with consensus group members.

4.5.2.6 Third consensus group review of the symptoms list

Attempts to arrange a third meeting of the consensus group prior to formatting the draft questionnaire were not successful due to group members' conflicting schedules. Findings from the patient telephone interviews, including relevance means, the percentage of women who described symptoms as troublesome and a summary of coded qualitative data for each symptom was circulated by email during February 2008. Potential changes to the list indicated by the data were also circulated. Group members were asked to forward their final comments or suggestions for the draft questionnaire by the end of March 2008.

4.5.3 Results

4.5.3.1 Results of preliminary revision of the symptoms list

Preliminary review of the 349 symptoms generated from the literature resulted in a list of 82 symptoms. Appendix 8 provides details of each revision and reasons for deletions. There was one instance of an American term (hot flashes) being replaced by an English term (hot flushes). Several items were deleted due to a lack of specificity to ovarian cancer or use of medical terminology. Items were grouped into seven categories for the first consensus group meeting: 1) abdominal symptoms, 2) gastrointestinal symptoms, 3) pelvic symptoms, 4) gynaecological symptoms, 5) urinary symptoms, 6) respiratory symptoms and 7) general symptoms.

4.5.3.2 Results of the first consensus group review of the symptoms list

Revisions to the symptoms list suggested during the first consensus group meeting are summarised in tables for each group of symptoms. Table 4.4 lists abdominal symptoms following preliminary review and as revised by the consensus group. The group decided to remove the symptoms swollen abdomen, abdominal swelling and abdominal distension as it was felt that these symptoms were covered by increased abdominal size. Tense abdomen was deleted as the group thought this term was unclear. In order to keep the terminology consistent it was

decided to replace stomach cramping with abdominal cramping. All other symptoms in the abdominal group remained unchanged.

Table 4.4. *Abdominal symptoms, preliminary and consensus group revision*

As per preliminary review	**As revised by first consensus group**
Abdominal bloating	Abdominal bloating
Abdominal fullness	Abdominal fullness
Abdominal swelling	Increased abdominal size
Swollen abdomen	Abdominal tightening
Abdominal tightening	Hard abdomen
Increased abdominal size	Able to feel abdominal mass/lump
Abdominal distension	Abdominal discomfort
Hard abdomen	Abdominal pain
Tense abdomen	Abdominal pressure
Able to feel abdominal mass/lump	Abdominal cramping
Abdominal discomfort	
Abdominal pain	
Stomach cramping	
Abdominal pressure	

Table 4.5 lists gastrointestinal symptoms following preliminary review and consensus group revision. The group decided to separate indigestion or heartburn into two items as it was considered these are different symptom experiences. Feeling sick was added to nausea, and being sick was added to vomiting, as it was thought that these changes would improve interpretation among women with low literacy levels. The group changed belching/gas to burping as it was thought that this term is more commonly used among older women.

Table 4.5. *Gastrointestinal symptoms, preliminary and consensus group revision*

As per preliminary review	As revised by first consensus group
Indigestion or heartburn	Indigestion
Nausea	Heartburn
Vomiting	Nausea/feeling sick
Reflux	Vomiting/being sick
Belching, gas	Reflux of food
Taste changes	Burping
Feeling full quickly after beginning to eat	Taste changes
Loss of appetite	Feeling full quickly after beginning to eat
Change in bowel habit	Loss of appetite
Bowel irregularity	Change in bowel habit
Constipation	Constipation
Diarrhoea	Diarrhoea
Passing wind/gas/flatulence	Excessive passing of wind/flatulence
Difficulty opening bowels	Difficulty opening bowels
Pain when opening bowels	Pain before, during or after opening bowels
Rectal pain	Rectal pain
Rectal bleeding	Rectal bleeding
Abdominal discomfort	Urgent need to open bowel
Abdominal pain	Bowel incontinence
Stomach cramping	
Abdominal pressure	

The group suggested changing the wording of passing wind/gas/flatulence to excessive passing of wind/flatulence as it was thought that the terms wind or gas may be confused with upper GI wind. The word excessive was added to this item in recognition that passing wind is a normal bodily function. Pain when opening bowels was clarified to pain before, during or after opening bowels. Bowel irregularity was removed as this was considered non-specific. It was decided to add urgent need to open bowel, and bowel incontinence, as some group members commented that women with ovarian cancer report these symptoms.

Table 4.6 lists pelvic symptoms after preliminary review and as revised by the consensus group. The group discussed whether women are physically able to feel masses or lumps within the pelvis. It was suggested that internal examination is required for manual detection of masses within the pelvis. Nevertheless, the group decided to leave this item in the list until feedback was received from health

professionals in the next phase of the research. The wording of this item was clarified and expanded from lump to able to feel mass or lump. All other pelvic symptoms remained unchanged.

Table 4.6. *Pelvic symptoms, preliminary and consensus group revision*

As per preliminary review	As revised by first consensus group
Lump	Able to feel mass or lump
Pelvic discomfort	Pelvic discomfort
Pelvic pain	Pelvic pain
Pelvic cramping	Pelvic cramping
Pelvic pressure	Pelvic pressure
Pelvic fullness	Pelvic fullness
Pelvic heaviness	Pelvic heaviness

There was considerable discussion among group members regarding the level of understanding women have about the terms abdomen and pelvis. It was suggested that many women may be unable to differentiate between these terms. To avoid confusion, it was decided to include a mannequin of a woman's body in the finalised OCSq.

The gynaecological symptoms revised during preliminary review and by the first consensus group are listed in Table 4.7. Rather than asking women if they have abnormal vaginal bleeding the group suggested that the questionnaire should ask if women have vaginal bleeding. A similar recommendation was made to replace abnormal vaginal discharge with vaginal discharge. The group suggested that as the questionnaire is being developed for postmenopausal women, this is more appropriate terminology. It was also suggested that the questionnaire should include a question about HRT to clarify this information. Prolapse was added to the gynaecological symptoms as group members cited examples of ovarian cancer patients presenting with this symptom.

There was lively discussion of the terms intercourse and sexual intercourse. Some group members felt that the term intercourse excludes other types of sexual behaviour that may also cause pain symptoms in women with ovarian tumours. However, other group members thought that changing the wording to pain during sexual intercourse or other sexual activities was too general. After much

discussion, it was agreed to alter the wording from painful intercourse to pain during or after sexual intercourse.

Table 4.7. *Gynaecological symptoms, preliminary and consensus group revision*

As per preliminary review	As revised by first consensus group
Abnormal vaginal discharge	Vaginal discharge
Abnormal vaginal bleeding	Vaginal bleeding
Vaginal pain	Vaginal pain
Painful intercourse	Pain during/after sexual intercourse
Bleeding during/after intercourse	Bleeding during/after intercourse
	Prolapse

Urinary symptoms as revised during preliminary review and by the first consensus group are listed in Table 4.8. Urinary urgency was deleted as it was considered urgent need to pass urine covered the same issue. Similarly, passing urine more often was deleted as urinary frequency covered the same issue. Urinary frequency was re-phrased to passing urine frequently. Pressure on the bladder was re-worded to feeling of pressure on the bladder. Urinary incontinence was re-worded to leakage of urine as the group thought that this is more readily understandable. Urinary burning was clarified to burning on passing urine and soreness was deleted from pain or soreness on passing urine as the group considered that soreness was already covered by the term burning. Urinary tract infection was removed as it is a medical term and the group thought burning on passing urine or pain on passing urine adequately captured this information.

Table 4.8. *Urinary symptoms, preliminary and consensus group revision*

As per preliminary review	As revised by first consensus group
Urinary urgency Urgent need to pass urine Urinary frequency Passing urine more often Pressure on the bladder Urinary incontinence Difficulty emptying bladder Urinary burning Pain or soreness on passing urine Urinary tract infection	Urgent need to pass urine Passing urine frequently Feeling of pressure on the bladder Leakage of urine Difficulty emptying bladder Burning on passing urine Pain on passing urine

The group discussed at length whether any respiratory symptoms should be included in the OCSq. There was consensus that respiratory symptoms are only seen in advanced ovarian cancer, therefore it would be little use to include them in a questionnaire seeking to identify women with early stage disease. However, the group decided to leave respiratory symptoms in the list until feedback was received from health professionals. Table 4.9 lists respiratory symptoms as revised by preliminary review and the consensus group. Breathlessness was removed as the group decided that shortness of breath covered the same symptom.

Table 4.9. *Respiratory symptoms, preliminary and consensus group revision*

As per preliminary review	As revised by first consensus group
Chest pain Breathlessness Difficulty breathing Shortness of breath Coughing	Chest pain Difficulty breathing Shortness of breath Cough

Table 4.10 lists general symptoms associated with ovarian cancer, following preliminary review and consensus group revision. Pain in the hip/buttock/outside leg was added to the list as some group members commented that they have known ovarian cancer patients to complain of pain in this area. The group decided to remove swollen lymph nodes, reasoning that women may not know where the lymph nodes are, or to be able to interpret them as swollen. The term lump in neck

was inserted to capture metastases in the neck, which the group considered a rare but serious sign of ovarian cancer.

Malaise was replaced by generally feeling unwell as the group thought this terminology was more readily understandable. Fever was clarified by adding raised temperature. Flu-like symptoms was deleted as the group thought this was non-specific. Weight gain and weight loss were qualified by adding without trying, in order to exclude intentional changes in weight. Lump in breast was added as group members considered this an important sign of cancer, even if breast metastases are rare in ovarian cancer. Difficulty sleeping was added as group members recalled women describing being unable to sleep as a result of increased abdominal size and discomfort. Panic attacks was replaced with feeling tense or anxious as this was thought to be more accurate. Finally, one group member suggested changing the depression item to the two short depression screening questions recommended by NICE for use in primary care populations.[193] After discussion, the group agreed with this suggestion.

Table 4.10. *General symptoms, preliminary and consensus group revision*

As per preliminary review	As revised by first consensus group
Backache	Backache
Back pain	Back pain
Shoulder pain	Shoulder pain
Pain in side of trunk, flank	Pain in side of trunk, flank
Aching limbs	Pain in the hip/buttock/outside leg
Leg cramps	Aching limbs
Leg pain	Leg cramps
Leg swelling	Pain in legs
Ankle swelling	Leg swelling
Swollen lymph nodes	Ankle swelling
Fever	Lump in neck
Flu-like symptoms	Fever/raised temperature
Tiredness	Tiredness
Fatigue	Fatigue
Lack of energy	Lack of energy
Malaise	Generally feeling unwell
Weight loss	Weight loss without trying
Weight gain	Weight gain without trying
Hot flushes	Hot flushes
Night sweats	Night sweats
Breast swelling	Breast swelling
Breast pain	Breast pain
Panic attacks	Lump in breast
Depression*	Difficulty sleeping
	Feeling tense or anxious
	Feeling down, depressed or hopeless
	Little interest or pleasure doing things

** Removed as a symptom but agreed to include in finalised questionnaire as depression screening questions*

By the conclusion of the first consensus group meeting, the symptoms list had been reduced to 80 items. The review process confirmed the validity of individual items and the comprehensiveness of the list. Revisions suggested by the group ensured that symptoms were linguistically relevant and easily understood by persons with an average level of literacy. Amendments to the list were made prior to formatting the questionnaire for interviews with health professionals.

4.5.3.3 Results of interviews with health professionals

Table 4.11 lists the number of interviews conducted with health professionals in the five regional gynaecological oncology centres. Seven of the 21 interviews were conducted with consultant gynaecological oncologists, six with research nurses, three with nurse consultants, three with nurse specialists and two with registrars.

Table 4.11. *Number of health professional interviews in each site*

Site	**n**
Belfast	6
Gateshead	6
London	3
North Wales	4
Portsmouth	2
Total	*21*

Appendix 9 lists mean relevance scores and the percentage of health professionals who prioritised each of the 80 symptoms. Table 4.12 lists the top ten symptoms according to relevance mean. Table 4.13 lists the top ten symptoms sorted first by the percentage of health professionals who prioritised the item for inclusion in a questionnaire, then by relevance mean. Abdominal bloating and increased abdominal size had the equal highest mean relevance scores (3.57) and were prioritised by the largest number of health professionals (91%). Abdominal fullness had the next highest mean relevance, (3.29) although this symptom was not among the ten most commonly prioritised for inclusion in a questionnaire.

Table 4.12. *Health professional interviews top ten symptoms by relevance means*

Symptom	Relevance Mean	Percentage Prioritised
Abdominal bloating	3.57	91
Increased abdominal size	3.57	91
Abdominal fullness	3.29	57
Generally feeling unwell	3.14	86
Abdominal discomfort	3.10	81
Passing urine frequently	3.10	76
Fatigue	3.05	71
Tiredness	3.00	57
Lack of energy	2.95	48
Change in bowel habit	2.95	81

There were some differences in the types of symptoms considered most relevant and those prioritised for a questionnaire. For example, change in bowel habit had a lower mean relevance (2.95) than passing urine frequently (3.10), but was prioritised by a larger number of health professionals. Indigestion and weight gain were not within the top ten symptoms according to relevance score but they were among the ten symptoms most frequently prioritised for a questionnaire.

Table 4.13. *Health professional interviews top ranking symptoms prioritised for questionnaire*

Symptom	Relevance Mean	Percentage Prioritised
Abdominal bloating	3.57	91
Increased abdominal size	3.57	91
Generally feeling unwell	3.14	86
Change in bowel habit	2.95	81
Abdominal discomfort	3.10	81
Passing urine frequently	3.10	76
Indigestion	2.76	71
Feeling of pressure on the bladder	2.76	71
Fatigue	3.05	71
Weight gain without trying	2.67	67

The ten symptoms described by health professionals as having the lowest relevance to ovarian cancer are listed in Table 4.14. From the list of 80 symptoms the three breast symptoms had the lowest mean relevance scores and none of these were prioritised for inclusion in a questionnaire. Chest pain, leg cramps, pain in legs and taste changes were also regarded as having very low relevance to an ovarian cancer diagnosis.

Table 4.14. *Health professional interviews, lowest ranking symptoms*

Symptom	Relevance Mean	Percentage Prioritised
Breast pain	1.10	0
Lump in breast	1.14	0
Breast swelling	1.14	0
Chest pain	1.14	0
Leg cramps	1.29	5
Pain in legs	1.33	0
Taste changes	1.33	0
Hot flushes	1.38	0
Fever/raised temperature	1.38	0
Bowel incontinence	1.38	0

As there were 152 pages of coded data from the semi-structured interviews this is not included as a full appendix. However, an example of the coding results is shown in appendix 10. This details comments made by health professionals when they were asked why they considered the relevance of breast pain as a symptom of ovarian cancer. The coding results for each symptom that had a low mean relevance, and those prioritised by few health professionals for inclusion in a questionnaire, were presented during the second consensus group meeting.

Ten interviewees discussed additional symptoms, or suggested slight changes to the wording of symptoms (Table 4.15). With the exception of IBS symptoms, all health professionals who suggested additional symptoms noted that these symptoms were very rare.

Table 4.15. *Additional symptoms described by health professionals*

Symptom	n	Comments
Clothes feel tighter around middle, increased girth, trousers feeling tighter	2	Commonly mentioned by women. Patients often say that their trousers have felt tighter.
Discharge from umbilicus; sudden, unprovoked DVT	1	Discharge from umbilicus seen in one patient. DVT seen but very rare and only in those with advanced disease.
Exhaustion	1	Term exhaustion or exhausted used rather than fatigue.
Feeling 'out of sorts'	1	Patients often use this term rather than 'generally feeling unwell'.
Generalised oedema	1	Only seen in a couple of patients.
Had to purchase new wardrobe as clothes no longer fit	1	Mentioned by many women, although these women also notice their abdomens have increased in size rather than just put on weight.
Hirsutism, excess facial hair or baldness	1	Very rare but has been seen.
IBS symptoms	1	Some patients with knowledge or past experience of IBS have mentioned IBS-type symptoms.
Rectal discharge, but only seen in one patient	1	Mucus discharge mentioned by only one patient but it was an unusual symptom.

4.5.3.4 Results of the second consensus group review of the symptoms list

The second consensus group meeting started with a discussion of the meaning of abdominal bloating and abdominal fullness. It was agreed that these terms are very similar and could be used interchangeably. This was reflected in the comment by a research nurse, '*Fullness, I've put it on the same lines as the bloating really, I think it's the same feeling to the woman as bloating*.' (Research Nurse, Site 5). After discussion, the group decided to merge these to one symptom, abdominal bloating/fullness. Table 4.16 lists abdominal symptoms presented to health professionals and amendments made during the second meeting of the consensus group.

Table 4.16. *Abdominal symptoms as revised by the second consensus group*

Presented to health professionals	As revised by second consensus group
Abdominal bloating Abdominal fullness Increased abdominal size Abdominal tightening Hard abdomen Able to feel abdominal mass/lump Abdominal discomfort Abdominal pain Abdominal pressure Abdominal cramping	Abdominal bloating/fullness Increased abdominal size/waistband feels tighter Able to feel abdominal mass/lump Abdominal discomfort, pain or pressure

Increased abdominal size was re-worded, in line with suggestions made by health professionals, to increased abdominal size/waistband feels tighter. Abdominal tightening and hard abdomen had moderate relevance scores but low priority scores. Comments by interview participants supported deletion of these issues. For example, '*I think it's the general use of words from the ladies I've seen. It's usually bloating followed by fullness, but tightening is not really mentioned at all*' (Research Nurse, Site 2) and, '*Nobody has actually said that they felt their abdomen was hard*' (Research Nurse, Site 3). The consensus group also noted that abdominal tightening may be confused by clothes feeling tighter around the abdomen.

The group discussed how women might interpret similar types of sensations as abdominal discomfort, abdominal pain or pressure depending on their previous experiences and personal outlook. For this reason the group decided to merge abdominal discomfort, pain and pressure. Abdominal cramping was deleted as it had a low relevance score of 1.62 and was not prioritised by any health professionals. The group noted health professionals' comments, which suggested that women with ovarian cancer do not use the term cramping to describe abdominal discomfort. For example, '*Nobody has ever described it as a cramping pain, they say it's more of an ache, more of a, you know, an ache or discomfort or pain, but nobody has ever called it a cramp as such*'. (Research Nurse, Site 3).

Table 4.17 lists gastrointestinal symptoms presented to health professionals and revised by the second consensus group. The group discussed the unlikely event of a woman with ovarian cancer being sick without feeling nauseous beforehand. It was noted that projectile vomiting is not described as symptom of ovarian cancer in any previous research. The group also noted that many previous studies combined nausea and vomiting. For these reasons it was decided to merge nausea/feeling sick and vomiting/being sick.

Table 4.17. *Gastrointestinal symptoms as revised by the second consensus group*

Presented to health professionals	**As revised by second consensus group**
Indigestion	Indigestion
Heartburn	Heartburn
Nausea/feeling sick	Nausea/feeling sick or vomiting/being sick
Vomiting/being sick	Feeling full quickly after beginning to eat
Reflux of food	Change in appetite
Burping	Change in bowel habit
Taste changes	Excessive passing of wind/flatulence
Feeling full quickly after beginning to eat	Difficulty emptying bowels
Loss of appetite	Pain before, during or after opening bowels
Change in bowel habit	
Constipation	
Diarrhoea	
Excessive passing of wind/flatulence	
Difficulty opening bowels	
Pain before, during or after opening bowels	
Rectal pain	
Rectal bleeding	
Urgent need to open bowel	
Bowel incontinence	

Loss of appetite was re-worded to change in appetite as the group recalled women with ovarian cancer reporting both increased and decreased appetite. Reflux of food had a mean relevance score of 2.05 and was prioritised by only one health professional. Given this information, and the fact that reflux is very similar to vomiting, the group decided to delete the item. Similarly, burping had a low mean relevance of 1.43 and was prioritised by one health professional. Interview participants suggested that burping was unrelated to ovarian cancer, or was such a

rare symptom that it is of little use to collect this information. Taste changes also had a low mean relevance of 1.33, and was not prioritised by any health professional. Interview participants noted the symptom is non-specific, very rare and probably related to indigestion or vomiting rather than being a separate symptom in itself. For example, '*Taste changes, I know it does happen sometimes but it's very rare. It's very non-specific*' (Registrar, Site 1) and, '*I heard of one lady but it was more taste changes as in a bad taste in her mouth, due to being nauseated and having indigestion all the time* (Research Nurse, Site 1).

Constipation and diarrhoea were deleted as the group felt that change in bowel habit adequately covered both symptoms. Difficulty opening bowels was re-worded to difficulty emptying bowels as women who participated in the Ovacome survey used this wording. Rectal pain was deleted as it had a low relevance mean of 1.76 and was prioritised by only one health professional. The group agreed with comments made by health professionals that patients can experience bowel symptoms but rectal pain is rarely reported. For example, '*Although I see people with bowel symptoms they don't mention rectal pain to me*' (Nurse Specialist, Site 1).

Rectal bleeding had a low relevance mean of 1.43 and was prioritised by 10% of health professionals. While some interviewees commented that rectal bleeding is an important 'flag' symptom, the group noted that rectal bleeding is rare in ovarian cancer, '*I think an ovarian tumour is unlikely to penetrate into the bowel itself, it may encase the surface of the bowel but we don't generally see rectal bleeding. The only time we come across it in gynae-oncology is if there's an extensive tumour infiltrating the bowel*' (Consultant, Site 3).

Urgent need to open bowel was deleted as the group thought change in bowel habit would adequately capture this information. Bowel incontinence had a low relevance mean of 1.38 and was not prioritised by any health professionals. The consensus group noted that health professionals described this symptom as very rare, and when it does occur, it only occurs in advanced ovarian cancer, '*I haven't come across that, not in the early stages. In the later stages, yes, but not in the early stages*' (Research Nurse, Site 4). However, one health professional reasoned

that this may be due to women being too embarrassed to disclose bowel incontinence during gynaecological consultations, '*Very few patients will tell you about incontinence, even when they are incontinent. So it's a symptom they tend to ignore or suppress. If you ask colorectal surgeons they'd say a lot more patients, 24 percent say, are incontinent with faeces but never admit it … because it's sort of a cleanliness thing'* (Consultant, Site 2). After considerable discussion the group decided to delete this as it was thought change in bowel habit would sufficiently capture information on bowel incontinence.

Excessive passing of wind/flatulence was considered for removal as it had a low mean of 1.71 and only one health professional prioritised the symptom for a questionnaire. The group discussed deleting the issue but noted that the low relevance and priority scores may reflect patients being embarrassed about the symptom and therefore reluctant to tell their doctor or nurse. Additionally, it was noted that a small number of Ovacome survey participants reported this symptom. It was therefore decided to leave the issue in the list for feedback from ovarian cancer patients.

Table 4.18 lists pelvic symptoms presented to health professionals and as revised by the second consensus group. The group noted that the word pelvic is likely to be poorly understood by women. It was agreed to add the term lower abdominal to all pelvic symptoms, and to include a mannequin in the finalised questionnaire, to help women understand which part of the body this refers to.

A lengthy debate centred on the symptom able to feel a mass or lump in the pelvis. The group agreed with the comment of one health professional, *'I don't think the patients would be able to feel or examine themselves, to that extent, so they can't actually feel something in the pelvis*' (Consultant, Site 2). Other health professionals suggested that a tumour in the pelvis would have to be very large for a woman to be able to feel. The group noted that any mass/lump a woman is able to feel herself is, by definition, located outside the pelvis. It was therefore decided to delete this as relevant information would be covered by able to feel mass or lump in the abdomen.

Table 4.18. *Pelvic symptoms as revised by the second consensus group*

Presented to health professionals	As revised by second consensus group
Able to feel mass or lump Pelvic discomfort Pelvic pain Pelvic cramping Pelvic pressure Pelvic fullness Pelvic heaviness	Lower abdominal or pelvic discomfort, pain or pressure Lower abdominal or pelvic fullness Lower abdominal or pelvic heaviness

Paralleling the re-wording of the abdominal symptoms, the group decided that discomfort, pain and pressure may describe similar sensations. These separate symptom issues were merged into one issue and re-worded as lower abdominal/pelvic discomfort, pain or pressure. Pelvic cramping was removed from the list as it had a low mean relevance score of 1.76 and was prioritised by only one person. The consensus group agreed with the comment, '*They don't really talk about cramping very much. They talk about pain, discomfort, they very rarely describe their pain as crampy pain … it's not something that they would describe their pain as being, as a crampy nature*' (Lead Nurse, Site 1). Furthermore, the group agreed that the sensation of pelvic cramping would be covered by lower abdominal/pelvic discomfort, pain or pressure.

Table 4.19 lists gynaecological symptoms presented to health professionals during interviews and as revised during the second consensus group. The group discussed deleting vaginal discharge, although it was eventually decided to leave this in the list as a small number of women reported the symptom in the Ovacome survey. The word abnormal was added to vaginal bleeding and vaginal discharge in consideration of the fact that women participating in finalised questionnaires may be taking HRT.

Table 4.19. *Gynaecological symptoms as revised by the second consensus group*

Presented to health professionals	**As revised by second consensus group**
Vaginal discharge Vaginal bleeding Vaginal pain Pain during/after sexual intercourse Bleeding during/after intercourse Prolapse	Abnormal vaginal discharge Abnormal vaginal bleeding Pain during/after sexual intercourse

Vaginal pain had a mean relevance of 1.52 and only one health professional prioritised it for a questionnaire. Following discussion of health professional comments, the group agreed to delete this issue. Bleeding during/after sexual intercourse was also deleted. This had a low relevance mean of 1.38 and interviewees frequently commented that they had not come across this symptom among women with ovarian cancer. For example, '*Bleeding with intercourse is associated with cancer of the cervix rather than ovarian cancer*' (Consultant, Site 5). Prolapse had a low relevance score of 1.71 but was not prioritised by any health professionals. Interview participants described prolapse as a rare, late-stage symptom usually preceded by ascites, '*It does happen with ascites, so I do see it, but by the time they've got prolapse they've got so many other symptoms that they'd mention that as part of huge bloating and pressure and all the rest of it*' (Consultant, Site 5). The group acknowledged that prolapse is a medical term that some women may not understand. After discussion, prolapse was deleted from the list.

Table 4.20 lists urinary symptoms presented to health professionals and as revised during the second consensus group. Two urinary symptoms were deleted: burning on passing urine and leakage of urine. While burning on passing urine had a slightly higher mean relevance score compared to pain on passing urine, the group agreed that pain would also cover burning sensations. Leakage of urine had a relevance mean of 2.0 and was prioritised by one health professional. The consensus group agreed with the comments of several health professionals that urinary incontinence is very common among healthy postmenopausal women and is not specific to ovarian cancer. For example, '*Leakage of urine I haven't given a*

high score because that's quite common in the older age group, they'll have some sort of stress incontinence when they sneeze or something like that' (Research Nurse, Site 2).

Table 4.20. *Urinary symptoms as revised by the second consensus group*

Presented to health professionals	As revised by second consensus group
Urgent need to pass urine Passing urine frequently Feeling of pressure on the bladder Leakage of urine Difficulty emptying bladder Burning on passing urine Pain on passing urine	Urgent need to pass urine Passing urine frequently Feeling of pressure on the bladder Difficulty emptying bladder Pain on passing urine

Three of the four respiratory symptoms presented to health professionals were deleted (Table 4.21). Chest pain, cough and difficulty breathing had relevance means of 1.14, 1.38 and 1.71 respectively. Chest pain was not prioritised by any health professionals for a questionnaire, one person prioritised cough and 14% prioritised difficulty breathing. However, the group decided to remove these three symptoms as health professionals commented they are only relevant in late-stage ovarian cancer. For example, '*We don't usually see chest metastases in early ovarian tumours. So usually you've got to be very distended with ascites to have difficulty breathing, etcetera*.' (Consultant, Site 2).

Table 4.21. *Respiratory symptoms as revised by the second consensus group*

Presented to health professionals	As revised by second consensus group
Chest pain Cough Difficulty breathing Shortness of breath	Shortness of breath

Table 4.22 lists general symptoms presented to health professionals and as revised during the second consensus group meeting. Several symptoms were deleted from the list as they had low relevance and priority scores and health professionals commented that they were not specific to ovarian cancer. Backache and back pain

were merged to form one item as some health professionals commented that women with ovarian cancer describe backache while others commented that women tend to experience back pain. Aching limbs had a relevance mean of 1.48 and was not prioritised by any health professionals. However, the patient peer group representative could remember women with ovarian cancer describing this symptom. It was therefore decided to leave this symptom in the list for feedback from women with ovarian cancer.

Table 4.22. *General symptoms as revised by the second consensus group*

Presented to health professionals	**As revised by second consensus group**
Backache	Backache or pain
Back pain	Pain in side of trunk, flank
Shoulder pain	Aching limbs
Pain in side of trunk, flank	Pain in legs
Pain in the hip/buttock/outside leg	Leg swelling
Aching limbs	Tiredness, fatigue or lack of energy
Leg cramps	Generally feeling unwell
Pain in legs	Weight loss without trying
Leg swelling	Weight gain without trying
Ankle swelling	Feeling down, depressed or hopeless
Lump in neck	Little interest or pleasure doing things
Fever/raised temperature	
Tiredness	
Fatigue	
Lack of energy	
Generally feeling unwell	
Weight loss without trying	
Weight gain without trying	
Hot flushes	
Night sweats	
Breast swelling	
Breast pain	
Lump in breast	
Difficulty sleeping	
Feeling tense or anxious	
Feeling down, depressed or hopeless	
Little interest or pleasure doing things	

While leg swelling was left in the list, ankle swelling was deleted as the group agreed with the comments of health professionals who suggested that ankle

swelling is non-specific. '*So many people have ankle swelling, even young people have ankle swelling if they've been sedentary for a while. I think it's so non-specific, it's not too pertinent to ovarian tumours, but leg swelling, when you've got generalised oedema as a result of low albumin, I think it is more important*' (Consultant, Site 2).

Tiredness, fatigue and lack of energy were merged to form one symptom as the group agreed each of these terms describe similar experiences. One health professional commented that women with ovarian cancer describe exhaustion rather than fatigue. This was noted by the group, although it was not added to tiredness, fatigue or lack of energy as the group considered this was sufficiently descriptive to also capture information on exhaustion.

By the conclusion of the second consensus group, the symptom list had been reduced from 80 to 34 items. The next phase entailed formatting the 34 item list into a questionnaire to be used as a basis for telephone interviews with women with ovarian cancer.

4.5.3.5 Results of telephone interviews with ovarian cancer patients

Thirty-eight women were identified in the selected UKCTOCS regional centres as diagnosed with primary malignant ovarian cancer within the past three years. Two women were excluded because their consultants considered them too ill to participate and one woman had died (notification of her death had not yet been received by the UKCTOCS coordinating centre). These exclusions resulted in a total of 35 women being sent a letter inviting them to participate in a telephone interview. Twenty-nine women responded, and four subsequently declined participation. Two of these women telephoned to say that they had terminal ovarian cancer and were too ill to participate, one woman was recently bereaved and too upset to participate and the fourth woman wrote a letter to explain that she had recovered from ovarian cancer and no longer wished to dwell on her diagnosis. This gave a total of 25 interview participants. Table 4.23 lists the stage of ovarian cancer at diagnosis for women invited to participate, and those who took part in an interview.

Table 4.23. *Stage of ovarian cancer, women invited and participants*

Stage	Invited	Participated
Stage I	19	12
Stage II	4	3
Stage III	9	9
Unknown	3	1
Total	35	25

The median duration of time from date of diagnosis to participation in a telephone interview was 17.8 months (range 1.3-35.5, IQR 9.5-26.6) and median age was 64 years (range 58-76, IQR 62-69).

One participant reported she was asymptomatic leading up to her ovarian cancer diagnosis. Appendix 11 lists the relevance mean scores for each of the 34 items discussed with patients during telephone interviews. The percentage of women who described a symptom as 'causing the most trouble' is also given. Table 4.24 lists the top nine symptoms according to mean relevance.

Table 4.24. *Ovarian cancer patients top ranking symptoms by relevance mean*

Symptom	Relevance Mean	Caused the Most Trouble (%)
Tiredness, fatigue or lack of energy	2.04	4
Lower abdominal/pelvic discomfort, pain or pressure	1.96	24
Increased abdominal size/waistband feels tighter	1.88	4
Passing urine frequently	1.80	8
Weight gain without trying	1.72	0
Abdominal bloating or fullness	1.68	8
Indigestion	1.56	4
Urgent need to pass urine	1.48	12
Excessive passing of wind/flatulence	1.48	0

The lowest ranking symptoms based on relevance score were abdominal mass/lump, pelvic heaviness, pain when passing urine, pain during/after sexual intercourse and pelvic fullness.

Pelvic discomfort, pain or pressure was the second most relevant symptom and was most frequently (24%) described as a symptom which caused the most trouble. By contrast, abdominal discomfort/pain or pressure had a relevance mean of only 1.16 and no woman prioritised it as a symptom which caused the most trouble.

There were a number of discrepancies between the rankings of items based on mean relevance score compared to the percentage of women who described the symptom as causing the most trouble. Urinary urgency was ranked eighth on mean relevance score but second in terms of the number of women who described it as causing the most trouble. Four symptoms shared equal third ranking as a symptom that caused women the most trouble: urinary frequency, abdominal bloating/fullness, feeling full and pressure on the bladder, yet feeling full and pressure on the bladder only had moderate relevance scores. This suggests that

these two symptoms were fairly uncommon but, among those who experienced them, they were quite troublesome.

Nineteen of the 34 symptoms were not prioritised by any woman as a symptom that caused the most trouble (appendix 11). These included symptoms with relatively high relevance scores such as weight gain, excessive passing of wind/flatulence, difficulty emptying bowels and backache/pain.

Five participants stated that they experienced additional symptoms (not already in the list) during the period leading up to their diagnosis (Table 4.25). None of the additional symptoms were mentioned by more than one woman. All of the participants who described additional symptoms also reported that they experienced three to 14 symptoms already in the list.

Table 4.25. *Additional symptoms reported by women*

Symptom	Interview No.
Leakage of urine, feeling of pressure/discomfort in the rectum	4
Hair became very unmanageable	14
Hair and nails became thin, became very emotional	16
Cough when trying to sing	17
Skin became noticeably darker	23

Participants were asked if any additional symptoms caused them the most trouble during the time leading up to their diagnosis. With the exception of leakage of urine and feeling of pressure/discomfort in the rectum, none of the symptoms caused women particular trouble.

4.5.3.6 Results of the third consensus group review of the symptoms list

Three symptoms (pain in side of trunk/flank, aching limbs and generally feeling unwell) were deleted from the list following review of data from interviews with ovarian cancer patients. While these symptoms did not have the lowest rankings, they did have relatively low scores and evidence from patient interviews supported their deletion.

Pain in side of trunk/flank had a mean relevance of 1.16 and was not described as a symptom which caused the most trouble by any woman. Findings from interviews suggested that women have difficulty understanding what area of the body the terms trunk and flank refer to. Several women sought clarification of these terms before they responded. Four women stated that they had a little pain in the side of trunk or flank prior to diagnosis but no participant had this symptom quite a bit or very much. For example, '*I did occasionally have pains, I suppose in my side but there was never any pattern. I might just have one then not have one for a few months … I mean I never ever considered going to the doctors. It never lasted. It was very spasmodic, I might have one, one week then another the next week then not for a couple of months. I might have one then the next in three weeks. You know, sort of very hit and miss, nothing that you could actually put your finger on and say there was a problem*'. (Patient interview 8) All of the women who described having pain in the side of trunk or flank also had either abdominal, pelvic or back pain. Taking all of these factors into consideration, the consensus group agreed to delete this symptom.

Aching limbs had a mean relevance score of 1.20 and was not described as a symptom which caused the most trouble by any participant. The decision to delete this symptom was supported by the finding that all telephone interview participants who had the symptom described aches in their legs but not in their arms. Additionally, when participants were asked about the next item on the list, leg pain, they described both leg ache and pain together, not as two separate symptoms, for example, '*I used to get lots of pains in my legs, at the top of my legs, it would ache for hours. Then some days I would walk up the road and my legs would be so heavy and achy and I thought, what is wrong with me*?' (Patient interview 18). The group agreed to delete aching limbs and change the wording of the leg pain to leg ache or pain.

The third issue that was deleted by the consensus group, generally feeling unwell, had a higher relevance score of 1.44 and was prioritised by one woman as a symptom which caused the most trouble. The decision to delete this item was based upon the consideration that it is not specific to ovarian cancer. All seven of the women who reported this symptom also reported other symptoms. The

consensus group also noted that inclusion of generally feeling unwell in any list of symptoms designed for identification of women for ovarian cancer screening would result in GP surgeries being swamped with worried-well women.

Following email discussion on the meaning of the term pressure, the consensus group decided to separate abdominal discomfort, pain or pressure into two symptoms: abdominal discomfort or pain, and abdominal pressure. It was also decided to separate lower abdominal/pelvic discomfort, pain or pressure into two symptoms. The group agreed that women may feel pressure but not necessarily discomfort or pain.

One other minor change was the decision to merge the symptoms indigestion and heartburn into one item. The consensus group decided that keeping these as separate symptoms would not necessarily improve the sensitivity of the finalised questionnaire. After the proposed changes were agreed by all group members a questionnaire was formatted for piloting. Wherever possible, symptoms were phrased using the terminology of validated EORTC questionnaires.

Decisions to delete, merge or separate certain items reduced the symptoms list from 34 to 32 items by the conclusion of the third consensus process. The 32 symptom list was formatted as a pilot questionnaire (appendix 12) which was subsequently field-tested in the UKCTOCS cohort. Findings from the questionnaire pilot are presented in the next section.

4.6 Stage IV – Pilot of the provisional ovarian cancer symptoms questionnaire

4.6.1 Aims

- To determine the validity and reliability of the draft OCSq
- To identify symptoms for potential removal from the questionnaire
- To seek feedback from UKCTOCS volunteers on the draft questionnaire and revise the according to these findings
- To format a finalised OCSq for a prospective study

4.6.2 Methods

4.6.2.1 Setting

The OCSq was piloted in the UKCTOCS cohort from 21 May to 3 December 2008. Women receiving screening, or enrolled as a UKCTOCS control, were invited to participate. Letters of invitation and questionnaires were posted to women from all 13 regional centres from the UKCTOCS coordinating centre in London.

GPs of women invited to participate were posted a GP study information letter (appendix 13). This letter described the aims of the research and included the names of all women registered at the practice who were invited to participate.

4.6.2.2 Sample size

For validation of the pilot OCSq, the research group took into account the need to maximise participant feedback within a short timescale and restricted budget. As the plan was to send the finalised questionnaire to 100,000 women, recruiting approximately one percent of this total (n = 1,000) for the pilot was considered sufficient for validation and the identification of potential problems in administering the OCSq. Given that the response rate for UKCTOCS follow-up questionnaires was 75%, it was calculated that approximately 1,333 volunteers should be invited to participate in the pilot.

The sample size required for test-retest reliability was considered separately. The project group acknowledged that retest validation would impose a slight burden on women, as they would be asked to complete a second questionnaire two days after their first questionnaire. This process may have been confusing or irritating for women. In order to reduce participant burden, it was agreed to send the minimum number of retest questionnaires dictated by statistical validity in order to assess the stability of item wording and the severity section (as women were instructed to only completed the frequency, duration and GP consultation sections if they experienced the symptom).

Within the questionnaire design literature there is debate regarding sample sizes required for retest validation. Streiner and Norman[130] note two previous studies which identified the need for 200 participants, and one study which identified a minimum sample of 300 for retest validation. This information, in parallel with sample size tables for the kappa statistic, was considered for calculation of the sample size required for reliability testing. For a two-tailed test assuming a null *k* value of 0.60 (as repeat test response should have a fairly high level of agreement with the initial test) the number of participants required at 80% power ranges from 126 to 335 to detect a kappa of 0.80, with the proportion of positive ratings ranging from 0.10 to 0.90.[194] Given UKCTOCS response rates, approximately 168 to 447 women should be invited to calculate test-retest kappa statistics. According to questionnaire design literature more generally, 267 to 400 participants should be invited for retest validation.

4.6.2.3 Pilot questionnaire sample

Two groups were invited to participate in the OCSq pilot: 1) UKCTOC controls and 2) women receiving screening in the multimodal or ultrasound arms of UKCTOCS. The second group was comprised of two sub-groups: a) women attending annual (Level 1) screening; and b) women recalled for repeat (Level 2) screening due to an abnormal finding on annual screen. Inclusion and exclusion criteria were as follows:

Inclusion criteria

- Women participating in UKCTOCS - as a control or receiving screening in the multimodal or ultrasound arms
- For controls – return of a UKCTOCS follow-up questionnaire within the past 12 months, in order to reduce the number of women already lost to follow-up

Exclusion criteria

- Withdrawal from UKCTOCS for any reason
- Women who had both ovaries surgically removed since joining UKCTOCS
- Women who had made a complaint relating to their participation in UKCTOCS
- For women in the multimodal or ultrasound arms - non-attendance of the screening appointment prior to their current appointment letter

UKCTOCS controls

A list of controls who met the inclusion and exclusion criteria was exported from the main UKCTOCS database and imported into SPSS version 12.0.1 (SPSS Inc., Chicago, USA). The random sample of cases function was used to select the UKCTOCS volunteer reference numbers of 25 controls from each of the 13 regional centres. A mail merge was conducted in Word then letters inviting control group women to participate were printed out and posted.

UKCTOCS volunteers in the multimodal and ultrasound arms

All UKCTOCS screening appointment letters are printed and posted from the research coordinating centre in London. Screening appointment letters are printed every Monday, Tuesday and Wednesday. These letters are printed by order of appointment type (either annual screen, repeat annual screen, Level 2 screen, repeat Level 2 screen or clinical decision), screening arm (multimodal then ultrasound), year of screening (in chronological order) and sequential regional site number. The repeat letters are new appointments for women who failed to attend their original appointment. Screening letters are sorted by administration staff into piles for each type of appointment. Annual screen and repeat letters are placed in an envelope stuffing machine then letters are franked and dispatched. Level 2 and clinical decision letters are given to a Nurse Consultant for checking prior to postage.

All repeat appointment letters were excluded to reduce the number of volunteers potentially lost to follow-up since their last screening appointment. The following process was then used to identify 15 women from each screening arm in the 13 regional centres sent an annual appointment and 24 women from each screening arm in the 13 regional centres sent a Level 2 appointment:

- Annual screen appointment letters were hand sorted, on a daily basis, into a multimodal and ultrasound group for each of the regional centres
- Every fifth annual appointment letter from each pile was selected until a sufficient number of women in the multimodal and ultrasound groups was selected for each regional centre
- Level 2 letters were first checked by a research nurse then, on a weekly basis, they were sorted in the same way as annual screen letters
- Every Level 2 letter was selected from each pile until a sufficient number of women in the multimodal and ultrasound groups was identified for each regional centre
- The volunteer reference numbers on all selected appointment letters were entered into a database, a mail merge was conducted in Word (daily for annual screening appointments and weekly for Level 2 appointments), then letters inviting women to participate in the questionnaire pilot were printed out

4.6.2.4 Test-retest validation sample

Prior to each mail merge, a group of women were selected to participate in test-retest validation of the pilot OCSq. Approximately every third woman was selected for test-retest validation. This group of women were invited to complete an initial (test) OCSq then complete a second (retest) OCSq two days later. As completion of two seven-page questionnaires was considered time-consuming and rather onerous, it was decided to stop selecting women for retest validation once

sufficient numbers of test-retest questionnaires were received back at the UKCTOCS coordinating centre.

4.6.2.5 Data collection

The pilot OCSq included 32 symptoms and a section for women to write the details of up to three 'other' symptoms (appendix 12). Women identified for the pilot were sent a letter of invitation (appendix 14), study information sheet (appendix 15), consent form (appendix 16) and the pilot OCSq (appendix 12). Women selected for the test-retest validation were sent a slightly different invitation letter (appendix 17), study information sheet (appendix 18) and two pilot OCSqs, one labelled questionnaire A and the other questionnaire B. The first 1,000 women across all groups were also sent a feedback form (appendix 19). Those who wished to take part in the research were asked to complete these documents then post them back in the pre-paid envelope provided.

The pilot OCSq elicited information on symptom severity, frequency and duration, as well as GP consultations for symptoms. Respondents were asked if they experienced each of the 32 symptoms in the last week, using a Likert scale to assess severity (0 denoted not at all, 1 a little, 2 quite a bit and 3 very much). If women experienced the symptom during the last week they were asked about its frequency, whether the symptom was experienced 1-2 days, 3-5 days or 6-7 days. They were also asked about the duration of the symptom (less then 3 months, 3-6 months, 7-12 months or more than 12 months), and whether they had discussed the symptom with a GP in the last three months (yes or no). The questionnaire also included a section asking respondents about co-morbidities and whether they were currently using HRT. The two short depression screening questions were the final items in the questionnaire: 1) In the past month have you often been bothered by feeling down, depressed or hopeless? 2) In the past month have you often been bothered by little interest or pleasure doing things?

Women selected for test-retest validation were asked to complete two questionnaires two days apart. This time frame was adopted as symptoms should be relatively stable over this time and a two day period between questionnaires was considered sufficient to avoid women completing items based on memory of

their previous responses. In order to obtain accurate test-retest data the invitation letter and study information sheet sent to this group clearly requested them not to copy information from one questionnaire to the next: 'If you would like to take part in this study please complete the consent section then fill in questionnaire A. Two days later please complete questionnaire B. We would like to know about your symptom experiences on the two separate dates so please don't copy from questionnaire A.'

The feedback form asked respondents how long it took to complete the OCSq, if they had any difficulties answering questions, if they were upset by any questions and if they had any comments or other feedback on the study.

4.6.2.6 Data analysis

Data from the symptoms and feedback questionnaires was entered into SPSS version 12.0.1 (SPSS Inc., Chicago, USA). Detailed feedback comments were typed into Word then imported into QSR-Nvivo version 7 (QSR International, Doncaster, Australia) for coding using content analysis techniques.[190-192] Frequencies were run in SPSS to describe variables.

Factor analysis was described earlier in the chapter. This was not appropriate as a method of identifying variables for potential removal from the draft OCSq. However, relationships between symptoms were investigated using correlation analyses, with the aim of merging or removing highly correlated symptoms in order to reduce the length of the questionnaire.

Statistical analysis

Spearman's correlation coefficients were calculated to investigate correlations between ordinal symptoms data. Spearman coefficients of $r_s > 0.30$ indicate medium correlation and $r_s > 0.50$ large correlation. Correlation coefficients of $r_s > 0.90$ were considered potential candidates for merging prior to formatting the finalised questionnaire. Differences were accepted as significant at $p < 0.05$ for all statistical analyses and 95% confidence intervals were calculated where appropriate.

The intra-class correlation coefficient (ICC) is the preferred statistic for test-retest analyses of continuous data. However, this statistic was not appropriate for reliability testing of the OCSq as all data were binary or ordinal. Cohen's kappa coefficient was therefore the most appropriate statistic for this data. Quadratic weightings were applied to ordinal data as these approximate the intraclass correlation coefficient.[130 195-197]

Cohen's kappa statistic for binary data is represented by:

$$K = \frac{P_{(o)} - P_{(c)}}{1 - P_{(c)}}$$

where $P_{(o)}$ represents the proportion of observed agreement and $P_{(c)}$ is the proportion of agreement by chance. SPSS was utilised for the calculation of kappa coefficients for binary data.

Quadratic weighted kappas were calculated as a measure of agreement between ordinal test-retest data. The quadratic weighting set penalises disagreement by the square of the number of categories and is represented by:

$$w_i = 1 - \frac{i^2}{\left(k-1\right)^2}$$

This weighting set essentially treats disagreements between close responses (e.g. not at all and a little) as less important than disagreements between responses further apart on the scale (e.g. not at all and quite a bit). STATA version 10.0 (STATA Corp., College Station, USA) was used for the calculation of weighted kappas. Table 4.26 shows how quadratic weights were applied to test-retest data where respondents used all four Likert scale response categories.

Table 4.26. *Quadratic weights for ordinal data with four categories*

	Not at all	**A little**	**Quite a Bit**	**Very Much**
Not at all	1.0			
A little	0.8889	1.0		
Quite a Bit	0.5556	0.8889	1.0	
Very Much	0	0.5556	0.8889	1.0

Kappa coefficients from 0.21-0.40 were considered indicative of fair agreement, 0.41-0.60 as moderate agreement, 0.61 to 0.80 as substantial agreement and 0.81 or greater as excellent agreement.[198]

4.6.3 Results

This section describes the results of questionnaire validation and reliability analyses following the pilot. Results of symptoms analyses are presented separately in Chapter Five.

4.6.3.1 Validity of the questionnaire

A total of 1,339 women were posted the pilot OCSq and 829 women returned a questionnaire (61.9% response rate). A small number of women initially overlooked the consent section. These questionnaires were returned to women with a polite note asking them to provide written consent then return the signed questionnaire to the coordinating centre. All returned questionnaires were included in analyses.

Table 4.27 lists the number of women who missed each question. No data is given for pain during or after sexual intercourse as this was preceded by an instruction to participants to miss this question if they had not been sexually active during the past week. The symptoms with the largest amount of missing data were abdominal pressure (q8) and pelvic heaviness (q13), which were missed by 81 (9.8%) participants each.

Table 4.27. *Number of participants who missed each question*

Questionnaire item	n	%
Q1 Lower abdominal or pelvic discomfort or pain	53	6.4
Q2 Upper abdominal discomfort or pain	65	7.8
Q3 Indigestion or heartburn	51	6.2
Q4 Nausea or vomiting	66	8.0
Q5 Felt full quickly when eating	61	7.4
Q6 Change in appetite	65	7.8
Q7 Upper abdominal bloating or fullness	62	7.5
Q8 Upper abdominal pressure	81	9.8
Q9 Increased abdominal size	66	8.0
Q10 Abdominal to feel abdominal mass or lump	80	9.7
Q11 Lower abdominal or pelvic bloating or fullness	70	8.4
Q12 Lower abdominal or pelvic pressure	74	8.9
Q13 Lower abdominal or pelvic heaviness	81	9.8
Q14 Pain before, during or after opening bowels	67	8.1
Q15 Difficulty emptying bowels	61	7.4
Q16 Change in bowel habit	74	8.9
Q17 Excessive wind or flatulence	58	7.0
Q18 Passed urine frequently	66	8.0
Q19 Urgent need to pass urine	57	6.9
Q20 Pressure on the bladder	68	8.2
Q21 Difficulty emptying bladder	77	9.3
Q22 Pain when passing urine	75	9.0
Q23 Short of breath	77	9.3

Questionnaire item	n	%
Q24 Back ache or pain	61	7.4
Q25 Leg ache or pain	67	8.1
Q26 Leg swelling	67	8.1
Q27 Tiredness, fatigue or lack of energy	61	7.4
Q28 Weight gain without trying	71	8.6
Q29 Weight loss without trying	80	9.7
Q30 Abnormal vaginal bleeding	78	9.4
Q31 Abnormal vaginal discharge	76	9.2
Q32 Pain during or after sexual intercourse	n/a	n/a

The matrix in appendix 20 presents results of Spearman correlations. No two symptoms had correlations above $r_s = 0.90$, therefore no symptoms were candidates for merging. Pelvic pressure (q12) and pelvic heaviness (q13) were the two most highly correlated symptoms ($r_s = 0.64$, $p < 0.0001$), followed by urinary frequency (q18) and urinary urgency (q19) ($r_s = 0.63$, $p < 0.0001$), then pelvic discomfort/pain (q1) and pelvic pressure (q12) ($r_s = 0.59$, $p < 0.0001$). No symptoms were strongly negatively correlated, although there was a significant negative correlation between weight gain and weight loss ($r_s = -0.13$, $p < 0.0001$). Due to very few women reporting 'a little', 'quite a bit' or 'very much' weight loss, this negative correlation is not as large as would be expected if the response categories were restricted to yes or no for both variables.

From the 1,000 women posted a feedback form, 584 returned the form (58.4% response rate). A total of 452 (77.4%) replied that the OCSq took them 10-15 minutes to complete (Table 4.28). Six (1%) replied that they needed help to complete the questionnaire. Three of these women were helped by their spouse or partner, one by her daughter, one by her care coordinator and one by myself (over the telephone).

Table 4.28. *Time taken to complete symptoms questionnaire*

Time to complete questionnaire	n	%
10-15 minutes	452	77.4
16-20 minutes	93	15.9
21-30 minutes	27	4.6
More than 30 minutes	4	0.7
Missing	8	1.4
Total	584	100.0

Sixty-six respondents (11%) replied that they had difficulty answering any questions, four women (0.7%) found one or more questions upsetting and 24 (4%) found one or more questions irrelevant. Table 4.29 lists the number of women who found each question difficult to answer, upsetting or irrelevant. Participants were also asked to write the reasons why they found symptoms difficult to answer, upsetting or irrelevant.

Table 4.29. *Number of women, question difficult to answer, upsetting or irrelevant*

Questionnaire item	Difficulty	Upsetting	Irrelevant
	n	***n***	***n***
Q1 Lower abdominal or pelvic discomfort or pain	9	0	2
Q2 Upper abdominal discomfort or pain	8	0	2
Q3 Indigestion or heartburn	7	0	1
Q4 Nausea or vomiting	1	0	2
Q5 Felt full quickly when eating	2	0	3
Q6 Change in appetite	6	0	3
Q7 Upper abdominal bloating or fullness	8	0	4
Q8 Upper abdominal pressure?	7	0	3
Q9 Increased abdominal size	8	0	2
Q10 Able to feel abdominal mass or lump	3	0	2
Q11 Lower abdominal or pelvic bloating or fullness	10	0	2
Q12 Lower abdominal or pelvic pressure	9	0	3
Q13 Lower abdominal or pelvic heaviness	9	0	4
Q14 Pain before, during or after opening bowels	2	0	2
Q15 Difficulty emptying bowels	12	0	2
Q16 Change in bowel habit	6	0	2
Q17 Excessive wind or flatulence	15	0	1
Q18 Passed urine frequently	10	0	1
Q19 Urgent need to pass urine	7	0	2
Q20 Pressure on bladder	4	0	1

Questionnaire item	Difficulty	Upsetting	Irrelevant
Q21 Difficulty emptying bladder	2	0	2
Q22 Pain when passing urine	2	0	1
Q23 Short of breath	4	0	4
Q24 Back ache or pain	9	0	3
Q25 Leg ache or pain	12	0	4
Q26 Leg swelling	5	0	2
Q27 Tiredness, fatigue or lack of energy	9	0	2
Q28 Weight gain without trying	3	1	2
Q29 Weight loss without trying	2	0	1
Q30 Abnormal vaginal bleeding	2	1	2
Q31 Abnormal vaginal discharge	1	1	2
Q32 Pain during or after sexual intercourse	0	0	13

Participants explained that the reason they had difficulty answering questions was due to interpretation of their bodily experiences in terms of the symptoms described in the questionnaire. For example, '*I couldn't decide whether I felt bloated or full or whether it was pressure I felt*'. Difficulties also arose when respondents attempted to attribute symptoms, rather than simply reporting their experiences, '*With IBS and ulcerative colitis I often get feelings of discomfort or pain, bloating, fullness, pressure and heaviness. I have answered these questions regarding "unusual" feelings*'. The symptom women had the most difficulty answering was excessive wind/flatulence. Table 4.30 presents coded data relating to this symptom for the 13 women who wrote the reason why they had difficulty.

Table 4.30. *Reasons why women had difficulty answering question 17*

Coded data – reasons why q17 (excessive wind or flatulence) difficult to answer

Respondent 1, site 5
Have no idea how to quantify, I have a high fibre diet therefore virtually every day I have flatulence but it's part of life.

Respondent 1, site 6
Unsure as to whether the fact that I have been prescribed alendronic acid and calcium may affect answer.

Respondent 1, site 7
Since colectomy in 1997 I have a tendency to flatulence as normal. So wasn't sure whether it would count as 'excessive' when compared with average. The flatulence is of no anxiety.

Respondent 2, site 7
Re-phrase maybe – Have you had flatulence/wind at unusual times and excessive?

Respondent 1, site 9
Not sure how much is excessive.

Respondent 2, site 9
I have an ongoing problem with excessive wind, for which I have medication.

Respondent 1, site 11
I do not know how much flatulence is normal.

Respondent 2, site 11
Difficult to tick boxes as I had not experienced the problem over the past week, but just occasionally over the past year or more.

Respondent 3, site 11
Due to aspirin and other drugs, now taking omeprazole 10mg.

Respondent 1, site 13
Have for years been bothered by flatulence. Now break a lot of wind.

Respondent 1, site 17
Increased flatulence – embarrassingly due to age.

Respondent 2, site 17
I do have diverticular disease, but have not had an attack lately.

Most of the women who had difficulty answering question 15 explained that this was due to a long history of constipation. For example, '*I take fibre gel most nights. Constipation is something I have suffered with for 40 years*' (Respondent, site 2). Women who had difficulty responding to the leg pain question explained this was due to varicose veins, arthritis or injury. For example, '*I decided not to answer this question as I have pain in my left leg, on a regular basis, due to a*

broken ankle three and a half years ago. I felt that this would be irrelevant or misleading to the survey' (Respondent, site 11).

From the list of 32 symptoms only one woman found two questions (abnormal vaginal bleeding and abnormal vaginal discharge) upsetting. This participant wrote, '*Could be re-phrased "have you had any vaginal bleeding" and "have you had vaginal discharge", then list why these might be occurring'*. This response suggests that the respondent was not particularly upset by these questions.

With the exception of pain during or after sexual intercourse (q32), few women reported that any symptom was irrelevant. The 13 women who found q32 irrelevant wrote that this was because they were not sexually active. For example, '*Not sexually active as I am a widow*' (Respondent, site 5), and *'My husband and I are not sexually active any longer*' (Respondent, site 13).

Two women ticked that they were they were upset by q34, the co-morbidities section of the questionnaire. However their responses indicated that they were not particularly upset by the question. For example, the first woman wrote, '*Very glad to say I haven't had any health problems that needed treatmen*t' (Respondent, site 3) and the second, '*I have not been diagnosed with any of the symptoms stated*' (Respondent, site 9). Eight women had difficulty answering the co-morbidities section (Table 4.31). Women explained that they had difficulties fitting what they had been told by their doctor to a diagnosis listed in the questionnaire. For example, '*Have had both hips replaced (no other arthritis) should I have ticked the arthritis box? If so, please do so on my behalf*' (Respondent, site 3) and '*I have never been told I have heart failure but had a triple by-pass in May 2000*' (Respondent, site 9).

Table 4.31. *Difficulties answering other parts of the questionnaire, number of women*

Questionnaire item	Difficulty	Upsetting	Irrelevant
	n	n	n
Q34 Co-morbidities	8	0	2
Q35 Taking HRT	1	0	2
Q36 Feeling down, depressed or hopeless	6	2	1
Q37 Little interest or pleasure doing things	5	3	1

Two of the three women who ticked that they found q37 (little interest or pleasure doing things) upsetting also ticked that they found q36 upsetting (feeling down, depressed or hopeless). These women found the questions upsetting due to recent bereavement and a history of depression. '*I just felt very sad as a much beloved dog had to be put to sleep*' (Respondent, Site 5). '*I have lost my husband this year and am still at the tearful stage*' (Site 6) and '*I am a very up and down person, it seems to be my personality. I am often low but fight to keep up. Talking or thinking about it upsets me*' (Site 14).

4.6.3.2 Acceptance of the study among GPs

None of the 1,325 GPs who were posted a study information letter raised concerns about the research with the study supervisor or myself. The details of 14 volunteers' GPs were insufficient to post a letter about the research. One GP telephoned to inform the UKCTOCS team that a patient sent the OCSq had recently been diagnosed with ovarian cancer. This patient was participating as a control in UKCTOCS and was diagnosed two months before the letter was sent to the GP. Confirmation of the diagnosis was not yet received by the coordinating centre. A total of 27 GPs returned study information letters with a note stating that the patient named in the letter was no longer registered at the practice.

4.6.3.3 Reliability of the questionnaire

A total of 409 women (135 controls, 132 multimodal, 142 ultrasound) were sent two questionnaires for reliability analyses, and 220 returned at least one questionnaire (53.7% response rate). Of these, 214 complied with the retest exercise by completing both questionnaires. Compliance among controls was 50.4%, 53.0% among women in the multimodal group and 54.2% in the ultrasound group.

Of the 170 women who wrote the date on both questionnaires, 128 completed questionnaire B two days after questionnaire A (Table 4.32). A total of 42 participants wrote the date on questionnaire A only. Table 4.33 lists the days between the date questionnaire A was completed, and the date both questionnaires were received back at the research centre for those respondents who failed to date questionnaire B. Two participants did not date either questionnaire: one woman's questionnaires were received back at the coordinating centre within nine days of being posted out and the other woman's questionnaires within 19 days.

Table 4.32. *Days between questionnaire A and B*

Days between QA & QB	**n**
2 days	128
3 days	32
4 days	6
5 days	1
7 days	1
10 days	1
13 days	1
Total	*170*

Table 4.33. *Days between questionnaire A and received*

Days between QA & received	n
4 days	6
5 days	4
6 days	3
7 days	6
8 days	5
9 days	6
10 days	4
11 days	3
13 days	2
18 days	1
26 days	1
35 days	1
Total	*42*

Inclusion criteria for test-retest reliability analyses

- Where questionnaires A and B were both dated, all participants who completed questionnaire B within four days of questionnaire A were included
- Where there was no date on questionnaire B, those whose questionnaires were received back within 10 days of the date on questionnaire A were included
- Where neither questionnaire A or B were dated, those whose questionnaires were received back at the research coordinating centre within 14 days of being sent to the participant were included

Exclusion of questionnaires not eligible for reliability analyses resulted in a sample of 201 participants.

Reliability of symptom severity assessments

Sample sizes for the calculation of individual severity kappas ranged from 189 for short of breath (q23) and urgent need to pass urine (q19), to 198 for abdominal discomfort/pain (q2) and increased abdominal size (q9). A sample of 74 respondents was included in the calculation of the kappa for pain during/after sexual intercourse (q32). Kappa coefficients for test-retest reliability of severity items are listed in Table 4.34, Table 4.35 and Table 4.36.

Quadratic kappas were lowest for abdominal pressure (q8) $k = 0.63$ and pelvic pressure (q12) $k = 0.67$. There was almost perfect agreement between test and retest questionnaires for pain during or after sexual intercourse ($k = 0.97$). Quadratic kappa 95% confidence intervals were widest for abdominal mass/lump (q10), abnormal vaginal bleeding (q30) and abnormal vaginal discharge (q31). Alternately, confidence intervals were tightest for excessive flatulence (q17), leg swelling (q26), pelvic discomfort/pain (q1), heartburn or indigestion (q3), difficulty emptying bowels (q15), backache/pain (q24) and leg ache/pain (q25).

Table 4.34. *Kappa coefficients for 4x4 severity data*

Questionnaire item	n	Agreement unweighted %	Unweighted k	95% CI	Agreement quadratic weighted %	Quadratic weighted k	95% CI
Q1 Lower abdominal or pelvic discomfort or pain	196	88.3	0.74	0.65-0.84	98.7	0.87	0.81-0.92
Q2 Upper abdominal discomfort or pain	198	92.4	0.77	0.66-0.87	98.5	0.85	0.72-0.92
Q3 Indigestion or heartburn	197	86.8	0.76	0.69-0.85	98.4	0.88	0.82-0.93
Q4 Nausea or vomiting	196	92.4	0.65	0.49-0.81	99.0	0.80	0.63-.091
Q5 Felt full quickly when eating	196	93.9	0.78	0.63-0.88	99.2	0.89	0.79-0.95
Q6 Change in appetite	193	95.9	0.74	0.53-0.89	99.5	0.83	0.66-0.95
Q7 Upper abdominal bloating or fullness	192	83.3	0.61	0.50-0.72	97.6	0.78	0.66-0.86
Q8 Upper abdominal pressure	192	90.1	0.54	0.36-0.72	98.4	0.63	0.39-0.80
Q9 Increased abdominal size	198	84.9	0.68	0.57-0.77	97.5	0.81	0.69-0.88
Q11 Lower abdominal or pelvic bloating or fullness	193	87.6	0.67	0.54-0.78	98.5	0.87	0.78-0.92
Q12 Lower abdominal or pelvic pressure	195	90.8	0.65	0.47-0.77	98.3	0.67	0.49-0.82

Questionnaire item	n	Agreement unweighted %	Unweighted k	95% CI	Agreement quadratic weighted %	Quadratic weighted k	95% CI
Q13 Lower abdominal or pelvic heaviness	193	89.6	0.61	0.46-0.75	98.2	0.75	0.55-0.87
Q15 Difficulty emptying bowels	196	91.8	0.79	0.68-0.88	99.1	0.89	0.82-0.94
Q16 Change in bowel habit	194	92.8	0.71	0.55-0.83	98.9	0.83	0.67-0.92
Q17 Excessive wind or flatulence	195	86.2	0.76	0.68-0.84	98.5	0.89	0.84-0.93
Q18 Passed urine frequently	191	83.3	0.71	0.61-0.79	96.8	0.82	0.71-0.89
Q19 Urgent need to pass urine	189	87.8	0.79	0.70-0.86	98.0	0.90	0.82-0.95
Q20 Pressure on bladder	192	92.2	0.71	0.57-0.83	98.0	0.78	0.59-0.91
Q21 Difficulty emptying bladder	191	99.0	0.92	0.76-1.00	99.7	0.90	0.61-1.00
Q23 Short of breath	189	94.7	0.72	0.55-0.86	99.1	0.79	0.60-0.92
Q24 Back ache or pain	195	83.6	0.72	0.63-0.81	97.5	0.86	0.80-0.91
Q25 Leg ache or pain	194	87.1	0.75	0.65-0.84	98.4	0.89	0.82-0.93
Q26 Leg swelling	195	96.4	0.86	0.73-0.95	99.6	0.94	0.88-0.98

Questionnaire item	n	Agreement unweighted %	Unweighted k	95% CI	Agreement quadratic weighted %	Quadratic weighted k	95% CI
Q27 Tiredness, fatigue or lack of energy	194	79.9	0.70	0.62-0.79	97.1	0.85	0.78-0.90
Q28 Weight gain without trying	195	91.3	0.81	0.73-0.88	98.7	0.90	0.82-0.95
Q31 Abnormal vaginal discharge	193	98.4	0.87	0.69-1.00	99.4	0.74	0.43-1.00

Table 4.35. *Kappa coefficients for 3x3 severity data*

Questionnaire item	n	Agreementun weighted %	Unweighted k	95% CI	Agreement quadratic weighted %	Quadratic weighted k	95% CI
Q10 Able to feel abdominal mass or lump	193	98.5	0.57	0.25-1.00	99.6	0.77	0.00-0.89
Q14 Pain before, during or after opening bowels	193	90.7	0.74	0.63-0.85	97.7	0.85	0.77-0.91
Q29 Weight loss without trying	192	99.0	0.90	0.66-1.00	99.4	0.85	0.51-1.00
Q32 Pain during or after sexual intercourse	74	98.7	0.95	0.81-1.00	99.7	0.97	0.84-1.00

Table 4.36. *Kappa coefficients for binary severity data*

Questionnaire item	n	% Agreement	Unweighted k	95% CI
Q22 Pain when passing urine	192	99.5	0.91	0.72-1.00
Q30 Abnormal vaginal bleeding	191	99.0	0.66	0.22-1.00

Reliability of symptom frequency assessments

The reliability of frequency, duration and GP data was considered secondary to the need for the questionnaire to collect reliable severity data. This was because the severity section, most importantly, collected data on the prevalence of symptoms. Women were instructed to only complete the frequency, duration and GP consultation components if they experienced the symptom, thus several items had small numbers of test-rest questionnaires included in analyses.

Kappa coefficients for frequency items are listed in Table 4.37 and Table 4.38. Frequency data was not collected for three items: abdominal mass/lump (q10), weight gain (q28) and weight loss (q29), as these symptoms generally have temporal stability over a one-week reference period. There was insufficient data to calculate kappas for pain when passing urine (q22) and abnormal vaginal bleeding (q30).

Quadratic weighted kappa coefficients ranged from $k = 0.62$ to $k = 0.94$. However, kappa calculations for difficulty emptying the bladder (q21), abnormal vaginal discharge (q31) and pain during/after sexual intercourse (q32) should be interpreted with caution due to the small number of test-retest questionnaires included in analyses. Items with substantial numbers of test-retest questionnaires and the highest kappas for frequency reliability were urinary frequency (q18) $k = 0.87$, pelvic bloating/fullness (q11) $k = 0.85$, pelvic discomfort/pain (q2) $k = 0.84$ and urinary urgency (q19) $k = 0.83$.

Reliability of symptom duration assessments

Kappa coefficients for test-retest reliability of symptom duration items are listed in Table 4.39 and Table 4.40. There was insufficient data to calculate kappa coefficients for six items: abdominal mass/lump (q10), difficulty emptying bladder (q21), pain when passing urine (q22), weight loss without trying (q29), abnormal vaginal bleeding (q30) and abnormal vaginal discharge (q31). Quadratic kappas for all other symptom durations were $k \geq 0.65$. Items with the highest reliability scores for duration, and the largest number of test-retest questionnaires included in analysis, were abdominal bloating/fullness (q7) $k = 0.95$ and pelvic bloating/fullness (q11)) $k = 0.94$.

Reliability of GP symptom reporting assessments

Table 4.41 lists kappa coefficients for test-retest reliability of the GP consultations component of the questionnaire. There was insufficient data to calculate kappas for four items: change in appetite (q6), abdominal mass/lump (q10), pain when passing urine (q22) and abnormal vaginal bleeding (q30). Five GP consultation items had perfect test-retest agreement. However, four of these were calculated from fewer than 20 women. One item, increased abdominal size (q9), included 47 women and had perfect agreement k = 1.00. The item with the lowest reliability for GP consultation was difficulty emptying bladder (q21) k = 0.62, although only 10 women were included in the calculation.

Reliability of depression screening questions

Question 36, which asked women if they were bothered by feeling down, depressed or hopeless during the past month had excellent test-retest agreement, k = 0.91 (95% CI 0.84-0.98), as did q37, which asked women if they were bothered by little interest or pleasure doing things during the past month k = 0.89 (95% CI 0.81-0.96).

Table 4.37. *Kappa coefficients for 3x3 frequency data*

Questionnaire item	n	Agreement unweighted %	Unweighted k	95% CI	Agreement quadratic weighted %	Quadratic weighted k	95% CI
Q1 Lower abdominal or pelvic discomfort or pain	44	75.0	0.60	0.37-0.80	92.1	0.77	0.57-0.90
Q2 Upper abdominal discomfort or pain	29	86.2	0.77	0.54-1.00	94.0	0.84	0.59-0.98
Q3 Indigestion or heartburn	63	68.3	0.45	0.23-0.63	92.1	0.68	0.52-0.80
Q4 Nausea or vomiting	18	66.7	0.39	-0.01-0.78	91.7	0.60	0.13-0.91
Q5 Felt full quickly when eating	24	79.2	0.69	0.46-0.91	94.8	0.85	0.66-0.97
Q6 Change in appetite	37	76.9	0.65	0.03-1.00	94.2	0.79	0.40-1.00
Q7 Upper abdominal bloating or fullness	37	83.8	0.75	0.55-0.91	93.9	0.82	0.61-0.95
Q8 Upper abdominal pressure	14	71.4	0.59	0.29-1.00	92.9	0.78	0.50-1.00
Q9 Increased abdominal size	41	73.2	0.60	0.38-0.79	93.3	0.81	0.69-0.91
Q10 Able to feel abdominal mass or lump	n/a*						
Q11 Lower abdominal or pelvic bloating or fullness	32	84.4	0.74	0.53-0.92	93.8	0.85	0.63-0.97

Questionnaire item	n	Agreement unweighted %	Unweighted k	95% CI	Agreement quadratic weighted %	Quadratic weighted k	95% CI
Q12 Lower abdominal or pelvic pressure	18	83.3	0.71	0.41-1.00	95.8	0.91	0.78-1.00
Q13 Lower abdominal or pelvic heaviness	21	85.7	0.76	0.47-1.00	96.4	0.91	0.77-1.00
Q14 Pain before, during or after opening bowels	31	67.7	0.43	0.19-0.72	91.9	0.66	0.40-0.84
Q15 Difficulty emptying bowels	34	67.7	0.49	0.21-0.74	89.7	0.65	0.33-0.84
Q16 Change in bowel habit	17	76.5	0.61	0.25-1.00	89.7	0.72	0.18-0.96
Q17 Excessive wind or flatulence	64	73.4	0.58	0.40-0.74	89.8	0.65	0.44-0.83
Q18 Passed urine frequently	56	87.5	0.80	0.66-0.93	95.5	0.87	0.74-0.96
Q19 Urgent need to pass urine	54	79.6	0.69	0.50-0.84	93.5	0.83	0.68-0.93
Q20 Pressure on bladder	18	77.8	0.65	0.32-1.00	94.4	0.81	0.62-0.96
Q21 Difficulty emptying bladder	9	77.8	0.66	0.18-1.00	94.4	0.86	0.55-1.00
Q22 Pain when passing urine	n/a[†]						
Q23 Short of breath	14	85.7	0.77	0.43-1.00	96.4	0.92	0.76-1.00

Questionnaire item	n	Agreement unweighted %	Unweighted k	95% CI	Agreement quadratic weighted %	Quadratic weighted k	95% CI
Q24 Back ache or pain	61	78.7	0.69	0.54-0.82	93.4	0.80	0.65-0.90
Q25 Leg ache or pain	46	71.7	0.58	0.39-0.75	91.3	0.73	0.53-0.87
Q26 Leg swelling	19	79.0	0.68	0.43-0.91	94.7	0.85	0.67-0.97
Q27 Tiredness, fatigue or lack of energy	84	71.4	0.57	0.43-0.71	92.9	0.80	0.72-0.87
Q28 Weight gain without trying	n/a*						
Q29 Weight loss without trying	n/a*						
Q31 Abnormal vaginal discharge	10	90.0	0.84	0.46-1.00	97.5	0.94	0.74-1.00

** Frequency data not collected*

† Insufficient data, kappa calculation not possible

Table 4.38. *Kappa coefficients for binary frequency data*

Questionnaire item	n	% Agreement	Unweighted k	95% CI
Q30 Abnormal vaginal bleeding	n/a[†]			
Q32 Pain during or after sexual intercourse	10	90.0	0.62	-0.05-1.00

[†] *Insufficient data, kappa calculation not possible*

Table 4.39. *Kappa coefficients for 4x4 duration data*

Questionnaire item	n	Agreement unweighted %	Unweighted k	95% CI	Agreement quadratic weighted %	Quadratic weighted k	95% CI
Q1 Lower abdominal or pelvic discomfort or pain	43	90.7	0.86	0.72-0.97	96.1	0.89	0.68-0.99
Q2 Upper abdominal discomfort or pain	29	89.7	0.84	0.65-1.00	95.8	0.86	0.55-1.00
Q3 Indigestion or heartburn	57	84.2	0.74	0.55-0.89	97.1	0.92	0.81-0.97
Q4 Nausea or vomiting	14	92.9	0.90	0.64-1.00	92.9	0.73	0.10-1.00
Q5 Felt full quickly when eating	22	77.3	0.69	0.44-0.93	89.4	0.66	0.24-0.98
Q6 Change in appetite	10	80.0	0.72	0.34-1.00	88.9	0.65	0.05-1.00
Q7 Upper abdominal bloating or fullness	35	88.6	0.83	0.63-0.96	98.7	0.95	0.86-0.99
Q8 Upper abdominal pressure	13	76.9	0.63	0.18-1.00	97.4	0.92	0.75-1.00
Q9 Increased abdominal size	43	83.7	0.77	0.60-0.91	94.1	0.81	0.54-0.97
Q10 Able to feel abdominal mass or lump	n/a[†]						
Q11 Lower abdominal or pelvic bloating or fullness	31	83.9	0.77	0.55-0.93	98.2	0.94	0.88-0.99

Questionnaire item	n	Agreement unweighted %	Unweighted k	95% CI	Agreement quadratic weighted %	Quadratic weighted k	95% CI
Q12 Lower abdominal or pelvic pressure	19	89.5	0.85	0.61-1.00	98.8	0.97	0.89-1.00
Q13 Lower abdominal or pelvic heaviness	20	85.0	0.79	0.54-1.00	98.3	0.96	0.88-1.00
Q14 Pain before, during or after opening bowels	29	79.3	0.70	0.48-0.90	96.6	0.89	0.76-0.97
Q15 Difficulty emptying bowels	30	80.0	0.67	0.45-0.89	96.7	0.90	0.72-0.97
Q16 Change in bowel habit	17	64.7	0.48	0.19-0.82	94.1	0.77	0.34-0.93
Q17 Excessive wind or flatulence	54	92.6	0.89	0.76-0.97	97.5	0.92	0.75-0.99
Q18 Passed urine frequently	55	92.7	0.88	0.72-0.97	97.6	0.91	0.71-0.99
Q19 Urgent need to pass urine	55	90.9	0.84	0.68-0.96	97.2	0.87	0.69-0.98
Q20 Pressure on bladder	19	89.5	0.86	0.61-1.00	98.9	0.95	0.85-1.00
Q21 Difficulty emptying bladder	n/a†						
Q22 Pain when passing urine	n/a†						
Q23 Short of breath	14	71.4	0.59	0.22-0.90	90.5	0.74	0.29-0.98

Questionnaire item	n	Agreement unweighted %	Unweighted k	95% CI	Agreement quadratic weighted %	Quadratic weighted k	95% CI
Q24 Back ache or pain	63	85.7	0.77	0.62-0.90	94.5	0.84	0.68-0.96
Q25 Leg ache or pain	42	88.1	0.81	0.64-0.95	97.9	0.93	0.84-0.99
Q26 Leg swelling	20	90.0	0.85	0.63-1.00	94.4	0.83	0.45-1.00
Q27 Tiredness, fatigue or lack of energy	82	78.1	0.69	0.56-0.81	94.2	0.81	0.65-0.92
Q28 Weight gain without trying	50	80.0	0.69	0.49-0.86	97.8	0.89	0.80-0.95
Q29 Weight loss without trying	n/a†						
Q30 Abnormal vaginal bleeding	n/a†						
Q31 Abnormal vaginal discharge	n/a†						

† *Insufficient data, kappa calculation not possible*

Table 4.40. *Kappa coefficients for 3x3 duration data*

Questionnaire item	n	Agreement unweighted %	Agreement unweighted %	95% CI	Agreement quadratic weighted %	Quadratic weighted k	95% CI
Q32 Pain during or after sexual intercourse	10	90.0	0.80	0.0-1.00	97.5	0.89	0.00-1.00

Table 4.41. *Kappa coefficients for binary GP symptom reporting data*

Questionnaire item	n	% Agreement	Unweighted k	95% CI
Q1 Lower abdominal or pelvic discomfort or pain	47	91.5	0.73	0.48-0.97
Q2 Upper abdominal discomfort or pain	29	82.8	0.65	0.39-0.91
Q3 Indigestion or heartburn	62	96.8	0.91	0.78-1.00
Q4 Nausea or vomiting	18	88.9	0.77	0.48-1.00
Q5 Felt full quickly when eating	23	95.7	0.78	0.36-1.00
Q6 Change in appetite	n/a[†]			
Q7 Upper abdominal bloating or fullness	36	94.4	0.84	0.62-1.00
Q8 Upper abdominal pressure	14	100.0	1.00	1.00-1.00
Q9 Increased abdominal size	47	100.0	1.00	1.00-1.00
Q10 Able to feel abdominal mass or lump	n/a[†]			
Q11 Lower abdominal or pelvic bloating or fullness	31	96.8	0.90	0.72-1.00
Q12 Lower abdominal or pelvic pressure	19	100.0	1.00	1.00-1.00
Q13 Lower abdominal or pelvic heaviness	20	100.0	1.00	1.00-.100

Questionnaire item	n	% Agreement	Unweighted k	95% CI
Q14 Pain before, during or after opening bowels	31	93.6	0.79	0.52-1.00
Q15 Difficulty emptying bowels	36	94.4	0.80	0.54-1.00
Q16 Change in bowel habit	16	87.5	0.75	0.44-1.00
Q17 Excessive wind or flatulence	63	96.8	0.73	0.38-1.00
Q18 Passed urine frequently	61	96.7	0.86	0.66-1.00
Q19 Urgent need to pass urine	60	96.7	0.88	0.72-1.00
Q20 Pressure on bladder	18	100.0	1.00	1.00-1.00
Q21 Difficulty emptying bladder	10	90.0	0.62	-0.05-1.00
Q22 Pain when passing urine	n/a[†]			
Q23 Short of breath	15	86.7	0.71	0.34-1.00
Q24 Back ache or pain	69	94.2	0.87	0.75-0.99
Q25 Leg ache or pain	46	97.8	0.95	0.86-1.00
Q26 Leg swelling	21	90.5	0.81	0.56-1.00

Questionnaire item	n	% Agreement	Unweighted k	95% CI
Q27 Tiredness, fatigue or lack of energy	87	94.3	0.85	0.72-0.98
Q28 Weight gain without trying	50	92.0	0.75	0.52-0.98
Q29 Weight loss without trying	9	88.9	0.73	0.24-1.00
Q30 Abnormal vaginal bleeding	n/a[†]			
Q31 Abnormal vaginal discharge	9	100.0	1.00	1.00-1.00
Q32 Pain during or after sexual intercourse	11	100.0	1.00	1.00-1.00

[†] *Insufficient data, kappa calculation not possible*

4.6.4 Formatting the finalised questionnaire

A fourth consensus group meeting was held on 2 October 2008 to agree content for the finalised OCSq. Pilot findings up to this date were presented to the group, including missing data, correlations between symptoms, retest reliability kappa coefficients and feedback from respondents relating to specific questions.

The group decided to continue with the 'past week' timeframe for all questions, except weight loss and weight gain. For these two items it was agreed to ask women about the 'past year'. It was also agreed to add the wording 'during the past week' or 'during the past year' to all individual questions rather than just have this information at the top of each page.

To improve readability, it was decided to change the direction of the text in the severity column (e.g. not at all, a little, quite a bit and very much) to a horizontal direction and change 'not at all' to 'no'. The group decided to revise the questionnaire so that it appeared less cluttered, removing the arrows and the numbers under the boxes for not at all, a little, etc. It was agreed to experiment with shading the columns and to seek feedback on the questionnaire's readability prior to final formatting.

No questions were removed on the basis of correlation with another question. The group agreed that removal of any symptom with a correlation coefficient of less than $r_s = 0.90$ with another symptom would potentially result in information being missed by the finalised questionnaire. As all kappa correlations indicated moderate or higher reliability, no symptoms were deleted on the basis of poor reliability.

The group noted that women were confused by the ordering of shortness of breath (q23) on the same page, and directly after, the five urinary symptoms (q18-q22). Several women wrote comments similar to the following on their feedback forms: '*I get short of breath but not when I pass urine*' (Respondent, Site 3) and '*Shortness of breath is not something I associate with passing urine, and its position in the questionnaire seemed to refer to urination. Was it included as a joke perhaps?*' (Respondent, Site 6). The group therefore decided to reorder

shortness breath, placing it before the urinary symptoms. The order of all other questions remained unchanged.

The group noted that only 15 out of 829 women (2%) wrote more than one 'other' symptom in the space provided. The symptoms reported by these women were dry skin, headache, sore throat and other symptoms not specific to ovarian cancer. It was decided to remove the space where respondents could write second and third 'other' symptoms in order to reduce the length of the questionnaire.

The group decided to add diverticulitis to the co-morbidities section as several women wrote similar comments to, '*I'm not sure if diverticulitis is classed as inflammatory bowel disease'* (Respondent, Site 13). It was also agreed to add a section to the questionnaire where participants can write relevant information about their symptoms.

The finalised OCSq was formatted according to the decisions of the fourth consensus group. Several weeks after the meeting, a questionnaire was received from a participant who commented that she specifically remembered the date of onset of a symptom as it started whilst she was on holiday. The duration of the symptom was 6.5 months, which made it difficult for the respondent to decide whether to tick 4-6 months or 7-12 months, so both durations were ticked. After receiving this feedback it was decided to change the duration options to: <3 months, 3-6 months, 6-12 months and >12 months. This improved the consistency of the symptom duration assessment as the pilot OCSq covered durations of 3.5 months (e.g. <3 months and 3-6 months) but not 6.5 months.

Four drafts with different shading schemes were presented to a convenience sample of 14 women aged over 50 years. These women were asked to select the questionnaire they found most visually appealing and easiest to read. A majority (six of the 14 women) preferred shading format B (appendix 21), thus this was adopted for the finalised OCSq (appendix 22).

By the conclusion of stage IV the draft OCSq had been piloted with 829 women, validity analyses confirmed the questionnaire was acceptable to women and reliability analyses demonstrated its stability over time. The finalised OCSq was

formatted and planning commenced for the prospective research described in Chapter Six.

4.7 Discussion

The process of developing a valid and reliable questionnaire for any research topic is resource and time intensive. The absence of a previously validated and readily available ovarian cancer symptoms questionnaire necessitated the research described in this chapter. Unfortunately, it is not possible to compare the findings of my own research with the two earlier studies which described the use of a validated questionnaire,[7 70] as they did not publish findings of their validation, or provide details when requested.

Face and content validation was conducted throughout the development process. Each component of this process was guided by input from experts, including women living with ovarian cancer, nurses who provide care to ovarian cancer patients, gynaecological oncology surgeons, questionnaire design specialists and UKCTOCS volunteers. Generation of the symptoms list from ovarian cancer symptoms papers ensured that its contents were relevant to the intended topic. Consensus group review and feedback from health professionals and women with ovarian cancer further validated the content of the symptoms list.

The OCSq layout was based upon a combination of the formatting used by Vine *et al.*[16] and Goff *et al.*[18 23] for their respective questionnaires. The questionnaire review in stage II identified these previously developed questionnaires as having as the most visually-appealing, user-friendly formats. Wider research has shown that user-friendly formats and the exclusion of difficult or objectionable items increase response rates.[199] To reduce 'question threat',[129] more intimate questions about symptoms of vaginal discharge, vaginal bleeding and sexual intercourse were placed towards the end of the questionnaire, and an instruction was included for women to respond to the question about painful sexual intercourse only if they had been sexually active in the past week.

Further content validation was achieved through the analysis of completed pilot questionnaires and feedback forms. This found less than 10% of respondents

missed any question on the OCSq, indicating a reasonable degree of acceptability. Fayers & Machin[169] suggest questions with 3-4% missing data should be re-examined with a view to rewording. However, this proportion of missing data relates to questionnaires completed in the presence of the researcher. It is to be expected that the proportion of missing data for each question will be higher for postal questionnaires. Piloting of the OCSq found a maximum of 15 women had difficulty replying to any question. The consensus group discussed this finding but decided against re-wording questions due to the due to the fact that women did not have trouble understanding wording. Rather, their difficulty was associated with their indecision whether to respond positively to questions for symptoms which they had experienced for many years.

No symptoms were excluded on the basis of correlation with another item, as the highest Spearman coefficient was $r_s = 0.64$. All 32 symptoms in the draft OCSq therefore remained in the finalised OCSq. This number of symptoms is considerably more than the next largest checklists reported in the literature, such as the questionnaire used by Goff *et al.*[23] which included 23 symptoms and Igoe's[7] questionnaire which included 21. However, the consensus group considered it important to include as comprehensive a list as possible in the finalised OCSq, as asking about specific symptoms elicits reporting through memory-cueing effects.[129 141] A comprehensive list of symptoms is also important as it provides a common frame of reference for all respondents. This reduces the arbitrariness of symptom recall associated with questionnaires which elicit information using open questions. As discussed in chapter three, this was the principal flaw of the Ovacome Patient Survey.

Construct validation was not appropriate as all women who participated in the questionnaire pilot were apparently healthy at the time. Construct validation would only be appropriate when sufficient numbers of women who complete the OCSq are diagnosed with ovarian cancer.

Factor analysis was not appropriate in the development of the OCSq as it is not a psychometric tool. Moreover, as the women recruited for the pilot did not yet have the outcome of interest (ovarian cancer), it would be impossible to determine

underlying symptom factors associated with ovarian cancer. Criterion validation was also not attempted as there is no gold standard ovarian cancer symptoms measure.

Likert scales for symptom severity ranged from not at all to very much. This four-point scale is the same as the Likert scales used in EORTC Quality of Life questionnaires. This is less than the 5-7 or 7-10 response categories described in the literature as having the greatest accuracy.[129-130] Rather than increase the number of response categories the consensus group decided to adhere to EORTC questionnaire formatting for the measurement of symptom severity. Consensus group members noted that the four-category scale has been well-validated among cancers patients in several different countries.[178 181 185 200-204] Moreover, the wider questionnaire design literature is largely based upon psychological studies where nuanced information elicited by 7-10 point scales may be more relevant than in a symptoms study.

The consensus group also discussed whether the symptom frequency column (e.g. 1-2 days, 3-5 days, 6-7 days) should be broken down into seven categories for the seven days of the week. It was debated whether to increase the number of response categories for symptom duration into shorter timeframes (e.g. one month, two to three months, three to four months, etc.), or expand these to include durations of longer than 12 months. However, the group decided that this would not necessarily increase the accuracy of the data given the study population (i.e. women aged 50 to 80 years). Also, increased response options may create greater confusion among respondents. It was therefore decided to limit the symptom severity to four categories, frequency to three categories and duration to four.

The reference period selected for assessment of symptom prevalence/severity and frequency was one week. This timeframe was selected after reviewing the literature on ovarian cancer symptoms, questionnaire design and the measurement of symptoms in diverse patient populations. The literature review in Chapter Two revealed the persistent nature of ovarian cancer symptoms and a recent paper by the Goff group demonstrated the temporal stability of key symptoms over several months.[26] Thus, a one-week reference period was considered sufficient to capture

information on symptom prevalence. A one-week, rather than one-month, reference period was selected as it is less susceptible to exponential memory decay.[129 147 151] Evidence indicates one to two-week periods have similar reliability to daily symptom diaries,[131 149 162] while one-month recall can be half as accurate as daily reports for symptoms such as tiredness, indigestion or back pain.[160] The consensus group also considered that women would not be able to accurately remember detailed information on symptom severity and frequency over a one-month period. While research suggests that severe symptoms are often remembered in the medium to long-term, minor symptoms are likely to be forgotten after short lapses of time.[132 205-206] Restricting the reference period to one week had the additional advantage of limiting telescoping, which refers to the tendency for patients to misplace symptom events in time.[129 133]

A daily symptoms diary was rejected as they present a considerable burden to research participants. Studies have also found conditioning effects associated with symptom diaries, where participants tend to under-report symptoms they associate with long-term disease.[149] Other disadvantages of symptom diaries include reporting-fatigue and higher rates of attrition compared to one-off questionnaires.[207]

Our aim to recruit a sufficiently large sample of participants for reliability analyses was balanced by a consideration to limit participant burden. After exclusion of ineligible questionnaires, test-retest validation was conducted using data from a sample of 201 respondents. Streiner & Norman[130] demonstrated that a sample of 200 participants yields a 95% confidence interval with a width of 0.15 for reliability coefficients. Confidence intervals for kappa coefficients could have been narrower had the response rate been higher than 53% among women invited to complete a retest questionnaire. However, it would have been difficult to improve this given the fact that the questionnaire was conducted via post, and that at seven pages in length, it was fairly onerous for women to complete twice. Furthermore, our sample size of 201 is greater than the 194 women who participated in test-retest validation of an EORTC questionnaire for assessing quality of life in ovarian cancer patients (QLQ-OV28[185]) and approximately four times the number of subjects included in reliability analyses of the Women's

Health Questionnaire (WHQ) and a questionnaire designed to assess bowel and lower urinary tract symptoms.[208-209]

Test-retest reliability analyses produced an overall median quadratic weighted (or unweighted where quadratic weighting was not possible for binary data) kappa of k = 0.85 (range 0.60-1.00) for the questionnaire as a whole, indicating excellent stability over time. The median quadratic weighted kappa for symptom severity was k = 0.85 (range 0.63-0.97) and the median for symptom frequency was k = 0.81 (range 0.60-0.94), while symptom duration had a median of k = 0.89 (range 0.65-0.97). Kappa scores for the reliability of GP consultation data ranged from 0.62-1.00 with a median of k = 0.85. Only one item, frequency of nausea and vomiting (q4) (k = 0.60), had a kappa just under the minimum score of k = 0.61 described by Landis & Koch[198] as indicative of substantial agreement.

The very high percentage agreement and substantially lower kappa scores of some questionnaire items (e.g. severity of abdominal pressure (q8) k = 0.63) are an example of the 'paradox of kappa'.[210] This arises when the prevalence of the outcome being measured is either very high or very low, resulting in an imbalance in the marginal or horizontal totals of a 2 x 2 table. Over 81% of women replied 'not at all' to the severity section of abdominal pressure (Q8) on their test-retest questionnaires. Prevalence of 'a little', 'quite a bit' or 'very much' responses was very low, which produced an imbalance in the table for this item. This was also the case for a number of frequency, duration and GP consultation items.

Several frequency, duration and GP consultation items had small numbers of test-retest questionnaires included in kappa calculations and some (e.g. pain when passing urine (q22) had too few questionnaires to enable calculation. Items with both small numbers of test-retest questionnaires and imbalanced 2 x 2 tables had wide 95% confidence intervals. Small numbers for frequency, duration and GP consultation items are to be expected as women were instructed to complete these sections only if they experienced the symptom during the past week. The primary purpose of reliability analyses was assessment of the stability of symptom wording and prevalence measures (i.e. the severity component). From the outset we appreciated that we would not have the time or resources to collect sufficient

test-retest data to validate the stability of all frequency, duration and GP consultation components of the questionnaire.

Quadratic kappa coefficients were considerably higher than the minimum coefficient of 0.5 described by Streiner & Norman[130] as acceptable for health measures, although they are in a similar range to that reported for the Women's Health Questionnaire.[208] It is plausible that high kappa coefficients resulted from some women directly copying information from questionnaire A to questionnaire B. However, we tried to avoid this by including an instruction in the cover letter specifically requesting women not to simply copy information from their first questionnaire.

During the first consensus group it was agreed to remove depression from the symptoms list, but to add two short depression screening questions which have been validated and are recommended by NICE for use in primary care settings.[193] In the interest of brevity, the group decided against the use of a separate depression screening tool such as the Short Form 36, Beck Depression Inventory or the General Health Questionnaire (GHQ-12).

The two depression screening questions included in the questionnaire were: 1) During the past month have you often been bothered by feeling down, depressed or hopeless? and 2) During the past month have you often been bothered by little interest or pleasure doing things? These questions were originally developed by Spitzer *et al.*[211] as part of the PRIME-MD tool, designed to screen for mental health disorders in primary care populations. Research has shown that these two questions have a sensitivities ranging from 68-96% and specificities of 57-84% for identifying depression in hospital out-patients, primary and palliative care populations and pregnant women.[212-217] A recent meta-analysis concluded that a positive response on one of the two questions identifies eight out of 10 cases of depression.[218] These questions were included in the questionnaire as they are short, easily comprehended by research participants and recommended to screen for depression in primary care.

Study strengths

Strengths of the research include feedback from experts in each sequential stage of the questionnaire's development and recruitment of a large sample of women for the OCSq pilot. The review of existing questionnaires also helped to identify examples of good questionnaire design for inclusion in the OCSq.

Study limitations

Unfortunately, the study was limited by a moderate response rate (53%) among women asked to complete test and retest questionnaires, which may have introduced an element of selection bias. The project group decided against sending women a reminder letter as we recognised that two seven page questionnaires represent a burden to women and we wished to maintain good relations with UKCTOCS volunteers.

Selection bias is also likely to have occurred during the telephone interview component. We were advised by consultants that two of the 38 women initially identified as candidates for telephone interviews were too ill to be approached for invitation. Perhaps a greater proportion of those who agreed to participate had symptoms compared to other women diagnosed with ovarian cancer in UKCTOCS. We attempted to limit recall bias in the telephone interview component by inviting women who were diagnosed with ovarian cancer within the past three years. However, women who were diagnosed with late stage disease may have already died within this time-frame, resulting in further selection bias.

4.8 Summary

In this chapter I have described the sequential development of the OCSq, from generation of the initial ovarian cancer symptoms list, up to formatting of the finalised questionnaire. Although this process was time-consuming, it succeeded in developing a robust, valid and reliable questionnaire for use in the prospective study. Analyses of symptoms data collected during the OCSq pilot are presented in the next chapter.

Chapter Five – Symptoms Reported by Women Who Participated in the OCSq Pilot

5.0 Introduction

The literature review in Chapter Two described the absence of any genuinely prospective ovarian cancer symptoms research. Three studies assessed symptoms prior to women undergoing surgery for possible ovarian lesions.[18 23 46] However, these studies collected symptoms information from patients who were aware of the presence of a serious abnormality and, undoubtedly, the possibility of malignancy. The research described in this chapter attempts to address this gap in existing knowledge by investigating symptoms in apparently healthy women, then correlating symptoms with results of ovarian cancer screening.

The data presented in this chapter were collected during the course of piloting the OCSq. The methods are the same as those described for the pilot of the provisional OCSq in Chapter Four. However, the aims and data analysis sections differ. The chapter begins with the aims of symptoms analyses. Data analysis methods are documented and results are presented. Findings are reviewed in the discussion and compared to the literature on ovarian cancer symptoms. Strengths and limitations of the research are considered, then the final section of the chapter summarises the main findings.

5.1 Aims

- To estimate the prevalence of 'key symptoms' in apparently healthy women participating in the pilot of the OCSq
- To correlate symptoms data with: 1) participation in screening, 2) abnormal results on ovarian cancer screening, 3) diagnosis of ovarian/fallopian tube cancer, 4) awareness of a possible ovarian lesion due to the need to have repeat tests following annual screen, and 5) depression screening status

- To develop models based on symptoms to detect ovarian abnormalities and to establish the performance characteristics of the generated and previously published indices
- To generate a preliminary hypothesis of symptom reporting that will be tested in the final phase of the research

5.2 Methods

The methods of the OCSq pilot are fully described in Chapter Four. A summary of this information is provided below. Data cleaning and analysis methods unique to this chapter are also described.

5.2.1 Setting

The OCSq was piloted in the UKCTOCS cohort. To summarise, women invited to participate were: 1) UKCTOC controls, 2) women receiving screening in the multimodal or ultrasound groups of UKCTOCS. Women in the screening groups were either: 1) attending annual (Level 1) screening, or 2) recalled for repeat (Level 2) screening due to an abnormal finding on annual screen.

5.2.1.1 Summary of UKCTOCS screening

Chapter One details the design of UKCTOCS, including screening algorithms for the multimodal and ultrasound groups. A summary of this information is given below.

Multimodal group

Women in the multimodal group receive an annual CA125 blood test and a risk of ovarian cancer (ROC) score is calculated (Chapter One, Figure 1.3). The ROC score is then classified as either: 1) normal, 2) intermediate or 3) elevated (>0.2578%). Women with an intermediate ROC are recalled for repeat CA125 in 12 weeks. Women with an elevated ROC are recalled for Level 2 screen in 6-8 weeks when they have another CA125 test and a transvaginal ultrasound. They are then triaged according to their results to: 1) annual screening, 2) repeat Level 2 if the scan is normal or unsatisfactory, or 3) clinical assessment.[219]

Ultrasound group

Women in the ultrasound group receive an annual transvaginal ultrasound (Chapter One, Figure 1.4). Results are classified as: 1) unsatisfactory, 2) normal, or 3) abnormal. Any of the following are abnormal: a single simple cyst over 5cms diameter, more than one cyst including more than one inclusion cyst in one ovary, complex morphology (solid areas, septae or cysts with irregular outline or anechoic contents). Women with abnormal ultrasound results are recalled for a Level 2 ultrasound in 6-8 weeks and those with highly suspicious findings are recalled earlier. Level 2 screens are also categorised as: 1) unsatisfactory, 2) normal, or 3) abnormal. Women with normal results are referred back to annual screening, unsatisfactory results are recalled for a repeat Level 2 in 6-8 weeks and those with abnormal scans are referred for clinical assessment with a gynaecological oncology consultant.

5.2.2 Sample

In the control group, only women who returned their UKCTOCS follow up questionnaires in the last 12 months were eligible (Chapter 4). A random sample of 25 controls from each of the 13 regional centres was mailed the OCSq.

In the screen group, in order to enrich the population with those with possible ovarian abnormalities, 60% of the women mailed were those who were being sent a Level 2 screen appointment. Women were identified for mailing as described in Chapter 4.

5.2.3 Data collection

The pilot OCSq is described in Chapter Four and presented in appendix 12. All questionnaires were date stamped on receipt. Questionnaires without the written consent section completed were considered ineligible. These were returned to women with a second reply-stamped envelope and letter requesting them to provide consent if they wished their questionnaire to be included in the study.

The UKCTOCS data collection instruments are described in Chapter One. Participants completed the UKCTOCS baseline questionnaire at initial recruitment and the follow-up questionnaire approximately 3.5 years later.

Demographic and reproductive history data from the questionnaires were exported from the main UKCTOCS Trial Management System on 28 April 2009 and included in analyses described in this chapter.

In addition to symptoms data, the OCSq elicited information on current HRT use and co-morbidities (including past non-ovarian cancer diagnoses) previously diagnosed by a doctor. Two depression screening questions, validated by international groups and recommended for use in primary care by NICE, were included in the final section of the OCSq.

Screening, surgery, ovarian cancer diagnoses and outcomes data were exported from the main UKCTOCS Trial Management System on 26 June 2009. This data included an NHS Information Centre for Health and Social Care in England and Wales cancer registry notification update received at the UKCTOCS coordinating centre on 30 January 2009 and a notification received 17 February 2009 from the Northern Ireland Central Services Agency and Cancer Registry.

5.2.4 Data cleaning

- An estimated completion date was calculated for respondents who did not write the date on their questionnaire. This was based upon the overall median number of days between the date of questionnaire completion and receipt date for all participants.
- Where respondents completed the frequency section (ticking either: 1-2 days, 3-5 days or 6-7 days during the past week), the duration section (ticking either: less than 3 months, 3-6 months, 6-12 months or more than 12 months) or ticked yes to reported to GP section but did not complete the severity section (either: no, a little, quite a bit or very much) the symptom was coded as present during the past week but without a severity rating.
- Where respondents did not complete the severity, frequency or duration sections but ticked no to the discussed with GP section, the symptom was coded as not experienced during the past week.

5.2.5 Data analysis

OCSq data were entered directly into SPSS version 12.0.1 (SPSS Inc., Chicago, USA) on a daily basis until the final questionnaire was received. UKCTOCS baseline questionnaire, follow-up questionnaire and screening data were imported into the same SPSS database for analysis. Frequencies were run to describe the data and distributions of continuous variables were explored.

Screening results

UKCTOCS screening results concurrent with the OCSq were investigated for the multimodal and ultrasound groups. The concurrent screen was defined as the screening appointment given in the letter which accompanied the OCSq. If the respondent did not attend the scheduled appointment, the concurrent screen was the first screening appointment attended after the date the questionnaire was posted to the volunteer.

Concurrent screening results were categorised as either normal or abnormal based on the 'action' generated following classification and triage on UKCTOCS (Table 5.1).

Table 5.1. *Criteria for categorising UKCTOCS concurrent screening results*

Screening action	Coded for analysis
Return to annual screening	Normal
Repeat screen (repeat Level 1, Level 2 or repeat Level 2 screen)	Abnormal
Referred to gynaecological oncologist for assessment	Abnormal

In addition to the classification of results in Table 5.1, results were also explored in the multimodal group by comparing: 1) those with elevated ROC scores (risk >0.2578%) versus those with normal and intermediate ROC scores (<0.2578%), and 2) those with CA125 ≥30 U/mL (traditional cut-off adopted in clinical practice in postmenopausal women) versus those with CA125 <30 U/mL.

Ultrasound results were available for women in the ultrasound group and those attending Level 2 appointments in the multimodal group. In the UKCTOCS trial

ultrasonographers report whether ovaries are visualised or not. In women where ovaries are visualised, the morphology on ultrasound of each ovary (right and left separately) is described as: 1) normal, 2) simple cysts, or 3) complex morphology (as described in Chapter One). Left and right ovary morphology and volumes were investigated for all respondents where this information was available.

End of study outcomes

In all participants, the UKCTOCS database was searched for further information with regard to annual or repeat screening, referrals to gynaecological oncologists, trial surgery, cancer registrations, deaths and reasons for withdrawal from the trial. Histopathology and hospital notes of women who underwent surgery were reviewed to ascertain any ovarian pathology and morphology, stage and grade of ovarian/fallopian tube cancer. GP notes were requested for women diagnosed with ovarian/fallopian tube cancer.

For the purpose of this analysis, all participants were censored on the date of surgery during which ovaries were removed, diagnosis of ovarian cancer, death or withdrawal from UKCTOCS. The date of data export from the UKCTOCS Trial Management System was used as the censorship date for participants who were continuing as a control, or continuing to receive screening in the UKCTOCS trial. Number of days follow-up was calculated for each woman from the questionnaire completion date to the date of censorship and total person-years of follow-up was calculated for all respondents.

Symptoms reported by OCSq respondents

Symptoms were investigated using four different approaches to classify ‘positive’ symptoms:

1 Symptoms reported at any level of severity.

2 Symptoms reported at level 2-3 severity. This pragmatic approach was adopted based on the hypothesis that it is difficult to define ‘a little’ in terms of symptoms and women are unlikely to consult their doctor about mild symptoms.

3 Symptoms reported at any level of severity with ≥12 days per month frequency and <12 months duration as described in the Goff Index (detailed in Chapter Two).[23] This approach was utilised as symptoms included in the Goff index had a similar frequency (>12 days during the past month) and equivalent duration criteria.

4 Symptoms with a frequency ≥12 days per month, <12 months duration and level 2-3 severity.

Symptoms reported by all respondents were investigated and symptoms were compared between women receiving screening and controls using the four approaches.

Symptoms and concurrent screen results

Concurrent screen results were investigated using the four approaches to symptoms analysis.

- Symptoms were compared in respondents with abnormal and normal screen results (Table 5.1)
- Symptoms were compared in respondents with elevated ROC scores versus those with normal and intermediate ROC scores
- Symptoms were compared in respondents with concurrent CA125 ≥30 U/mL and those with CA125 <30 U/mL
- Symptoms were compared in respondents with complex morphology in one or both ovaries and those with normal morphology or non-visualised ovaries
- In women with an ultrasound detected ovarian abnormality, symptoms were investigated according to estimated ovarian volume (calculated during ultrasound)

Multivariate analysis of symptoms associated with abnormal results on concurrent screen

Symptoms associated with abnormal results on each of the four univariate approaches were entered into backwards stepwise multivariate logistic regression

models. A backwards method was chosen as forwards regression has a higher risk of Type II error (acceptance of the null hypothesis when in reality there is a genuine effect within a population).

Model 1 included symptoms associated with abnormal results at any level of severity, model 2 at level 2-3 severity, model 3 at ≥12 days frequency and <12 months duration and model 4 at ≥12 days, <12 months and level 2-3 severity. Co-morbidities associated with an abnormal result on univariate analyses were also entered into models, with age and total number of symptoms entered as continuous variables (when associated with an abnormal result on univariate analyses). The likelihood ratio statistic $p = 0.05$ was the criterion for entry into models and $p = 0.1$ for removal. Variables with missing cells were excluded due to confidence intervals of odds ratios being inestimable.

Performance of the models for detecting abnormal results

Models 1-4 developed using this dataset

Receiver operating curves were plotted from the predicted values for the four models and the area under the curve was calculated to assess the goodness-of-fit. Receiver operating curves typically plot the performance of diagnostic tests, demonstrating the sensitivity (true positive rate) versus one-minus specificity (true negative rate) of a test. The sensitivity of the receiver operating curves plotted for the four models refers to the ability of the symptoms in the final models to predict an abnormal ovarian cancer screening result. One-minus specificity refers to the proportion of women the symptoms model predicts will have a normal screening result. A symptoms model which perfectly predicts an abnormal result at all levels of the test would have an area under the curve equal to one, and models which perform no better than chance would have an area equal to 0.5.

Goff Symptom Index

Women who had either pelvic discomfort/pain (q1), abdominal discomfort/pain (q2), feeling full (q5), abdominal bloating (q7) or increased abdominal size (q9) for 3-5 or 6-7 days during the past week and where the symptom had a duration of <3, 3-6 or 7-12 months, were considered positive on the Goff symptom index

(detailed in Chapter Two).[23] This gave an approximate frequency of ≥12 days, which was similar to the stated frequency in the Goff index of >12 days per month. It is to be noted that one item on the Goff index, difficulty eating, was not included in the OCSq. Reasons for exclusion are discussed in Chapter Four.

Lurie Symptom Index

Women who had either abdominal pain (q1), increased abdominal size (q9), abdominal mass or lumps (q10) or abnormal vaginal bleeding (q30) were considered positive on the Lurie symptom index (described in Chapter Two).[25] The Lurie index included hard abdomen but no data were available for this symptom as the item was not included in the OCSq.

Performance of the Goff and Lurie indices for detecting abnormal concurrent screen results was assessed by calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Performance of symptoms models for detecting ovarian cancer

Performance of the four symptoms models, and the Goff and Lurie indices, for identifying women with ovarian/fallopian tube cancer was assessed. The number of women with and without malignancy who were identified by each model was determined and the sensitivity, specificity, PPV and NPV were calculated.

Symptom reporting according to prior awareness of a possible ovarian lesion

All women in the UKCTOCS control group were categorised as unaware of a possible ovarian lesion as they had not undergone any screening. Women in the multimodal and ultrasound groups were categorised into unaware or aware depending on whether their OCSq was posted with their annual or Level 2 screening appointment. Where women completed the OCSq after being informed of the result of their concurrent screening appointment, awareness was adjusted based upon their concurrent screen result.

Symptoms were analysed according to women's awareness of a possible ovarian lesion prior to receipt of the OCSq. It was hypothesised that awareness of the possibility of an ovarian lesion, raised by the need to have repeat tests, would

make women more aware of symptoms and perhaps cause a certain level of anxiety.

Odds ratios were calculated for symptoms reported by aware vs. unaware respondents using the four approaches: 1) any severity, 2) level 2-3 severity, 3) ≥12 days and <12 months duration, 4) ≥12 days, <12 months duration and level 2-3 severity. Using the same approaches, symptoms were analysed in a sub-group of unaware women receiving screening compared to controls.

Symptoms reported to GPs

Symptoms most commonly reported to GPs during the three months prior to the OCSq were investigated. The percentage of respondents who consulted their GP was calculated from the number of women who were positive for the symptom on each of the four approaches. Women were excluded from these analyses if they did not provide both symptom and GP consultation information.

Symptoms and depression screening status

In accordance with the literature discussed in Chapter Four, respondents who replied positively to one or both depression screening questions were categorised as depression screen positive. Prior awareness of a possible ovarian lesion and symptom reporting were investigated according to depression screening status. The same four approaches to classify positive symptoms were utilised for this analysis.

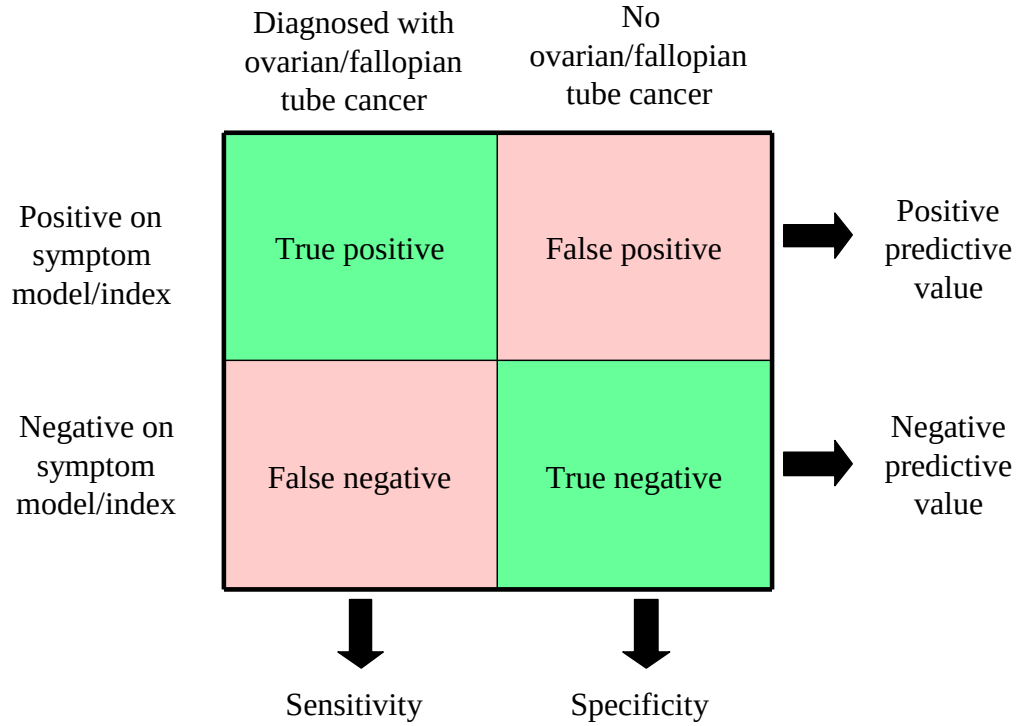
Statistical analysis

Chi-square or Fisher's exact statistics were used to investigate univariate relationships between categorical variables and odds ratios with 95% confidence intervals were calculated. Mann-Whitney *U* tests were used to test differences between two groups for non-parametric continuous data. Effect sizes were calculated and interpreted according to Cohen's criteria of $r = 0.3$ for a medium effect and $r = 0.5$ for a large effect. Differences were accepted as significant at $p < 0.05$ for all tests.

Sensitivity and specificity

Sensitivity refers to the number of respondents who had the defined outcome (abnormal result or ovarian/fallopian tube cancer) who were positive on each symptom model (true positives) divided by the total number of respondents with ovarian/fallopian tube cancer (Figure 5.1 depicts sensitivity, specificity, NPV and PPV of symptom models or indices for detecting ovarian/fallopian tube cancer). Specificity refers to the number of respondents who did not have the specified outcome who were negative on each symptom model (true negatives) divided by the total number of respondents who did not have the defined outcome. The PPV is the number of respondents with the defined outcome identified by the model divided by the total number of respondents with the defined outcome. The NPV is the number of respondents who did not have the defined outcome who were negative on the model divided by the total number of respondents who did not have the defined outcome.

Figure 5.1. *Sensitivity, specificity, PPV and NPV of symptom models for detecting ovarian/fallopian tube cancer*



5.3 Results

5.3.1 Response rates

A total of 1,339 UKCTOCS volunteers (325 from the control group and 507 women from each of the screening groups) were posted the pilot OCSq between 21 May 2008 and 3 December 2008 (Chapter Four). This included 103 women from each of the 13 regional centres (25 controls, 39 multimodal and 39 ultrasound group women). Completed questionnaires were received between 23 May and 3 February 2009. No women were excluded from analysis on the basis of ineligible data as all provided written consent. Ten women initially overlooked completing the consent section. All subsequently provided written consent after their questionnaire was returned to them.

A total of 829 women returned the OCSq, giving an overall response rate of 61.9%. Response rates varied across the 13 regional centres (Table 5.2), with a significant difference between Bristol, which had the highest response rate, and Liverpool, which had the lowest (74.8% *vs*. 54.4%, $\chi^2(1) = 9.4$, $p = 0.002$). A larger proportion of women in the screening groups responded compared to controls (65.2% *vs*. 51.7%, $\chi^2(1) = 19.0$, $p < 0.0001$) and a larger proportion of women attending for Level 2 appointments responded compared to those attending for annual screening (67.8% *vs*. 61.0%, $\chi^2(1) = 4.8$, $p = 0.028$) (Table 5.3).

Table 5.2. *OCSq response rates by regional centre*

Centre	**Invited (n)**	**Responded (n)**	**Response Rate (%)**
Belfast	103	64	62.1
Bristol	103	77	74.8
Cardiff	103	64	62.1
Derby	103	59	57.3
East London (St Bart's)	103	59	57.3
Gateshead	103	67	65.0
Liverpool	103	56	54.4
Manchester	103	69	67.0
Middlesbrough	103	62	60.2
North London (Royal Free)	103	57	55.3
North Wales	103	63	61.2
Nottingham	103	61	59.2
Portsmouth	103	71	68.9
Total	*1,339*	*829*	*61.9*

Table 5.3. *OCSq - Number of women invited, number who responded and response rates*

Group	**Control**		**Annual Screening**		**Repeat Screening**	
	Responded (Invited)	%	Responded (Invited)	%	Responded (Invited)	%
Controls	168 (325)	51.7	-	-	-	-
Multimodal	-	-	117 (195)	60.0	202 (312)	64.7
Ultrasound	-	-	121 (195)	62.1	221 (312)	70.8
Total	*168 (325)*	*51.6*	*238 (390)*	*61.0*	*423 (624)*	*67.8*

Nineteen respondents (5 controls, 8 multimodal and 6 ultrasound) did not have a completion date for the OCSq. The median time from OCSq completion to receipt in the remaining 810 respondents was seven days (range 1-133, IQR 4-15). For the respondents with a missing completion date, an estimated completion date was calculated by subtracting seven days from the stamped receipt date.

5.3.2 Demographics and co-morbidities

5.3.2.1 Reported on OCSq

Mean age was 65.6 years (range 53-80, SD = 5.6), with no difference in the age of controls compared to respondents receiving screening (Table 5.4). Sixty (7.2%) respondents were using hormone replacement therapy (HRT) at the time of the OCSq, with fewer controls reporting current HRT use compared to the other groups ($\chi^2(2) = 6.5$, $p = 0.04$).

A total of 268 (32.2%) women reported they had been diagnosed with arthritis, 124 (15.0%) with depression, 120 (14.5%) with irritable bowel syndrome (IBS), 73 (8.8%) with hiatus hernia and 39 (4.7%) with inflammatory bowel disease (Table 5.4). There were no significant differences in the proportion of women who reported each of the co-morbidities across the three groups. Excluding basal cell carcinomas (BCCs), 74 women (8.9%) reported having a history of cancer, of whom 46 were diagnosed with breast cancer, six with colon or bowel cancer, four

with cervical cancer, three with malignant melanoma and two with non-Hodgkin's lymphoma. One woman each reported being diagnosed with lung cancer, head and neck cancer, multiple myeloma, oesophagus cancer, sarcoma, face cancer or adenocarcinoma of rectum. Six women did not specify cancer type.

5.3.2.2 Reported on UKCTOCS baseline questionnaire

A majority of the respondents (98.4%) were of white ethnic origin. All were postmenopausal, with median of 15.7 years (range 3.1-44.6, IQR 10.4-21.7) since last menstruation at recruitment to UKCTOCS (Table 5.5). A total of 169 (20.4%) were using HRT at recruitment and 147 (17.7%) reported that they had a hysterectomy. Respondents reported a median of two viable pregnancies (range 0-8, IQR 2-3) and 506 (61.0%) reported ever using the oral contraceptive pill (OCP). The groups were well balanced with regard to demographics (Table 5.5). While fewer women in the control group reported HRT use, and more women in the ultrasound group reported hysterectomy, these differences were not significant.

5.3.2.3 Reported on UKCTOCS follow-up questionnaire

Information about education was not collected at baseline. This omission was corrected in the UKCTOCS follow-up questionnaire. As a result of the study design, only women in the control group who completed this questionnaire in the previous 12 months were eligible. Among the 661 women in the screen group, 160 had not completed a follow-up questionnaire when this analysis was undertaken. In the 669 women who had completed a follow-up questionnaire, there was no significant difference in education level between controls and the screen group, although controls had fewer missing data for education (Table 5.6).

Table 5.4. *OCSq demographic and co-morbidity data*

OCSq	**Controls n=168 n (% or SD)**	**Multimodal Group n=319 n (% or SD)**	**Ultrasound Group n=342 n (% or SD)**	**Overall n=829 n (% or SD)**
Age at questionnaire†	64.2 (SD 5.3)	66.2 (SD 5.6)	65.7 (SD 5.7)	65.6 (SD 5.6)
Current HRT use	5 (3.0)	24 (7.5)	31 (9.1)	60 (7.2)
Personal history of cancer*	9 (5.4)	38 (11.9)	27 (7.9)	74 (8.9)
Personal history of breast cancer	6 (3.6)	21 (6.6)	17 (5.0)	46 (5.5)
Diagnosed with hiatus hernia	11 (6.5)	29 (9.1)	33 (9.6)	73 (8.8)
Diagnosed with IBS	19 (11.3)	56 (17.6)	45 (13.2)	120 (14.5)
Diagnosed with inflammatory bowel disease	7 (4.2)	13 (4.1)	19 (5.6)	39 (4.7)
Diagnosed with arthritis	51 (30.4)	113 (35.4)	104 (30.4)	268 (32.2)
Diagnosed with depression	30 (17.9)	46 (14.4)	48 (14.0)	124 (15.0)

** Excluding BCCs/skin cancer*

† Mean

Table 5.5. *UKCTOCS baseline questionnaire demographic data and reproductive history*

UKCTOCS baseline questionnaire	**Controls n=168 n (% or IQR)**	**Multimodal Group n=319 n (% or IQR)**	**Ultrasound Group n=342 n (% or IQR)**	**Overall n=829 n (% or IQR)**
Ethnic origin				
White	166 (98.8)	313 (98.1)	337 (98.5)	816 (98.4)
Black	1 (0.1)	2 (0.6)	4 (1.2)	7 (0.8)
Asian	0	0	0	0
Other	0	3	0	3
Missing	1	1	1	3
Height at recruitment (cm)[†]	162.6 (157.5-65.1)	162.6 (157.5-167.6)	162.6 (157.5-167.6)	162.6 (157.5-167.6)
Weight at recruitment (kg)[†]	67.8 (60.3-76.2)	66.7 (60.3-77.2)	66.7 (60.3-73.0)	66.7 (60.3-76.2)
Median Body Mass Index (BMI) at recruitment	26.0 (23.0-30.0)	25.4 (23.0-30.0)	25.0 (23.0-28.0)	25.4 (23.0-29.0)
BMI group[†]				
Under-weight (BMI <18.5)	0	3 (0.9)	0	3 (0.4)
Optimal weight (BMI 18.5-25.0)	73 (43.5)	142 (44.5)	170 (49.7)	385 (46.4)
Over-weight (BMI 25.1-30.0)	54 (32.1)	98 (30.7)	121 (35.4)	273 (32.9)
Obese (BMI >30.0)	38 (22.6)	71 (22.3)	48 (14.0)	157 (18.9)
Missing	3 (1.8)	5 (1.6)	3 (0.9)	11 (1.3)

UKCTOCS baseline questionnaire	Controls n=168 n (% or IQR)	Multimodal Group n=319 n (% or IQR)	Ultrasound Group n=342 n (% or IQR)	Overall n=829 n (% or IQR)
Years since last menstruation	14.4 (9.5-20.0)	16.5 (10.5-21.7)	16.5 (10.5-22.7)	15.7 (10.4-21.7)
Ever use oral contraceptive pill (OCP)	110 (65.5)	180 (56.4)	216 (63.2)	506 (61.0)
Duration of OCP (years) if applicable	5.0 (2.0-10.0)	5.0 (2.0-10.0)	5.5 (2.0-10.0)	5.0 (2.0-10.0)
Ever use hormone replacement therapy (HRT) at	25 (14.9)	74 (23.2)	70 (20.5)	169 (20.4)
Miscarriages (pregnancies < 6 months)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Number of children (pregnancies ≥ 6 months)	2 (1-3)	2 (2-3)	2 (2-3)	2 (2-3)
Hysterectomy	27 (16.1)	46 (14.4)	73 (21.6)	147 (17.7)

† Median

Table 5.6. *UKCTOCS follow-up questionnaire education data*

UKCTOCS follow up questionnaire	**Controls n=168 n (%)**	**Multimodal Group n=234 n (%)**	**Ultrasound Group n=267 n (%)**	**Overall n= 669 n (%)**
Education level				
No qualification	41 (24.4)	64 (27.4)	74 (27.7)	179 (26.8)
O level	23 (13.7)	24 (10.3)	35 (13.1)	82 (12.3)
A level	8 (4.8)	8 (3.4)	21 (7.9)	37 (5.5)
Clerical qualification	43 (25.6)	59 (25.2)	58 (21.7)	160 (23.9)
Professional qualification	15 (8.9)	27 (11.5)	19 (7.1)	61 (9.1)
Degree level	35 (20.8)	41 (17.5)	37 (13.9)	113 (16.9)
Missing	3 (1.8)	11 (4.7)	23 (8.6)	37 (5.5)

5.3.3 Screening results

Screen results concurrent with the questionnaire were available for 643 of the 661 respondents from the screening groups, of whom 380 (59.1%) had a normal result and 263 (40.9%) had an abnormal result (Table 5.7). There was an association between concurrent screen result and self-reported history of cancer diagnosis (excluding BCCs) but there were no other associations between screening result and co-morbidities. Women reporting a history of cancer were significantly more likely to have an abnormal concurrent screen result compared to women with no history of cancer (54.0% *vs*. 39.5%, $\chi^2(1) = 4.9$, $p = 0.026$). Among women with abnormal results, 23 from the multimodal group and 107 from the ultrasound group were referred to a gynaecological oncologist for clinical assessment.

Table 5.7. *Concurrent screening results by group*

Group	**Normal n (%)**	**Abnormal n (%)**
Multimodal	182	131
Ultrasound	198	132
Total	*380 (59.1)*	*263 (40.9)*

Among the 313 women in the multimodal group with a concurrent screen result, median serum CA125 level was 16.5 U/mL (range 4.0-187.0, IQR 12.3-22.6) and 35 women had a CA125 level ≥30. The median ROC score was 0.034% (range 0-100.0, IQR 0.016-0.235) and 74 respondents had an elevated ROC.

Table 5.8 lists the concurrent ultrasound result for women in the ultrasound group and women in the multimodal group who underwent a scan as part of the Level 2 screen. Overall, 172 women had complex morphology in one or both ovaries and 336 women had non visualised or normal ovaries, or simple ovarian cysts.

Table 5.8. *Ultrasound results*

Result	**Left ovary n**	**Right ovary n**
Not visualised	125	97
Normal	277	271
Simple cyst	17	25
Complex morphology	89	115
Total	*508*	*508*

Left ovarian volume was available for 360 women, with a median of 11.7 cm^2 (range 0.6-7878.9, IQR 6.8-22.7) and right ovarian volume was available for 374 women, with a median of 13.9 cm^2 (range 1.4-4487.3, IQR 8.2-27.2).

5.3.4 End-of-study outcomes

There was a median of 329 (range 0-400, IQR 288-353) days between the date of OCSq completion and censorship date, and a total of 710.4 person-years of follow-up. One woman was diagnosed with ovarian cancer and one with fallopian tube cancer. Fifteen women had pelvic surgery during follow-up and seven were diagnosed with benign tumours (Table 5.9).

Table 5.9. *Outcomes at end of study*

Outcome	**n=829**	**%**
Continuing as control	166	20.0
Continuing with annual screening	539	65.0
Level 2 screening	71	8.6
Referred to gynaecological oncologist	17	2.1
Surgery - ovary looked normal, no histology	1	0.1
Surgery - oophorectomy – normal ovaries	3	0.4
Surgery - oophorectomy - benign ovarian neoplasm	7	0.8
Surgery - ovarian or fallopian tube cancer	2	0.2
Non-UKCTOCS surgery - oophorectomy, awaiting details	2	0.2
Died - other reason	1	0.1
Withdrawn - controls	2	0.2
Withdrawn - screening groups	18	2.2
Total	*829*	*100*

Ovarian cancer case

The one case of ovarian cancer was diagnosed seven weeks after the volunteer completed the OCSq. The volunteer was in the UKCTOCS ultrasound screening group and had attended for an annual scan on 21 June 2008. A complex cyst (with papillations and an irregular wall) was detected on the left ovary. A symptoms questionnaire was posted to the volunteer on 2 July 2008 with a Level 2 appointment letter. The questionnaire was completed on 14 July 2008 and the volunteer was assessed by a gynaecological oncology consultant on 21 August 2008 (during the scheduled Level 2 appointment). The ultrasound conducted at this appointment found a 32 mm x 26 mm x 34 mm tumour with an estimated volume of 4.8 cm^2. The volunteer was referred for surgery, which took place on 2 September 2008. Pre-operative CA125 was 8.18 U/mL. A tumour was removed

during bilateral salpingo-oophorectomy and a diagnosis of Stage IA, Grade III, clear cell ovarian cancer was confirmed on histopathology. The respondent was 79 years of age, had been previously diagnosed with arthritis, inflammatory bowel disease and emphysema, and answered no to both depression screening questions.

Symptoms reported by the volunteer diagnosed with ovarian cancer are listed in Table 5.10. As can be seen in the table, 23 of the 32 symptoms in the questionnaire were reported. The volunteer also described three 'other' symptoms. The respondent ticked that she reported 14 of the 32 standardised symptoms to her GP. Eleven of these were recorded in her GP notes during the three months prior to the date of OCSq completion. On 22 April 2008 the woman was referred by her GP for an abdominal and pelvic ultrasound. The scan was conducted 9 May 2008, finding a small area of fatty infiltration on the liver and a 26 mm cyst in the left adnexal region. There was no referral recorded in the notes to a specialist gynaecological oncologist. The volunteer was already receiving specialist respiratory and orthopaedic care at the time of her ovarian cancer diagnosis.

Fallopian tube cancer case

One woman was diagnosed with fallopian tube cancer during the follow-up period. The volunteer was in the multimodal group and was posted the OCSq on 21 June 2008 with a Level 2 appointment letter. The questionnaire was completed on 25 June 2008 and the volunteer attended the scheduled appointment on 21 August 2008. At Level 2 screening the volunteer's CA125 level was 43.9 U/mL and the ROC value was elevated (2.68%). No cysts were detected on ultrasound and the result was normal, with an ultrasound-estimated left ovary volume of 9.4 cm^2 and right ovary volume of 6.4 cm^2. The volunteer was referred to a gynaecological oncology consultant for clinical assessment following Level 2 investigations. Clinical assessment was conducted on 24 September 2008, whereupon the woman was referred for surgery. The volunteer underwent laparotomy and bilateral salpingo-oophorectomy on 27 January 2009. A tumour measuring 40 mm x 20 mm x 10 mm was removed from the left fallopian tube. A diagnosis of Stage I, Grade III, poorly differentiated invasive adenocarcinoma of the fallopian tube was confirmed on histopathology. No malignant cells were

detected in the left ovary or right fallopian tube and ovary. On 19 March 2009 the volunteer underwent completion surgery (hysterectomy). Histology findings from the second surgery confirmed that there were no malignant cells.

At the time of OCSq completion, the respondent was aged 74 years, was taking HRT, had been previously diagnosed with arthritis and answered no to both depression screening questions. The one symptom reported by the volunteer was urinary frequency (Table 5.11).

Table 5.10. *Symptoms reported on OCSq by the respondent diagnosed with ovarian cancer*

Symptom	Severity	Frequency	Duration	Symptom reported to GP	GP consultation confirmed by notes (date if confirmed)
Pelvic discomfort or pain	Quite a bit	3-5 days	>12 months	Yes	Yes (22/04/08)
Abdominal discomfort or pain	Very much	6-7 days	3-6 months	Yes	Yes (22/04/08)
Indigestion or heartburn	A little	1-2 days	3-6 months	Yes	Not recorded
Pelvic bloating or fullness	Very much	6-7 days	3-6 months	Yes	Yes (22/04/08)
Abdominal pressure	Very much	6-7 days	3-6 months	Yes	Not recorded
Increased abdominal size	Very much	6-7 days	3-6 months	Yes	Yes (22/04/08)
Pelvic bloating or fullness	Quite a bit	3-5 days	>12 months	No	-
Pelvic pressure	Quite a bit	3-5 days	7-12 months	No	-
Pelvic heaviness	Quite a bit	6-7 days	7-12 months	No	-
Pain before, during or after opening bowels	Quite a bit	6-7 days	>12 months	No	-
Change in bowel habit	Quite a bit	6-7 days	>12 months	No	-
Excessive flatulence	Very much	3-5 days	>12 months	No	-

Symptom	Severity	Frequency	Duration	Symptom reported to GP	GP consultation confirmed by notes (date if confirmed)
Urinary frequency	Quite a bit	6-7 days	>12 months	Yes	Yes (22/04/08)
Urinary urgency	Very much	6-7 days	>12 months	Yes	Not recorded
Pressure on the bladder	Quite a bit	1-2 days	3-6 months	No	-
Difficulty emptying the bladder	Quite a bit	6-7 days	7-12 months	No	Yes (22/04/08)
Pain when passing urine	A little	missing	missing	missing	Yes (22/04/08)
Shortness of breath	Very much	6-7 days	>12 months	Yes	Yes (several 2/04/08-04/06/08)
Back ache or pain	Very much	6-7 days	>12 months	Yes	Yes (07/07/08)
Leg ache or pain	Very much	6-7 days	>12 months	Yes	Yes (07/07/08)
Leg swelling	Quite a bit	3-5 days	7-12 months	Yes	Yes (07/07/08)
Tiredness, fatigue or lack of energy	Quite a bit	6-7 days	>12 months	Yes	Not recorded
Weight gain	Very much	-	>12 months	Yes	Not recorded
Other – ‘pressure on lungs’	Quite a bit	6-7 days	>12 months	Yes	Yes (06/05/08)
Other – ‘excessive bruising’	Very much	6-7 days	7-12 months	Yes	Not recorded

Symptom	Severity	Frequency	Duration	Symptom reported to GP	GP consultation confirmed by notes (date if confirmed)
Other – 'lower back pain'	Very much	6-7 days	>12 months	Yes	Yes (18/03/08)

Table 5.11. *Symptoms reported on the OCSq by the respondent diagnosed with fallopian tube cancer*

Symptom	Severity	Frequency	Duration	Symptom reported to GP	GP consultation confirmed by notes
Urinary frequency	Quite a bit	3-5 days	<3 months	No	N/A*

** GP notes not yet received*

5.3.5 Symptoms reported by OCSq respondents

A total of 739 (89.1%) women reported any of the 32 symptoms during the past week, with a median of 5.0 (range 0-26, IQR 2.0-9.50) symptoms reported at any level. Ninety (10.9%) women were asymptomatic. Table 5.12 lists the ten most commonly reported symptoms at any level of severity, frequency or duration. Of note, while abdominal bloating/fullness and increased abdominal size were reported by approximately 28% of respondents, pelvic symptoms did not feature in the top ten.

Table 5.12. *Most common symptoms reported by OCSq respondents*

Symptom at any level	**n=829**	**%**
Tiredness, fatigue or lack of energy	443	53.4
Back ache or pain	365	44.0
Excessive flatulence	345	41.6
Leg ache or pain	329	39.7
Indigestion or heartburn	329	39.7
Urinary urgency	326	39.3
Urinary frequency	312	37.6
Weight gain	242	29.2
Abdominal bloating or fullness	233	28.1
Increased abdominal size	232	28.0

A total of 457 (55.1%) women reported at least one of the following symptoms: abdominal or pelvic discomfort/pain, increased abdominal size, abdominal or pelvic bloating/fullness, change in appetite or feeling full. Addition of urinary frequency or urgency increased this number to 577 (69.6%). Abdominal or pelvic discomfort/pain, increased abdominal size, abdominal or pelvic bloating/fullness, change in appetite, feeling full or abnormal vaginal bleeding was reported by 461 (55.6%).

A total of 493 (50.5%) women reported symptoms at level 2-3 severity (quite a bit or very much) with a median of zero symptoms (range 0-17, IQR 0-1.0) at this level. The 10 most common symptoms experienced at level 2-3 severity were the same as the 10 most common symptoms overall, although the order was slightly different (Table 5.13).

Table 5.13. *Most common symptoms reported by OCSq respondents at level 2-3 severity*

Symptom at level 2-3 severity	**n=829**	**%**
Tiredness, fatigue or lack of energy	190	22.9
Back ache or pain	161	19.4
Urinary frequency	161	19.4
Leg ache or pain	157	18.9
Excessive flatulence	154	18.6
Urinary urgency	153	18.5
Indigestion or heartburn	102	12.3
Weight gain	95	12.3
Increased abdominal size	86	10.4
Abdominal bloating or fullness	71	8.6

A total of 404 (48.7%) respondents reported symptoms at a frequency of ≥12 days during the past month and <12 months duration, with median of zero symptoms (range 0-20, IQR 0-2.0) reported with this frequency and duration. Difficulty emptying bowels was the most common symptom in this group, but it was not among the ten most common symptoms at any level of severity or at level 2-3 severity (Table 5.14).

Table 5.14. *Most common symptoms reported by OCSq respondents at ≥12 days frequency & <12 months duration*

Symptom ≥12 days & <12 months	**n=829**	**%**
Difficulty emptying bowels	118	14.2
Tiredness, fatigue or lack of energy	117	14.1
Weight gain	115	13.9
Leg ache or pain	76	9.2
Urinary frequency	69	8.3
Excessive flatulence	68	8.2
Increased abdominal size	61	7.4
Urinary urgency	59	7.1
Back ache or pain	57	6.9
Abdominal bloating or fullness	46	5.5

There were 237 (28.9%) respondents who reported any symptom at a frequency of ≥12 days during the past month, <12 months duration and at level 2-3 severity, with a median of zero symptoms (range 0-17, IQR 0-1.0) meeting these criteria. Pelvic discomfort/pain was among the ten most common symptoms using this approach, but not the other three approaches (Table 5.15).

Table 5.15. *Most common symptoms reported by OCSq respondents at ≥12 days frequency, <12 months duration & level 2-3 severity*

Symptom ≥12 days, <12 months & level 2-3 severity	**n=829**	**%**
Tiredness, fatigue or lack of energy	73	8.8
Difficulty emptying bowels	56	6.8
Leg ache or pain	48	5.8
Excessive flatulence	47	5.7
Weight gain	39	4.7
Urinary frequency	38	4.6
Urinary urgency	36	4.3
Increased abdominal size	34	4.1
Back ache or pain	30	3.6
Pelvic discomfort or pain	27	3.3

5.3.5.1 Symptoms reported by screening group respondents vs. controls

There was no difference in the proportion of screened women who reported any symptoms compared to controls (89.9% *vs.* 86.3%, *ns*). However, a greater proportion of screened women reported any symptoms at level 2-3 severity (63.1% *vs.* 50.9%, $\chi^2(1) = 8.2$, $p = 0.004$), any symptoms with a frequency of ≥12 days and <12 months duration (51.6% *vs.* 42.2%, $\chi^2(1) = 4.5$, $p = 0.035$) and any symptoms with a frequency of ≥12 days, <12 months duration and severity level 2-3 (30.9% *vs.* 22.4%, $\chi^2(1) = 4.5$, $p = 0.033$). There was no difference in the median number of symptoms reported by screened women compared to controls on each of the four approaches.

Screened women were more likely to report six individual symptoms at any level of severity, frequency and duration (Table 5.16), although only one symptom - tiredness/fatigue at ≥12 days, <12 months and level 2-3 severity. None of the differences in symptom reporting among screened women vs. controls were consistent across all four levels of analysis, although tiredness/fatigue was significant at three levels. Controls were more likely to report only one symptom, pain during or after sexual intercourse, at any level of severity, frequency or duration.

Table 5.16. *Symptoms reported by screening group vs. controls*

Symptom reported	n	Screening groups n (%)	Controls n (%)	OR (95% CI)	p-value
At any level					
Pelvic discomfort or pain	780	199 (31.8)	32 (20.6)	1.80 (1.18-2.74)	0.006
Feeling full quickly	771	139 (22.6)	20 (12.9)	1.97 (1.19-3.26)	0.008
Change in appetite	766	73 (12.0)	9 (5.7)	2.24 (1.09-4.58)	0.02
Pelvic pressure	757	97 (16.1)	14 (9.0)	1.95 (1.08-3.52)	0.02
Pelvic heaviness	750	86 (14.5)	13 (8.3)	1.86 (1.01-3.43)	0.04
Difficulty emptying the bladder	752	49 (8.2)	5 (3.2)	2.71 (1.06-6.91)	0.03
Pain during or after sexual intercourse	247	17 (9.0)	11 (19.0)	0.42 (0.19-0.96)	0.04
Level 2-3 severity					
Pelvic discomfort or pain	776	64 (10.3)	6 (3.9)	2.83 (1.20-6.66)	0.01
Difficulty emptying bowels	768	58 (9.5)	7 (4.4)	2.30 (1.03-5.15)	0.04
Tiredness, fatigue or lack of energy	768	164 (26.8)	26 (16.8)	1.81 (1.15-2.86)	0.01

Symptom reported	n	Screening groups n (%)	Controls n (%)	OR (95% CI)	p-value
≥12 days & <12 months					
Abdominal bloating or fullness	733	43 (7.4)	3 (2.0)	3.94 (1.20-12.87)	0.02
Difficulty emptying bowels	740	103 (17.6)	15 (9.6)	2.01 (1.13-3.57)	0.02
Change in bowel habit	730	32 (5.6)	2 (1.3)	4.47 (1.06-18.87)	0.03
Tiredness, fatigue or lack of energy	670	101 (19.1)	16 (11.4)	1.82 (1.04-3.21)	0.03
Weight gain*	726	103 (17.9)	12 (8.1)	2.48 (1.32-4.65)	0.004
≥12 days, <12 months & level 2-3 severity					
Tiredness, fatigue or lack of energy	670	65 (12.3)	8 (5.7)	2.31 (1.08-4.93)	0.03

** Reported at <12 months duration only as frequency data not collected*

5.3.6 Symptoms and concurrent screen results

5.3.6.1 Symptoms associated with abnormal screen results

There were 263 respondents with an abnormal concurrent screen result and 380 with a normal result. Women with abnormal results were more likely than those with normal results to report any symptoms across three of the four levels of analysis (Table 5.17), with the largest odds ratio for report of symptoms at any level of severity, frequency or duration (OR 2.07, 95% CI 1.15-3.75). There was no association between concurrent screening result and report of any symptoms at ≥12 days frequency, <12 months duration and level 2-3 severity.

Women with abnormal results also reported a greater number of symptoms overall (*Mdn* 6.0 *vs*. *Mdn* 5.0, $U = 42687.5$, $p = 0.002$, $r = -0.12$) and a greater number of symptoms at level 2-3 severity (*Mdn* 2.0 *vs*. *Mdn* 1.0, $U = 44323.0$, $p < 0.01$, $r = -0.10$). However, there was no association between concurrent result and the number of symptoms at ≥12 days and <12 months or ≥12 days, <12 months and level 2-3 severity (Table 5.17).

Table 5.17. *Symptom reporting in women with abnormal vs. normal concurrent screen results*

Symptom reported	n	Abnormal result n (% or IQR)	Normal result n (% or IQR)	Odds ratio (95% CI)	p-value
At any level					
Reported	643	247 (93.9)	335 (88.2)	2.07 (1.15-3.75)	0.014
Median		6.0 (3.0-11.0)	5.0 (2.0-9.0)	-	0.002
Range		0-26	0-23	-	
Level 2-3 severity					
Reported	632	179 (69.1)	222 (59.5)	1.52 (1.09-2.13)	0.014
Median		2.0 (0-4.0)	1.0 (1.0-3.0)	-	0.012
Range		0-21	0-18	-	
≥12 days & <12 months					
Reported	631	151 (59.0)	175 (46.7)	1.64 (1.19-2.27)	0.002
Median		1.0 (0-3.0)	0 (0-2.0)	-	ns
Range		0-20	0-18	-	

Symptom reported	n	Abnormal result n (% or IQR)	Normal result n (% or IQR)	Odds ratio (95% CI)	p-value
≥12 days, <12 months & level 2-3 severity					
Reported	632	90 (35.0)	107 (28.5)	ns	ns
Median		0 (0-1.0)	0 (0-1.0)	-	ns
Range		0-17	0-11	-	

Odds ratios were significant between those with abnormal results compared to those with normal results for nine symptoms at any level, four symptoms at level 2-3 severity and five at ≥12 days and <12 months and four when level 2-3 severity was added to this criteria (Table 5.18). Increased abdominal size and abdominal or pelvic pressure were significant across three of the four approaches. Abdominal pressure (OR 5.38, 95% CI 1.11-26.15) and shortness of breath (OR 5.29, 95% CI 1.09-25.70) had the largest odds ratios, although small numbers resulted in wide confidence intervals. Women with normal results were not more likely to report any of the 32 symptoms in the OCSq.

The symptoms pelvic bloating/fullness, pelvic pressure and pelvic heaviness were combined into a single variable for further analysis and abdominal bloating/fullness, abdominal pressure and increased abdominal size were also combined into a single variable. Significantly more women with abnormal results reported pelvic symptoms at any level (34.6% *vs*. 26.4%, $\chi^2(1) = 4.6$, $p = 0.021$) and at level 2-3 severity (5.0% *vs*. 1.7%, $\chi^2(1) = 5.3$, $p = 0.032$). However, there was no association between concurrent screen result and pelvic symptoms at ≥12 days frequency and <12 months duration, or when level 2-3 severity was added to these criteria. There was also no association between concurrent screen result and the combined abdominal symptoms on three of the levels of analysis. A larger proportion of women with abnormal concurrent screen results reported abdominal symptoms at ≥12 days frequency, <12 months duration and level 2-3 severity compared to those with normal results (8.4% *vs*. 4.5%, $\chi^2(1) = 5.3$, $p = 0.042$), although this had borderline significance.

Table 5.18. *Symptoms associated with abnormal results*

Symptom reported	n	Abnormal n (%)	Normal n (%)	OR (95% CI)	p-value
At any level					
Change in appetite	594	42 (17.1)	30 (8.6)	2.20 (1.33-3.63)	0.002
Increased abdominal size	593	92 (38.0)	94 (26.8)	1.68 (1.18-2.38)	0.004
Pelvic pressure	585	51 (21.7)	44 (12.6)	1.93 (1.24-3.00)	0.003
Pelvic heaviness	578	45 (19.3)	39 (11.3)	1.88 (1.18-2.99)	0.007
Excessive flatulence	601	128 (53.1)	149 (41.4)	1.60 (1.15-2.23)	0.005
Urinary urgency	600	121 (49.4)	142 (40.0)	1.46 (1.05-2.03)	0.02
Leg ache or pain	598	122 (50.6)	142 (39.8)	1.55 (1.12-2.16)	0.009
Tiredness, fatigue or lack of energy	600	159 (65.7)	194 (54.2)	1.62 (1.16-2.27)	0.005
Abnormal vaginal bleeding	583	6 (2.5)	0	∞	0.005
Level 2-3 severity					
Increased abdominal size	589	37 (15.4)	31 (8.9)	1.85 (1.12-3.08)	0.007

Symptom reported	n	Abnormal n (%)	Normal n (%)	OR (95% CI)	p-value
Level 2-3 severity					
Pelvic bloating or fullness	586	31 (13.0)	20 (5.8)	2.44 (1.35-4.39)	0.002
Excessive flatulence	597	63 (26.1)	63 (17.7)	1.65 (1.11-2.45)	0.01
Shortness of breath	583	22 (9.3)	16 (4.6)	2.11 (1.08-4.11)	0.03
Symptom ≥12 days & <12 months					
Nausea or vomiting	586	10 (4.2)	4 (1.1)	3.77 (1.17-12.17)	0.02
Abdominal pressure	567	12 (5.2)	7 (2.1)	2.61 (1.01-6.75)	0.04
Pelvic pressure	563	15 (6.6)	7 (2.1)	3.33 (1.33-8.29)	0.007
Pelvic heaviness	557	14 (6.3)	8 (2.4)	2.73 (1.13-6.62)	0.02
Leg ache or pain	553	36 (16.1)	29 (8.8)	2.00 (1.19-3.37)	0.008
≥12 days, <12 months & level 2-3 severity					
Abdominal pressure	552	7 (3.2)	2 (0.6)	5.38 (1.11-26.15)	0.03
Increased abdominal size	550	17 (7.9)	11 (3.3)	2.51 (1.15-5.47)	0.02

Symptom reported	n	Abnormal n (%)	Normal n (%)	OR (95% CI)	p-value
≥12 days, <12 months & level 2-3 severity					
Shortness of breath	564	7 (3.1)	2 (0.6)	5.29 (1.09-25.70)	0.04
Leg swelling	563	14 (6.1)	7 (2.1)	3.00 (1.19-7.54)	0.02

5.3.6.2 Symptoms associated with CA125 level

Thirty-five (11.2%) of the 313 women with a concurrent CA125 result had a level ≥30 U/mL and 273 (87.2%) had a CA125 <30 U/mL. There were no associations between CA125 level and report of symptoms overall across the four approaches. There was also no difference in the number of symptoms reported by women with CA125 levels ≥30 U/mL compared to those with levels <30 U/mL on any of the four approaches.

When individual symptoms were analysed, odds ratios were significant between those with CA125 levels ≥30 U/mL compared to those with CA125 <30 U/mL for difficulty emptying the bladder at level 2-3 severity (OR 16.83, 95% CI 1.48-191.36), and urinary frequency (OR 3.43, 95% CI 1.30-9.06) and shortness of breath (OR 4.62, 95% CI 1.30-16.44) at ≥12 days frequency and <12 months duration. At ≥12 days, <12 months and level 2-3 severity, odds ratios were significant for change in appetite (OR 5.85, 95% CI 1.25-27.41), urinary frequency (OR 4.46, 95% CI 1.42-14.02), shortness of breath (OR 6.78, 95% CI 1.44-31.96) and backache or pain (OR 4.68, 95% CI 1.32-16.65) (appendix 23).

5.3.6.3 Symptoms associated with elevated ROC scores

Concurrent ROC scores were available for 313 women, of whom 74 (23.6%) had an elevated score. There were no associations between ROC scores and report of symptoms overall, at level 2-3 severity or ≥12 days, <12 months and level 2-3 severity. However, respondents with elevated ROCs were 1.80 (95% CI 1.05-3.09) times more likely to report symptoms with a frequency of ≥12 days and <12 months duration, although the lower confidence limit indicates marginal significance. There was no association between elevated ROCs and either the Goff or Lurie indices.

There was no difference in the number of symptoms reported overall, at level 2-3 severity, or with a frequency of ≥12 days and <12 months duration, by respondents with elevated ROCs compared to others. However, a greater number of symptoms were reported by respondents with elevated ROCs at ≥12 days, <12 months and level 2-3 severity (*Mdn* 3.0 *vs*. *Mdn* 1.0, $U = 742.0$, $p = 0.02$, $r =$ -

0.23). This effect size indicates a small increase in symptom reporting at this severity, frequency and duration, associated with elevated ROC scores.

Appendix 24 lists individual symptoms which were associated with elevated ROCs. The largest odds ratio was for increased abdominal size (OR 4.70, 95% CI 1.67-13.18) at ≥12 days, <12 months and level 2-3 severity, followed by indigestion or heartburn (OR 4.06, 95% CI 1.32-12.50) at ≥12 days and <12 months. No single symptom was significant on all four approaches, although increased abdominal size was associated with elevated ROC score on three of the four approaches.

5.3.6.4 Symptoms associated with complex ovarian morphology

Symptoms were compared in 172 women with complex ovarian morphology and 336 women with normal findings (ovaries not visualised, ovaries normal or simple cysts). There was no difference in the proportion of women with complex masses compared to those with normal findings who reported symptoms overall (91.3% *vs*. 90.2%, *ns*), at level 2-3 severity (63.4% *vs*. 64.0%, *ns*), at ≥12 days frequency and <12 months duration (50.6% *vs*. 52.1%, *ns*) or at level 2-3 severity, ≥12 days and <12 months (30.2% *vs*. 31.8%, *ns*). There was also no difference in the number of symptoms reported by women with complex ovarian morphology compared to others (both *Mdn* 6.0), at level 2-3 severity (both *Mdn* 1.0), at ≥12 days and <12 months (both *Mdn* 2.0) or when level 2-3 severity was added to this frequency and duration (both *Mdn* 2.0).

Pelvic pressure (OR 1.88, 95% CI 1.15-3.09) at any level and change in bowel habit (OR 2.34, 95% CI 1.11-4.94) at level 2-3 severity were the only symptoms which women with complex ovarian morphology were more likely to report (appendix 25). Surprisingly, there was no association between complex ovarian morphology and pelvic bloating/fullness, pressure or heaviness on any of the four approaches when these symptoms were combined into a single variable.

5.3.6.5 Symptoms associated with abnormal ovarian volume

Of the 172 women with an ovarian abnormality (complex ovarian morphology), ovarian volume was recorded for 55 of the 57 women who had a left-sided lesion,

77 of the 83 women with a right-sided lesion and 30 of the 32 women with bilateral ovarian abnormalities. Median ovarian volume in the 172 women with an ovarian abnormality was 25.26 cm^2 (range 2.6-7878.9, IQR 12.5-57.5).

Women who reported abdominal bloating/fullness and urinary frequency at any level, or at level 2-3 severity, had larger median total ovarian volumes compared to women who did not report the symptoms (Table 5.19). Effect sizes for these symptoms indicate a moderate increase in reporting with increasing total ovarian volume. No pelvic symptoms were associated with total ovary volume, even after combining pelvic bloating/fullness, heaviness and pressure into a single variable. Interestingly, women who reported leg swelling ≥12 days during the past month and onset within the past 12 months had smaller median total ovarian volumes.

Table 5.19. *Symptoms associated with total ovary volume*

Symptom at any level	**n**	**Symptom reported Median volume cm^2 (IQR)**	**Symptom not reported Median volume cm^2 (IQR)**	***U***	**p-value**	***r***
Urinary frequency	29	129.2 (57.3-270.0)	59.5 (27.2-89.4)	53.0	0.023	-0.42
Abdominal bloating or fullness	29	117.3 (27.5-342.4)	76.7 (41.8-139.5)	9.0	0.032	-0.40
Level 2-3 severity						
Urinary frequency	29	143.4 (78.7-234.1)	59.7 (27.4-116.9)	40.0	0.032	-0.40
≥12 days & <12 months						
Leg swelling	27	27.5 (18.3-43.4)	88.8 (52.9-142.8)	9.0	0.036	-0.40

Note: there were no associations between total ovary volume and symptoms ≥12 days, <12 months & level 2-3 severity

5.3.7 Multivariate analysis of symptoms associated with abnormal results

5.3.7.1 Symptoms at any level of severity predictive of an abnormal result – Model 1

Eight symptoms with significant odds ratios on univariate analyses were entered into the regression model with previous cancer diagnosis and the continuous variables age and total number of symptoms at any level of severity, frequency or duration. Symptoms included in the model were: 1) change in appetite, 2) increased abdominal size, 3) pelvic pressure, 4) pelvic heaviness, 5) excessive flatulence, 6) urinary urgency, 7) leg ache/pain, and 8) tiredness/fatigue. Abnormal vaginal bleeding was excluded from the model due to missing cells. The regression found age, pelvic pressure and tiredness/fatigue at any level of severity independently predicted an abnormal concurrent screening result (receiver operating curve = 0.62). Adjusted odds ratios for all symptoms models are listed in Table 5.20 and Figure 5.2 shows the receiver operating curves.

5.3.7.2 Symptoms at any level 2-3 severity predictive of an abnormal result – Model 2

Four symptoms at level 2-3 severity associated with an abnormal result on univariate analyses, 1) increased abdominal size, 2) pelvic bloating/fullness, 3) excessive flatulence and 4) shortness of breath, were entered into a second model with previous cancer diagnosis, age and total number of symptoms at level 2-3 severity. This found that age, pelvic bloating and shortness of breath at level 2-3 severity were independently predictive of an abnormal result (receiver operating curve = 0.60).

5.3.7.3 Symptoms ≥ 12 days and <12 months predictive of an abnormal result - Model 3

Five symptoms, 1) nausea or vomiting, 2) abdominal pressure, 3) pelvic pressure, 4) pelvic heaviness, and 5) leg ache/pain, reported at ≥12 days during the past month and <12 months duration associated with an abnormal concurrent screen

result were entered into a third logistic regression model with previous cancer diagnosis. Age was entered as a continuous variable. Total number of symptoms reported ≥12 days and <12 months was not included as univariate analyses found this was not associated with screening result. The regression identified age, pelvic pressure and leg ache/pain as independent predictors of an abnormal result when experienced ≥12 days and <12 months (receiver operating curve = 0.61). However, leg ache/pain had marginal significance.

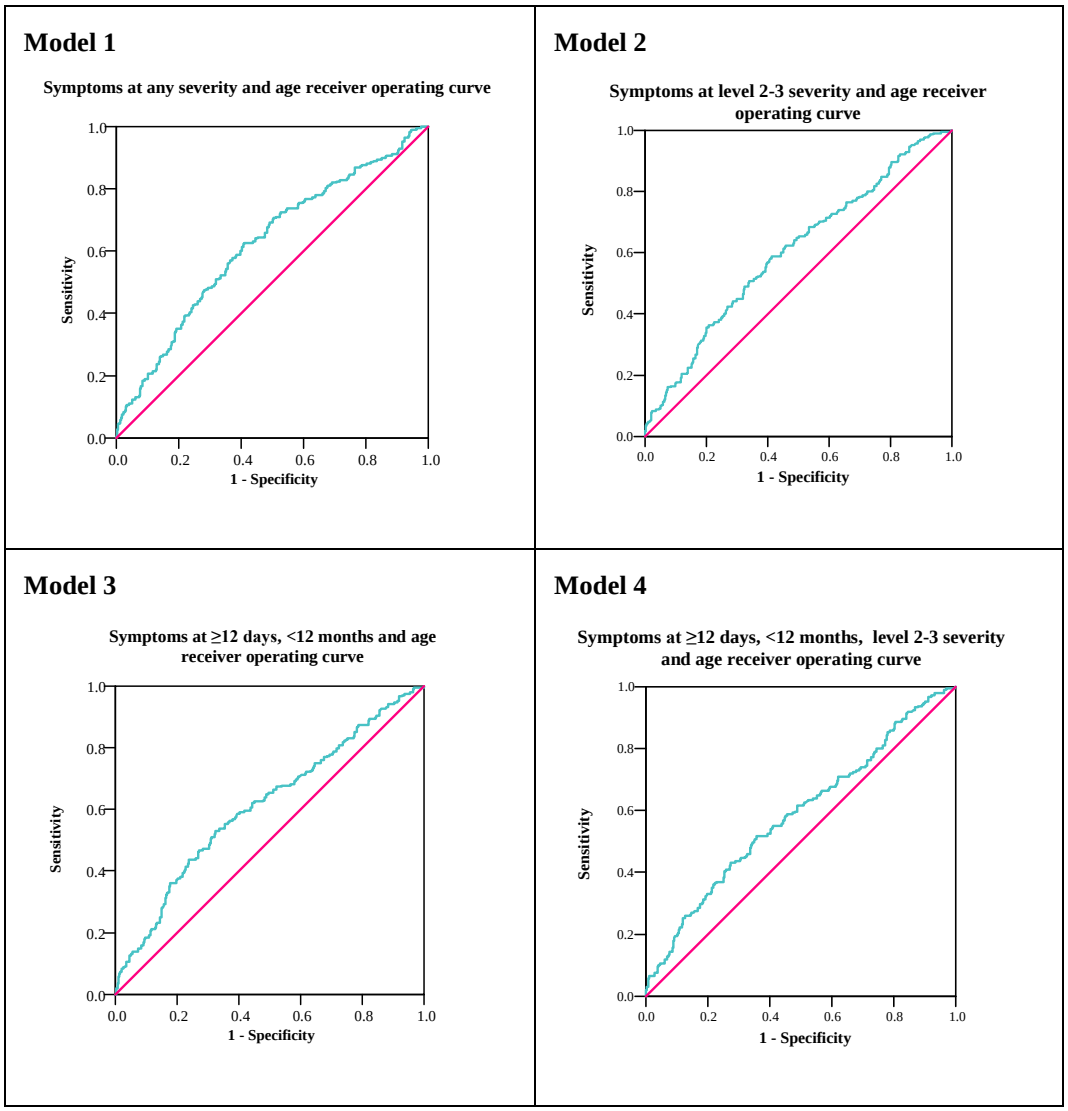
5.3.7.4 Symptoms ≥ 12 days, <12 months and level 2-3 severity predictive of an abnormal result – Model 4

Four symptoms, 1) abdominal pressure, 2) increased abdominal size, 3) shortness of breath, and 4) leg swelling, experienced at ≥12 days, <12 months and level 2-3 severity were entered into a fourth backwards stepwise logistic regression model with previous cancer diagnosis, and age as a continuous variable. Total number of symptoms reported ≥12 days, <12 months and at level 2-3 severity was not included as this was not associated with screening result on univariate analysis. The regression identified abdominal pressure, shortness of breath and age as independent predictors of an abnormal result (receiver operating curve = 0.59). However, the confidence intervals for these symptoms were wide and the area under the curve was slightly smaller than the model using frequency and duration criteria alone.

Table 5.20. *Results of multivariate logistic regression of symptoms and abnormal screening results*

Multivariate logistic regression models predictive of abnormal results	**n**	**Exp β (95% CI)**	**p-value**
Symptoms at any level - model 1			
Pelvic pressure	539	1.93 (1.16-3.21)	0.011
Tiredness, fatigue or lack of energy		1.58 (1.09-2.28)	0.015
Age		1.05 (1.02-1.09)	0.001
Symptoms at level 2-3 severity - model 2			
Pelvic bloating or fullness	561	2.37 (1.25-4.49)	0.008
Shortness of breath		2.33 (1.13-4.83)	0.023
Age		1.05 (1.02-1.08)	0.004
Symptoms ≥12 days & <12 months - model 3			
Pelvic pressure	495	3.31 (1.22-8.96)	0.019
Leg ache or pain		1.78 (1.00-3.15)	0.049
Age		1.05 (1.01-1.08)	0.005
Symptoms ≥12 days, <12 months & level 2-3 severity - model 4			
Abdominal pressure	491	9.33 (1.10-78.80)	0.04
Shortness of breath		12.94 (1.52-109.40)	0.019
Age		1.10 (1.02-1.09)	0.003

Figure 5.2. *Receiver operating curves for the models*



5.3.8 Performance of the Goff Symptom Index for detecting an abnormal screen result

A total of 129 women (15.6%) were positive on the Goff index. Of these, 110 were from the screening group and 57 had an abnormal concurrent result. The index had a sensitivity of 21.7% and a specificity of 86.1% for detecting an abnormal result. The PPV was 51.8% and NPV was 61.4%.

5.3.9 Performance of the Lurie Symptom Index for detecting an abnormal screen result

The Lurie symptom index identified 325 women (39.2%), of whom 261 were from the screening group and 125 had an abnormal result. The index had a sensitivity of 46.8% and a specificity of 63.9% for detecting respondents with abnormal screen results. The PPV was 46.8% and NPV was 63.9%.

5.3.10 Performance of symptom models and indices for detecting ovarian cancer

As there were only two women diagnosed with ovarian/fallopian tube cancer, the following analyses were conducted mainly to assess the specificity of symptom models. Other performance characteristics are included to demonstrate how we intend to assess the performance of symptoms models in follow-up analyses of the 100,000 women study (Chapter Six).

Table 5.21 details the performance of the four models which predicted an abnormal screen result, in addition to the Goff and Lurie indices, for detecting ovarian/fallopian cancer. The respondent diagnosed with fallopian tube cancer reported only one symptom, urinary frequency, and was therefore negative on all models. The respondent diagnosed with ovarian cancer was positive on all models. Thus all six models had a sensitivity of 50.0%.

Model 1 identified 460 women without ovarian cancer (including four of the seven women with benign masses), resulting in the lowest specificity (44.4%) among the six models. Model 4 identified 20 women without ovarian/fallopian cancer, resulting in the highest specificity at 97.6%. The Goff index ranked fourth on specificity (84.5%) while the Lurie index ranked fifth (60.8%).

Table 5.21. *Performance of symptoms models for predicting ovarian/fallopian tube cancer*

Model	Ovarian/ fallopian cancer n=2	Non-cancer cases n=827	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Model 1 Any pelvic pressure or tiredness/fatigue	1	460	50.0% (9.5%-90.5%)	44.4% (44.1%-47.8%)	0.2% (0.04%-1.2%)	99.7% (98.5%-99.95%)
Model 2 Pelvic bloating/fullness or shortness of breath at level 2-3 severity	1	92	50.0% (9.5%-90.5%)	88.9% (86.6%-90.8%)	1.1% (0.2%-5.8%)	99.9% (99.2%-99.98%)
Model 3 Pelvic pressure or leg ache/pain at ≥12 days & <12 months	1	88	50.0% (9.5%-90.5%)	89.4% (87.1%-91.3%)	1.1% (0.2%-6.1%)	99.9% (99.2%-99.98%)
Model 4 Abdominal pressure or shortness of breath at level 2-3 severity, ≥12 days & <12 months	1	20	50.0% (9.5%-90.5%)	97.6% (96.3%-98.4%)	4.8% (0.8%-22.7%)	99.9% (99.3%-99.98%)
Goff index Pelvic discomfort/pain, abdominal discomfort/pain, feeling full quickly, abdominal bloating or increased abdominal size at ≥12 days & <12 months	1	128	50.0% (9.5%-90.5%)	84.5% (81.9%-86.8%)	0.8% (0.1%-4.3%)	61.4% (99.2%-99.97%)

Model	Ovarian/ fallopian cancer n=2	Non-cancer cases n=827	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Lurie index Any abdominal pain, increased abdominal size, abdominal mass/lump or abnormal vaginal bleeding	1	325	50.0% (9.5%-90.5%)	60.8% (57.3%-57.0%)	0.3% (0.1%-1.7%)	99.8% (98.9%-99.96%)

5.3.11 Symptom reporting according to prior awareness of a possible ovarian abnormality

Awareness was based on previous screen results. All 168 controls and the 238 screen group women who were sent the OCSq with their annual screen appointments were initially classified as unaware of any abnormality. The 423 women who were sent the OCSq along with their Level 2 appointment were initially classified as aware of a possible ovarian lesion as they had been asked to attend for repeat testing. However, 34 women from the screening groups (15 multimodal and 19 ultrasound) completed their questionnaires after being informed of the result of their concurrent screening appointment (defined as greater than two days after the result letter was posted for the multimodal group and equal to or greater than the appointment date in the ultrasound group). In these women, awareness status was altered to reflect concurrent results. This identified 416 (50.2%) women as unaware and 413 (49.8%) who were aware of a possible ovarian lesion.

5.3.11.1 Symptoms reporting in aware vs. unaware respondents

There was no association between awareness and symptom reporting at any level of severity, frequency or duration (90.8% *vs.* 87.5%, *ns*). However, women who were aware of the possibility of an ovarian abnormality were more likely (OR 1.81, 95% CI 1.37-2.40) to report symptoms at level 2-3 severity compared to unaware women. They were also more likely to report symptoms of ≥12 days frequency and <12 months duration (OR 1.41, 95% CI 1.07-1.85) and symptoms at ≥12 days, <12 months and level 2-3 severity (OR 1.61 95% CI 1.19-2.18). Aware women were also more likely to be positive on the Goff symptom index (OR 1.95, 95% CI 1.32-2.87) and the Lurie index (OR 1.48 95% CI 1.11-1.97).

There was no difference in the median number of symptoms reported at level 2-3 severity (*Mdn* 1.0 in both groups). However, the median number of symptoms reported at any level (*Mdn* 6.0 *vs. Mdn* 4.0, $U = 72136.0$, $p < 0.0001$, $r = -0.14$), at ≥12 days and <12 months (*Mdn* 3.0 *vs. Mdn* 1.0, $U = 15517.5$, $p < 0.0001$, $r = -0.15$) and ≥12 days, <12 months and level 2-3 severity (*Mdn* 2.0 *vs. Mdn* 1.0, $U =$

5414.5, p = 0.004, r = -0.10) was greater among those aware of an abnormality, although the effect sizes indicate awareness had a minimal impact on the number of symptoms reported.

Women who were aware of an abnormality were significantly more likely to report 19 symptoms at any level of severity, frequency and duration compared to unaware women (Table 5.22). Eight symptoms were more likely to be reported by aware respondents at level 2-3 severity, 13 at ≥12 days and <12 months, and five when level 2-3 severity was added to this criteria. Change in bowel habit at ≥12 days, <12 months and level 2-3 severity had the highest odds ratio (OR 6.81, 95% CI 1.99-23.34) across the four approaches, although the confidence limits were wide. Pelvic heaviness was among the two highest odds ratios on three of the four approaches, with odds ratios ranging from 2.61 (95% CI 1.66-4.11) to 6.00 (95% CI 2.04-17.67). Interestingly, women who were aware of a possible ovarian lesion were more likely to report both weight gain and weight loss.

Table 5.22. *Symptom reporting in aware vs. unaware respondents*

Symptom reported	n	Aware of possible ovarian abnormality n (%)	Unaware n (%)	OR (95% CI)	p-value
At any level					
Pelvic discomfort or pain	780	133 (34.5)	98 (24.8)	1.60 (1.17-2.18)	0.003
Abdominal discomfort or pain	766	80 (21.1)	58 (15.0)	1.52 (1.05-2.20)	0.028
Change in appetite	766	54 (14.4)	28 (7.2)	2.18 (1.35-3.53)	0.001
Increased abdominal size	767	130 (34.9)	102 (25.9)	1.53 (1.12-2.09)	0.007
Abdominal mass or lump	749	14 (3.8)	5 (1.3)	3.04 (1.08-8.52)	0.027
Pelvic bloating or fullness	764	108 (28.9)	67 (17.2)	1.96 (1.39-2.76)	<0.0001
Pelvic pressure	757	71 (19.3)	40 (10.3)	2.09 (1.37-3.17)	<0.0001
Pelvic heaviness	750	68 (8.6)	31 (8.1)	2.61 (1.66-4.11)	<0.0001
Pain before, during or after opening bowels	766	97 (26.0)	60 (15.3)	1.95 (1.36-2.79)	<0.0001
Change in bowel habit	759	81 (22.0)	50 (12.8)	1.92 (1.31-2.83)	0.001

Symptom reported	n	Aware of possible ovarian abnormality n (%)	Unaware n (%)	OR (95% CI)	p-value
At any level					
Excessive flatulence	775	187 (49.5)	158 (39.8)	1.48 (1.11-1.97)	0.007
Urinary frequency	765	175 (46.8)	137 (35.0)	1.63 (1.22-2.18)	0.001
Urinary urgency	775	183 (47.9)	143 (36.4)	1.61 (1.21-2.14)	0.001
Difficulty emptying the bladder	752	36 (9.9)	18 (4.7)	2.24 (1.25-4.03)	0.006
Shortness of breath	755	85 (23.2)	52 (13.4)	1.95 (1.33-2.85)	0.001
Leg ache or pain	769	182 (48.3)	147 (37.5)	1.56 (1.17-2.07)	0.003
Tiredness, fatigue or lack of energy	772	234 (62.1)	209 (52.9)	1.46 (1.09-1.94)	0.01
Weight gain	762	135 (36.4)	107 (27.4)	1.52 (1.12-2.06)	0.007
Weight loss	749	30 (8.3)	17 (4.4)	1.97 (1.07-3.63)	0.028
Level 2-3 severity					
Pelvic discomfort or pain	776	44 (11.5)	26 (6.6)	1.84 (1.11-3.06)	0.017

Symptom reported	n	Aware of possible ovarian abnormality n (%)	Unaware n (%)	OR (95% CI)	p-value
Level 2-3 severity					
Pelvic bloating or fullness	759	42 (11.4)	18 (4.6)	2.64 (1.49-4.68)	0.001
Pelvic heaviness	748	25 (6.9)	10 (2.6)	2.77 (1.31-5.86)	0.005
Difficulty emptying bowels	768	44 (11.9)	21 (5.3)	2.42 (1.41-4.16)	0.001
Change in bowel habit	755	32 (8.8)	12 (3.1)	3.03 (1.53-5.97)	0.001
Excessive flatulence	771	94 (25.1)	60 (15.1)	1.89 (1.31-2.70)	0.001
Urinary frequency	763	94 (25.2)	67 (17.2)	1.62 (1.14-2.31)	0.007
Urinary urgency	772	92 (24.1)	61 (15.6)	1.75 (1.22-2.50)	0.003
≥12 days & <12 months					
Pelvic discomfort or pain	752	30 (8.1)	14 (3.7)	2.33 (1.22-4.47)	0.009
Increased abdominal size	715	40 (11.7)	21 (5.6)	2.22 (1.28-3.85)	0.004
Pelvic pressure	732	19 (5.4)	5 (1.3)	4.21 (1.55-11.39)	0.002

Symptom reported	n	Aware of possible ovarian abnormality n (%)	Unaware n (%)	OR (95% CI)	p-value
≥12 days & <12 months					
Pelvic heaviness	728	21 (6.0)	4 (1.1)	6.00 (2.04-17.67)	<0.0001
Change in bowel habit	730	24 (6.9)	10 (2.6)	2.72 (1.28-5.78)	0.007
Feeling of pressure on the bladder	725	22 (6.3)	11 (2.9)	2.22 (1.06-4.64)	0.03
Pain when passing urine	740	6 (1.7)	0	∞	0.01
Shortness of breath	731	15 (4.3)	5 (1.3)	3.35 (1.20-9.31)	0.014
Leg ache or pain	709	51 (14.8)	25 (6.9)	2.35 (1.42-3.89)	0.001
Leg swelling	733	30 (8.5)	14 (3.7)	2.40 (1.25-4.61)	0.007
Tiredness, fatigue or lack of energy	670	68 (21.3)	49 (14.0)	1.66 (1.11-2.48)	0.014
Weight gain*	726	69 (19.7)	46 (12.2)	1.76 (1.17-2.64)	0.006
Weight loss*	744	24 (6.7)	8 (1.9)	3.38 (1.50-7.62)	0.002

Symptom reported	n	Aware of possible ovarian abnormality n (%)	Unaware n (%)	OR (95% CI)	p-value
≥12 days, <12 months & level 2-3 severity					
Pelvic discomfort or pain	776	19 (5.0)	8 (2.0)	2.53 (1.09-5.84)	0.025
Increased abdominal size	713	24 (7.0)	10 (2.7)	2.72 (1.28-5.78)	0.007
Difficulty emptying bowels	740	38 (10.8)	18 (4.7)	2.47 (1.38-4.42)	0.002
Change in bowel habit	730	18 (5.1)	3 (0.8)	6.81 (1.99-23.34)	<0.0001
Excessive flatulence	711	32 (9.4)	15 (4.0)	2.48 (1.32-4.67)	0.004

** Reported at <12 months duration only as frequency data not collected*

5.3.11.2 Symptoms reported by screening group women vs. controls in the unaware group

Sub-group analysis of 416 women in the unaware group found that there was no difference between screened women and controls for symptoms at any level of severity, frequency or duration (88.3% *vs*. 86.3%, *ns*), at level 2-3 severity (54.0% *vs*. 50.0%, *ns*), at ≥12 days frequency and <12 months duration (46.4% *vs*. 41.7%, *ns*), or ≥12 days, <12 months and level 2-3 severity (25.0% *vs*. 22.0%, *ns*).

When individual symptoms were analysed, larger proportions of screened women reported feeling full at any level (21.9% *vs*. 12.9%, $\chi^2(1) = 5.1$, $p = 0.024$) compared to controls. However, greater proportions of controls reported nausea or vomiting at any level (7.2% *vs*. 14.2%, $\chi^2(1) = 5.1$, $p = 0.024$) and backache or pain at level 2-3 severity, ≥12 days and <12 months (1.3% *vs*. 6.0%, $\chi^2(1) = 6.2$, $p = 0.013$). There was no difference between these groups for reports of other symptoms.

5.3.11.3 Symptoms reported by aware respondents with abnormal vs. normal concurrent screen results

A concurrent screen result was available for 407 of the 413 women who were aware of a potential abnormality. There was no association between report of symptoms overall (92.9% *vs.* 88.4%, *ns*), symptoms at level 2-3 severity (68.3% *vs.* 64.5%, *ns*) or symptoms at level 2-3 severity, ≥12 days frequency and <12 months duration (33.7% *vs.* 32.9%, *ns*) and abnormal concurrent screen results. However, women who reported any symptoms at ≥12 days frequency and <12 months duration were more likely (OR 1.60, 95% CI 1.07-2.40) to have an abnormal concurrent screen result. There was no difference in the median number of symptoms at each of the four levels of analysis in women who had abnormal concurrent screen results compared to those with normal results.

The most frequently reported symptom among aware women with an abnormal concurrent result was tiredness/fatigue followed by backache or pain, excessive flatulence, urinary urgency and leg ache or pain (Table 5.23). The number of women reporting abnormal vaginal bleeding was small (n = 5), but all had an

abnormal result. Similarly, 10 of the 14 women who reported an abdominal mass or lump had an abnormal screen result.

Table 5.23. *Most frequently reported symptoms in aware women who had a concurrent screen result*

Symptom at any level	**n=407**	**%**
Tiredness, fatigue or lack of energy	231	56.8
Back ache or pain	186	45.7
Excessive flatulence	184	45.2
Urinary urgency	180	44.2
Leg ache or pain	179	44.0
Urinary frequency	173	42.5
Indigestion or heartburn	170	41.8
Weight gain	134	32.9
Pelvic discomfort or pain	131	32.2
Increased abdominal size	129	31.7

Table 5.24 shows the proportion of aware women who reported symptoms who went on to have either a normal or abnormal concurrent screen result. Increased abdominal size and change in appetite or feeling full was associated with abnormal concurrent screen results on two of the four levels of analysis. The largest odds ratio was for feeling full at a frequency of ≥12 days and <12 months duration. Women who reported this were 3.55 (95% CI 1.02-12.37) times more likely to have an abnormal concurrent screen result. However, the lower confidence limit was close to zero. There was a trend for women who were positive on the Goff or the Lurie symptom indices to have abnormal concurrent screen results, although this was not significant.

Table 5.24. *Symptom reporting in aware respondents who had a concurrent result (n=407)*

Symptom at any level	**n**	**Abnormal concurrent result (%)**	**Normal concurrent result (%)**	**OR (95% CI)**	**p-value**
Change in appetite	370	41 (17.6)	12 (8.8)	2.22 (1.13-4.40)	0.019
Increased abdominal size	368	90 (39.0)	39 (28.5)	1.60 (1.02-2.53)	0.041
Leg ache or pain	372	120 (52.4)	59 (41.3)	1.57 (1.03-2.39)	0.036
Level 2-3 severity					
Increased abdominal size	364	37 (16.1)	9 (6.7)	2.66 (1.24-5.71)	0.009
≥12 days & <12 months					
Feeling full quickly	347	17 (7.8)	3 (2.3)	3.55 (1.02-12.37)	0.035
Symptom indices					
Positive on Goff symptom index*	381	55 (23.3)	25 (17.2)	ns	ns
Positive on Lurie symptom index**	388	117 (48.5)	60 (40.8)	ns	ns

** Pelvic discomfort/pain, abdominal discomfort/pain, feeling full quickly, abdominal bloating or increased abdominal size at ≥12 days and <12 months*

*** Abdominal pain, increased abdominal size, abdominal mass or lumps or abnormal vaginal bleeding*

5.3.12 Symptoms reported to GPs

A total of 350 (42%) women consulted their GP about at least one of the 32 symptoms during the past three months, with a median of two symptoms being discussed with GPs (range 1-21, IQR 1-5). The symptoms most commonly reported to GPs were backache or pain, leg ache or pain and tiredness or fatigue (Table 5.25).

Table 5.25. *Symptoms most commonly reported to GPs*

Symptom at any level	**n=829**	**%**
Back ache or pain	109	13.1
Leg ache or pain	104	12.5
Tiredness, fatigue or lack of energy	99	11.9
Indigestion or heartburn	84	10.1
Leg swelling	69	8.3
Excessive flatulence	56	6.8
Pelvic discomfort or pain	52	6.3
Urinary frequency	51	6.2
Shortness of breath	49	5.9
Urinary urgency	48	5.8

Table 5.26 lists the number of women who reported symptoms and the proportion who consulted a GP about the symptom during the past three months. Shaded boxes indicate the largest proportion of women who consulted their GP about symptoms across the four approaches. The top ten symptoms based on any severity, and with no specified frequency or duration, for which a GP consultation had been undertaken were: leg swelling (53.5%), abnormal vaginal bleeding (50.0%), abdominal mass or lump (46.2%), nausea or vomiting (45.2%), shortness of breath (42.3%), abdominal discomfort or pain (40.3%), abnormal vaginal

discharge (40.0%), leg ache or pain (35.0%), pain when passing urine (33.3%) and back ache or pain (33.1%).

Level 2-3 severity was the most important factor determining a GP visit, with 22 of the 32 symptoms more likely to be reported to GPs when experienced at level 2-3 severity. Eleven symptoms were more likely to be reported to GPs when experienced at a frequency of ≥12 days, <12 months duration & level 2-3 severity.

Table 5.26. *Symptoms reported to GPs during the past three months*

Symptom reported	At any level		Level 2-3 severity		≥12 days & <12 months		≥12 days, <12 months & level 2-3 severity	
	n	Consulted GPn (%)	n	Consulted GPn (%)	n	Consulted GPn (%)	n	Consulted GPn (%)
Pelvic discomfort or pain	123	26 (21.1)	39	14 (35.9)	28	7 (25.0)	17	6 (35.3)
Abdominal discomfort or pain	72	29 (40.3)	30	20 (66.7)	14	6 (42.9)	11	5 (45.5)
Indigestion or heartburn	150	46 (30.7)	48	22 (45.8)	20	5 (25.0)	11	5 (45.5)
Nausea or vomiting	42	19 (45.2)	8	5 (83.3)	11	5 (45.5)	8	3 (35.7)
Feeling full quickly	74	18 (24.3)	26	10 (38.5)	20	5 (25.0)	8	3 (35.7)
Change in appetite	44	13 (29.5)	11	6 (54.5)	23	9 (39.1)	9	5 (55.6)
Abdominal bloating or fullness	104	23 (23.1)	33	11 (33.3)	27	9 (33.3)	14	6 (42.9)
Abdominal pressure	43	13 (30.2)	17	7 (41.2)	13	4 (30.8)	5	3 (60.0)
Increased abdominal size	107	16 (15.0)	41	6 (14.6)	36	5 (13.9)	22	4 (18.2)
Abdominal mass or lump	13	6 (46.2)	3	2 (66.7)	7*	2 (28.6)*	2*	1 (50.0)*
Pelvic bloating or fullness	96	16 (16.7)	39	11 (28.2)	21	1 (4.8)	12	1 (8.3)

Symptom reported	At any level		Level 2-3 severity		≥12 days & <12 months		≥12 days, <12 months & level 2-3 severity	
Pelvic pressure	68	10 (14.7)	25	7 (28.0)	19	3 (15.8)	9	3 (33.3)
Pelvic heaviness	59	11 (18.6)	20	6 (30.0)	20	3 (15.0)	9	3 (33.3)
Pain before, during or after opening bowels	81	21 (25.9)	24	8 (33.3)	14	3 (21.4)	10	2 (20.0)
Difficulty emptying bowels	100	24 (24.0)	39	16 (41.0)	65	19 (29.2)	35	15 (42.9)
Change in bowel habit	68	18 (26.5)	28	13 (46.4)	24	8 (33.3)	18	8 (44.4)
Excessive flatulence	165	28 (17.0)	82	18 (22.0)	37	8 (21.6)	30	6 (20.0)
Urinary frequency	149	26 (17.4)	78	18 (23.1)	39	6 (15.4)	20	2 (10.0)
Urinary urgency	160	26 (16.3)	79	18 (22.8)	35	7 (20.0)	23	5 (21.7)
Pressure on the bladder	66	15 (22.7)	24	8 (33.3)	21	5 (23.8)	6	2 (33.3)
Difficulty emptying bladder	31	7 (22.6)	7	3 (42.9)	8	2 (25.0)	3	1 (33.3)
Pain when passing urine	9	3 (33.3)	2	2 (100.0)	5	2 (40.0)	1	1 (100.0)
Shortness of breath	71	30 (42.3)	26	21 (80.8)	13	6 (46.2)	7	6 (85.7)
Back ache or pain	163	54 (33.1)	73	43 (58.9)	32	12 (37.5)	17	9 (52.9)

Symptom reported	At any level		Level 2-3 severity		≥12 days & <12 months		≥12 days, <12 months & level 2-3 severity	
Leg ache or pain	157	55 (35.0)	73	43 (58.9)	47	12 (25.5)	27	10 (37.0)
Leg swelling	71	38 (53.5)	29	19 (65.5)	29	12 (41.4)	16	9 (56.3)
Tiredness, fatigue or lack of energy	200	52 (26.0)	95	31 (32.6)	65	16 (24.6)	41	12 (29.3)
Weight gain	109	20 (18.3)	43	13 (30.2)	64*	8 (12.5)*	22*	6 (27.3)*
Weight loss	25	8 (32.0)	7	3 (42.9)	22*	7 (31.8)*	5*	2 (40.0)*
Abnormal vaginal bleeding	4	2 (50.0)	0	0	0	0	0	0
Abnormal vaginal discharge	20	8 (40.0)	4	3 (75.0)	4	4 (100.0)	3	3 (100.0)
Pain during or after sexual intercourse	28	4 (14.3)	9	2 (22.2)	1	0	1	0

*Note: Shaded cells indicate the largest proportion of women who reported the symptom to a GP across the four approaches to analysis. *Reported at <12 months duration only as frequency data not collected*

5.3.13 Symptoms and depression screening status

There were 192 (23.2%) women who reported feeling down, depressed or hopeless during the past month and 170 (20.5%) who reported little interest or pleasure doing things, with a total of 220 (26.5%) being depression screen positive (answering yes to one or both questions).

Women who were depression screen positive were more likely to report symptoms with odds ratios ranging from 2.84 (95% CI 2.04-3.95) for symptoms at ≥12 days and <12 months, up to 7.02 (95% CI 2.81-17.57) for report of symptoms at any level (Table 5.27). Depression screen positive women were also more likely to have discussed symptoms with a GP during the past three months (OR 2.63, 95% CI 1.91-3.61) and to be positive on the Goff (OR 2.80, 95% CI 1.89-4.15) and Lurie symptom indices (OR 2.65, 95% CI 1.91-3.68).

Depression screen positive women reported a greater number of symptoms overall (*Mdn* 9.0 *vs*. *Mdn* 4.*0*, $U = 34791.0$, $p < 0.0001$, $r = -0.43$) and a greater number of symptoms at ≥12 days frequency and <12 months duration (*Mdn* 1.0 *vs*. *Mdn* 0, $U = 43693.0$, $p < 0.0001$, $r = -0.30$) (Table 5.27). Effect sizes indicate a moderate increase in the number of symptoms with depression screen positive status.

A larger proportion of screening group women responded yes to one or both depression questions compared to controls (29.2% *vs*. 20.5%, $\chi^2(1) = 5.0$, $p = 0.026$). However, there was no difference in the proportion of unaware women in the screen group compared to controls who were depression screen positive (25.9% *vs*. 20.5%, *ns*). Among those who had prior awareness of a possible ovarian lesion, 31.1% screened positive for depression compared to 23.7% unaware or control women ($\chi^2(1) = 5.6$, $p = 0.018$). Most importantly, there was no association between concurrent screen result and depression status in all women, or in the subgroup of those who were aware of the possibility of an ovarian lesion.

Table 5.27. *Symptoms in depression screen positive vs. depression screen negative women*

Symptom reported	n	Depression screen positive (% or IQR)	Depression screen negative (% or IQR)	Odds ratio (95% CI)	p-value
At any level					
Reported	804	215 (97.7)	502 (86.0)	7.02 (2.81-17.57)	<0.0001
Median		9.0 (5.0-15.0)	4.0 (2.0-8.0)	-	<0.0001
Range		0-26	0-24	-	
Level 2-3 severity					
Reported	789	176 (80.0)	301 (51.5)	4.09 (2.79-6.00)	<0.0001
Median		0 (0-2.0)	0 (0-0)	-	-
Range		0-17	0-17	-	
≥12 days & <12 months					
Reported	789	146 (66.4)	245 (42.0)	2.84 (2.04-3.95)	<0.0001
Median		1.0 (0-2.0)	0 (0-1.0)	-	<0.0001
Range		0-20	0-19	-	

Symptom reported	n	Depression screen positive (% or IQR)	Depression screen negative (% or IQR)	Odds ratio (95% CI)	p-value
≥12 days, <12 months & level 2-3 severity					
Reported	790	99 (46.0)	129 (22.4)	2.95 (2.12-4.11)	<0.0001
Median		0 (0-4.0)	0 (0-1.0)	-	-
Range		0-17	0-17	-	

Depression screen positive women were more likely to report all 32 symptoms at any level and at level 2-3 severity they were more likely to report 27 symptoms. However, there was no association between depression status and report of abdominal mass or lump, pain passing urine, weight loss, abnormal vaginal bleeding and abnormal vaginal discharge at level 2-3 severity.

Table 5.28 lists the proportion of depression screen positive and negative women who reported symptoms at ≥12 days frequency and <12 months duration and ≥12 days, <12 months and level 2-3 severity. In the interest of brevity, symptoms more likely to be reported at any level and at level 2-3 severity are omitted from the table. Interestingly, abdominal discomfort/pain had the highest odds ratio (OR 10.12, 95% CI 3.68-27.83) for symptoms at ≥12 days and <12 months, yet the odds ratio for pelvic discomfort or pain was much lower (OR 3.12, 95% CI 1.67-5.81). At level 2-3 severity, ≥12 days and <12 months abdominal discomfort/pain also had the highest odds ratio (OR 9.49, 95% CI 3.05-29.45), followed by shortness of breath (OR 8.92, 95% CI 2.38-33.30) and pressure on the bladder (OR 7.82 (2.05-29.80).

Feeling full was more likely to be reported by depression screening positive respondents on three of the four approaches, with the exception being for the symptom at level 2-3 severity, ≥12 days and <12 months. However, as reported earlier, this symptom was not associated with elevated ROC score, abnormal ovarian morphology, ovarian volume or overall abnormal screen result.

Table 5.28. *Symptoms reported by depression screen positive vs. negative respondents*

Symptom reported	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
≥12 days & <12 months					
Pelvic discomfort or pain	735	22 (11.2)	21 (3.9)	3.12 (1.67-5.81)	<0.0001
Abdominal discomfort or pain	738	17 (8.6)	5 (0.9)	10.12 (3.68-27.83)	<0.0001
Indigestion or heartburn	743	17 (8.5)	13 (2.4)	3.82 (1.81-8.01)	<0.0001
Nausea or vomiting	739	12 (6.1)	5 (0.9)	6.97 (2.42-20.04)	<0.0001
Feeling full quickly	717	19 (10.2)	17 (3.2)	3.41 (1.73-6.72)	<0.0001
Change in appetite	727	19 (10.0)	15 (2.8)	3.87 (1.92-7.78)	<0.0001
Abdominal bloating or fullness	720	25 (13.2)	20 (3.8)	3.89 (2.11-7.20)	<0.0001
Abdominal pressure	726	16 (8.4)	7 (1.3)	6.95 (2.81-17.17)	<0.0001
Increased abdominal size	705	26 (14.2)	35 (6.7)	2.30 (1.35-3.95)	0.002
Pelvic bloating or fullness	720	15 (8.1)	17 (3.2)	2.69 (1.31-5.50)	0.005
Pelvic pressure	720	11 (5.9)	12 (2.3)	2.71 (1.18-6.26)	0.015

Symptom reported	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
≥12 days & <12 months					
Pelvic heaviness	717	14 (7.8)	11 (2.0)	4.03 (1.80-9.05)	<0.0001
Pain before, during or after opening bowels	736	13 (6.8)	8 (1.5)	4.90 (2.00-12.02)	<0.0001
Difficulty emptying bowels	728	46 (24.1)	69 (12.8)	2.15 (1.42-3.27)	<0.0001
Change in bowel habit	718	18 (9.6)	15 (2.8)	3.64 (1.79-7.37)	<0.0001
Excessive flatulence	700	28 (15.3)	39 (7.5)	2.21 (1.32-3.72)	0.002
Urinary frequency	689	27 (14.8)	39 (7.7)	2.09 (1.24-3.53)	0.005
Urinary urgency	690	26 (14.5)	33 (6.5)	2.46 (1.43-4.25)	0.001
Pressure on the bladder	714	16 (8.6)	16 (3.0)	2.99 (1.46-6.10)	0.002
Pain when passing urine	728	6 (3.2)	0	∞	<0.0001
Shortness of breath	719	15 (8.0)	5 (0.9)	9.19 (3.29-25.66)	<0.0001
Back ache or pain	713	27 (14.4)	27 (5.1)	3.12 (1.78-5.47)	<0.0001

Symptom reported	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
≥12 days & <12 months					
Leg ache or pain	696	28 (15.0)	46 (9.0)	1.77 (1.07-2.93)	0.024
Leg swelling	721	19 (10.1)	23 (4.3)	2.49 (1.33-4.69)	0.004
Tiredness, fatigue or lack of energy	658	64 (36.8)	49 (10.1)	5.17 (3.37-7.91)	<0.0001
Weight gain*	716	49 (25.9)	65 (12.3)	2.49 (1.64-3.77)	<0.0001
≥12 days, <12 months & level 2-3 severity					
Pelvic discomfort or pain	758	16 (7.8)	10 (1.8)	4.56 (2.04-10.23)	<0.0001
Abdominal discomfort or pain	738	13 (6.6)	4 (0.7)	9.49 (3.05-29.45)	<0.0001
Indigestion or heartburn	743	11 (5.5)	5 (0.9)	6.31 (2.16-18.39)	<0.0001
Nausea or vomiting	738	9 (4.6)	4 (0.7)	6.47 (1.97-21.27)	0.001
Change in appetite	727	9 (4.7)	6 (1.1)	4.40 (1.55-12.53)	0.005
Abdominal bloating or fullness	720	14 (7.4)	10 (1.9)	4.17 (1.82-9.55)	<0.0001

Symptom reported	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
≥12 days, <12 months & level 2-3 severity					
Increased abdominal size	703	16 (8.7)	18 (3.5)	2.67 (1.33-5.36)	0.004
Pelvic bloating or fullness	720	8 (4.3)	8 (1.5)	2.98 (1.10-8.05)	0.038
Pelvic pressure	720	7 (3.7)	5 (0.9)	4.11 (1.29-13.10)	0.017
Pelvic heaviness	718	8 (4.4)	5 (0.9)	4.92 (1.59-15.24)	0.006
Pain before, during or after opening bowels	736	9 (4.7)	5 (0.9)	5.34 (1.77-16.14)	0.003
Difficulty emptying bowels	728	24 (12.6)	30 (5.6)	2.43 (1.38-4.27)	0.002
Change in bowel habit	718	10 (5.3)	10 (1.9)	2.92 (1.20-7.13)	0.014
Excessive flatulence	700	25 (13.7)	21 (4.1)	3.74 (2.04-6.86)	<0.0001
Pressure on the bladder	715	8 (4.3)	3 (0.6)	7.82 (2.05-29.80)	0.002
Shortness of breath	719	9 (4.8)	3 (0.6)	8.92 (2.38-33.30)	<0.0001
Back ache or pain	713	15 (8.0)	13 (2.5)	3.44 (1.61-7.38)	0.001

Symptom reported	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
≥12 days, <12 months & level 2-3 severity					
Leg ache or pain	696	21 (11.2)	26 (5.1)	2.35 (1.29-4.29)	0.004
Tiredness, fatigue or lack of energy	658	43 (24.7)	27 (5.6)	5.60 (3.33-9.41)	<0.0001
Weight gain*	717	17 (9.0)	21 (4.0)	2.39 (1.23-4.63)	0.008

**Reported at <12 months duration only as frequency data not collected*

5.4 Discussion

The findings of this pilot suggest that ovarian cancer symptom reporting is very complex. It is influenced by a number of factors including participation in screening, age, awareness of a possible ovarian lesion and positive depression screening status, in addition to the presence of a screen-detected abnormality. Results indicate that awareness of the possibility of an ovarian lesion is an overriding factor which influences both symptom reporting and depression screening status. We were unable to test this hypothesis in multivariate logistic regression models as awareness was not an independent variable (i.e. it was based upon previous screen result which was strongly correlated with the dependent outcome variable - concurrent screen result). Awareness of the possibility of an ovarian lesion is likely to be a proxy for anxiety. Unfortunately, the study design did not permit assessment of anxiety generated by the need for further testing.

Symptom prevalence

The proportion of women who reported any symptoms was considerably higher than previous studies. For example, 86% of women in the control group were symptomatic compared to 42% and 52% reported by two US studies which recruited community dwelling women as controls.[16-17] When the analysis was restricted to approximately similar symptoms, 40% of OCSq control group women reported bloating/fullness or pressure in the abdomen or pelvis, while Olson *et al*.[17] found 9% of controls reported this for the 6-12 months prior to interview. Differences were more dramatic for the combination of abdominal or pelvic discomfort/pain, pressure or heaviness, which was reported by 32% of OCSq controls during the past week compared to 10% of controls who reported this during the two weeks prior to interview in Vine *et al*.[16] Similarly, increased abdominal size was reported by 25% of OCSq controls compared to 3% in a recent US study.[25]

The higher prevalence of symptoms in our research is likely to be due to the inclusion of a comprehensive list of 32 symptoms in the OCSq. Women in the Olson *et al*.[17] and Vine *et al*.[16] studies were asked about similar types of pelvic

and abdominal symptoms grouped together into a single item, while, for example, the OCSq listed five separate items to elicit information on abdominal or pelvic discomfort/pain, pressure or heaviness. Asking women about specific symptoms in separate items is likely to increase reporting due to either an acquiescent or memory cueing effect.[129 141] The high prevalence of symptoms among women in our research may also be due to older age, as ≥50% of controls in the two comparative studies were aged under 50 years. It is unlikely that symptom reporting was related to increased prevalence of underlying disease, as UKCTOCS volunteers have lower overall and disease-specific mortality rates.[220]

The large proportion of symptomatic women among those with normal concurrent screen results (88%) highlights the need to increase specificity by restricting the number of symptoms, adding severity or frequency and duration criteria, or a combination of these, to investigate symptoms associated with ovarian cancer in follow-up analyses of the 100,000 women study. Restricting analyses to the key symptoms of abdominal or pelvic discomfort/pain, increased abdominal size, abdominal or pelvic bloating/fullness and change in appetite or feeling full reduced the proportion of symptomatic women to 55%, although this still identified nearly half (46%) of those who had a normal screen result.

Symptoms associated with abnormal screening results

The most frequently reported symptoms among the postmenopausal women surveyed were tiredness/fatigue, backache/pain, leg ache/pain, excessive flatulence, weight gain, indigestion/heartburn and urinary frequency/urgency. In comparison, women with abnormal screen results were more likely to report increased abdominal size, abdominal or pelvic pressure, pelvic bloating/fullness, pelvic heaviness and shortness of breath.

Many studies have described abdominal or pelvic pain as among the three most common symptoms of ovarian cancer, with research indicating that these symptoms often have the largest odds ratios between ovarian cancer cases and controls.[9 12 16 19-21 23 46-47 50-51 72-73 121 124] Although one of the two women diagnosed with cancer reported both abdominal and pelvic discomfort/pain, these symptoms were not associated with abnormal concurrent screen result, elevated CA125,

elevated ROC, complex ovarian morphology or increased ovarian volume at any level of analysis. This contrasts with Rufford *et al.*[221] who reported abdominal discomfort/pain in 18 out of 23 women with an ovarian abnormality detected on ultrasound and 10 out of 13 women with raised CA125. Unfortunately, the only other study to-date which investigated symptoms associated with CA125 results did not report the percentage of women with abdominal or pelvic discomfort/pain among those with elevated CA125 levels.[24]

Multivariate analyses identified abdominal or pelvic pressure as the only symptoms which independently predicted an abnormal screen result on three of the four approaches, although shortness of breath was included in the final models on two approaches. All four symptom models performed only marginally better than chance for identifying abnormal screen results, as the largest area under the curve was 0.62 (for pelvic pressure and tiredness/fatigue at any severity, frequency and duration). Given the ubiquity of tiredness/fatigue among postmenopausal women it is unsurprising that the model with the highest area under the curve for detecting an abnormal result had the lowest specificity for detecting ovarian cancer.

With the exception of urinary symptoms and shortness of breath, symptoms associated with elevated CA125 level differed to those associated with elevated ROC scores. This may be due to the higher sensitivity of ROC scores for the detection of ovarian cancer compared to CA125 level alone. Women with elevated ROCs were more likely to report symptoms previously described as associated with ovarian cancer, including increased abdominal size, pelvic bloating/fullness and urinary symptoms.[12 14-16 18 20 22-23 46 50]

Pelvic pressure and change in bowel habit were the only two symptoms associated with complex ovarian morphology. Ten percent of women with complex masses reported change in bowel habit, which is less than the 27% who reported constipation, and 18% who reported diarrhoea, in another study which investigated symptoms associated with complex ovarian morphology detected on ultrasound.[222] Analysis of symptoms associated with ultrasound-estimated total ovarian volume in those with complex morphology identified urinary frequency

and abdominal bloating as associated with larger volumes, which seems plausible on a physiological basis. However, the former was reported by both women with screen detected cancers, despite relatively small ultrasound-estimated ovarian volumes. The association between smaller volumes and leg swelling is more difficult to interpret and may be a spurious finding.

Feeling full was notable in that it was associated with abnormal concurrent screen result in the sub-group of aware women. Several studies have described early satiety or difficulty eating as a symptom of ovarian cancer.[8 13 15-16 18 23 46 48 124] Its importance as a key symptom is reflected by its inclusion in the Goff symptom index and both the US and UK symptoms consensus statements.[30 32] It is to be noted that neither of the two women diagnosed with cancer reported this symptom, although it is possible that this is a reflection of the low volume early stage disease detected on screening.

Performance of symptom models and indices for identifying ovarian cancer

In this pilot of 829 apparently healthy postmenopausal women, only 1-2 ovarian/tubal cancers were expected. The four models which independently predicted an abnormal result were investigated for their usefulness in detecting these cancers, and the results were compared with the Goff and Lurie symptom indices. All the models and indices had a sensitivity of 50.0%, with very wide confidence intervals reflecting the small number of cases. However it was possible to better estimate specificity, which ranged from 44.4%, for Model 1, up to 97.6 for Model 4 (abdominal pressure and shortness of breath at level 2-3 severity, ≥12 days frequency and <12 months duration). With a specificity of 84.5%, the Goff symptom index performed similarly in our sample compared to the authors' original study, where a sensitivity of 56.7% was reported for early-stage ovarian cancer with specificities ranging from 86-90%.[23] The Lurie index had a lower specificity (60.8%) among our sample than was reported in the authors' own research, where their four-symptom model had a specificity of 71%. These preliminary findings emphasise the importance of exploring a range of different indices. They also underscore the likelihood that a symptoms index

developed from prospective research may differ from previously published indices.

Impact of screening and awareness of an ovarian lesion on symptom reporting

Women who participated in the OCSq pilot were either UKCTOCS controls or screening group women scheduled to receive annual or repeat (Level 2) screening within 4-6 weeks. Comparison of symptoms between the groups revealed screened women were 1.4-1.6 times more likely to report symptoms at three of the four levels of analysis. They were also more likely to report key symptoms of ovarian cancer, including pelvic discomfort or pain, abdominal bloating/fullness, feeling full and change in bowel habit, although they were not more likely to be positive on the Goff or Lurie symptom indices. As severity, frequency and duration criteria were added to individual symptoms, the number of symptoms associated with screening was reduced. Lower symptom reporting among controls was not related to lower education levels as educational attainment was equivalent across the groups, as were other baseline characteristics, this being a randomised controlled trial. The finding could be related to women undergoing ovarian cancer screening being better informed (either through contact with screening staff, literature displayed in clinics or their own information searches prompted by screening) and paying more attention to symptoms associated with ovarian cancer. Alternatively, this finding may reflect subtle symptoms related to the presence of abnormalities as half the screen group were respondents scheduled for repeat screening due to the detection of a possible abnormality on annual screening.

In order to explore this difference in symptom reporting between women undergoing screening and no intervention (controls), symptoms were analysed in relation to awareness of a possible ovarian lesion. Women who were aware of a possible ovarian lesion were more likely to report symptoms across three of th[9]e four levels of analysis. Analysis of individual symptoms revealed that aware women were more likely to report key symptoms listed in the literature, such as pelvic or abdominal discomfort/pain, increased abdominal size, urinary symptoms and change in bowel habit. In contrast, there was no significant difference

between the proportion of screened women attending for annual screening (unaware of an abnormality) and controls who reported symptoms overall across the four approaches. Unaware screened women were more likely than controls to report feeling full and controls were more likely to report, backache/pain and nausea/vomiting. It is difficult to ascertain why these differences arose but it must be noted that the lower confidence limits in all these cases were close to one.

To further elucidate the relationship between awareness, symptom reporting and the presence of ovarian lesions, symptoms were investigated according to concurrent screen results in aware women. This analysis revealed that aware women (ie. those who had a previously abnormal screen result) with change in appetite, feeling full, increased abdominal size or leg ache/pain were more likely to have an abnormal concurrent screen result. This finding is similar to retrospective and medical records research which has reported increased abdominal size, change in appetite or feeling full are among the most common symptoms reported by women with ovarian cancer.[13 16 18 23 25 46-47 51] Increased abdominal size is also commonly reported by women with benign, borderline and early stage tumours.[16 18 22 50-51 121 123] Medical and insurance records studies also indicate that increased abdominal size is commonly experienced several months prior to diagnosis,[20 72 121 123] with one study finding an elevated odds ratio for the symptom in medical notes up to 30 months before diagnosis.[21]

To control for the effect of awareness on symptom reporting, a useful analysis would be investigating symptoms reported by unaware respondents who went on to have an abnormal concurrent screen result. Unfortunately, numbers were too small (n = 18) to conduct this analysis, although it is expected that there will be sufficient numbers for analysis in the larger study described in Chapter Six.

It is highly plausible that anxiety increased symptom reporting among screen group women who were aware of a possible ovarian lesion. Anxiety may have heightened women's attention to bodily sensations and knowledge seeking behaviours such as searching websites for information about ovarian cancer symptoms. Regrettably, we overlooked inclusion of a question on the OCSq about health information searches related to ovarian cancer. Anxiety associated with

awareness could have been measured by asking all respondents to complete a Hospital Anxiety and Depression Scale (HADS) or Speilberger Trait Anxiety Inventory (STAIT) questionnaire at the same time as OCSq. However, there is a parallel study collecting detailed information on anxiety and other psychosocial morbidity resulting from screening (described in Chapter One). Women in the pilot who were attending repeat screening would have been sent the HADS questionnaire as part of this study. We did not wish to confuse women and contaminate the existing data collection by asking them to complete two anxiety measures. In due course this data should be available in the 51% of respondents who were in the aware group. This is not ideal and arrangements could have been made to send the questionnaire to the remaining respondents if such a large effect had been anticipated.

Symptoms associated with depression screening status

The finding that 27% of respondents screened positive for depression is considerably higher than the 6% of women 65 years or older who screened positive for depression in a large US study,[223] 8% of women aged over 60 in an Australian study,[224] and 10% of people aged 65 years or over in a UK study.[225] This high prevalence of depression persisted, even when comparisons were limited to respondents from the control group. One explanation is that the two-question depression screening method used in our research may have lower specificity compared to multi-factorial depression screening tools such as the Patient Health Questionnaire (PHQ) used in the other studies, although the two-questions have been previously found to have specificities ranging from 57-84%.[212-215 217-218 226] Goff *et al*.[23] also used a comprehensive depression screening measure consisting of 20 items on a four-point Likert scale (the Center for Epidemiologic Studies Depression Scale - CES-D), although the authors do not report the percentage of women who screened positive for depression.

The finding that women who screened positive for depression were more likely to report symptoms, and reported a greater number of symptoms, is congruent with the findings of the recent Goff study.[23] However, in contrast to the Goff study, neither of the two women diagnosed with malignancy screened positive for

depression. These two women, like those in Goff series, were attending for further investigations and were aware of an abnormality at the time of completing the OCSq .

There was also no association between depression screening status and abnormal concurrent screen results. However, respondents who had prior awareness of a possible abnormality were more likely to screen positive for depression. This suggests Goff *et al.*'s[23] finding that depression was significantly associated with cancer is likely to be the product of heightened awareness of the possibility of malignancy, or anxiety related to impending surgery, rather than a product of physiological changes associated with the disease. It also adds weight to our impression that awareness has a psychological impact in the absence of specific data on anxiety.

In contrast to the Goff group, we did not enter depression screening status into multivariate analyses. In their confirmatory logistic regression, Goff *et al.*[23] found depression was independently predictive of ovarian cancer in women under 50 years of age. This analysis appears methodologically flawed as the authors did not take into account the impact of awareness of the possibility of malignancy on depression screening results. Moreover, the inclusion of depression status into a predictive model for ovarian cancer fails to acknowledge the complex relationship between depression and symptom reporting.[227-234]

Symptoms reported to GPs

The top symptoms out of the list of 32 for which the GP was consulted were backache/pain, leg ache/pain and tiredness/fatigue. The pilot confirmed our intuitive impression that respondents were most likely to consult their GP when symptoms were experienced at level 2-3 severity. Only in the case of postmenopausal bleeding did women consult their GP, irrespective of severity. This has significant implications for our attempts to improve time to diagnosis of ovarian cancer. Previous research has shown frequency and recent onset of symptoms as the main issues to be considered in women with ovarian cancer.[17-18] [20] [23] [46] In contrast, only one published study reported severity was of significance,[18] although recent PhD research found both higher level severity and

increased frequency characterised key symptoms such as bloating/increased abdominal size, pelvic/abdominal pain, loss of appetite and fatigue in ovarian cancer cases compared to controls.[34]

Severity is not a feature of either the US or the UK symptoms consensus statements.[30 32] However, our pilot revealed that abdominal or pelvic pain, increased abdominal size and feeling full were discussed with the GP only when experienced at level 2-3 severity. This suggests that women and GPs need to be educated about the importance of frequency and duration criteria alone if current initiatives are to make a real impact.

Study strengths

A unique strength of the research described in this chapter was the use of a valid and reliable questionnaire (as demonstrated from the analyses presented in Chapter Four), developed specifically to elicit information on ovarian cancer symptoms. The robustness of the instrument is reflected by the fact that no respondents were excluded from analysis on the basis of illegible data.

The study recruited a large number of women (n = 829). The response rate was slightly higher than the 60% generally considered acceptable for postal surveys,[235] although it was equivalent to the median reported in medical journals.[236] Women were recruited from 13 centres throughout England, Wales and Northern Ireland, ensuring a regionally and socially heterogeneous study population.

Prospective data collection is a chief strength of the research. While other studies have attempted to collect data prospectively, this is the first study to include symptom data collection in women who were aware of the possibility of an abnormality but who were not yet assessed by a gynaecological oncologist. The women in the control group were similar to healthy controls in other studies that used community-based populations.

The conduct of this study within an ovarian cancer screening trial is a foremost strength of the study. This facilitates the detection of ovarian cancer at early stage when the disease volume is low. The enrichment of ovarian cancer cases with early stage disease where prompt diagnosis can make a real impact is crucial. In many studies reported in the literature, symptoms one year prior to diagnosis are

correlated with the stage of disease at diagnosis. At present, there is insufficient evidence to prove disease progression over time, although studies implicitly assume that stage of disease was static during the pre-diagnosis period.

The OCSq elicited symptoms data using a one-week reference period. This timeframe is another advantage of the study, as research indicates that asking participants about events during the past seven days yields more accurate data than one-month or longer time periods.[131 160 205]

Study limitations

The findings of this chapter are limited by higher response rates among women attending screening compared to controls, and among women attending repeat screening compared to those attending annual screening. This is likely to have biased the findings through the recruitment of women who have enhanced knowledge of the symptoms of ovarian cancer. It is also possible that different response rates resulted in the recruitment of women who were anxious about their screening and were therefore more attuned to symptoms. This is likely to have resulted in over-reporting bias, which is another factor which may explain the large percentage of symptomatic women. However, this is likely to have occurred in all previous questionnaire studies of ovarian cancer symptoms.

Unfortunately, it was not possible to measure anxiety as this was an existing component of the UKCTOCS trial. Data on anxiety may have led to important insights about symptom reporting associated with different levels of screening investigations.

As the aim of the pilot was validation of an ovarian cancer symptoms questionnaire, we deliberately enriched the population with a large proportion of women who had an abnormality detected on their previous screen. We considered that these women would be able to provide feedback on the wording of symptoms rarely experienced by healthy women, such as abdominal mass or lumps. However, as discussed earlier, this is likely to have led to over-reporting bias. While this was unavoidable in the pilot, the final study described in Chapter Six should succeed in recruiting sufficient numbers of women who are unaware of an abnormality, and thus reduce this source of bias.

5.5 Summary

The analyses presented in this chapter found variation in the types of symptoms associated with abnormal ovarian cancer screening results. No symptoms were associated with abnormality on all screening modalities, although increased abdominal size, abdominal or pelvic pressure and urinary frequency or urgency were frequently associated with abnormal results. Stronger associations were observed between awareness of a possible ovarian lesion or depression status and symptom reporting, than abnormal concurrent screen result and symptom reporting. However, symptom reporting in aware women may be a result of early physiological changes associated with malignant or benign masses, rather than awareness of the possibility of an ovarian lesion per se. Symptom indices described by other groups had lower sensitivity and specificity among OCSq respondents, although sensitivity analyses were greatly restricted by the small number of cancer cases. Lastly, the types of symptoms found to be associated with abnormal screen results differed across the four levels of analysis. These inconsistencies will be further explored in the larger study described in Chapter Six.

Chapter Six – Analysis of Baseline Data from the OCSq Survey of 100,000 Postmenopausal Women

6.0 Introduction

This chapter describes the methods and preliminary findings of the prospective symptoms study using the finalised OCSq. Earlier chapters of this thesis described the paucity of research utilising validated questionnaires and the urgent need for a prospective study, designed to collect symptoms data prior to women being assessed by specialist gynaecological oncologists. Many studies have described abdominal or pelvic pain, increased abdominal size, bloating, change in appetite, urinary frequency or urgency, change in bowel habit and tiredness or fatigue as key symptoms of ovarian cancer.[8-10 13-19 22-23 46-47 50-51 73 121] However, Chapter Five demonstrated that women who are aware of the possibility of an ovarian lesion are more likely to report these symptoms, even though few were subsequently diagnosed with malignancy during follow-up. Several questions arose from these analyses, including whether symptoms are related to pre-malignant pathological changes, or whether knowledge of the possibility of malignancy prompts greater attention to, and perception of, key symptoms.

6.1 Aims

- To estimate the prevalence of 'key symptoms' in apparently healthy women participating in the finalised OCSq study
- To investigate symptoms reported by women receiving ovarian cancer screening compared to controls
- To explore symptoms according to awareness of the possibility of an ovarian lesion

- To describe GP consultations for symptoms and assess consultation behaviour associated with symptom severity, frequency and duration
- To describe depression screening status and investigate symptoms associated with depression screening positive status

6.2 Methods

6.2.1 Study power

A power calculation was conducted in 2006, prior to the original ethics application. At this time, the estimated 75% response rate was based upon the response rate to the first UKCTOCS follow-up questionnaire (described in Chapter One). Incidence of ovarian cancer was estimated at approximately 50 cases per year per 100,000 women aged over 50. Therefore 1.5 years of follow-up may be expected to result in 75 women diagnosed with ovarian cancer. However, a healthy volunteer effect has since been confirmed in the UKCTOCS cohort.[220] This would reduce the number of cases to 49, given a 75% response rate. As the pilot found a response rate of 52%, the number of cases may be further reduced to 25.

Power estimates based on testing a difference in proportions (normal approximation) between cases and non-cases with alpha = 0.05 and a two-sided test were calculated for key symptoms of ovarian cancer. This calculation used the difference in proportions from retrospective questionnaire research which recruited community-based healthy women as controls.[16] The power of the test was very close to one for bloating, increased abdominal size and abdominal/pelvic pain, regardless of the response rate, as the anticipated differences between the two proportions for these symptoms was large. However, the pilot data analyses confirmed earlier reservations regarding tests using the difference in proportions of symptoms at any level of severity, frequency or duration. This inflates the proportion of healthy women with key symptoms of ovarian cancer. Addition of level 2-3 severity criteria, or ≥12 days frequency and <12 months duration, reduces the proportion of healthy women with key symptoms to similar levels reported by other research.

6.2.2 Sample selection

A total of 100,000 randomly selected UKCTOCS volunteers were posted the finalised OCSq. This group included 55,000 controls, 22,500 multimodal and 22,500 ultrasound group women.

Inclusion criteria

- Volunteers in the UKCTOCS control, multimodal and ultrasound groups

Exclusion criteria

- Volunteers who had died
- Volunteers who had previously undergone UKCTOCS trial surgery
- Volunteers who had both ovaries removed outside the trial
- Volunteers who had registered a complaint about previous questionnaires
- Volunteers who had requested no further contact from UKCTOCS for any reason
- Volunteers who had been lost to follow-up due to moving home

6.2.3 Data collection

The finalised OCSq (described in Chapter Four and presented in appendix 22), cover letter (appendix 26), information sheet (appendix 27), instruction page (appendix 28) and return stamped envelope were posted to randomly selected UKCTOCS volunteers. Walledge Associates, a direct mailing and data capture company, organised postage of the OCSq, although the Gynaecological Cancer Research Centre address and telephone number was printed on all documents.

All questionnaires were date stamped on receipt and were manually entered by Walledge Associates staff. Questionnaires incorrectly returned to the research coordinating centre were also manually entered.

Demographic data were obtained from baseline questionnaires, completed at UKCTOCS recruitment. Education data were obtained from UKCTOCS follow-up questionnaires. Both questionnaires are described in Chapter One.

6.2.4 Data cleaning

An estimated completion date was calculated for respondents who did not write the date on their questionnaire (as described in Chapter Five). This was based upon the overall median number of days between the date of questionnaire completion and receipt back at Walledge Associates, or the research coordinating centre, for all participants. Where the completion date was either written incorrectly by the respondent or entered incorrectly onto the database (e.g. 23.03.2004 instead of 23.04.2009), an estimated completion date was calculated using the same method.

The OCSq database was set-up so that symptom prevalence/severity was entered as follows: 0 = no, 1 = a little, 2 = quite a bit, 3 = very much, 9 = missing data. Frequency: 1 = 1-2 days, 2 = 3-5 days, 3 = 6-7 days, 9 = missing data. Duration: 1 = less than 3 months, 2 = 3-6 months, 3 = 6-12 months, 4 = more than 12 months, 9 = missing data. GP consultation: 1 = yes, 0 = no, 9 = missing data.

The data cleaning protocol was as follows:

- Where 4 was incorrectly entered for symptom severity, this was re-coded as 3 (very much)
- Where 4 was incorrectly entered for symptom frequency, this was re-coded as 3 (6-7 days)
- Where 0 was incorrectly entered for frequency or duration, this was re-coded as 9 (missing data)
- Where GP consultation was incorrectly entered as 2 or 3, this was re-coded as 1 (yes).

- Where respondents completed the frequency section (ticking either 1-2 days, 3-5 days or 6-7 days during the past week), the duration section (ticking either less than 3 months, 3-6 months, 6-12 months or more than 12 months) or ticked yes to the GP reported section but did not complete the severity section, the symptom was coded as experienced but without a severity rating.
- Where respondents did not complete the severity, frequency or duration sections but ticked no to GP reported section, the symptom was coded as not experienced during the past week.

6.2.5 Data analysis

UKCTOCS baseline and follow-up questionnaires, together with OCSq data, were exported from the main UKTOCS database on Monday 3 August 2009 and imported into SPSS version 12.0.1 (SPSS Inc., Chicago, USA) for analysis. Frequencies were run to describe the data and distributions of continuous variables were explored. Respondents who reported a diagnosis of ovarian cancer on the OCSq (q35) were excluded from further analysis.

The same four approaches that were utilised in Chapter Five to classify 'positive' symptoms were also utilised for analyses described in this chapter. To reiterate: 1) symptoms reported at any level of severity; 2) symptoms reported at level 2-3 severity; 3) symptoms reported at any level of severity with ≥12 days per month frequency and <12 months duration; and 4) symptoms with a frequency ≥12 days per month, <12 months duration and level 2-3 severity.

Women who had either pelvic discomfort/pain (q1), abdominal discomfort/pain (q2), feeling full (q5), abdominal bloating (q7) or increased abdominal size (q9) for 3-5 or 6-7 days during the past week and where the symptom had a duration of <12 months were considered positive on the Goff *et al.*[23] symptom index (described in Chapter Two).

Women who had either abdominal pain (q2), increased abdominal size (q9), abdominal mass/lumps (q10) or abnormal vaginal bleeding (q30) were considered

positive on the Lurie *et al.*[25] symptom index (described in Chapter Two). Hard abdomen was not included as this was not listed in the OCSq.

Symptom Model 4 described in Chapter Five and identified as having the best performance for identifying ovarian cancer in the pilot was also investigated. This model included abdominal pressure (q8) or shortness of breath (q18) at level 2-3 severity, ≥12 days frequency & <12 months duration.

Symptom reporting according to screening group

Using the four approaches, symptoms were investigated in the control, multimodal and ultrasound groups. Symptoms were also explored in the screening group (multimodal plus ultrasound) compared to controls.

Symptom reporting according to awareness of a possible ovarian lesion

All controls were classified as unaware of a possible ovarian lesion. Screening group women whose last screening 'action' prior to completing the OCSq was 'return to annual screening' were also classified as unaware of a possible ovarian lesion. Women recalled for repeat screening (repeat blood test or ultrasound or Level 2 screening), referred to a gynaecological oncologist for clinical evaluation, or referred for surgery, were classified as aware. Symptoms were compared in the two groups.

GP consultations for symptoms

Symptoms most frequently reported to GPs were explored and GP consultations for symptoms were investigated across the four levels of analysis. Only women who completed the required sections (e.g. frequency and duration sections plus GP consultation section for assessment of GP consultations for symptoms at ≥12 days frequency and <12 months duration) were included in analyses.

Symptoms and depression screening status

Respondents who replied positively to one or both depression screening questions were categorised as depression screen positive and those who responded negatively to both questions were categorised as depressions screen negative. This is in accordance with the literature.[213-218] [237] Depression screening status was investigated according to prior awareness of a possible ovarian lesion. Using the

four approaches to classify positive symptoms, symptoms were investigated according to depression screening status.

Statistical analysis

Relationships between variables were investigated using the chi-square statistic and Mann-Whitney *U* tests were used to test differences between two groups for non-parametric continuous data. Effect sizes were calculated and interpreted according to Cohen's criteria of $r = 0.3$ for a medium effect and $r = 0.5$ for a large effect. Differences were accepted as significant at $p < 0.05$ for all tests.

6.3 Results

6.3.1 Response rates

A total of 100,000 UKCTOCS volunteers (55,000 controls, 22,500 multimodal and 22,500 ultrasound group women) were posted the pilot OCSq over an eight week period from 12 March to 13 May 2009. There were 51,019 completed questionnaires received between 18 March and 31 July 2009, giving an overall response rate of 51.0%. This included 25,823 controls (47.0%), 12,646 multimodal (56.2%) and 12,550 (55.7%) ultrasound group women. Response rates being significantly higher among women in the screening groups compared to the control group (56.0% *vs*. 47.0%, $\chi^2(1) = 809.4$, $p < 0.0001$).

Response rates varied across the 13 regional centres. As in the pilot, Bristol had the highest response rate and Liverpool had the lowest (57.0% *vs*. 47.0%, $\chi^2(1) = 123.1$, $p < 0.0001$) (Table 6.1). Questionnaires were still being received at the time of data analysis, therefore final response rates will be higher.

Table 6.1. *OCSq response rates by regional centre*

Centre	Invited n	Responded n	Response rate %
Belfast	6,851	3,396	49.6
Bristol	8,127	4,635	57.0
Cardiff	8,271	4,114	49.7
Derby	7,554	3,980	52.7
East London (St Bart's)	9,572	4,509	47.1
Gateshead	8491	4,302	50.7
Liverpool	4,904	2,306	47.0
Manchester	8,155	4,107	50.4
Middlesbrough	5,004	2,534	50.6
North London (Royal Free)	8,429	4,124	48.9
North Wales	7,088	3,662	51.7
Nottingham	8,202	4,270	52.1
Portsmouth	9,352	5,080	54.3
Total	*100,000*	*51,019*	*51.0*

After preliminary data exploration, 12 questionnaires (9 controls, 2 multimodal, 1 ultrasound) were excluded due to self-reported diagnosis of ovarian cancer on question 35. This resulted in a final data set of 51,007 questionnaires. No ovarian cancer diagnosis was registered on the UKCTOCS database for the 12 women. However, they may have been very recently diagnosed. The information provided by these women, and their contact details, was passed on to the appropriate UKCTOCS staff member for follow-up.

There were 10,018 (19.6%) respondents (5,221 controls, 2,407 multimodal and 2,390 ultrasound) who did not have a completion date for the OCSq and 142 (0.3%) had an incorrect date (62 controls, 36 multimodal and 44 ultrasound). The

median time from OCSq completion to receipt in the remaining 40,847 respondents was four days (range 1-109, IQR 2-6). An estimated completion date was calculated by subtracting four days from the stamped receipt date for respondents who did not date their questionnaire, or had an incorrect date.

6.3.2 Demographics and co-morbidities

Reported on OCSq

Mean age was 66.1 years (range 53.7-82.3, SD = 6.0) with no difference in age between the groups (Table 6.2). A total of 4,995 (9.8%) women were using HRT at the time of the OCSq, with an equivalent proportion of controls (9.9%), multimodal (9.3%) and ultrasound (10.0%) group respondents reporting HRT use.

Self-reported history of cancer was equivalent across the groups, with 7.9% of controls, 7.3% of multimodal and 7.6% of ultrasound group women reporting that they had been diagnosed with cancer in the past (Table 6.2). Approximately 10% had been diagnosed with hiatus hernia, 13.3% with IBS, 2.3% with inflammatory bowel disease, 33.7% with arthritis and 14.0% with depression. There were no differences in the proportion of respondents in each group who self-reported these co-morbidities.

Reported on UKCTOCS baseline questionnaire

An equal proportion (approximately 98%) of women in each group reported a white ethnic background (Table 6.3).

Approximately 35% in each group were overweight and approximately 17% were obese. There was a median of 16.2 years (range 3.5-42.8, IQR 10.4-22.4) since respondents' last menstrual periods. A median of zero miscarriages (range 0-12, IQR 0-1) and two pregnancies (range 0-9, IQR 2-3) in each group, and an equivalent proportion (approximately 63%) of controls, multimodal and ultrasound group respondents reported a history of OCP use.

Reported on UKCTOCS follow-up questionnaire

Of the total 51,007 women, 40,048 (78.5%) completed the UKCTOCS follow-up questionnaire. Education levels were equivalent across the three groups, with approximately 3% of women reporting A level qualifications, 25% clerical qualifications, 10% professional qualifications and 23% degree level qualifications (Table 6.4). Small differences between the groups were not significant.

Table 6.2. *Demographic and co-morbidity data reported on OCSq*

OCSq	**Controls n=25,814 n (% or SD)**	**Multimodal Group n=12,644 n (% or SD)**	**Ultrasound Group n=12,549 n (% or SD)**	**Overall n=51,007 n (% or SD)**
Age at questionnaire†	66.1 (SD=6.0)	66.2 (SD=6.0)	66.0 (SD=5.9)	66.1 (SD=6.0)
Current HRT use	2,557 (9.9)	1,170 (9.3)	1,268 (10.1)	4,995 (9.8)
Personal history of cancer*	2,030 (7.9)	924 (7.3)	950 (7.6)	3,917 (7.7)
Personal history of breast cancer	1,306 (5.1)	566 (4.5)	628 (5.0)	2,500 (4.9)
Diagnosed with hiatus hernia	2,575 (10.0)	1,293 (10.2)	1,200 (9.6)	5,068 (9.9)
Diagnosed with IBS	3,384 (13.1)	1,695 (1.4)	1,687 (13.4)	6,766 (13.3)
Diagnosed with inflammatory bowel disease	584 (2.6)	292 (2.3)	273 (2.2)	1,149 (2.3)
Diagnosed with arthritis	8,661 (33.6)	4,304 (34.0)	4,209 (33.5)	17,174 (33.7)
Diagnosed with depression	3,573 (13.8)	1,772 (14.0)	1,771 (14.1)	7,116 (14.0)

** Excluding basal cell carcinoma/skin cancer*

† Mean

Table 6.3. *Demographic data reported on UKOCTOCS baseline questionnaire*

UKCTOCS baseline questionnaire	**Controls n=25,814 n (% or IQR)**	**Multimodal Group n=12,644 n (% or IQR)**	**Ultrasound Group n=12,549 n (% or IQR)**	**Overall n=51,007 n (% or IQR)**
Ethnic origin				
Bangladeshi	5 (0.02)	1 (0.007)	0	6 (0.01)
Black African	52 (0.2)	27 (0.2)	25 (0.2)	104 (0.2)
Black Caribbean	124 (0.5)	83 (0.7)	74 (0.6)	281 (0.6)
Black other	12 (0.05)	4 (0.03)	7 (0.05)	23 (0.05)
Chinese	41 (0.2)	19 (0.2)	19 (0.2)	79 (0.2)
Indian	90 (0.4)	36 (0.3)	44 (0.4)	170 (0.3)
Pakistani	9 (0.03)	2 (0.02)	7 (0.06)	18 (0.04)
White	25,235 (97.8)	12,346 (97.6)	12,240 (97.5)	49,833 (97.7)
Other	127 (0.5)	65 (0.5)	76 (0.6)	268 (0.5)
Missing	119 (0.5)	61 (0.5)	57 (0.5)	237 (0.5)
Height at recruitment (cm)	162.6 (157.5-167.6)	162.6 (157.5-167.6)	162.6 (157.5-167.6)	162.6 (157.5-167.6)
Weight at recruitment (kg)	67.0 (60.3-76.2)	67.0 (60.3-76.2)	66.7 (60.3-76.0)	66.7 (60.3-76.2)
Median Body Mass Index (BMI) at recruitment	25.5 (23.1-28.7)	25.6 (23.2-28.7)	25.5 (23.1-28.5)	25.5 (23.1-28.7)

UKCTOCS baseline questionnaire	**Controls n=25,814 n (% or IQR)**	**Multimodal Group n=12,644 n (% or IQR)**	**Ultrasound Group n=12,549 n (% or IQR)**	**Overall n=51,007 n (% or IQR)**
BMI group Under-weight (BMI <18.5) Optimal weight (BMI 18.5-25.0) Over-weight (BMI 25.1-30.0) Obese (BMI >30.0) Missing	 186 (0.7) 11,438 (44.3) 9,081 (35.2) 4,445 (17.2) 664 (2.6)	 106 (0.8) 5,516 (43.6) 4,485 (35.5) 2,242 (17.7) 295 (2.3)	 99 (0.8) 5,565 (44.3) 4,466 (35.6) 2,155 (17.2) 264 (2.1)	 391 (0.8) 22,520 (44.1) 18,032 (35.4) 8,842 (17.3) 1,223 (2.4)
Years since last menstruation	16.2 (10.4-22.6)	16.3 (10.4-23.1)	16.2 (10.3-22.4)	16.2 (10.4-22.5)
Ever use oral contraceptive pill (OCP)	16,271 (63.0)	7,915 (62.6)	8,019 (63.9)	32,205 (63.1)
Duration of OCP (years) if applicable	5.0 (2.0-10.0)	5.0 (2.0-10.0)	5.0 (2.0-10.0)	5.0 (2.0-10.0)
Ever use hormone replacement therapy (HRT) at recruitment	5,055 (19.6)	2,439 (19.3)	2,477 (19.7)	9971 (19.5)
Miscarriages (pregnancies <6 months)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Number of children (pregnancies ≥6 months)	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)
Hysterectomy	4,461 (17.3)	2,297 (18.2)	2,207 (17.6)	8965 (17.6)

Table 6.4. *Demographic data reported on UKCTOCS follow-up questionnaire*

UKCTOCS follow-up questionnaire	**Controls n=20,123 n (%)**	**Multimodal Group n=10,054 n (%)**	**Ultrasound Group n=9,871 n (%)**	**Overall n=40,048 n (%)**
Education level				
No qualification	4,521 (22.5)	2,456 (24.4)	2,407 (24.4)	9384 (23.4)
O level	2,335 (11.6)	1,124 (11.7)	1047 (10.6)	4506 (11.3)
A level	692 (3.4)	340 (3.4)	306 (3.1)	1338 (3.3)
Clerical qualification	4,951 (24.6)	2,502 (24.9)	2,434 (24.7)	9887 (24.7)
Professional qualification	2,148 (10.7)	1,020 (10.1)	946 (9.6)	4114 (10.3)
Degree level	4,681 (23.3)	2,151 (21.4)	2,240 (22.7)	9072 (22.7)
Missing	795 (4.0)	461 (4.6)	491 (5.0)	1747 (4.4)

6.3.3 Symptoms reported by OCSq respondents

A total of 45,140 (88.5%) women reported symptoms at any level of severity, with a median of 5.0 (range 0-32, IQR 2-9) symptoms reported. Tiredness/fatigue was the most commonly reported symptom overall (52.6%), followed by back ache or pain (46.5%) and leg ache or pain (37.9%) (Table 6.5). Both urinary urgency and urinary frequency were among the ten most commonly reported symptoms at any level but no pelvic or abdominal symptoms were among the top ten at any level of severity, frequency or duration.

Table 6.5. *Most common symptoms at any level of severity*

Symptom at any level	n	%
Tiredness, fatigue or lack of energy	26,830	52.6
Back ache or pain	23,726	46.5
Leg ache or pain	19,334	37.9
Urinary urgency	18,309	35.9
Indigestion or heartburn	18,117	35.5
Excessive flatulence	17,850	35.0
Weight gain	17,284	33.9
Urinary frequency	16,064	31.5
Shortness of breath	12,201	23.9
Difficulty emptying bowels	11,651	22.8

There were 28,402 (55.7%) respondents who reported symptoms at level 2-3 severity, with a median of 1.0 symptom at this level (range 0-28, IQR 0-3). The types of symptoms most commonly reported at level 2-3 severity were similar to those most commonly reported at any level of severity (Table 6.6). However, shortness of breath was not among the ten most commonly reported symptoms at level 2-3 severity, and abdominal bloating/fullness was the ninth most common symptom at this level of severity.

Table 6.6. *Most common symptoms at level 2-3 severity*

Symptom at level 2-3 severity	n	%
Tiredness, fatigue or lack of energy	10,850	21.3
Back ache or pain	9,535	18.7
Leg ache or pain	8,581	16.8
Urinary urgency	8,581	15.5
Urinary frequency	7,669	15.0
Weight gain	7,374	14.5
Excessive flatulence	7,289	14.3
Indigestion or heartburn	4,706	9.2
Abdominal bloating or fullness	3,622	7.1
Difficulty emptying bowels	3,325	6.5

There were 21,250 (41.7%) respondents who reported any symptoms with a frequency of ≥12 days during the past month and a duration of <12 months (Mdn 0, range 0-25, IQR 0-1). Seven of the 10 most commonly reported symptoms at ≥12 days frequency & <12 months duration were also among the most commonly reported symptoms overall or at level 2-3 severity (Table 6.7). Increased abdominal size was the ninth most common at ≥12 days frequency & <12 months duration but this was not among the ten most common symptoms on the other three approaches.

Table 6.7. *Most common symptoms at ≥12 days & <12 months*

Symptom ≥12 days & <12 months	n	%
Weight gain*	7,600	14.9
Tiredness, fatigue or lack of energy	5,906	11.6
Leg ache or pain	4,303	8.4
Back ache or pain	4,222	8.3
Excessive flatulence	3,101	6.1
Urinary urgency	2,893	5.7
Urinary frequency	2,877	5.6
Pelvic discomfort or pain	2,190	4.3
Increased abdominal size	2,136	4.2
Weight loss*	2,083	4.1

**Reported at <12 months duration only as frequency data not collected*

A total of 12,548 (24.6%) women reported any symptoms with a frequency of ≥12 days, <12 months and level 2-3 severity (Mdn 0, range 0-25, IQR 0-0). The most common symptoms reported at this level of frequency, duration and severity were similar to those reported on the other three approaches, with tiredness/fatigue (6.6%), weight gain (5.5%) and leg ache/pain (4.8%) being the most commonly reported symptoms.

Table 6.8. *Most common symptoms at ≥12 days, <12 months and level 2-3 severity*

Symptom ≥12 days, <12 months & level 2-3 severity	n	%
Tiredness, fatigue or lack of energy	3,376	6.6
Weight gain*	2,781	5.5
Leg ache or pain	2,466	4.8
Back ache or pain	2,377	4.7
Excessive flatulence	1,807	3.5
Urinary frequency	1,708	3.2
Urinary urgency	1,628	3.2
Indigestion or heartburn	1,073	2.1
Pelvic discomfort or pain	1,045	2.0
Abdominal bloating or fullness	1,036	2.0

**Reported at <12 months duration only as frequency data not collected*

Table 6.9 lists the prevalence of key symptoms of ovarian cancer according to the four levels of analysis. Pelvic pain was reported by 22.6% of women at any level of severity, frequency and duration, and was more common than abdominal pain across the four approaches. Surprisingly, feeling full at any level of severity (18.1%) was nearly as common as increased abdominal size (19.9%), and was twice as common as change in appetite (9.5%).

Table 6.9. *Prevalence of key symptoms of ovarian cancer*

Symptom reported	At any level		Level 2-3 severity		≥12 days & <12 months		≥12 days, <12 months & level 2-3 severity	
	n	(%)	n	(%)	n	(%)	n	(%)
Pelvic discomfort or pain	11,507	22.6	3,171	6.2	2,190	4.3	1,045	2.0
Abdominal discomfort or pain	9,804	19.2	2,188	4.3	1,384	2.7	684	1.3
Feeling full quickly	9,208	18.1	2,876	5.6	1,710	3.4	928	1.8
Change in appetite	4,867	9.5	900	1.8	909	1.8	357	0.7
Abdominal bloating or fullness	11,627	22.8	3,622	7.1	1,912	3.7	1,036	2.0
Increased abdominal size	10,146	19.9	3,238	6.3	2,136	4.2	939	1.8
Abdominal mass or lump	2,211	4.3	274	0.5	317*	0.6	126*	0.2
Pelvic bloating or fullness	9,452	18.5	2,853	5.6	1,602	3.1	750	1.5
Change in bowel habit	8,221	16.1	1,416	2.8	1,078	2.1	447	0.9
Urinary frequency	16,064	31.5	7,669	15.0	2,877	5.6	1,708	3.3
Urinary urgency	18,309	35.9	7,928	15.5	2,893	5.7	1,628	3.2

Symptom reported	At any level		Level 2-3 severity		≥12 days & <12 months		≥12 days, <12 months & level 2-3 severity	
Abnormal vaginal bleeding	705	1.4	51	0.1	59	0.1	14	0.03

** Reported at <12 months duration only as frequency data not collected*

6.3.3.1 Prevalence of symptom indices

There were 5,728 (11.2%) women who were positive on the Goff symptom index and 16,829 (33.0%) who were positive on the Lurie index. A total of 1,131 (2.2%) women were positive for symptom Model 4, identified from the pilot analyses in Chapter Five and consisting of abdominal pressure or shortness of breath at level 2-3 severity, ≥12 days and <12 months.

6.3.3.2 Symptom reporting in controls, multimodal and ultrasound group respondents

There was no difference in the proportion of controls, multimodal or ultrasound group women who were positive for symptoms on the four approaches overall (Table 6.10). Approximately 89% of each group reported symptoms at any level of severity, 61% at level 2-3 severity, 53% at ≥12 days frequency and <12 months duration, and 25% at level 2-3 severity, ≥12 days frequency and <12 months duration. There was no difference in the median number of symptoms reported by women in each group on the four approaches (Table 6.10).

There was no association between screening group and the number of women who were positive on Goff symptom index (controls 11.9% *vs*. multimodal 11.4% *vs*. ultrasound 11.2%, *ns*) or Model 4 (controls 2.4% *vs*. multimodal 2.1% *vs*. ultrasound 2.5%, *ns*). However, there was an association between screening group and the Lurie index (controls 35.2% *vs*. multimodal 33.9% *vs*. ultrasound 32.8%, $p < 0.0001$).

There was an association between UKTOCS study group and report of eight individual symptoms at any level of severity, nine at level 2-3 severity, two at ≥12 days frequency and <12 months duration and one when severity level 2-3 was added to this frequency and duration criteria (Table 6.11). Interestingly, and in contrast to the findings of the pilot, control group respondents were slightly more likely to report symptoms. Change in bowel habit at level 2-3 severity, ≥12 days and <12 months was the only symptom which screening group respondents were more likely to report. Differences were statistically significant for the symptoms in Table 6.11, but fairly small in practical terms. For example, the largest difference was observed for abdominal discomfort/pain at any level of severity. This was reported by 21.1% of controls compared to 19.3% of ultrasound group respondents, a difference of 1.8 percentage points.

Table 6.10. *Prevalence of symptoms in controls, multimodal and ultrasound group women*

Symptom reported	n	Controls (% or IQR)	Multimodal Group (% or IQR)	Ultrasound Group (% or IQR)	Overall (% or IQR)
At any level					
Reported	50,553	22,851 (89.3%)	11,170 (89.1%)	11,119 (89.4%)	45,140 (89.3)
Median		5.0 (2.0-10.0)	5.0 (2-0-9.0)	5.0 (2-0-9.0)	5.0 (2.0-10.0)
Range		0-32	0-30	0-30	0-32
Level 2-3 severity					
Reported	46,204	14,433 (61.7)	6,974 (61.0)	6,995 (61.4)	28,402 (61.5)
Median		1.0 (0-3.0)	1.0 (0-3.0)	1.0 (0-3.0)	1.0 (0-3.0)
Range		0-28	0-25	0-25	0-28
≥12 days & <12 months					
Reported	40,372	10,771 (52.6)	5,257 (52.7)	5,222 (52.7)	21,250 (52.6)
Median		1.0 (0-2.0)	1.0 (0-2.0)	1.0 (0-2.0)	1.0 (0-2.0)
Range		0-23	0-25	0-25	0-25

Symptom reported	n	Controls (% or IQR)	Multimodal Group (% or IQR)	Ultrasound Group (% or IQR)	Overall (% or IQR)
≥12 days, <12 months & level 2-3 severity					
Reported	50,553	6,399 (25.0)	3,062 (24.4)	3,087 (24.8)	12,548 (24.8)
Median		0 (0-1.0)	0 (0-0)	0 (0-0)	0 (0-0)
Range		0-22	0-25	0-18	0-25

Note: Overall column included instead of p-values as there were no associations between screening group and symptom reporting

Table 6.11. *Symptoms associated with screening group*

Symptom reported	n	Controls	Multimodal	Ultrasound	p-value
At any level					
Pelvic discomfort or pain	48,542	6,013 (24.5)	2,760 (22.9)	2,734 (22.9)	<0.0001
Abdominal discomfort or pain	48,266	5,140 (21.1)	2,367 (19.8)	2,297 (19.3)	<0.0001
Abdominal bloating or fullness	47,607	6,009 (24.9)	2,832 (24.0)	2,786 (23.8)	0.031
Increased abdominal size	47,559	5,258 (21.8)	2,502 (21.2)	2,386 (20.4)	0.009
Abdominal mass or lump	47,032	1,188 (5.0)	513 (4.4)	510 (4.4)	0.01
Pelvic bloating or fullness	47,595	4,926 (20.5)	2,285 (19.4)	2,241 (19.1)	0.004
Pelvic pressure	48,069	2,933 (12.1)	1,355 (11.4)	1,302 (11.0)	0.007
Pelvic heaviness	48,043	3,248 (13.4)	1,463 (12.3)	1,419 (12.0)	<0.0001
Level 2-3 severity					
Pelvic discomfort or pain	39,385	1,676 (8.4)	793 (8.1)	702 (7.3)	0.003
Abdominal discomfort or pain	38,509	1,164 (6.0)	525 (5.5)	499 (5.2)	0.023

Symptom reported	n	Controls	Multimodal	Ultrasound	p-value
Level 2-3 severity					
Feeling full quickly	38,867	1,527 (7.8)	653 (6.8)	696 (7.2)	0.006
Abdominal bloating or fullness	38,715	1,899 (9.7)	876 (9.1)	847 (8.8)	0.04
Pelvic bloating or fullness	38,248	1,509 (7.8)	693 (7.3)	651 (6.9)	0.02
Excessive flatulence	40,108	3,791 (18.7)	1,743 (17.6)	1,755 (17.7)	0.024
Shortness of breath	38,214	1,527 (7.9)	666 (7.0)	677 (7.1)	0.007
Difficulty emptying the bladder	36,869	388 (2.1)	153 (1.7)	157 (1.7)	0.022
Leg swelling	38,231	1,420 (7.4%)	641 (6.7)	630 (6.7)	0.044
≥12 days & <12 months					
Pelvic discomfort or pain	48,542	1,169 (4.8)	509 (4.2)	512 (4.3)	0.028
Abdominal discomfort or pain	48,266	748 (3.1)	337 (2.8)	299 (2.5)	0.012

Symptom reported	n	Controls	Multimodal	Ultrasound	p-value
≥12 days & <12 months & level 2-3 severity					
Change in bowel habit	48,187	195 (0.8)	114 (1.0)	138 (1.2)	0.003

6.3.3.3 Symptoms reported by screening group respondents compared to controls

An equal proportion of screened women and controls reported symptoms overall at any level (89.3% *vs*. 89.3%), at level 2-3 severity (61.2% *vs*. 61.7%), at ≥12 days frequency and <12 months duration (52.7% *vs*. 52.6%) and at ≥12 days, <12 months and level 2-3 severity (24.6% *vs*. 25.0%). Screened women and controls also reported the same number of symptoms at any level (Mdn 5.0), at level 2-3 severity (Mdn 1.0), at ≥12 days frequency and <12 months duration (Mdn 0) and ≥12 days, <12 months and level 2-3 severity (Mdn 0).

When individual symptoms were investigated, screened women were less likely to report 13 symptoms at any level, 11 at level 2-3 severity, three at ≥12 days frequency and <12 months duration, and one symptom when severity level 2-3 was added to this criteria (Table 6.12). However, differences in the proportion of women in each group who reported symptoms were small and upper confidence intervals were close to one. Change in bowel habit at level 2-3 severity, ≥12 days and <12 months was the only symptom screened women were more likely to report (OR 1.33 95% CI 1.10-1.60).

Table 6.12. *Symptoms reported by screened women vs. controls*

Symptom reported	n	Screening groups n (%)	Controls n (%)	OR (95% CI)	p-value
At any level					
Pelvic discomfort or pain	48,542	5,494 (22.9)	6,013 (24.5)	0.91 (0.88-0.96)	<0.0001
Abdominal discomfort or pain	48,66	4,664 (19.6)	5,140 (21.1)	0.91 (0.87-0.95)	<0.0001
Abdominal bloating or fullness	47,607	5,618 (23.9)	6,009 (24.9)	0.95 (0.91-0.99)	0.009
Increased abdominal size	47,559	4,888 (20.8)	5,252 (21.8)	0.94 (0.90-0.98)	0.008
Abdominal mass or lump	47,032	1,023 (4.4)	1,188 (5.0)	0.88 (0.80-0.96)	0.003
Pelvic bloating or fullness	47,595	4,526 (19.3)	4,926 (20.5)	0.93 (0.89-0.97)	0.001
Pelvic pressure	48,069	2,657 (11.2)	2,933 (12.1)	0.92 (0.87-0.97)	0.003
Pelvic heaviness	48,043	2,882 (12.1)	3,248 (13.4)	0.90 (0.85-0.95)	<0.0001
Excessive flatulence	48,670	8,681 (36.1)	9,169 (37.2)	0.96 (0.92-0.99)	0.017
Pressure on the bladder	47,053	3,513 (15.1)	3,776 (15.8)	0.95 (0.90-0.99)	0.031
Difficulty emptying the bladder	46,834	1,036 (4.5)	1,165 (4.9)	0.91 (0.83-0.99)	0.027

Symptom reported	n	Screening groups n (%)	Controls n (%)	OR (95% CI)	p-value
At any level					
Pain when passing urine	47,097	2,338 (10.0)	2,555 (10.7)	0.81 (0.70-0.94)	0.017
Leg swelling	48,230	5,101 (21.4)	5,441 (22.3)	0.95 (0.91-0.99)	0.017
Level 2-3 severity					
Pelvic discomfort or pain	39,385	1,495 (7.7)	1,676 (8.4)	0.91 (0.84-0.98)	0.008
Abdominal discomfort or pain	38,509	1,024 (5.4)	1,164 (6.0)	0.89 (0.82-0.97)	0.008
Feeling full quickly	38,867	1,349 (7.0)	1,527 (7.8)	0.89 (0.83-0.96)	0.003
Abdominal bloating or fullness	38,715	1,723 (9.0)	1,899 (9.7)	0.92 (0.86-0.98)	0.014
Increased abdominal size	38,287	1,538 (8.1)	1,700 (8.8)	0.92 (0.85-0.99)	0.018
Pelvic bloating or fullness	38,248	1,344 (7.1)	1,509 (7.8)	0.90 (0.84-0.98)	0.01
Excessive flatulence	40,108	3,498 (17.6)	3,791 (18.7)	0.93 (0.89-0.98)	0.007
Shortness of breath	38,214	1,343 (7.1)	1,527 (7.9)	0.88 (0.82-0.95)	0.002
Difficulty emptying the bladder	36,869	310 (1.7)	388 (2.1)	0.81 (0.70-0.94)	0.006

Symptom reported	n	Screening groups n (%)	Controls n (%)	OR (95% CI)	p-value
Level 2-3 severity					
Leg swelling	38,231	1,271 (6.7)	1,420 (7.4)	0.91 (0.84-0.98)	0.013
Abnormal vaginal discharge	36,757	18 (0.1)	33 (0.2)	0.55 (0.31-0.98)	0.04
≥12 days & <12 months					
Pelvic discomfort or pain	48,542	1,021 (4.3)	1,169 (4.8)	0.89 (0.82-0.97)	0.008
Abdominal discomfort or pain	48,266	636 (2.7)	748 (3.1)	0.87 (0.78-0.97)	0.009
Abdominal bloating or fullness	47,607	894 (3.8)	1,018 (4.2)	0.90 (0.82-0.98)	0.020
≥12 days, <12 months & level 2-3 severity					
Pelvic discomfort or pain	48,542	477 (2.0)	568 (2.3)	0.86 (0.76-0.97)	0.014
Change in bowel habit	48,187	252 (1.1)	195 (0.8)	1.33 (1.10-1.60)	0.003

6.3.4 Symptom reporting according to prior awareness of a possible ovarian lesion

There were 1,989 (3.9%) women who were aware of a possible ovarian lesion based on their screen result prior to completing the OCSq. Unaware women (n = 49,018) included all controls (n = 25,814) and screening group women who were returned to annual screening (n = 23,204) after their previous screen.

There was no association between awareness and report of symptoms at any severity, frequency and duration or level 2-3 severity (Table 6.13). However, women who were aware of the possibility of an ovarian lesion were more likely to report symptoms at ≥12 days frequency and <12 months duration (OR 1.18, 95% CI 1.07-1.31) and at level 2-3 severity, ≥12 days and <12 months (OR 1.17, 95% CI 1.06-1.29).

Aware women reported a greater number of symptoms at any level (*Mdn* 6.0 *vs*. *Mdn* 5.0, U = 45,584,146.0, p = 0.003, r = -0.1), although, the effect size indicates a rather negligible increase symptom reporting due to awareness of a possible ovarian lesion. The median number of symptoms reported by aware and unaware women was the same on the other three levels of analysis (Table 6.13).

Women who were aware of the possibility of an ovarian lesion were also more likely to be positive on the Goff (OR 1.31, 95% CI 1.15-1.49) and Lurie indices (OR 1.11, 95% CI 1.01-1.23). There was no association between awareness and women being positive on symptom Model 4.

Table 6.13. *Symptoms reported by aware vs. unaware women*

Symptom reported	n	Aware (% or IQR)	Unaware (% or IQR)	Odds ratio (95% CI)	p-value
At any level					
Reported	50,553	1,771 (90.6)	43,369 (89.2)	ns	ns
Median		6.0 (2.0-10.0)	5.0 (2.0-9.0)	-	0.003
Range		0-32	0-32	-	
Level 2-3 severity					
Reported	46,204	1,123 (62.8)	27,279 (61.4)	ns	ns
Median		1.0 (1.0-2.0)	1.0 (1.0-2.0)	-	-
Range		0-25	0-28	-	
≥12 days & <12 months					
Reported	40,372	894 (56.6)	20,356 (52.5)	1.18 (1.07-1.31)	0.001
Median		1.0 (0-3.0)	1.0 (0-3.0)	-	-
Range		0-23	0-25	-	

Symptom reported	n	Aware (% or IQR)	Unaware (% or IQR)	Odds ratio (95% CI)	p-value
≥12 days, <12 months & level 2-3 severity					
Reported	50,553	542 (27.7)	12,006 (24.7)	1.17 (1.06-1.29)	0.002
Median		0 (0-1.0)	0 (0-0)	-	-
Range		0-22	0-25	-	

Investigation of individual symptoms according to awareness group found significant differences for seven symptoms at any level, five at level 2-3 severity, 14 at ≥12 days frequency and <12 months duration and 12 when severity level 2-3 was added to this frequency and duration criteria (Table 6.14).

Pain when passing urine at level 2-3 severity, ≥12 days and <12 months had the highest odds ratio among aware compared to unaware women (OR 2.18, 95% CI 1.06-4.50), although the lower confidence limit was close to one and the symptom was not associated with awareness on the other levels of analysis. Pelvic discomfort/pain was significant on all four approaches, with odds ratios ranging from 1.22 (95% CI 1.03-1.46) at level 2-3 severity to 1.53 (95% CI 1.27-1.84) at ≥12 days and <12 months. Pelvic pressure was reported by higher proportions of aware women on all four levels, with odds ratios ranging from 1.21 (95% CI 1.06-1.38) at any level of severity to 1.57 (95% CI 1.22-2.02) at ≥12 days and <12 months. Interestingly, abdominal mass/lump was also more likely to be reported by aware women on all four approaches. The symptom had the second highest odds ratio overall at level 2-3 severity, ≥12 days <12 months duration (OR 2.14, 95% CI 1.12-4.09).

Table 6.14. *Report of individual symptoms in aware vs. unaware women*

Symptom reported	n	Aware n (%)	Unaware n (%)	OR (95% CI)	p-value
At any level					
Pelvic discomfort or pain	48,542	534 (28.4)	10,973 (23.5)	1.29 (1.17-1.43)	<0.0001
Abdominal bloating or fullness	47,607	495 (26.8)	11,132 (24.3)	1.14 (1.02-1.26)	0.017
Abdominal mass or lump	47,032	120 (6.6)	2,091 (4.6)	1.45 (1.20-1.75)	<0.0001
Pelvic bloating or fullness	47,595	419 (22.6)	9,033 (19.7)	1.19 (1.06-1.33)	0.003
Pelvic pressure	48,069	253 (13.6)	5,337 (11.5)	1.21 (1.06-1.38)	0.006
Difficulty emptying the bladder	46,834	104 (5.8)	2,097 (4.7)	1.25 (1.02-1.53)	0.031
Tiredness, fatigue or lack of energy	49,076	1,090 (57.3)	2,5740 (54.6)	1.12 (1.02-1.22)	0.020
Level 2-3 severity					
Pelvic discomfort or pain	39,385	148 (9.6)	3,023 (8.0)	1.22 (1.03-1.46)	0.02
Abdominal pressure	37,439	76 (5.2)	1,399 (3.9)	1.35 (1.07-1.72)	0.012
Abdominal mass or lump	36,749	21 (1.5)	253 (0.7)	2.06 (1.32-3.23)	0.001

Symptom reported	n	Aware n (%)	Unaware n (%)	OR (95% CI)	p-value
Level 2-3 severity					
Pelvic pressure	38,231	88 (5.9)	1,596 (4.3)	1.39 (1.12-1.74)	0.003
Urinary urgency	39,192	341 (22.4)	7,587 (20.1)	1.14 (1.01-1.29)	0.033
≥12 days & <12 months					
Pelvic discomfort or pain	48,542	124 (6.6)	2,066 (4.4)	1.53 (1.27-1.84)	<0.0001
Abdominal bloating or fullness	47,607	95 (5.1)	1,817 (4.0)	1.31 (1.06-1.62)	0.012
Abdominal pressure	47,237	28 (1.5)	395 (0.9)	1.76 (1.20-2.59)	0.004
Increased abdominal size	47,559	110 (5.9)	2,026 (4.4)	1.36 (1.12-1.66)	0.002
Abdominal mass or lump*	47,032	21 (1.2)	296 (0.7)	1.76 (1.12-2.74)	0.011
Pelvic bloating or fullness	47,595	81 (4.4)	1,521 (3.3)	1.33 (1.06-1.67)	0.015
Pelvic pressure	48,069	66 (3.6)	1,063 (2.3)	1.57 (1.22-2.02)	<0.0001
Pelvic heaviness	48,043	62 (3.3)	986 (2.1)	1.58 (1.22-2.05)	0.001
Change in bowel habit	48,187	57 (3.1)	1,021 (2.2)	1.40 (1.07-1.84)	0.014

Symptom reported	n	Aware n (%)	Unaware n (%)	OR (95% CI)	p-value
≥12 days & <12 months					
Excessive flatulence	48,670	157 (8.4)	2,944 (6.3)	1.36 (1.15-1.61)	<0.0001
Urinary frequency	47,427	136 (7.4)	2,741 (6.0)	1.25 (1.04-1.49)	0.015
Back ache or pain	49,033	198 (10.4)	4,024 (8.5)	1.25 (1.07-1.45)	0.004
Tiredness, fatigue or lack of energy	49,076	271 (14.2)	5,635 (11.9)	1.22 (1.07-1.40)	0.003
Weight gain*	48,556	328 (17.5)	7,272 (15.6)	1.15 (1.02-1.30)	0.021
≥12 days, <12 months & level 2-3 severity					
Pelvic discomfort or pain	48,542	55 (2.9)	990 (2.1)	1.39 (1.06-1.83)	0.018
Abdominal bloating or fullness	47,607	53 (2.9)	983 (2.1)	1.34 (1.01-1.78)	0.038
Abdominal pressure	47,237	55 (3.0)	802 (1.8)	1.72 (1.30-2.26)	<0.0001
Abdominal mass or lump*	47,032	10 (0.5)	116 (0.3)	2.14 (1.12-4.09)	0.018
Pelvic bloating or fullness	47,595	43 (2.3)	707 (1.5)	1.51 (1.11-2.06)	0.009
Pelvic pressure	48,069	35 (1.9)	484 (1.0)	1.82 (1.28-2.57)	0.001

Symptom reported	n	Aware n (%)	Unaware n (%)	OR (95% CI)	p-value
≥12 days, <12 months & level 2-3 severity					
Pelvic heaviness	48,043	33 (1.8)	432 (0.9)	1.92 (1.34-2.74)	<0.0001
Pain before, during or after opening bowels	48,262	33 (1.8)	459 (1.0)	1.81 (1.27-2.58)	0.001
Urinary frequency	47,427	86 (4.7)	1,622 (3.6)	1.33 (1.06-1.66)	0.012
Urinary urgency	47,689	88 (4.8)	1,540 (3.4)	1.44 (1.16-1.80)	0.001
Pressure on the bladder	47,053	39 (2.1)	583 (1.3)	1.68 (1.21-2.33)	0.002
Pain when passing urine	47,097	8 (0.4)	92 (0.2)	2.18 (1.06-4.50)	0.032

** Reported at <12 months duration only as frequency data not collected*

6.3.4.1 Symptoms reported by screening group women vs. controls in the unaware group

Symptoms were investigated in screening group women compared to controls among the 49,018 unaware women. These analyses found no association between screening group and report of symptoms overall (89.1% *vs*. 89.3%, *ns*), at level 2-3 severity (61.1% *vs*. 61.7%, *ns*), ≥12 days frequency and <12 months duration (52.3% *vs*. 52.6%, *ns*), or ≥12 days, <12 months and level 2-3 severity (24.4% *vs*. 25.0%, *ns*). However, a slightly higher proportion of controls were positive on the Goff (11.9% *vs*. 11.0%, $\chi^2(1) = 8.4$, $p = 0.004$), and Lurie (35.2% *vs*. 33.1%, $\chi^2(1) = 22.6$, $p < 0.0001$) indices. There was no association between screening group and symptom Model 4 (2.3% *vs*. 2.4%, *ns*).

When individual symptoms were investigated, odds ratios were significant between the groups for 16 symptoms at any level, 13 at level 2-3 severity, seven at ≥12 days and <12 months and four at level 2-3 severity, ≥12 days and <12 months (Table 6.15). However, it must be noted that odds ratios were close to one for many symptoms, indicating little practical difference between the groups for these symptoms. Screening group women were more likely to report only one symptom, change in bowel habit (OR 1.31, 95% CI 1.08-1.58) at level 2-3 severity, ≥12 days and <12 months.

Table 6.15. *Report of individual symptoms in unaware screened women vs. unaware controls*

Symptom reported	n	Screening groups n (%)	Controls n (%)	OR (95% CI)	p-value
At any level					
Pelvic discomfort or pain	46,665	4,960 (22.4)	6,013 (24.5)	0.89 (0.85-0.93)	<0.0001
Abdominal discomfort or pain	46,398	4,262 (19.4)	5,140 (21.1)	0.90 (0.86-0.94)	<0.0001
Abdominal bloating or fullness	45,757	5,123 (23.7)	6,009 (24.9)	0.93 (0.89-0.97)	0.002
Abdominal pressure	45,400	2,638 (12.3)	3,095 (12.9)	0.94 (0.89-0.99)	0.031
Increased abdominal size	45,709	4,463 (20.6)	5,258 (21.8)	0.93 (0.89-0.97)	0.002
Abdominal mass or lump	45,206	903 (4.2)	1,188 (5.0)	0.84 (0.77-0.92)	<0.0001
Pelvic bloating or fullness	45,741	4,107 (19.0)	4,926 (20.5)	0.91 (0.87-0.95)	<0.0001
Pelvic pressure	46,213	2,404 (11.0)	2,933 (12.1)	0.90 (0.85-0.95)	<0.0001
Pelvic heaviness	46,185	2,624 (12.0)	3,248 (13.4)	0.88 (0.84-0.93)	<0.0001
Change in bowel habit	46,324	3,641 (16.6)	4,231 (17.4)	0.95 (0.90-0.99)	0.028
Excessive flatulence	46,795	7,961 (36.0)	9,169 (37.2)	0.95 (0.91-0.98)	0.006

Symptom reported	n	Screening groups n (%)	Controls n (%)	OR (95% CI)	p-value
At any level					
Pressure on the bladder	45,232	3,231 (15.1)	3,776 (15.8)	0.74 (0.70-0.78)	0.027
Difficulty emptying the bladder	45,027	932 (4.4)	1,165 (4.9)	0.89 (0.81-0.97)	0.007
Pain when passing urine	45,273	2,136 (10.0)	2,555 (10.7)	0.92 (0.87-0.98)	0.008
Back ache or pain	47,137	10, 658 (47.7)	12,114 (48.8)	0.96 (0.92-0.99)	0.016
Leg swelling	46,368	4,687 (21.3)	5,441 (22.3)	0.94 (0.90-0.99)	0.012
Level 2-3 severity					
Pelvic discomfort or pain	37,848	1,347 (7.5)	1,676 (8.4)	0.89 (0.82-0.95)	0.001
Abdominal discomfort or pain	37,005	935 (5.3)	1,164 (6.0)	0.88 (0.81-0.96)	0.005
Feeling full quickly	37,364	1,237 (7.0)	1,527 (7.8)	0.89 (0.82-0.96)	0.003
Abdominal bloating or fullness	37,191	1,576 (8.9)	1,899 (9.7)	0.91 (0.85-0.98)	0.009
Increased abdominal size	36,807	1,410 (8.1)	1,700 (8.8)	0.72 (0.67-0.78)	0.014
Pelvic bloating or fullness	36,740	1,217 (7.0)	1,509 (7.8)	0.89 (0.82-0.96)	0.003

Symptom reported	n	Screening groups n (%)	Controls n (%)	OR (95% CI)	p-value
Level 2-3 severity					
Pelvic heaviness	36,620	671 (3.9)	833 (4.3)	0.89 (0.80-0.99)	0.025
Excessive flatulence	38,547	3,194 (17.5)	3,791 (18.7)	0.92 (0.88-0.97)	0.002
Shortness of breath	36,728	1,226 (7.0)	1,527 (7.9)	0.91 (0.84-0.98)	0.001
Urinary frequency	37,026	3,380 (19.3)	3,968 (20.3)	0.94 (0.89-0.98)	0.01
Difficulty emptying the bladder	35,441	282 (1.7)	388 (2.1)	0.80 (0.68-0.93)	0.004
Leg swelling	36,750	1,163 (6.7)	1,420 (7.4)	0.90 (0.83-0.97)	0.009
Abnormal vaginal discharge	35,331	14 (0.1)	33 (0.2)	0.47 (0.25-0.87)	0.014
≥12 days & <12 months					
Pelvic discomfort or pain	46,665	897 4.1)	1,169 4.8)	0.85 (0.77-0.92)	<0.0001
Abdominal discomfort or pain	46,398	748 (3.1)	577 (2.6)	0.76 (0.77-0.95)	0.005
Abdominal bloating or fullness	45,757	799 (3.7)	1,018 (4.2)	0.87 (0.79-0.96)	0.004
Abdominal pressure	45,400	341 (1.6)	461 (1.9)	0.82 (0.71-0.94)	0.006

Symptom reported	n	Screening groups n (%)	Controls n (%)	OR (95% CI)	p-value
≥12 days & <12 months					
Pelvic pressure	46,213	466 (2.1)	597 (2.5)	0.86 (0.76-0.98)	0.019
Excessive flatulence	46,795	1,332 (6.0)	1,612 (6.5)	0.92 (0.85-0.99)	0.02
Shortness of breath	45,443	795 (3.7)	981 (4.1)	0.90 (0.82-0.99)	0.027
≥12 days, <12 months & level 2-3 severity					
Pelvic discomfort or pain	46,665	422 (1.9)	568 (2.3)	0.82 (0.72-0.93)	0.002
Abdominal bloating or fullness	45,757	426 (2.0)	557 (2.3)	0.85 (0.75-0.96)	0.012
Increased abdominal size	45,709	390 (1.8)	502 (2.1)	0.86 (0.76-0.99)	0.031
Change in bowel habit	46,324	229 (1.0)	195 (0.8)	1.31 (1.08-1.58)	0.006

6.3.5 Symptoms reported to GPs

A total of 23,271 (45.6%) women discussed at least one of the 32 symptoms with a GP during the past three months, with a median of 3.0 symptoms (range 1-29, IQR 1-6) being discussed by these women. The three symptoms most commonly reported to GPs were backache/pain, tiredness/fatigue and leg swelling (Table 6.16).

Table 6.16. *Symptoms most commonly reported to GPs*

Symptom at any level	n	%
Back ache or pain	8,198	16.1
Tiredness, fatigue or lack of energy	7,205	14.1
Leg swelling	6,544	12.8
Leg ache or pain	6,247	12.2
Urinary frequency	5,801	11.4
Shortness of breath	5,419	10.6
Abdominal discomfort or pain	4,869	9.5
Pain when passing urine	4,357	8.5
Indigestion or heartburn	4,276	8.4
Urinary urgency	3,941	7.7

A substantially higher proportion of women who were Goff index positive (64.9% *vs*. 44.0%, $\chi^2(1) = 892.9$, $p < 0.0001$) or Lurie index positive (65.7% *vs*. 36.4%, $\chi^2(1) = 3803.8$, $p < 0.0001$) visited their GP about symptoms during the past three months compared to women who were negative on these indices.

Table 6.17 lists the number of women who reported symptoms and the proportion who consulted a GP about the symptom during the past three months. Shaded boxes denote the largest proportion of women who consulted their GP about symptoms across the four approaches. Women with pain when passing urine at any level of severity were most likely to consult their GP (91.7%), followed by

women with an abdominal mass/lump (82.6%) and abnormal vaginal bleeding (73.7%).

Women were more likely to consult their GP when symptoms were at level 2-3 severity (16 of the 32 symptoms), although they were more likely to consult their GP for 11 of the 32 symptoms at any level of severity. Women were least likely to consult their GP when symptoms were experienced at ≥12 days frequency and <12 months duration.

Table 6.17. *Symptoms most likely to be reported to GPs*

Symptom reported	At any level		Level 2-3 severity		≥12 days & <12 months		≥12 days, <12 months & level 2-3 severity	
	n	Consulted GP n (%)	n	Consulted GP n (%)	n	Consulted GP n (%)	n	Consulted GP n (%)
Pelvic discomfort or pain	10,592	3,669 (34.6)	2,963	1,343 (45.3)	2,073	815 (39.3)	998	496 (49.7)
Abdominal discomfort or pain	8,722	4,869 (55.8)	2,039	1,108 (54.3)	1,304	624 (47.9)	656	372 (56.7)
Indigestion or heartburn	15,380	4,276 (27.8)	4,265	1,587 (37.2)	1,802	476 (26.4)	1,023	298 (29.1)
Nausea or vomiting	5,080	2,358 (46.4)	616	317 (51.5)	486	207 (42.6)	211	108 (51.2)
Feeling full quickly	7,767	1,676 (21.6)	2,584	664 (25.7)	1,579	249 (15.8)	863	161 (18.7)
Change in appetite	4,326	2,437 (56.3)	3,879	332 (41.4)	864	173 (20.0)	346	104 (30.1)
Abdominal bloating or fullness	9,847	2,372 (24.1)	3,254	1,045 (32.1)	1,781	400 (22.5)	979	274 (28.0)
Abdominal pressure	5,093	2,556 (50.2)	1312	565 (43.1)	795	239 (30.1)	397	145 (36.5)
Increased abdominal size	8,338	1,151 (13.8)	2,839	452 (15.9)	1,967	210 (10.7)	871	133 (15.3)
Abdominal mass or lump	2,120	1,752 (82.6)	251	117 (46.6)	275*	99 (36.0)	113*	52 (46.0)

Symptom reported	At any level		Level 2-3 severity		≥12 days & <12 months		≥12 days, <12 months & level 2-3 severity	
Pelvic bloating or fullness	8,164	2,202 (27.0)	2,565	824 (32.1)	1,470	346 (23.5)	704	206 (29.3)
Pelvic pressure	4,877	1,904 (39.0)	1,536	754 (49.1)	1,039	370 (35.6)	487	229 (47.0)
Pelvic heaviness	5,399	2,192 (40.6)	1,431	559 (39.1)	971	255 (26.3)	435	138 (31.7)
Pain before, during or after opening bowels	7,975	3,185 (39.9)	1,868	755 (40.4)	1,028	323 (31.4)	467	179 (38.3)
Difficulty emptying bowels	9,709	2,722 (28.0)	2,916	924 (31.7)	1,387	300 (21.6)	690	179 (25.9)
Change in bowel habit	7,158	3,823 (53.4)	1,255	561 (44.7)	1,015	247 (24.3)	427	137 (32.1)
Excessive flatulence	1,4890	3,838 (25.8)	6,457	1,479 (22.9)	2,898	411 (14.2)	1,708	285 (16.7)
Shortness of breath	10,530	5,419 (51.5)	2,602	1,438 (55.3)	1,723	638 (37.0)	737	352 (47.8)
Urinary frequency	13,222	5,801 (43.9)	6,540	2,550 (39.0)	2,672	789 (29.5)	1,619	572 (35.3)
Urinary urgency	14,723	3,941 (26.8)	6,831	1,896 (27.8)	2,653	580 (21.9)	1,526	381 25.0%
Pressure on bladder	5,877	1,607 (27.3)	2,282	674 (29.5)	1,225	275 (22.4)	568	158 (27.8)
Difficulty emptying bladder	1,846	578 (31.3)	606	181 (29.9)	400	103 (25.8)	146	49 (33.6)
Pain when passing urine	4,749	4,357 (91.7)	305	209 (68.5)	213	111 (52.1)	95	67 (70.5)

Symptom reported	At any level		Level 2-3 severity		≥12 days & <12 months		≥12 days, <12 months & level 2-3 severity	
Back ache or pain	20,511	8,198 (40.0)	8,667	4,080 (47.1)	3,928	1,355 (34.5)	2,263	945 (41.8)
Leg ache or pain	16,481	6,247 (37.9)	7,699	3,514 (45.6)	4,008	1,381 (34.5)	2,342	986 (42.1)
Leg swelling	9,383	6,544 (69.7)	2,410	1,473 (61.1)	1,311	653 (49.8)	626	386 (61.7)
Tiredness, fatigue or lack of energy	22,224	7,205 (32.4)	9,654	3,443 (35.7)	5,569	1,335 (24.0)	3,243	935 (28.8)
Weight gain	13,896	2,991 (21.5)	6,326	1,229 (19.4)	6,714*	967 (14.4)	2,480*	452 (18.2)
Weight loss	2,836	922 (32.5)	942	338 (35.9)	1,831*	557 (30.4)	516*	223 (43.2)
Abnormal vaginal bleeding	639	471 (73.7)	42	27 (64.3)	56	32 (57.1)	14	10 (71.4)
Abnormal vaginal discharge	1,148	324 (28.2)	180	75 (41.7)	366	101 (27.6)	78	31 (39.7)
Pain during or after sexual intercourse	2,033	818 (40.2)	485	138 (28.5)	69	8 (11.6)	23	5 (21.7)

*Note: Shaded cells indicate the largest proportion of women who reported the symptom to a GP across the four approaches to analysis. *Reported at <12 months duration only as frequency data not collected.*

6.3.5.1 Symptoms and depression screening status

There were 12,451 (24.4%) women who responded yes to the question, 'During the past month have you often been bothered by feeling down, depressed or hopeless?' and 8,500 (16.7%) women who responded yes to, 'During the past month have you often been bothered by little interest or pleasure doing things?' A total of 13,733 (26.9%) women responded yes to one or both questions, indicating they were depression screen positive, 28,983 (56.8%) answered no to both questions, indicating they were depression screen negative, while 8,291 (16.3%) women did not respond to both questions.

Women who were depression screen positive were more likely to report any symptoms overall (OR 7.30, 95% CI 6.49-8.22), symptoms at level 2-3 severity (OR 4.39, 95% CI 4.18-4.62), at ≥12 days and <12 months (OR 1.89, 95% CI 1.81-1.98) and when level 2-3 severity was added to this frequency and duration criteria (OR 2.79, 95% CI 2.67-2.92) (Table 6.18). Depression screen positive women were also more likely to be positive on the Goff (OR 2.59, 95% CI 2.44-2.75) and Lurie indices (OR 3.44, 95% CI 3.39-3.59), and Model 4 (described in Chapter Five) (OR 4.64, 95% CI 4.03-5.33). There was no association between awareness of the possibility of an ovarian lesion and depression screening positive status (32.8% *vs.* 32.1%, ns).

The median number of symptoms reported by depression screen positive women was more than double the number reported by depression screen negative women at any level (*Mdn* 9.0 *vs*. *Mdn* 4.0, $U = 97495120.5$, $p < 0.0001$, $r = -0.41$), at level 2-3 severity (*Mdn* 3.0 *vs*. *Mdn* 1.0, $U = 98464780.5$, $p < 0.0001$, $r = -0.38$) and at ≥12 days frequency and <12 months duration (*Mdn* 1.0 *vs*. *Mdn* 0, $U = 109514721.5$, $p < 0.0001$, $r = -0.19$). Effect sizes for symptoms at any level and level 2-3 severity indicate a moderate increase in the number of symptoms associated with depression screen positive status, while the effect size for symptoms at ≥12 days and <12 months indicates a small increase in the number of symptoms associated with depression screen positive status.

Table 6.18. *Symptoms reported by depression screen positive vs. depression screen negative women*

Symptom reported	n	Depression screen positive (% or IQR)	Depression screen negative (% or IQR)	Odds ratio (95% CI)	p-value
At any level					
Reported	42,624	13,413 (97.8)	24,752 (85.6)	7.30 (6.49-8.22)	<0.0001
Median		9.0 (5.0-14.0)	4.0 (1.0-7.0)	-	<0.0001
Range		0-32	0-28	-	
Level 2-3 severity					
Reported	40,475	10,473 (80.7)	13,410 (48.8)	4.39 (4.18-4.62)	<0.0001
Median		3.0 (1.0-6.0)	0 (0-2.0)	-	<0.0001
Range		0-28	0-25	-	

Symptom reported	n	Depression screen positive (% or IQR)	Depression screen negative (% or IQR)	Odds ratio (95% CI)	p-value
≥12 days & <12 months					
Reported	34,860	8,025 (63.8)	10,765 (48.3)	1.89 (1.81-1.98)	<0.0001
Median		1.0 (0-3.0)	0 (0-1.0)	-	<0.0001
Range		0-25	0-21	-	
≥12 days, <12 months & level 2-3 severity					
Reported	42,624	5,472 (39.9)	5,555 (19.2)	2.79 (2.67-2.92)	<0.0001
Median		0 (0-1.0)	0 (0-0)	-	<0.0001
Range		0-25	0-16	-	

Analysis of individual symptoms found no association between depression screening status and report of abnormal vaginal bleeding at level 2-3 severity and at ≥12 days, <12 months and level 2-3 severity (appendix 29). All other symptoms were strongly associated with depression screening status, with significance values of all but one symptom being < 0.0001. Pain during or after sexual intercourse at level 2-3 severity, ≥12 days frequency and <12 months duration was $p = 0.008$.

All symptoms which were associated with depression screening status were more likely to be reported by depression screening positive women. The highest odds ratio was for pain when passing urine at any level of severity (OR 10.84, 95% CI 9.67-12.14) and the lowest odds ratio was for weight gain at <12 months duration (frequency data not collected), (OR 1.71, 95% CI 1.62-1.80). Depression screen positive women were more likely to report key symptoms of ovarian cancer including pelvic pain (OR 2.56, 95% CI 2.33-2.81), abdominal pain (OR 2.82, 95% CI 2.51-3.18), abdominal bloating/fullness (OR 2.97, 95% CI 2.69-3.28) and increased abdominal size (OR 2.91, 95% CI 2.66-3.19) at ≥12 days frequency and <12 months duration.

6.4 Discussion

Findings relating to symptom prevalence, symptoms associated with prior awareness of a possible ovarian lesion, GP consultations for symptoms and symptoms associated with depression screening status parallel the findings of the pilot OCSq, presented in Chapter Five. However, findings on symptom reporting in women receiving ovarian cancer screening compared to controls contrast with the results of Chapter Five.

Prevalence of symptoms

The overall prevalence of symptoms was high (89%) considering the cohort was comprised of apparently healthy postmenopausal women. It is striking that this proportion is similar to the 90-95% of women with ovarian cancer who report symptoms.[120] In contrast, 42-52% of community-based controls have been previously found to report ovarian cancer associated symptoms during the 12 months prior to interview.[16-17] Unfortunately, Goff *et al.*[23] do not provide information on the proportion of symptomatic women among those receiving screening in the Ovarian Cancer Early Detection Study (OCEDS), although the median of 5.0 symptoms in this group is equivalent to that among OCSq respondents.

The large proportion of symptomatic women may be due to the older age of UKCTOCS volunteers compared to the Vine *et al.*[16] and Olson *et al.*[17] studies, where ≥50% of controls were aged under 50 years. However, a more likely explanation is enhanced symptom recall over the one-week reference period and an acquiescent effect arising from a comprehensive symptoms checklist.[140-141 147 151 160 238] This is corroborated by research which recruited UKCTOCS volunteers as controls in a case-control study of ovarian cancer symptoms, where a shorter symptom checklist and 12 month reference period found a considerably reduced proportion (62%) of symptomatic controls.[34]

These findings emphasise the need to add severity, frequency and duration criteria to symptoms in order to enhance the power of the study to detect significant differences in key symptoms in ovarian cancer cases compared to controls in

follow-up analyses. Restricting analyses to symptoms at level 2-3 reduced the prevalence of key symptoms of ovarian cancer within the cohort. Pelvic pain at any level of severity, frequency or duration was reported by 23% of women, while 6% reported the symptom at level 2-3 severity and 4% at ≥12 days frequency and <12 months duration. Similarly, feeling full was reduced from 18% to 6% and 3%. Adding severity or frequency and duration criteria to symptoms in this way may increase the positive predictive value of symptoms in the final analyses by reducing their prevalence among women who do not develop ovarian cancer.

The imperative to include symptom severity or frequency and duration criteria in the final analyses is underscored by the ubiquity of some key symptoms of ovarian cancer among healthy women. For example, a large postal survey in the UK study found 61% of women reported urinary urgency,[239] while US research indicates 24% of community-dwelling women report abdominal discomfort/pain and 19% report abdominal bloating or distension.[240]

Symptom indices

Follow-up data on ovarian cancer diagnoses were not available at the time of analysis, therefore it was not possible to calculate the sensitivity and specificity of symptom indices. However, preliminary findings indicate the Goff index may have lower specificity among OCSq respondents as 11% of women were positive on the index compared to just 1% of women aged ≥50 years attending primary care in the Goff research.[23] Alternatively, 33% of OCSq respondents were positive on the four-symptom Lurie index compared to 47% in the original study.[25]

Sixty-five percent of women who were positive on the Goff index had attended primary care for any OCSq symptoms in the past three months. If, as ovarian cancer advocacy groups are urging, all women who were positive on the Goff index consulted their doctor, this would represent a 54% increase in consultations (from 3,719 to 5,728 women) among this group. This increase may have serious time and resource implications when considered at a population level.

Impact of screening and awareness of an ovarian lesion on symptom reporting

Findings relating to symptom reporting in women receiving ovarian cancer screening compared to controls contrast with the findings of the pilot OCSq. While there was no difference between controls and screened women for report of symptoms overall, or the number of symptoms reported at each level of analysis, controls were more likely to report key symptoms of ovarian cancer. This finding may have arisen due to the different methods used. Forty-seven percent of women invited to take part in the pilot were attending Level 2 screening and therefore had heightened awareness of the possibility of an ovarian lesion. In contrast, women in the final study were posted the OCSq independently of screening appointment letters. Perhaps the OCSq raised anxiety among controls who were not reassured by the results of previous screening investigations, resulting in higher levels of some symptoms.

Controls were more likely than screened women to report abdominal/pelvic pain, abdominal and pelvic bloating/fullness, increased abdominal size, abdominal mass/lump and feeling full. While these differences were statistically significant, they were fairly meaningless in practical terms as there was less then one percentage point between the proportion of controls and screened women for the majority of symptoms.

Women who were aware of the possibility of an ovarian lesion were more likely to report any symptoms at ≥12 days frequency and <12 months duration or when level 2-3 severity was added to this criteria. They were more likely to be positive on the Goff index and to report pelvic pain, pelvic pressure, pelvic heaviness, pelvic and abdominal bloating/fullness, abdominal mass/lump, increased abdominal size, urinary frequency or urgency and pressure on bladder. However, the odds ratios for these symptoms were fairly small.

Awareness of the possibility of an ovarian lesion will be investigated according to study outcome in the final analyses. This should answer the question whether symptoms reported by aware women are associated with diagnosis of cancer or awareness of the possibility of abnormality.

GP consultations

In contrast to the pilot, several symptoms were more likely to be reported to GPs when experienced at any level of severity, rather than level 2-3 severity. These included change in appetite, abdominal pressure, pelvic heaviness, change in bowel habit and excessive flatulence, which seem less salient than flag symptoms such as abnormal vaginal bleeding. The reasons for this are unclear, although the majority of respondents in the pilot were scheduled to attend screening within approximately six weeks. Perhaps this offered women some reassurance that they could discuss minor symptoms with screening staff during their appointment. The absence of an impending screening appointment in the finalised OCSq may have increased the willingness of women to seek medical advice for certain symptoms, even when these were experienced at a low level of severity.

Symptoms associated with depression screening status

The proportion of women who screened positive for depression (27%) was equal to the pilot. Women who were depression screen positive were 7.30 times more likely to report symptoms and 4.39 times more likely to report symptoms at level 2-3 severity. They were also 2.59 times more likely to be positive on the Goff index and 3.44 times more likely to be positive on the Lurie index. Similarly, to Goff *et al.*[23], depression screen positive women reported a greater number of symptoms overall, and at higher severity. Surprisingly, and in contrast to the pilot, there was no association between awareness of the possibility of an ovarian lesion and depression screening positive status. However, this may be due to the OCSq being sent separately to screening appointments. In contrast, pilot questionnaires were posted with appointment letters, including letters requesting the women to attend repeat screening due to an abnormality detected on annual screening.

Women who were depression screen positive were more likely to report all 32 symptoms at any level of severity and at a frequency of ≥12 days and <12 months duration, although there was no association between depression status and abnormal vaginal bleeding at level 2-3 severity or when frequency and duration was added to this severity criteria. These findings parallel wider research which

has indicated depression and negative affectivity is associated with increased attention to and reporting of, symptoms.[37 39 241-243]

Study strengths

The fundamental strength of the study is collection of genuinely prospective symptoms data. This is the first study to attempt this methodology. Symptoms reported by apparently healthy women will be correlated with diagnosis of benign and malignant ovarian/fallopian tube tumours in the 18 months following completion of the questionnaire. Women will be excluded from the final analyses if they completed the OCSq after being clinically assessed by a gynaecological oncologist. This will eliminate recall bias from the study.

A second core strength of the study is its direct access to UKCTOCS screening, surgery and histopathology data, and regular updates of cancer diagnoses from regional cancer registries. This will reduce misclassification bias when follow-up analyses are conducted and enable accurate calculation of the sensitivity and specificity of various symptom complexes.

Other strengths of the study include the use of a comprehensive, valid and reliable questionnaire, and the recruitment of a large sample of women. Demographics and co-morbidities were equivalent across the screening groups, indicating that differences in symptom reporting were unlikely to be due to differences in age, education levels or pre-existing conditions.

Study limitations

The response rate at the time of data analysis was 51%, although the final figure will be higher as questionnaires were still being received at the time of writing. While the 51% response rate is lower than the 60% generally considered acceptable for questionnaires, it is substantially higher than the average 45% response rate previously described for UK postal health surveys,[235] and the 26% response rate for a large prospective study of lifestyle and cancer risk conducted in the US.[244] The one other ovarian cancer symptoms study which utilised postal questionnaires, conducted by Goff *et al.*[13], achieved a substantially higher response rate of 88%. However, the Goff study population was comprised of women diagnosed with ovarian cancer, a group which is likely to have greater

motivation to participate. While reminder telephone calls and letters have been found to increase response rates to approximately 70-80%,[245-246] this was not feasible or affordable due to the large sample size.

The age of the UKCTOCS study population needs to be taken into account when assessing the response rate. The average age of respondents was 66 years with a range of 54-82 years. A postal survey of physical activity among a similar age group in England found a comparatively lower response rate of 37.9%.[247] Previous research has indicated that older people are more likely to have difficulty comprehending questionnaires.[248] However, pilot of the OCSq proved its acceptability and readability, with small percentages of women reporting that they had difficulty responding to items. We anticipated increased prevalence of visual problems among the study population and would have liked to compensate for it by increasing the font size of the OCSq. However, this was not possible without either increasing the number of pages or changing the page format to a less user-friendly landscape style.

A second limitation of the research was recruitment of women who were already participating in an ovarian cancer screening study. This group are likely to have higher levels of knowledge about the symptoms of ovarian cancer compared to the general population of postmenopausal women, which may lead to increased attention to key symptoms and over-reporting bias. Evidence of this tendency may be observed in the finding that 18% reported feeling full, whereas other research has found only 3% of community-based controls report the symptom.[17] However, knowledge of this symptom may also be due to recent advocacy group awareness campaigns and media coverage of the UK consensus statement on ovarian cancer symptoms.

Research has indicated that approximately 47% of women in the general population are aware of increased abdominal size/bloating or feeling full as symptoms of ovarian cancer and 26% are aware of urinary frequency or urgency.[249] However, these findings are based upon an internet survey which is likely to have recruited younger, well educated women who have the knowledge and skills to allow them to readily access health information. Knowledge of the

symptoms of ovarian cancer among the general population of postmenopausal women in the UK is likely to be substantially lower.

A third limitation of the research was the higher response rate among women receiving screening compared to controls. Findings from the pilot indicated that this may result in over-reporting bias, due to screened women having greater awareness of symptoms. However, this may not be the case as the proportion of women who reported symptoms in the two groups was very similar in the finalised OCSq.

6.5 Summary

This chapter presented baseline data from the OCSq survey of 100,000 postmenopausal women. The prevalence of key symptoms of ovarian cancer was surprisingly high, with approximately one in five women reporting pelvic or abdominal discomfort/pain, feeling full or bloating/increased abdominal size during the past week. Moreover, one in ten women were positive on the Goff symptom index, which casts doubt upon the usefulness of symptom indices among community-based postmenopausal women. Similarly to the pilot, depression screening status and symptom reporting were strongly associated, with depression screening positive women more likely to report symptoms, and a greater number of symptoms, compared to those who screened negative for depression. The relationship between awareness of a possibility of an ovarian lesion and symptom reporting was weaker than in the pilot, nevertheless, women who were aware of the possibility of an abnormality were more likely to report key symptoms of ovarian cancer and were more likely to be positive on the Goff symptom index.

Chapter Seven – Discussion and Future Research Plans

7.0 Introduction

The research presented in this thesis set out to prospectively identify type, severity, frequency and duration of symptoms in a large cohort of apparently healthy postmenopausal women, then to correlate symptoms with diagnosis of ovarian cancer upon follow-up. The research is currently ongoing and while the goal of prospectively recording symptoms was achieved, this data has yet to be correlated with diagnosis of ovarian cancer, as insufficient time has passed for this information to become available. Though answers to fundamental questions about the pattern of symptoms prior to diagnosis of ovarian cancer are awaited, a number of important findings have resulted from this phase of the work and these are discussed in this chapter.

7.1 Main findings

7.1.1 The need for a validated ovarian cancer symptoms measure

Preliminary searches of the literature confirmed the absence of an existing, properly validated, questionnaire specifically designed to collect data on symptoms of ovarian cancer. While two groups described limited validation processes,[7 70] they did not provide full details of their findings or copies of questionnaires when requested. After learning this information we had two options. We could have expedited the research by adapting an existing questionnaire which had been supplied by another group, or we could follow a robust though lengthy process of developing and validating our own questionnaire. We chose the latter as a review of the literature generated a list of 349 symptoms described as associated with ovarian cancer, yet a maximum of 23 symptoms were listed in questionnaires used by other groups. The strong correlation between the number of symptoms listed in questionnaires and the median number of symptoms reported by women (described in Chapter Two) underscored the importance of ensuring questionnaire comprehensiveness whilst

avoiding inclusion of symptoms with low specificity to the disease. To achieve this goal we utilised rigorous questionnaire development methods described by the EORTC.

Development of the OCSq started with the very first literature search in October 2006 and concluded with final formatting in February 2009. The process involved experts in the fields of gynaecological oncology and questionnaire design, as well as women living with ovarian cancer. Validation of the OCSq confirmed the questionnaire's face and content validity and its reliability among postmenopausal women. This affords some degree of assurance that the symptoms data collected in the finalised study will be sufficiently robust to accurately identify prospective symptoms of ovarian cancer.

7.1.2 Symptoms reported retrospectively

The retrospective component of the research included symptoms data from a total of 213 women: 188 Ovacome survey respondents and 25 former UKCTOCS volunteers who were diagnosed with ovarian cancer.

The four symptoms most commonly reported by Ovacome survey respondents were:

- Abdominal or pelvic discomfort/pain
- Increased abdominal size/bloating
- Tiredness/fatigue
- Urinary frequency/urgency

However, tiredness or fatigue was not included in the four-symptom complex which identified the largest proportion of respondents:

- Abdominal or pelvic discomfort/pain
- Increased abdominal size/bloating
- Abnormal vaginal bleeding
- Urinary frequency/urgency

Analysis of data from telephone interviews with 25 UKCTOCS volunteers diagnosed with ovarian cancer revealed the most common symptoms were equivalent to the Ovacome data. The symptoms women identified as most relevant during the period leading up to their diagnosis were:

- Tiredness/fatigue
- Pelvic discomfort/pain/pressure
- Increased abdominal size/bloating
- Urinary frequency

Two principal conclusions may be drawn from the retrospective data. Firstly, the types of symptoms most commonly reported by women were equivalent to previous research. Secondly, and most importantly, the retrospective data suggest that existing symptom indices may not be as useful for identifying ovarian cancer compared to symptom complexes which include abnormal vaginal bleeding, change in bowel habit or urinary symptoms.

Given the prominence afforded to feeling full in the Goff index,[23] and both the US and the UK ovarian cancer consensus statements,[30 32] findings from the Ovacome data are somewhat controversial. Only one woman reported feeling full quickly and the prevalence of change in appetite or feeling full quickly combined was less than 1%. This finding contrasts with other UK research,[46-47] although, as discussed in Chapter Three, this may be due to the symptom lacking salience among women, and therefore being more likely to be forgotten over time. However, it is surprising that the symptom was so rare given that the majority of respondents were diagnosed with stage III or IV ovarian cancer and the symptom is often associated with advanced disease.[17-18 47] These findings emphasise the need to further explore the utility of early satiety for identifying ovarian cancer in the prospective research. It also raises important questions about the inclusion of a symptom associated with advanced disease in indices which aim to 'lead to detection at the earliest possible stage of the disease'.[30]

Within the literature, abnormal vaginal bleeding is usually described as a less common symptom of ovarian cancer, with two studies not mentioning the

symptom at all.[17 124] However, abnormal bleeding was included in the Lurie index,[25] and recent UK research indicates that the symptom may be more important than previously thought.[46-47] Findings from the Ovacome data are congruent with this research, as the symptom was included in the most prevalent three and four-symptom complexes. Crucially, the symptom was associated with early stage disease and prompt diagnosis. While women with unexplained postmenopausal bleeding meet Department of Health and NICE criteria for an urgent referral to specialist gynaecological oncology centres,[43-44] awareness of postmenopausal bleeding as a 'flag' symptom for gynaecological malignancy among women cannot be taken for granted.[250-252] Indeed, one-third of the women with the symptom did not report it as a symptom which prompted them to seek medical advice and one of the women with abnormal bleeding waited more than two years before consulting her doctor. As current advocacy group awareness campaigns do not include postmenopausal bleeding, this may result in missed opportunities to diagnose women at an early stage of the disease.

Change in bowel habit was identified as a key symptom of ovarian cancer among Ovacome survey respondents. While this symptom is mentioned in the Department of Health *Ovarian Cancer: key messages for health professionals* guidance, it is not listed as one of the three symptoms which can 'suggest' ovarian cancer.[33] However, the research also indicated that change in bowel habit was associated with late stage disease, which suggests that it may have limited relevance for early detection efforts.

Urinary frequency and urgency were commonly reported by both Ovacome survey respondents and UKCTOCS volunteers diagnosed with ovarian cancer. Additionally, urinary frequency/urgency were among the top three symptoms described as 'causing the most trouble'. While these symptoms are not included as key symptoms in the UK consensus statement or Department of Health key messages guidance,[32-33] they are mentioned in these documents and they are included in the four-symptom GCF consensus statement.[30] However, the specificity of urinary symptoms for detecting ovarian cancer is likely to be low given the 28-87% prevalence of these symptoms among community-based women.[239 253-257] Addition of severity criteria to these symptoms in the prospective

study may not improve the positive predictive value of urinary frequency/urgency as 18-29% of women aged over 50 years report severe urinary symptoms.[258]

7.1.3 Symptoms reported prospectively

Symptoms which were most commonly associated with abnormal screening results (overall abnormal result, elevated CA125, elevated ROC or complex ovarian morphology) were:

- Increased abdominal size
- Abdominal or pelvic pressure
- Abdominal or pelvic bloating/fullness
- Shortness of breath
- Urinary frequency

With the exception of shortness of breath and abnormal vaginal bleeding, these symptoms were equivalent to the retrospective data. They are also similar to symptoms reported in the literature, although shortness of breath is usually described as a symptom of advanced disease, not a symptom of early stage ovarian cancer or benign tumours.[9 16 20 51] The association between shortness of breath and abnormal screening results will be further explored in follow-up analyses.

An unexpected finding was the ubiquity of symptoms. Approximately 89% of women reported a median of 5-6 symptoms during the past week and 42-48% reported any symptoms onset within the past year which occurred ≥12 days during the past month. Surprisingly large proportions of women reported key symptoms such as abdominal (19%) or pelvic (23%) discomfort/pain, increased abdominal size (29%), bloating (23%) and feeling full (18%). Frequency and duration criteria reduced the prevalence of symptoms, nevertheless 11-16% of women were positive on the Goff symptom index. In contrast, only 2.6% of women attending primary care in Goff study were positive on the index.[23] This difference may stem from enhanced recall of symptoms over the one-week OCSq reference period compared to the one-month Goff index. Alternatively, a tendency for patients to focus upon the need to present their doctor with a single concern may have interfered with recall of symptoms in the index.[142] Moreover, this finding highlights the importance of further research into the usefulness of symptom indices among community-based women and women attending primary care.

If 11-16% of postmenopausal women sought urgent advice relating to Goff index symptoms, GPs would be swamped with 'worried well' women. This would have serious implications for primary care funding and GP workloads. It would also increase psychological morbidity among women (demonstrated in the pilot OCSq by the finding of an association between awareness and depression screening positive status), as well as anxiety for women's families. There is also the consideration that this may result in substantial increases in the number of women referred for potentially painful, expensive screening interventions and an increase in unnecessary surgery with the concomitant risk of complications. This increase in psychological morbidity, investigations, service costs, and surgery may not necessarily lead to reduced ovarian cancer mortality. Indeed, at the present time there is currently no evidence that the integration of ovarian cancer symptom indices into primary care would reduce the stage of disease at diagnosis for the 6,500 women diagnosed with ovarian cancer each year in the UK.

This was the first study to investigate symptoms according to ultrasound-estimated ovary volumes. While the numbers included in these analyses were small, women with complex ovarian morphology who reported urinary frequency and abdominal bloating/fullness were found to have substantially larger ovarian volumes. Urinary frequency was also associated with elevated CA125 levels while bloating/fullness and increased abdominal size was associated with elevated ROCs. These findings will be further explored in future analyses as research by Andersen *et al*.[24] indicated that combining a symptom index with CA125 may improve its sensitivity from approximately 50% to 81% for the detection of early stage ovarian cancer. This suggests that combining symptoms with CA125 may achieve the elusive goal of stage shift towards earlier diagnosis, which is the most important determinant of survival. However, at the present time, there is insufficient evidence to warrant introduction of symptoms assessment alongside CA125 testing. It must also be remembered that CA125 level has previously been described as poorly correlated with symptoms.[259]

The PPV of the Goff index for detecting an abnormal screen result was 52% and the NPV was 61%. However, the study population was enriched with women who had a previous abnormal screen result, therefore the PPV is likely to be considerably lower among the cohort of women followed-up over the next 12-18 months. Results of these future analyses should provide sufficient information to assess whether symptom indices yield sufficiently large PPVs to balance the risks of awareness campaigns.

An enlightening finding from the research was the discrepant symptoms associated with abnormal screen results when severity, frequency and duration criteria were added to analyses. No symptoms were consistently associated with abnormal results across the four approaches. This will be further explored in future analyses to determine whether a similar effect is observable in relation to symptoms associated with ovarian cancer, although the finding suggests that symptoms many previous studies described as associated with ovarian cancer may have been different if these criteria were added to analyses. This finding also indicates that the current focus upon frequency and duration in symptom awareness campaigns and indices may need to be revised.

Findings from the pilot suggest that symptom models including abdominal pressure or abdominal bloating/fullness with severity, frequency and duration criteria included may have superior performance for detecting early stage ovarian cancer compared to the Goff or Lurie indices. However, the number of cases detected during the pilot was too small to draw definite conclusions.

As discussed in the literature review, previous questionnaire research on the symptoms of ovarian cancer is limited by recall bias and reporting bias arising from knowledge of malignancy. Evidence of the tendency for research participants to selectively search illness relevant memory following confirmation of diagnosis,[144] or even information about the possibility of an abnormality, is observable in the increased symptom reporting among women who had previous awareness of the possibility of an ovarian lesion. In the pilot study, only two 'aware' women were diagnosed with ovarian or fallopian tube cancer during the follow-up period, yet as a group, aware women were significantly more likely to report symptoms, including key symptoms of ovarian cancer such as increased abdominal size, abdominal/pelvic bloating, pressure and heaviness. Importantly, women who were aware of the possibility of an ovarian lesion in the pilot study, and 100,000 women study, were more likely to be positive on the Goff and Lurie symptom indices. While previous studies have attempted to control for reporting and recall bias by interviewing women prior to surgery for a pelvic mass, none have explored the impact of awareness on symptom reporting.

The methodology of the research was not appropriate for a thorough assessment of psycho-social influences symptom perception, interpretation and communication. However, the findings suggested that reporting of symptoms of ovarian cancer is associated with depression screening positive status, and that this is strongly correlated with knowledge of a possible abnormality.

According to current Department of Health guidelines, one of the two women diagnosed with ovarian/fallopian tube cancer in the OCSq pilot would not have been urgently referred. The woman was not positive on the Goff or Lurie indices, or the UK consensus statement, although she was positive on the GCF consensus statement. This one case exemplifies the need to compare the performance of

symptom indices with the results of the UKCTOCS screening trial. This will be possible in 2014 when trial follow-up concludes.

The lengthy follow-up period required for sufficient ovarian cancer diagnoses to be confirmed is a limitation of the research. Unfortunately, due to the relatively low incidence of ovarian cancer, the considerable time interval required for follow-up analyses is unavoidable in a prospective study. Another shortcoming of the research is the possibility that women later diagnosed with malignancy may be asymptomatic at the time of OCSq completion but develop symptoms soon after. Unfortunately, the only way to avoid misclassification of symptoms in these cases would be to conduct a second OCSq study in approximately six months. However, this would not be possible due to the considerable financial resources required for a second mailing of the OCSq.

The research presented in this thesis presented many challenges. With the benefit of hindsight, some aspects of the study would have been approached differently. For example, it would have been ideal to alter the one-week OCSq reference period to one-month for a sub-study in the pilot. This would have facilitated direct comparison with the Goff symptom index and would have ruled-out the different time periods as a possible reason for increased symptom prevalence among OCSq respondents.

7.2 Future research plans

The aims of this project were: 1) to prospectively identify type, severity, frequency and duration of symptoms that precede ovarian cancer diagnosis in a pilot study using a cohort of apparently healthy postmenopausal women, and 2) to set up a prospective study to assess the performance characteristics of symptoms and symptom complexes for the diagnosis of ovarian cancer upon follow-up. This thesis reported on the important incremental steps made in achieving these aims within the timeframe of the three-year PhD. Preliminary analyses of the 100,000 women symptoms study were presented in Chapter Six, although analyses fundamental to the research will not be possible until 12-18 months has elapsed from the date on which the last questionnaires were posted out (13 May 2009).

May 2010 is the earliest date when follow-up surgery and diagnostic data can be matched to OCSq symptoms data. By this time it is anticipated approximately 19 women will have developed ovarian cancer. Waiting until mid November 2010 will result in approximately 25 cases. Future analyses will include:

- Analysis of symptoms in women diagnosed with benign masses
- Analysis of symptoms in women diagnosed with malignant ovarian or fallopian tube lesions
- Exploration of symptom complexes in women diagnosed with malignant ovarian/fallopian tube cancer
- Assessment of the performance characteristics (sensitivity, specificity, positive and negative predictive values) of symptom complexes derived from the data for detecting both an abnormal result upon follow-up and ovarian or fallopian tube cancer
- Assessment of the performance characteristics of symptom indices described by other research groups for detecting an abnormal result upon follow-up and for detecting ovarian or fallopian tube cancer
- Assessment of whether symptom indices can be combined with CA125, ultrasound or both screening methodologies to improve sensitivity and specificity
- Analysis of the predictive validity of the OCSq

7.3 Conclusion

The findings of this research suggest symptom reporting is influenced considerably by awareness of the possibility of an ovarian lesion and depression status. The research also shows that symptom severity, in addition to frequency and duration, may be an important discriminatory factor in identifying ovarian abnormalities. The results indicate that it may be premature to implement the use of symptom indices developed from retrospective studies. Further research is required to assess the performance of symptom complexes which include abnormal vaginal bleeding, abdominal or pelvic pressure or heaviness, urinary frequency/urgency and increased abdominal size/bloating, for detecting early stage ovarian cancer. The utility of including symptom assessments alongside CA125 testing also requires further exploration.

Appendices

Appendix I Ovarian Cancer Symptom Terms Generated from the Literature

Symptom term		Source reference
1	Abdominal bloating	6,14,14,15,17,21
2	Abdominal bloating or pressure	6
3	Bloated	3,4
4	Bloatedness	7
5	Bloating	2,8,10,14,20,36
6	Bloating/abdominal swelling	9
7	Bloating or feeling of fullness	33
8	Abdominal bloating or increased abdominal size	28
9	Unusual bloating, fullness and pressure in the abdomen or pelvis	24
10	Abdominal bloating, fullness, pressure	12
11	Abdominal distension/bloating/increased size/weight	8
12	Ascites	7,22,26
13	Abdominal fullness	20
14	Abdominal fullness or pressure	4
15	Pregnant feeling	4
16	Abdominal swelling	11,17,19,21,29,31,35
17	Abdominal swelling or tightening	34
18	Swollen abdomen	3,8

Symptom term		Source reference
19	Swelling	4
20	General abdominal swelling without a detectable mass	34
21	Increased abdominal circumference	35,36
22	Increased abdominal girth	4,7,16,23,36
23	Increased abdominal girdle	11
24	Increased abdomen size	15
25	Increased abdominal size	13,14
26	Persistent abdominal enlargement	2
27	Weight gain around middle	10
28	Abdominal distension	5,9,18
29	Distended or hard abdomen	33
30	Distended or tense abdomen	25
31	Distension	4
32	Abdominal mass	18,26,34
33	Mass in abdomen	28
34	Able to feel abdominal mass	14,15
35	Abdominal or pelvic mass	7
36	Palpable abdominal mass	5
37	Any mass the woman herself felt	35,36
38	Self-detected abdominal mass	23
39	Lumps in abdomen	20
40	Lump or mass	32,33
41	Lump	3

Symptom term		Source reference
42	Mass noted by woman	36
43	Patient-noticed abdominal mass	4
44	Mass	8
45	Palpable mass	1,2,13,17
46	Palpable tumour	9,11,31
47	Pelvic mass	37
48	Growth/movement in pelvis	9
49	Abdominal discomfort	21
50	Abdominal discomfort other than pain or bloating	12
51	Abdominal pain and distension	2
52	Pain	1,8,10,11,13,31,35,36
53	Pain (abdominal or pelvic)	4
54	Abdominal pain	3,8,10,11,12,13,14,15,17,18,19,21,29,30,31,34,36
55	Abdominal-back pains	23
56	Unusual abdominal or lower back pain	23
57	Pain in abdomen	20
58	Abdominal or pelvic pain	7,14,17
59	Abdominal/pelvic pain	9
60	Abdominal pain or discomfort	5,25,28
61	Right abdominal pain	8
62	Pain in abdomen or pelvis	27
63	Pain related to abdominal function	35
64	Ache and pain under right rib cage	8

Symptom term		Source reference
65	Abdominal pain or pressure	34
66	Abdominal pain (cramping pain)	36
67	Painful spots in abdomen	20
68	Abdominal pain not related to bowel dysfunction	36
69	Vague abdominal pain	20,21,37
70	Severe abdominal pain	33
71	Stomach/pelvic cramping	9
72	Stomach cramps	10
73	Sense of abdominal pressure	7
74	Abdominal pressure	21
75	Pelvic or abdominal discomfort such as heaviness, fullness, pressure or pain	32,33
76	Pelvic discomfort	6,32
77	Pelvic and or/abdominal pain not related to bowel function	35
78	Pelvic pain	12,13,22,28
79	Transient acute lower abdominal pain	4
80	Severe lower abdominal pain	4
81	Pain in lower abdomen	20
82	Period-type pain	8
83	Pelvic (lower abdomen) pain	15
84	Pelvic pressure	1,37
85	Lower abdominal pressure	16
86	Pelvic/rectal pressure	9

Symptom term		Source reference
87	Lower abdominal (pelvic) pressure or heaviness	17
88	Pelvic fullness	37
89	Pelvic symptoms	13,23
90	‘Popping’ in abdomen	8
91	Digestive difficulties	8
92	Indigestion	8,9,10,13,14,15,17,29
93	Indigestion problems	20
94	Indigestion or heartburn	28
95	Indigestion, dyspepsia, heartburn, GERD	12
96	Heartburn	11,17
97	Nausea	3,9,12,13,14,17,15,21,24,26,35,36
98	Nausea or vomiting	14,15,28
99	Vomiting	8,12,17,18,26,35,36
100	Reflux	21
101	Eructation	11
102	Hiccups	17
103	Gas	9
104	Gas or bloating	32
105	Intestinal gas	12
106	Flatulence	3
107	Gas, nausea, indigestion	33
108	Gastrointestinal symptoms	1,8,10,11,13,17,18,20,21,28,34,35,36
109	Non-specific gastrointestinal complaints	16

Symptom term		Source reference
110	Gastrointestinal tract problems	20
111	Gastroenteritis	12
112	Epigastric distress	6
113	Fluid in abdomen	20
114	Stomach problems	10
115	Abdominal symptoms	13,34
116	Meteorismus	11
117	Bowel symptoms	5
118	Other bowel symptoms	28
119	Altered bowel habit	18
120	Altered bowel habits	8
121	Bowel changes	36
122	Bowel changes/difficulty	9
123	Change in bowel habit	3,7,19
124	Defecation at night/early morning	2
125	Constipation/diarrhoea	29
126	Bowel muscles not working properly	8
127	Difficulty voiding	17
128	Pressure during voiding	17
129	Bowel irregularity	25,32
130	Bowel irregularity such as diarrhoea, constipation, gas or bloating	32
131	Bowel irregularity such as diarrhoea or constipation	33

Symptom term		Source reference
132	Constipation	1,9,10,12,13,14,15,17,20,21,26,28,32,33,35,36
133	Unusual constipation	24
134	Persistent constipation	8
135	Diarrhoea	9,10,12,13,14,15,28,32,33,35,36,37
136	Unusual diarrhoea	24
137	Diarrhoea with bloating	8
138	Bowel pain	32
139	Painful defecation	35,36
140	Rectal pain	12,27
141	Symptoms of bowel obstruction	6
142	Compression on the bladder or bowel	31
143	Rectal bleeding	9,25
144	Gynaecologic symptoms	1,36
145	Gynaecological symptoms	31,34,35
146	Gynaecological/hormonal symptoms	8
147	Gynecological–urological symptoms	23
148	Abnormal discharge	35,36
149	Excessive vaginal discharge	4
150	Increased vaginal discharge	23
151	Vaginal discharge	8,17
152	Bleeding	30
153	Bleeding or spotting (vaginal)	20
154	Vaginal bleeding	3,7,9,13,17,19,36

Symptom term		Source reference
155	Vaginal bleeding or discharge	11,32
156	Irregular bleeding	3
157	Irregular vaginal bleeding	29,35,36
158	Irregular premenopausal bleeding	21
159	Postmenopausal vaginal bleeding	4
160	Abnormal vaginal bleeding	2,21,23,28
161	Abnormal menstrual or vaginal bleeding or discharge	25,33
162	Heavy, painful periods	10
163	Menstrual irregularities	14,15,32
164	Menstrual irregularities/changes	8
165	Menstrual symptoms	5
166	Dysmenorrhoea	17,30
167	Menorrhagia	4,21
168	Metrorrhagia	22,29
169	Absent or very light menses	17
170	Missed periods	9
171	Bleeding after menopause	14,15
172	Postmenopausal bleeding	14,18,21
173	Bleeding during intercourse	20
174	Bleeding with intercourse	13,14,15
175	Bleeding after intercourse	8
176	Pain with intercourse	13
177	Dyspareunia or abdominal pain with sexual intercourse	4

Symptom term		Source reference
178	Pain during intercourse	3,14,15,28,32,33
179	Painful intercourse	8
180	Sexual problems	10
181	Genital pain	27
182	Dyspareunia	17
183	Vaginal pain	4
184	Secondary dyspareunia	35,36
185	Vaginal/rectal pain	9
186	Rapid vaginal delivery	17
187	Technical difficulty and pain with speculum exam	17
188	Bladder symptoms	35,36
189	Urinary/bladder symptoms	34
190	Change in urinating habit	3
191	Urinary problems	20
192	Urination problems	29
193	Urinary symptoms	5,7,17,18,21,34,35,36
194	Urinary tract symptoms	14
195	Lower urinary tract symptoms	16
196	Other urinary problems	32
197	Urinary problems (retention and pain)	2
198	Problem passing urine	10
199	Retention of urine	18
200	Urinary tract infection	3

Symptom term		Source reference
201	Urinary tract infection, cystitis	12
202	Urinary urgency	10,14,15
203	Frequent urination or urgency	25
204	Frequent urination, urgency, or burning	24
205	Frequent urination	8,14,15,17
206	Increased urinary frequency	21
207	Frequency or urgency of urination	33
208	Urinary frequency	1,9,10,12,13,14,15,16,28
209	Urinary frequency or dysuria	7
210	Urinary frequency or urgency	8
211	Urinary frequency/urgency	32
212	Urinary frequency, urgency or incontinence	37
213	Need to urinate more often than usual	32
214	Frequency of micturition	18
215	Frequent micturition	35,36
216	Urinary burning, dysuria	12
217	Dysuria	11,17,23
218	Irritative voiding	16
219	Painful urination	8,17
220	Bladder pressure or urinary frequency	4
221	Pressure on the bladder	20,35,36
222	Nocturia	16,17

Symptom term		Source reference
223	Incontinence	35,36
224	Urge incontinence	16
225	Urinary stress incontinence	21
226	Urinary incontinence	8,12,13,17,28
227	Breathlessness	3
228	Difficulty breathing	15
229	Breathing difficulties	8,20
230	Breathing problems	8
231	Respiratory difficulties	25,32
232	Respiratory symptoms	8,31
233	Short of breath	10
234	Shortness of breath	12,19,20,29,37
235	Shortness of breath with activity	17
236	Shortness of breath at rest	17
237	Pain in chest	20
238	Chest pain or respiratory difficulties	33
239	Coughing	20
240	Dyspnoea	11,17,23,35,36
241	Pleurisy	37
242	Pleural effusion	26,37
243	Fluid in chest	20
244	Local symptoms	35,36
245	General symptoms	23,35,36
246	Headache	12

Symptom term		Source reference
247	Headaches	17
248	Backache	19
249	Pain in back	20
250	Back pain	9,11,13,14,15,17,20,28,32,33,34
251	Back pain, upper back	12
252	Back pain, lower back	12
253	Back pain, both lower and upper	12
254	Lower back pain	27
255	Back pressure or pain	4
256	Pain in shoulder or shoulder blade pain	17
257	Pain outside the abdominal cavity	25
258	Pain, side of trunk, flank	12
259	Pain under ribs	8
260	Pain in the side or ribs	24
261	Pain - thoracic	17
262	Pain inside	8
263	Pain - other sites	17
264	Pain - site unspecified	17
265	Sense of raised body temperature	2
266	Elevated temperature	20
267	Fever	4,9,10,11,17,32
268	Flu-like virus	20
269	Aching joints or muscles	17
270	Leg cramps	20

Symptom term		Source reference
271	Leg pain	8
272	Thigh pain	14
273	Pain or swelling in legs	32
274	Leg swelling	14,15
275	Deep venous thrombosis	13,18
276	Ankle swelling	18
277	Swelling in ankles/legs	9
278	Swelling of the legs or feet	17
279	Oedema, diffuse swelling, fluid retention	12
280	Swollen lymph nodes	9
281	Malaise	17
282	General malaise	34
283	Extreme fatigue	35,36
284	Fatigue	3,4,6,9,10,11,13,14,15,17,20,29,31,32,36
285	Fatigue, lack of energy, general weakness	12
286	Fatigue/lethargy/tiredness	28
287	Ongoing fatigue	33
288	Persisting fatigue or weight loss	25
289	Exhaustion	8
290	Feeling weak	10
291	Unusual lack of energy	24
292	Tiredness	8
293	Dizziness	23

Symptom term		Source reference
294	Anorexia	12,21
295	Appetite loss	8,29
296	Change in appetite	3
297	Changed appetite	8
298	Decreased appetite	7,9,33
299	Lack of appetite/feeling full	8
300	Loss of appetite	12,17,32,35
301	Loss of appetite or difficulty eating	28
302	Loss of appetite and weight	36
303	Unusual lack of appetite	24
304	Early satiety	17
305	Difficulty eating	14
306	Feeling full quickly	15
307	Feeling full after a few bites of food	17
308	Unable to eat normally	13,14,15
309	Taste changes	17
310	Food intolerance	12
311	Food aversions	2
312	Weight loss	4,7,8,9,13,14,15,18,19,22,28,31,36
313	Nondeliberate weight loss	6
314	Unintentional weight loss	12
315	Unplanned weight loss	17
316	Loss of weight	35
317	Unplanned weight gain	17

Symptom term		Source reference
318	Getting fat	4
319	Weight gain	7,8,20
320	Gained weight	10
321	Obesity	12
322	Unexplained weight gain or loss	33
323	Change in weight	3
324	Weight loss or gain	32
325	Anaemia	36
326	Severe anaemia	35
327	Fluid in lungs	20
328	Non-menopausal hot flushes	2
329	Menopausal symptoms, hot flushes	12
330	Hot flashes	17,32
331	Insomnia	20
332	Night sweats	8,32
333	Anxiety, panic attacks	12
334	Panic attacks	9
335	Umbilical hernia	8
336	Breast swelling	17
337	Mammary swelling	11
338	Breast tenderness	17
339	Tenesmus	11
340	Difficulty moving legs	17
341	Paresthesia, numbness, burning, tingling	12

Symptom term		Source reference
342	Irritable bowel syndrome	12,13
343	Constitutional symptoms	1,13,17,28
344	Metastatic symptoms	6
345	Symptoms of mass effect	1
346	Systemic symptoms	6,31
347	Regional symptoms	6
348	Depression	9,13,15,17
349	Stress	13

Source reference		Symptoms questionnaire used?
1	Attanucci et al. (2004)	
2	Bankhead et al. (2005)*	
3	Bayne & Gilbert (2007)*	Yes
4	Beck et al. (2001)	Yes
5	Chan et al. (2003)	
6	DiSilvestro et al. (1998)	
7	Eltabbakh et al. (1999)	
8	Evans et al. (2006)	
9	Ferrell et al. (2003)	
10	Fitch et al. (2002)	
11	Flam et al. (1988)	
12	Friedman et al. (2005)	
13	Goff et al. (2000)	Yes
14	Goff et al. (2004)	Yes
15	Goff et al. (2007)	Yes
16	Goldberg et al. (2001)	
17	Igoe (1997)	Yes
18	Kennedy & Gordon (1981)	
19	Kirwan et al. (2002)	
20	Koldjeski et al. (2003)	Yes
21	Lataifeh et al. (2005)	
22	Mantzavinos et al. (1988)	
23	Nelson et al. (1999)	
24	Olson et al. (2001)	Yes

Source reference		Symptoms questionnaire used?
25	Paulsen et al. (2005)	
26	Piura et al. (1998)	
27	Portenoy et al. (1994)	Yes
28	Rufford et al. (2007)	
29	Smith & Anderson (1985)	Yes
30	Takeuchi et al. (2002)	
31	Thulesius et al. (2004)	
32	Vine et al. (2001)	Yes
33	Vine et al. (2003)	Yes
34	Webb et al. (2004)	Yes
35	Wikborn et al. (1993)	
36	Wikborn et al. (1996)	
37	Yawn et al. (2004)	

* *Conference abstract*

Appendix II Symptom Questionnaire for Health Professional Interviews

United Kingdom Collaborative Trial of Ovarian Cancer Screening

Site		Role		Number	

Health Professional Interviews to Develop an Ovarian Cancer Symptoms Questionnaire for a Prospective Study

We are asking for your help in developing a questionnaire which will be used to identify symptoms that precede a diagnosis of ovarian cancer. Here is a list of symptoms described in the literature as associated with ovarian cancer. Please indicate the extent to which you find each symptom relevant for post-menopausal women diagnosed with ovarian cancer. Please also select up to 25 issues which you would prioritise for inclusion in the final questionnaire.

Issue		Relevance				Priority for inclusion
		Not at all	A little	Quite a bit	Very much	Tick if yes
Abdominal symptoms						
1	Abdominal bloating	1	2	3	4	
2	Abdominal fullness	1	2	3	4	
3	Increased abdominal size	1	2	3	4	
4	Abdominal tightening	1	2	3	4	
5	Hard abdomen	1	2	3	4	
6	Able to feel abdominal mass/lumps	1	2	3	4	
7	Abdominal discomfort	1	2	3	4	
8	Abdominal pain	1	2	3	4	
9	Abdominal pressure	1	2	3	4	
10	Abdominal cramping	1	2	3	4	
Gastrointestinal symptoms						
1	Indigestion	1	2	3	4	
2	Heartburn	1	2	3	4	
3	Nausea/feeling sick	1	2	3	4	
4	Vomiting/being sick	1	2	3	4	
5	Reflux of food	1	2	3	4	
6	Burping	1	2	3	4	
7	Taste changes					
8	Feeling full quickly after beginning to eat					
9	Loss of appetite	1	2	3	4	
10	Change in bowel habit	1	2	3	4	
11	Constipation	1	2	3	4	
12	Diarrhoea	1	2	3	4	
13	Excessive passing of wind	1	2	3	4	
14	Difficulty opening bowels	1	2	3	4	
15	Pain before, during or after opening bowels	1	2	3	4	
16	Rectal pain	1	2	3	4	
17	Rectal bleeding	1	2	3	4	
18	Urgent need to open bowel	1	2	3	4	
19	Bowel incontinence	1	2	3	4	
Pelvic symptoms						
1	Able to feel mass or lump	1	2	3	4	
2	Pelvic discomfort	1	2	3	4	

Issue		Relevance				Priority for inclusion
		Not at all	A little	Quite a bit	Very much	Tick if yes
3	Pelvic pain	1	2	3	4	
4	Pelvic cramping	1	2	3	4	
5	Pelvic pressure	1	2	3	4	
6	Pelvic fullness	1	2	3	4	
7	Pelvic heaviness	1	2	3	4	
Gynaecological symptoms						
1	Vaginal discharge	1	2	3	4	
2	Vaginal bleeding	1	2	3	4	
3	Vaginal pain	1	2	3	4	
4	Pain during/after sexual intercourse	1	2	3	4	
5	Bleeding during/after intercourse	1	2	3	4	
6	Prolapse	1	2	3	4	
Urinary symptoms						
1	Urgent need to pass urine	1	2	3	4	
2	Passing urine frequently	1	2	3	4	
3	Feeling of pressure on the bladder	1	2	3	4	
4	Leakage of urine	1	2	3	4	
5	Difficulty emptying bladder	1	2	3	4	
6	Burning on passing urine	1	2	3	4	
7	Pain on passing urine	1	2	3	4	
Respiratory symptoms						
1	Chest pain	1	2	3	4	
2	Cough	1	2	3	4	
3	Difficulty breathing	1	2	3	4	
4	Shortness of breath	1	2	3	4	
General symptoms						
1	Backache	1	2	3	4	
2	Back pain	1	2	3	4	
3	Shoulder pain	1	2	3	4	
4	Pain in side of trunk, flank	1	2	3	4	
5	Pain in the hip/buttock/outside leg	1	2	3	4	
6	Aching limbs	1	2	3	4	
7	Pain in legs	1	2	3	4	
8	Leg cramps	1	2	3	4	
9	Leg swelling	1	2	3	4	
10	Ankle swelling	1	2	3	4	
11	Lump in neck	1	2	3	4	
12	Fever/raised temperature	1	2	3	4	
13	Tiredness	1	2	3	4	
14	Fatigue	1	2	3	4	
15	Lack of energy	1	2	3	4	
16	Generally feeling unwell	1	2	3	4	
17	Weight loss without trying	1	2	3	4	
18	Weight gain without trying	1	2	3	4	
19	Hot flushes	1	2	3	4	

Issue		Relevance				Priority for inclusion
		Not at all	A little	Quite a bit	Very much	Tick if yes
20	Night sweats	1	2	3	4	
21	Breast swelling	1	2	3	4	
22	Breast pain	1	2	3	4	
23	Lump in breast	1	2	3	4	
24	Difficulty sleeping	1	2	3	4	
25	Feeling tense or anxious	1	2	3	4	
26	Feeling down, depressed or hopeless?	1	2	3	4	
27	Little interest or pleasure doing things?	1	2	3	4	

Please write down any additional problems not covered in the list of issues:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Thank you for completing this questionnaire

Appendix III Letter of Invitation for Telephone Interviews with Women Diagnosed with Ovarian Cancer

United Kingdom Collaborative Trial of Ovarian Cancer Screening

Department of Gynaecological Oncology
Level 1, Maple House
149 Tottenham Court Road
London
W1T 7DN

Private and confidential

NAME
ADDRESS LINE 1
ADDRESS LINE 2
CITY
POSTCODE

DATE

Dear NAME,

We are writing to you about a new study that is being conducted as part of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). The study is hoping to recruit women who have had ovarian cancer detected in UKCTOCS. We are seeking the feedback of these women about a draft ovarian cancer symptoms questionnaire.

Please read the enclosed study information sheet and if you are willing to take part please complete the contact details information sheet and the consent section, and return them in the enclosed free post envelope. The researcher will sign the 'researcher' section of the consent form when received. Women who indicate they would like to take part will be asked to participate in a telephone interview about ovarian cancer symptoms.

If you would like more information about the study please Penny Allen on 0789 733 7573 or 0207 380 6919.

Thank you for taking the time to read this information.

Yours sincerely

Penny Allen

I _____ (insert name) am interested in participating in a telephone interview about an ovarian cancer symptoms questionnaire. I give permission for the researcher to telephone me to explain more about the study and, if I wish, to arrange an interview time and date that is convenient to me.

I can be contacted on _____ (insert telephone number) between the hours of _____ and _____.

_____

Name

_____

Signature

_____

Date

Please enclose this page in the pre-addressed, pre-paid envelope provided and send to:

Penny Allen
Department of Gynaecological Oncology
UCL Institute for Women's Health
Level 1, Maple House
149 Tottenham Court Road
London
W1T 7DN

Appendix IV Study Information Sheet for Women Invited to Participate in Telephone Interviews

United Kingdom Collaborative Trial of Ovarian Cancer Screening

Ovarian cancer symptoms study

As a previous participant in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) you are being asked to take part in research to develop a questionnaire which will ask women about ovarian cancer symptoms. Before you decide to take part it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

Previous research has reported that the early symptoms of ovarian cancer are subtle or non-specific. Due to this the majority of women are diagnosed with ovarian cancer after it has spread from the ovaries. The purpose of this study is to develop a questionnaire which will be used in a larger study of symptoms that precede a diagnosis of ovarian cancer.

Why have I been chosen?

This study is a sub-study of the United Kingdom Collaborative Trial of Ovarian Cancer Screening and you participated in UKCTOCS. We are inviting women who have received a diagnosis of ovarian cancer to participate in an interview about a symptoms questionnaire.

Do I have to fulfil any other criteria to take part?

No. The only criteria you need to fulfil are:

1. Participated in the United Kingdom Collaborative Trial of Ovarian Cancer Screening and have been diagnosed with ovarian cancer.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign a consent form. This form is different to the original consent form that you signed to enrol in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. If you decide to take part you are free to withdraw at any time and without giving a reason. This will not affect any medical care you receive.

What will happen to me if I take part?

Structured questionnaire telephone interview

If you would like to take part in this study please sign the enclosed consent form then send to the researcher, Penny Allen, in the enclosed pre-paid envelope. The consent form also asks for your permission to audio tape record the interview. The researcher will telephone you to discuss the study in greater detail, give you the opportunity to ask any questions and arrange a convenient time for you to participate in a telephone interview. If you decide to take part in an interview you can decline to

answer any questions that you are not comfortable answering and you are free to end the interview at any time without giving a reason.

What are the possible disadvantages of taking part?

1. Participation in the telephone interview will take 30-45 minutes of your time.
2. Discussing symptoms during interview may create anxiety or may make some women upset

What are the possible benefits of taking part?

- We cannot promise the study will help you directly but the information collected may, in the future, help to identify symptoms of ovarian cancer.

What if I become worried or anxious about any of the issues raised during the interview?

The researcher cannot give you any information or advice about your symptoms. If you are worried about any symptoms please discuss them with your GP or gynaecologist. If you would like the details of an ovarian cancer patient support group please ask the interviewer.

What if something goes wrong?

We consider there to be little risk associated with taking part in this study and it is not anticipated that anything will go wrong in the study as it only involves you discussing symptoms. It does not involve any tests.

You will always be able to contact the researcher to discuss your concerns about the study. Every care will be taken to ensure your safety during the course of the study. University College London (UCL), the Research Governance Sponsor, ha s indemnity (insurance) arrangements in place for non-negligent harm, in the event that something does go wrong and you are harmed as a result of taking part in this study. If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation but you may have to pay your legal costs.

Will taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. You will be asked not to use your name, address or personal details during the tape-recorded interview. We will not write your name or any personal details on any interview notes. Occasionally the research documentation and results will be looked at by the people funding the research programme to check that the study is being carried out properly. Any information which is viewed by people not directly related to the research team will not have your name and address on it.

What will happen to the results of the research study?

The results of the research will be used in a PhD study of the symptoms of ovarian cancer. Additionally, the results will be reviewed by medical professionals and published in the medical press. Individuals will not be identified in any publications.

Who is organising and funding the research?
The research is part of a PhD study that is linked to the United Kingdom Collaborative Trial of Ovarian Cancer Screening. The Medical Research Council is funding the study.

Complaints

If you have a concern about any aspect of this study you should ask to speak with Penny Allen or Dr Usha Menon (tel. 0207 380 6907) who will do their best to assist. If you remain unhappy, and wish to complain formally, you can do this by contacting the Research Governance Sponsor of this study, University College London. Please write to:

UCLH/UCL Joint Biomedical Research Unit
R&D Directorate
Rosenheim Wing, Ground Floor
25 Grafton Way
London WC1E 5DB

Contact for further information

For further information please telephone Penny Allen in the Department of Gynaecological Oncology on tel. 0789 733 7573 or 0207 380 6919. Alternatively, you can write to:

Penny Allen
Department of Gynaecological Oncology
UCL Institute for Women's Health
Level 1, Maple House
149 Tottenham Court Road
London
W1T 7DN

Thank you for taking the time to read this information.

Appendix V Consent Form Sent to Women Invited to Participate in Telephone Interviews

United Kingdom Collaborative Trial of Ovarian Cancer Screening

Department of Gynaecological Oncology
Maple House, 1st Floor
149 Tottenham Court Road
London
W1T 7NF

Centre Number: _____
Volunteer reference number: _____

CONSENT FORM

Title of Project: Prospective study of ovarian cancer symptoms.

Name of researcher: Penny Allen

		Please initial box
1.	I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study and have had the opportunity to ask questions.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected.	☐
3.	I understand that information collected by the UKCTOCS study may be looked at by the researcher where it is relevant to my taking part in the research. I give permission for the researcher to have access to my UKCTOCS records.	☐
4.	I give permission for my interview to be audio-taped.	☐
5.	I agree to take part in the above study.	☐

_____	_____	_____
Name of study volunteer	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Appendix VI Symptoms Questionnaire for Telephone Interviews with Women Diagnosed with Ovarian Cancer

United Kingdom Collaborative Trial of Ovarian Cancer Screening

Symptoms Questionnaire for Telephone Interviews with Women Diagnosed with Ovarian Cancer

Interview no: _____ Site: _____ Months since diagnosis: _____

Issue		Relevance				Symptoms that caused most trouble
		Not at all	A little	Quite a bit	Very much	
1	Abdominal bloating or fullness	1	2	3	4	
2	Increased abdominal size/waistband felt tighter	1	2	3	4	
3	Able to feel abdominal mass/lumps	1	2	3	4	
4	Abdominal discomfort, pain or pressure	1	2	3	4	
5	Indigestion	1	2	3	4	
6	Heartburn	1	2	3	4	
7	Nausea/feeling sick or vomiting/being sick	1	2	3	4	
8	Feeling full too quickly after beginning to eat	1	2	3	4	
9	Change in appetite	1	2	3	4	
10	Lower abdominal/pelvic discomfort, pain or pressure	1	2	3	4	
11	Pelvic heaviness	1	2	3	4	
12	Pelvic fullness	1	2	3	4	
13	Pain before, during or after opening bowels	1	2	3	4	
14	Difficulty emptying bowels	1	2	3	4	
15	Change in bowel habit	1	2	3	4	
16	Excessive passing of wind/flatulence	1	2	3	4	
17	Abnormal vaginal bleeding	1	2	3	4	
18	Abnormal vaginal discharge	1	2	3	4	
19	Pain during/after sexual intercourse	1	2	3	4	
20	Passing urine frequently	1	2	3	4	
21	Urgent need to pass urine	1	2	3	4	
22	Feeling of pressure on the bladder	1	2	3	4	
23	Difficulty emptying bladder	1	2	3	4	
24	Pain when passing urine	1	2	3	4	
25	Shortness of breath	1	2	3	4	
26	Back ache/pain	1	2	3	4	
27	Pain in side of trunk, flank	1	2	3	4	
28	Aching limbs	1	2	3	4	
29	Leg pain	1	2	3	4	
30	Leg swelling	1	2	3	4	
31	Tiredness, fatigue or lack of energy	1	2	3	4	
32	Generally feeling unwell	1	2	3	4	
33	Weight gain without trying	1	2	3	4	
34	Weight loss without trying	1	2	3	4	

Please identify 5 to 10 symptoms that caused the greatest trouble leading up to diagnosis (tick boxes).

Were any additional symptoms experienced during the time leading up to diagnosis that are not included in this list?

_____

Appendix VII Interview Guide for Telephone Interviews with Women Diagnosed with Ovarian Cancer

Prior to commencing interview check that the participant has the symptom list in front of them. Inform participant that their name will not be used once the tape starts recording, that they can refuse to answer any questions they are not comfortable answering and that they can end the interview at any time.

Identify the 18 month period prior to diagnosis before commencing the interview. Clarify date at the start of the 18 month period and the date of diagnosis. Use significant dates (e.g. Christmas, Easter, birthdays, holidays, etc.) to help participant remember the exact time period.

For each item:

- Did you experience the symptom in the 18 months leading up to your diagnosis?
- If yes, did you experience it a little, quite a bit or very much? (Circle)
- Can you tell me about the symptom?
- In your own words how would you describe it?
- When did you first notice it?
- What did it feel like?
- Where exactly in your body did you feel/see it?
- How often did it happen?
- Did you take anything for it?
- Did you go to the doctor about it?
- Did it change at all or stop altogether? If so, how and when?
- What do you think caused that symptom?

Can you think of any additional symptoms which you experienced during the 18 months leading up to your diagnosis that are not included in the list?

Which of these symptoms in the list, and any that you have mentioned yourself, troubled you the most during that time? Please identify up to 10 issues (tick boxes)

Do you have any other comments about these symptoms?

Thank interviewee for their time

Appendix VIII Results of Preliminary Revision of the Symptoms List

Symptom term		Revised to
1	Abdominal bloating	Abdominal bloating
2	Abdominal bloating or pressure	
3	Bloated	
4	Bloatedness	
5	Bloating	
6	Bloating/abdominal swelling	
7	Bloating or feeling of fullness	
8	Abdominal bloating or increased abdominal size	
9	Unusual bloating, fullness and pressure in the abdomen or pelvis	
10	Abdominal bloating, fullness, pressure	
11	Abdominal distension/bloating/increased size/weight	
12	Ascites	Deleted - medical terminology
13	Abdominal fullness	Abdominal fullness
14	Abdominal fullness or pressure	
15	Pregnant feeling	
16	Abdominal swelling	Abdominal swelling Swollen abdomen Abdominal tightening
17	Abdominal swelling or tightening	
18	Swollen abdomen	
19	Swelling	
20	General abdominal swelling without a detectable mass	

Symptom term		Revised to
21	Increased abdominal circumference	Increased abdominal size
22	Increased abdominal girth	
23	Increased abdominal girdle	
24	Increased abdomen size	
25	Increased abdominal size	
26	Persistent abdominal enlargement	
27	Weight gain around middle	
28	Abdominal distension	Abdominal distension Hard abdomen Tense abdomen
29	Distended or hard abdomen	
30	Distended or tense abdomen	
31	Distension	
32	Abdominal mass	Able to feel abdominal mass/lumps Lump
33	Mass in abdomen	
34	Able to feel abdominal mass	
35	Abdominal or pelvic mass	
36	Palpable abdominal mass	
37	Any mass the woman herself felt	
38	Self-detected abdominal mass	
39	Lumps in abdomen	
40	Lump or mass	
41	Lump	
42	Mass noted by woman	
43	Patient-noticed abdominal mass	
44	Mass	

Symptom term		Revised to
45	Palpable mass	
46	Palpable tumour	
47	Pelvic mass	
48	Growth/movement in pelvis	
49	Abdominal discomfort	Abdominal discomfort
50	Abdominal discomfort other than pain or bloating	
51	Abdominal pain and distension	Abdominal pain
52	Pain	
53	Pain (abdominal or pelvic)	
54	Abdominal pain	
55	Abdominal-back pains	
56	Unusual abdominal or lower back pain	
57	Pain in abdomen	
58	Abdominal or pelvic pain	
59	Abdominal/pelvic pain	
60	Abdominal pain or discomfort	
61	Right abdominal pain	
62	Pain in abdomen or pelvis	
63	Pain related to abdominal function	
64	Ache and pain under right rib cage	
65	Abdominal pain or pressure	
66	Abdominal pain (cramping pain)	
67	Painful spots in abdomen	

Symptom term		Revised to
68	Abdominal pain not related to bowel dysfunction	
69	Vague abdominal pain	
70	Severe abdominal pain	
71	Stomach/pelvic cramping	Stomach cramping Pelvic cramping
72	Stomach cramps	
73	Sense of abdominal pressure	Abdominal pressure
74	Abdominal pressure	
75	Pelvic or abdominal discomfort such as heaviness, fullness, pressure or pain	Pelvic discomfort
76	Pelvic discomfort	
77	Pelvic and or/abdominal pain not related to bowel function	Pelvic pain
78	Pelvic pain	
79	Transient acute lower abdominal pain	
80	Severe lower abdominal pain	
81	Pain in lower abdomen	
82	Period-type pain	
83	Pelvic (lower abdomen) pain	
84	Pelvic pressure	Pelvic pressure
85	Lower abdominal pressure	
86	Pelvic/rectal pressure	
87	Lower abdominal (pelvic) pressure or heaviness	Pelvic heaviness
88	Pelvic fullness	Pelvic fullness
89	Pelvic symptoms	Deleted - non-specific
90	‘Popping’ in abdomen	Deleted - non-specific

Symptom term		Revised to
91	Digestive difficulties	Indigestion or heartburn
92	Indigestion	
93	Indigestion problems	
94	Indigestion or heartburn	
95	Indigestion, dyspepsia, heartburn, GERD	
96	Heartburn	
97	Nausea	Nausea
98	Nausea or vomiting	
99	Vomiting	Vomiting
100	Reflux	Reflux
101	Eructation	Deleted - medical terminology
102	Hiccups	Deleted - non-specific
103	Gas	Belching, gas Passing wind/gas/flatulence
104	Gas or bloating	
105	Intestinal gas	
106	Flatulence	
107	Gas, nausea, indigestion	
108	Gastrointestinal symptoms	Deleted - non-specific
109	Non-specific gastrointestinal complaints	
110	Gastrointestinal tract problems	
111	Gastroenteritis	Deleted - medical terminology
112	Epigastric distress	Deleted - medical terminology
113	Fluid in abdomen	Deleted - non-specific
114	Stomach problems	

Symptom term		Revised to
115	Abdominal symptoms	
116	Meteorismus	Deleted - medical terminology
117	Bowel symptoms	Deleted - non-specific
118	Other bowel symptoms	Deleted - non-specific
119	Altered bowel habit	Change in bowel habit
120	Altered bowel habits	
121	Bowel changes	
122	Bowel changes/difficulty	
123	Change in bowel habit	
124	Defecation at night/early morning	
125	Constipation/diarrhoea	
126	Bowel muscles not working properly	Difficulty opening bowels
127	Difficulty voiding	
128	Pressure during voiding	
129	Bowel irregularity	Bowel irregularity
130	Bowel irregularity such as diarrhoea, constipation, gas or bloating	
131	Bowel irregularity such as diarrhoea or constipation	
132	Constipation	Constipation
133	Unusual constipation	
134	Persistent constipation	
135	Diarrhoea	Diarrhoea
136	Unusual diarrhoea	
137	Diarrhoea with bloating	

Symptom term		Revised to
138	Bowel pain	Pain when opening bowels
139	Painful defecation	
140	Rectal pain	Rectal pain
141	Symptoms of bowel obstruction	Deleted - non-specific
142	Compression on the bladder or bowel	Deleted - medical terminology
143	Rectal bleeding	Rectal bleeding
144	Gynaecologic symptoms	Deleted - non-specific
145	Gynaecological symptoms	
146	Gynaecological/hormonal symptoms	
147	Gynecological–urological symptoms	
148	Abnormal discharge	Abnormal vaginal discharge
149	Excessive vaginal discharge	
150	Increased vaginal discharge	
151	Vaginal discharge	
152	Bleeding	Abnormal vaginal bleeding
153	Bleeding or spotting (vaginal)	
154	Vaginal bleeding	
155	Vaginal bleeding or discharge	
156	Irregular bleeding	
157	Irregular vaginal bleeding	
158	Irregular premenopausal bleeding	
159	Postmenopausal vaginal bleeding	
160	Abnormal vaginal bleeding	

Symptom term		Revised to
161	Abnormal menstrual or vaginal bleeding or discharge	
162	Heavy, painful periods	
163	Menstrual irregularities	
164	Menstrual irregularities/changes	
165	Menstrual symptoms	
166	Dysmenorrhoea	
167	Menorrhagia	
168	Metrorrhagia	
169	Absent or very light menses	
170	Missed periods	
171	Bleeding after menopause	
172	Postmenopausal bleeding	
173	Bleeding during intercourse	Bleeding during/after intercourse
174	Bleeding with intercourse	
175	Bleeding after intercourse	
176	Pain with intercourse	Painful intercourse
177	Dyspareunia or abdominal pain with sexual intercourse	
178	Pain during intercourse	
179	Painful intercourse	
180	Sexual problems	Deleted - non-specific
181	Genital pain	Vaginal pain
182	Dyspareunia	
183	Vaginal pain	

Symptom term		Revised to
184	Secondary dyspareunia	
185	Vaginal/rectal pain	
186	Rapid vaginal delivery	Deleted - not relevant in postmenopausal women
187	Technical difficulty and pain with speculum exam	Deleted - not relevant for symptoms questionnaire
188	Bladder symptoms	Deleted - non-specific
189	Urinary/bladder symptoms	
190	Change in urinating habit	
191	Urinary problems	
192	Urination problems	
193	Urinary symptoms	
194	Urinary tract symptoms	
195	Lower urinary tract symptoms	
196	Other urinary problems	
197	Urinary problems (retention and pain)	Difficulty emptying bladder
198	Problem passing urine	
199	Retention of urine	
200	Urinary tract infection	Urinary tract infection
201	Urinary tract infection, cystitis	
202	Urinary urgency	Urinary urgency Urgent need to pass urine Urinary frequency Passing urine more often
203	Frequent urination or urgency	
204	Frequent urination, urgency, or burning	
205	Frequent urination	
206	Increased urinary frequency	

Symptom term		Revised to
207	Frequency or urgency of urination	
208	Urinary frequency	
209	Urinary frequency or dysuria	
210	Urinary frequency or urgency	
211	Urinary frequency/urgency	
212	Urinary frequency, urgency or incontinence	
213	Need to urinate more often than usual	
214	Frequency of micturition	
215	Frequent micturition	
216	Urinary burning, dysuria	Urinary burning
217	Dysuria	Pain or soreness on passing urine
218	Irritative voiding	
219	Painful urination	
220	Bladder pressure or urinary frequency	Pressure on the bladder
221	Pressure on the bladder	
222	Nocturia	Deleted - medical terminology
223	Incontinence	Urinary incontinence
224	Urge incontinence	
225	Urinary stress incontinence	
226	Urinary incontinence	
227	Breathlessness	Breathlessness
228	Difficulty breathing	Difficulty breathing
229	Breathing difficulties	
230	Breathing problems	

Symptom term		Revised to
231	Respiratory difficulties	Deleted - non-specific
232	Respiratory symptoms	
233	Short of breath	Shortness of breath
234	Shortness of breath	
235	Shortness of breath with activity	
236	Shortness of breath at rest	
237	Pain in chest	Chest pain
238	Chest pain or respiratory difficulties	
239	Coughing	Coughing
240	Dyspnoea	Deleted - medical terminology
241	Pleurisy	
242	Pleural effusion	
243	Fluid in chest	
244	Local symptoms	Deleted - non-specific
245	General symptoms	
246	Headache	Deleted - non-specific
247	Headaches	
248	Backache	Backache
249	Pain in back	Back pain
250	Back pain	
251	Back pain, upper back	
252	Back pain, lower back	
253	Back pain, both lower and upper	
254	Lower back pain	

Symptom term		Revised to
255	Back pressure or pain	
256	Pain in shoulder or shoulder blade pain	Shoulder pain
257	Pain outside the abdominal cavity	Deleted - non-specific
258	Pain, side of trunk, flank	Pain in side of trunk, flank
259	Pain under ribs	
260	Pain in the side or ribs	
261	Pain - thoracic	Deleted - medical terminology
262	Pain inside	Deleted - non-specific
263	Pain - other sites	
264	Pain - site unspecified	
265	Sense of raised body temperature	Fever
266	Elevated temperature	
267	Fever	
268	Flu-like virus	Flu-like symptoms
269	Aching joints or muscles	Aching limbs
270	Leg cramps	Leg cramps
271	Leg pain	Leg pain
272	Thigh pain	
273	Pain or swelling in legs	
274	Leg swelling	Leg swelling
275	Deep venous thrombosis	
276	Ankle swelling	Ankle swelling
277	Swelling in ankles/legs	
278	Swelling of the legs or feet	

Symptom term		Revised to
279	Oedema, diffuse swelling, fluid retention	Deleted - medical terminology
280	Swollen lymph nodes	Swollen lymph nodes
281	Malaise	Malaise
282	General malaise	
283	Extreme fatigue	Fatigue
284	Fatigue	
285	Fatigue, lack of energy, general weakness	
286	Fatigue/lethargy/tiredness	
287	Ongoing fatigue	
288	Persisting fatigue or weight loss	
289	Exhaustion	
290	Feeling weak	Lack of energy
291	Unusual lack of energy	
292	Tiredness	Tiredness
293	Dizziness	Deleted - non-specific
294	Anorexia	Loss of appetite
295	Appetite loss	
296	Change in appetite	
297	Changed appetite	
298	Decreased appetite	
299	Lack of appetite/feeling full	
300	Loss of appetite	
301	Loss of appetite or difficulty eating	
302	Loss of appetite and weight	

Symptom term		Revised to
303	Unusual lack of appetite	
304	Early satiety	Feeling full quickly after beginning to eat
305	Difficulty eating	
306	Feeling full quickly	
307	Feeling full after a few bites of food	
308	Unable to eat normally	
309	Taste changes	Taste changes
310	Food intolerance	Deleted - non-specific
311	Food aversions	Deleted - non-specific
312	Weight loss	Weight loss Weight gain
313	Nondeliberate weight loss	
314	Unintentional weight loss	
315	Unplanned weight loss	
316	Loss of weight	
317	Unplanned weight gain	
318	Getting fat	
319	Weight gain	
320	Gained weight	
321	Obesity	
322	Unexplained weight gain or loss	
323	Change in weight	
324	Weight loss or gain	
325	Anaemia	Deleted - medical terminology
326	Severe anaemia	Deleted - medical terminology

Symptom term		Revised to
327	Fluid in lungs	Deleted - medical terminology
328	Non-menopausal hot flushes	Hot flushes
329	Menopausal symptoms, hot flushes	
330	Hot flashes	
331	Insomnia	Deleted - non-specific
332	Night sweats	Night sweats
333	Anxiety, panic attacks	Panic attacks
334	Panic attacks	
335	Umbilical hernia	Deleted - medical terminology
336	Breast swelling	Breast swelling
337	Mammary swelling	
338	Breast tenderness	Breast pain
339	Tenesmus	Deleted - medical terminology
340	Difficulty moving legs	Deleted - non-specific
341	Paresthesia, numbness, burning, tingling	Deleted - medical terminology
342	Irritable bowel syndrome	Deleted - non-specific
343	Constitutional symptoms	
344	Metastatic symptoms	
345	Symptoms of mass effect	
346	Systemic symptoms	
347	Regional symptoms	
348	Depression	Depression
349	Stress	Deleted - non-specific

Appendix IX Results of Health Professionals Interviews

Symptom	Relevance Mean	Prioritised (%)
Abdominal bloating	3.57	91
Abdominal fullness	3.29	57
Increased abdominal size	3.57	91
Abdominal tightening	2.38	19
Hard abdomen	2.14	14
Able to feel abdominal mass/lumps (abdomen)	2.33	52
Abdominal discomfort	3.10	81
Abdominal pain	2.57	48
Abdominal pressure	2.57	24
Abdominal cramping	1.62	0
Indigestion	2.76	71
Heartburn	2.19	24
Nausea/feeling sick	2.43	67
Vomiting/being sick	2.10	24
Reflux of food	2.05	5
Burping	1.43	5
Taste changes	1.33	0
Feeling full quickly after beginning to eat	2.10	33
Loss of appetite	2.81	67
Change in bowel habit	2.95	81
Constipation	2.52	38

Symptom	Relevance Mean	Prioritised (%)
Diarrhoea	2.19	24
Excessive passing of wind/flatulence	1.71	5
Difficulty opening bowels	2.38	14
Pain before, during or after opening bowels	1.81	10
Rectal pain	1.76	5
Rectal bleeding	1.43	10
Urgent need to open bowel	2.10	5
Bowel incontinence	1.38	0
Able to feel mass or lump (pelvis)	2.14	29
Pelvic discomfort	2.71	57
Pelvic pain	2.48	33
Pelvic cramping	1.76	5
Pelvic pressure	2.38	29
Pelvic fullness	2.48	33
Pelvic heaviness	2.24	24
Vaginal discharge	1.71	14
Vaginal bleeding	2.14	43
Vaginal pain	1.52	5
Pain during/after sexual intercourse	1.76	19
Bleeding during/after intercourse	1.38	10
Prolapse	1.71	0
Urgent need to pass urine	2.57	33
Passing urine frequently	3.10	76

Symptom	Relevance Mean	Prioritised (%)
Feeling of pressure on the bladder	2.76	71
Leakage of urine	2.00	5
Difficulty emptying bladder	2.19	14
Burning on passing urine	1.62	0
Pain on passing urine	1.57	0
Chest pain	1.14	0
Cough	1.38	5
Difficulty breathing	1.71	14
Shortness of breath	1.95	52
Backache	2.43	52
Back pain	2.05	33
Shoulder pain	1.38	5
Pain in side of trunk, flank	2.05	14
Pain in the hip/buttock/outside leg	1.43	5
Aching limbs	1.48	0
Pain in legs	1.33	0
Leg cramps	1.29	5
Leg swelling	2.29	33
Ankle swelling	2.05	19
Lump in neck	1.43	10
Fever/raised temperature	1.38	0
Tiredness	3.00	57
Fatigue	3.05	71

Symptom	Relevance Mean	Prioritised (%)
Lack of energy	2.95	48
Generally feeling unwell	3.14	86
Weight loss without trying	2.62	48
Weight gain without trying	2.67	67
Hot flushes	1.38	0
Night sweats	1.48	0
Breast swelling	1.14	0
Breast pain	1.10	0
Lump in breast	1.14	0
Difficulty sleeping	2.00	10
Feeling tense or anxious	1.76	14
Feeling down, depressed or hopeless?	1.67	0
Little interest or pleasure doing things?	1.76	10

Appendix X Example of Coded Qualitative Data from Health Professional Interviews

Symptom: Breast pain
Coded data for breast pain
Lead Nurse, Site 1
I haven't heard of that.
Research Nurse, Site 1
Sometimes …I'm trying to remember now, the women who talked about breast pain had breast cancer in the past, but I couldn't say that for sure. But um, it tends to be on the ward rounds, that's the only location you hear about symptoms being in the breast.
Consultant 1, Site 1
I'm not aware of a patient ever having breast pain.
Nurse Specialist, Site 1
I can't remember anyone talking about breast pain to me.
Registrar, Site 1
Breast pain, never seen it.
Consultant 2, Site 1
Breast pain is totally irrelevant.
Nurse Specialist, Site 2
I haven't come across that.
Consultant 1, Site 2
I've not come across that really.
Consultant 2, Site 2
I don't see the relevance of that in the context of ovarian tumours, unless you're looking for metastases from the breast.
Research Nurse, Site 2
Breast pain, never.
Consultant, Site 3
An hormonally active tumour could produce mastalgia, or breast discomfort but they are relatively rare tumours. All I can say if that I've not had any patients complain of that.
Research Nurse, Site 3
I haven't heard anybody say it's led them to the doctor and the diagnosis … Not at all, no, nobody has said that they've had breast pain.
Consultant, Site 4
It's connected with other problems but not ovarian cancer.
Research Nurse, Site 4
I haven't seen that.

Consultant, Site 5

It's not something that I've seen women complaining of.

Appendix XI Results of Telephone Interviews with Women with Ovarian Cancer

Symptom	Relevance Mean	Symptom caused most trouble (%)
Pelvic fullness	1.00	0
Pain during/after sexual intercourse	1.06	0
Pain when passing urine	1.08	0
Pelvic heaviness	1.08	0
Able to feel abdominal mass or lumps	1.12	0
Abnormal vaginal discharge	1.12	4
Abdominal discomfort, pain or pressure	1.16	0
Pain in side of trunk, flank	1.16	0
Abnormal vaginal bleeding	1.16	4
Aching limbs	1.20	0
Difficulty emptying bladder	1.20	0
Leg swelling	1.20	0
Nausea/feeling sick or vomiting/being sick	1.20	0
Shortness of breath	1.20	0
Weight loss without trying	1.28	0
Feeling of pressure on the bladder	1.32	8
Leg pain	1.36	0
Feeling full quickly after beginning to eat	1.36	8
Change in bowel habit	1.40	0
Change in appetite	1.40	4

Symptom	Relevance Mean	Symptom caused most trouble (%)
Back ache/pain	1.44	0
Difficulty emptying bowels	1.44	0
Generally feeling unwell	1.44	4
Heartburn	1.44	4
Pain before, during or after opening bowels	1.44	4
Excessive passing of wind/flatulence	1.48	0
Urgent need to pass urine	1.48	12
Indigestion	1.56	4
Abdominal bloating or fullness	1.68	8
Weight gain without trying	1.72	0
Passing urine frequently	1.80	8
Increased abdominal size/waistband feels tighter	1.88	4
Lower abdominal/pelvic discomfort, pain or pressure	1.96	24
Tiredness, fatigue or lack of energy	2.04	4

Appendix XII Pilot Ovarian Cancer Symptoms Questionnaire (OCSq)

United Kingdom Collaborative Trial of Ovarian Cancer Screening

Please read the enclosed information sheet and sign the consent section before starting the questionnaire.

How to complete this questionnaire:

For each item please tick the extent to which you have experienced it during the past week (either not at all, a little, quite a bit or very much), tick the number of days in the past week it has been experienced, tick how many months since it first started and tick whether or not you have discussed it with a GP in the past three months.

If you have not had the symptom in the past week tick 'not at all' and move onto the next question.

Below is an example of how to fill in the questionnaire. This shows that the woman had hot flushes 'a little' for three to five days during the past week, has been having hot flushes for more than a year and has not discussed her hot flushes with the GP during the past three months.

During the past week:	not at all	a little	quite a bit	very much	Number of days present during past week	How many months have you had this?	Discussed with GP in past 3 months?
E.g. Have you had hot flushes?	☐ 0	☑ 1	☐ 2	☐ 3	☐ 1-2 days ☑ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☑ more than 12	☐ Yes ☑ No

Please feel free to leave out any question if you feel uncomfortable replying to it, or for any other reason.

The questionnaire has 7 pages and takes approximately 15 minutes to complete.

Please fill-in the consent section below before turning over the page to start the questionnaire

---

Please initial each box

1 I have read the understand the information sheet dated 3 April 2008, version 3. ☐

2 I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected. ☐

3 I understand that information collected by the UKCTOCS study may be looked at by the researcher where it is relevant to my taking part in the research. I give permission for the researcher to have access to my UKCTOCS records. ☐

4 I agree to take part in the study. ☐

Name _____ Date _____ Signature _____

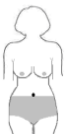
Date ☐☐ ☐☐ ☐☐☐☐ Volunteer Ref ☐☐☐☐☐☐☐☐☐☐

For each item please tick the extent to which you have experienced it during the past week, tick the number of days in the past week it has been experienced, tick how many months since it first started and tick whether or not you have discussed it with a GP in the past three months.

During the past week:		**not at all**	**a little**	**quite a bit**	**very much**	**Number of days present during past week**	**How many months have you had this?**	**Discussed with GP in past 3 months?**
Q1	Have you had lower abdominal or pelvic discomfort or pain?  shaded area indicates site of symptom	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
		if not at all move to next question →						
Q2	Have you had upper abdominal discomfort or pain?  shaded area indicates site of symptom	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
		if not at all move to next question →						
Q3	Have you had indigestion or heartburn?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
		if not at all move to next question →						
Q4	Have you had nausea or vomiting?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
		if not at all move to next question →						
Q5	Have you felt full quickly when eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
		if not at all move to next question →						

→

Volunteer Ref ☐☐☐☐☐☐☐☐☐

During the past week:	not at all	a little	quite a bit	very much	Number of days present during past week	How many months have you had this?	Discussed with GP in past 3 months?
Q6 Have you had a change in appetite?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question ←						
Q7 Have you had a feeling of upper abdominal bloating or fullness?  shaded area indicates site of symptom	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question ←						
Q8 Have you had a feeling of upper abdominal pressure?  shaded area indicates site of symptom	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question ←						
Q9 Have you had increased abdominal size or waistbands of clothes feeling too tight?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question ←						
Q10 Were you able to feel an abdominal mass or lump?	☐ 0	☐ 1	☐ 2	☐ 3	N/A	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question ←						
Q11 Have you had a feeling of lower abdominal or pelvic bloating or fullness?  shaded area indicates site of symptom	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question ←						

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Volunteer Ref ☐☐☐☐☐☐☐☐

During the past week:	not at all	a little	quite a bit	very much	Number of days present during past week	How many months have you had this?	Discussed with GP in past 3 months?
Q12 Have you had a feeling of lower abdominal or pelvic pressure?  shaded area indicates site of symptom	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question						
Q13 Have you had a feeling of lower abdominal or pelvic heaviness?  shaded area indicates site of symptom	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question						
Q14 Have you had pain before, during or after opening your bowels?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question						
Q15 Have you had difficulty emptying your bowels?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question						
Q16 Have you had a change in bowel habit?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question						
Q17 Have you had excessive passing of wind or flatulence?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question						

Volunteer Ref ☐☐☐☐☐☐☐☐☐☐

During the past week:	not at all	a little	quite a bit	very much	Number of days present during past week	How many months have you had this?	Discussed with GP in past 3 months?
Q18 Have you passed urine frequently?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						
Q19 When you felt the urge to pass urine did you have to hurry to get to the toilet?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						
Q20 Have you had a feeling of pressure on the bladder?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						
Q21 Have you had difficulty emptying the bladder?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						
Q22 Have you had pain when passing urine?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						
Q23 Were you short of breath?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						

→

Volunteer Ref ☐☐☐☐☐☐☐☐☐

During the past week:	not at all	a little	quite a bit	very much	Number of days present during past week	How many months have you had this?	Discussed with GP in past 3 months?
Q24 Have you had ache or pain in your back?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						
Q25 Have you had an ache or pain in one or both legs?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						
Q26 Have you had swelling in one or both legs?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						
Q27 Have you had a feeling of tiredness, fatigue or lack of energy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						
Q28 Have you gained weight without trying?	☐ 0	☐ 1	☐ 2	☐ 3	N/A	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						
Q29 Have you lost weight without trying?	☐ 0	☐ 1	☐ 2	☐ 3	N/A	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						

→

Volunteer Ref ☐☐☐☐☐☐☐☐☐

During the past week:	not at all	a little	quite a bit	very much	Number of days present during past week	How many months have you had this?	Discussed with GP in past 3 months?
Q30 Have you had abnormal vaginal bleeding?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						
Q31 Have you had abnormal vaginal discharge?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						

Please answer this question only if you have been sexually active during the past week:

Q32 Have you had pain during or after sexual intercourse?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No
	if not at all move to next question →						

During the past week have you experienced any other symptoms? If so, please make a note of the symptom(s) in the space(s) below and on the next page.

For each symptom(s) please tick the extent to which you have experienced it during the past week, tick the number of days in the past week it has been experienced, tick how many months since it first started and tick whether or not you have discussed it with a GP in the past three months

During the past week:	a little	quite a bit	very much	Number of days present during past week	How many months have you had this?	Discussed with GP in past 3 months?
33a _____	☐ 1	☐ 2	☐ 3	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12	☐ Yes ☐ No

→

33b _____ ☐ 1 ☐ 2 ☐ 3 ☐ 1-2 days ☐ 3-5 days ☐ 6-7 days ☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12 ☐ Yes ☐ No

33c _____ ☐ 1 ☐ 2 ☐ 3 ☐ 1-2 days ☐ 3-5 days ☐ 6-7 days ☐ less than 3 ☐ 3-6 months ☐ 7-12 months ☐ more than 12 ☐ Yes ☐ No

Q34 Have you ever been diagnosed by a doctor with any of the following conditions?

Please tick all that apply:

Heart failure	☐	Chronic bronchitis	☐	Hiatus hernia	☐
Irritable Bowel Disease (IBS)	☐	Emphysema	☐	Arthritis	☐
Inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis)	☐	Endometriosis	☐	Depression	☐
Cancer	☐				

Please specify type of cancer: _____

Q35. Are you currently taking hormone replacement therapy (HRT)?
Please tick yes or no
☐ Yes
☐ No

Q36. During the past month have you often been bothered by feeling down, depressed or hopeless?
Please tick yes or no
☐ Yes
☐ No

Q37. During the past month have you often been bothered by little interest or pleasure doing things?
Please tick yes or no
☐ Yes
☐ No

Thank you for taking the time to complete this questionnaire

Please remember this is only a survey, if you have any symptoms that are worrying or persistent please discuss them with your GP.

Appendix XIII GP Letter and Fact Sheet

United Kingdom Collaborative Trial of Ovarian Cancer Screening

UKCTOCS Coordinating Centre
Gynaecological Cancer Research Centre
Institute of Women's Health, UCL
Maple House, 1st Floor
149 Tottenham Court Road
London W1T 7DN

{GP Name}
{GP Address 1}
{GP Address 2}, {GP County}
{GP Postcode}

Date

MREC Reference No: 06/Q0505/103

Dear Dr {GP name},

Re: United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOC) sub-study: Prospective study of ovarian cancer symptoms

I am writing to let you know about a sub-study of UKCTOCS that is investigating symptoms that precede a diagnosis of ovarian cancer. This study has two objectives: 1) to develop a valid and reliable ovarian cancer symptoms questionnaire and; 2) to identify type, severity, frequency and duration of symptoms that precede a diagnosis of ovarian cancer in post-menopausal women using the UKCTOCS cohort. The study is funded by the MRC and will be co-ordinated by the Ovarian Cancer Screening Unit at University College London.

Healthy women, aged 50-74 years, who are already enrolled in the UKCTOCS study will be invited to participate in the ovarian cancer symptoms study. Women who wish to participate will be asked about symptoms found to be associated with ovarian cancer in previous studies. The participant information sheet states, 'Many of the symptoms listed in the questionnaire are common in healthy people or may be related to other conditions. However, if you are worried about any symptoms please contact your GP.' Participants in the sub-study will continue being followed-up as usual in the UKCTOCS study.

A fact sheet about the symptoms sub-study is attached. If you would like further information or have any questions about the study please do not hesitate to contact either Usha Menon or Ms Penny Allen on 0207 380 2125.

Yours sincerely

Usha Menon, MD, MRCOG
Director of Clinical Research

Prospective Study of Symptoms Preceding Ovarian Cancer Diagnosis Using the UKCTOCS Cohort – Fact Sheet

Funding bodies	MRC, Eve Appeal
Design	• Questionnaire development according to European Organisation for Research and Treatment of Cancer (EORTC) guidelines • Prospective study of symptoms that precede a diagnosis of ovarian cancer using a postal questionnaire sent to all three UKCTOCS groups (controls, multimodal group and ultrasound group)
Objectives	**Objective 1** • To develop a valid and reliable ovarian cancer symptoms questionnaire according to EORTC guidelines **Objective 2** • To identify type, severity, frequency, and duration of symptoms that precede a diagnosis of ovarian cancer in postmenopausal women
Endpoints/primary outcomes	Diagnosis of ovarian cancer and identification of symptom type, severity, frequency and duration prior to diagnosis
Inclusion/exclusion criteria	**Inclusion criteria** • Participation in UKCTOCS **Exclusion criteria** • Those who have been withdrawn from UKCTOCS
Recruitment	• Women will be posted invitations to participate in interviews to assist in the development of the symptoms questionnaire. • Women will be posted the finalised symptoms questionnaire. If they wish to participate they will be advised to sign the consent section and complete the questionnaire.
Planned sample size	• Interviews to assist in the development of the symptoms questionnaire: 15 interviews with clinicians, 15 interviews with women enrolled in UKCTOCS, 15 interviews with women who participated in UKCTOCS and had a confirmed diagnosis of ovarian cancer. • 1,000 women participating in UKCTOCS to field-test the draft symptoms questionnaire and provide feedback. • 100,000 women in the finalised prospective symptoms questionnaire study.

Follow-up	• Via UKCTOCS postal follow-up and ONS flagging
Study duration	February 2007 to March 2010
Contact details	Penny Allen or Dr Usha Menon Gynaecological Cancer Research Centre Institute of Women's Health University College London Maple House, 1st Floor 149 Tottenham Court Road London, W1T 7DN Telephone: 0207 380 2125, Email: p.allen@ucl.ac.uk

Appendix XIV Pilot OCSq Invitation Letter

United Kingdom Collaborative Trial of Ovarian Cancer Screening

Department of Gynaecological Oncology
Level 1, Maple House
149 Tottenham Court Road
London
W1T 7DN

(Name)
(Address line 1)
(Address line 2)
(Address line 3)

Date Volunteer Ref:

Dear (name),

We are writing to you about a new study that is being conducted as part of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). The study is inviting a group of randomly selected women who are participating in UKCTOCS to complete a draft symptoms questionnaire and provide feedback on its content.

If you wish to take part please read the enclosed study information sheet, sign the consent section and complete the questionnaire. Please return the completed questionnaire in the freepost envelope provided.

Please take care to complete both sides of the questionnaires as it is printed double-sided.

If you would like more information about the study please contact Penny Allen on 0207 380 6919 or 0789 733 7573.

Thank you for taking the time to read this information.

Yours sincerely

Penny Allen

Appendix XV Pilot OCSq Study Information Sheet

United Kingdom Collaborative Trial of Ovarian Cancer Screening

Prospective study of ovarian cancer symptoms

As a participant in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) you are being asked to take part in research to develop an ovarian cancer symptoms questionnaire. Before you decide to take part it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

Previous research has reported that the early symptoms of ovarian cancer are subtle or non-specific. Due to this the majority of women are diagnosed with ovarian cancer after it has spread from the ovaries. By then it is much more difficult to treat and as a consequence many women will die of the cancer. By contrast, treatment is more successful and the outlook can be good for women diagnosed before the cancer has spread. The purpose of this study is to develop a valid and reliable ovarian cancer symptoms questionnaire.

Why have I been chosen?

This study is a sub-study of the United Kingdom Collaborative Trial of Ovarian Cancer Screening and you are already participating in UKCTOCS. We are inviting a randomly selected group of women to take part in the questionnaire validation process.

Do I have to fulfil any other criteria to take part?

The only criteria you need to fulfil are:

- Already enrolled in the United Kingdom Collaborative Trial of Ovarian Cancer Screening.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign the consent section of the questionnaire and fill in the questionnaire and feedback form. The consent for this study is different to the original consent form that you signed to enrol in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. If you decide not to take part you do not have to give a reason. Deciding to participate or not will not affect any medical care you receive.

What will happen to me if I take part?

Symptoms Questionnaire

If you would like to take part in this study please complete the consent section of the questionnaire then fill in the questionnaire. Please also fill in the questionnaire feedback form and return both forms in the freepost envelope provided. If you have any questions please contact the researcher, Penny Allen, on the telephone number at the end of this form, who will discuss the study in greater detail and will give you the opportunity to ask any questions.

What are the possible disadvantages of taking part?

- Participation in the questionnaires will take approximately 20-30 minutes of your time.
- Thinking about symptoms may create anxiety in some women.

What are the possible benefits of taking part?

- There are no direct benefits of taking part although being asked about symptoms may help some women to remember symptoms that should be discussed with their doctor.

What if I have experienced any of the symptoms in the questionnaire or am worried about symptoms?

Please keep in mind that you have been randomly selected to participate in the survey, not for any other reason. Many of the symptoms listed in the questionnaire are common in healthy people or may be related to other conditions. If you are worried about any symptoms please contact your GP or gynaecologist.

What if something goes wrong?

It is not anticipated that anything will go wrong in this study as it only involves you filling in the enclosed questionnaire. It does not involve any tests or other questions.

You will always be able to contact the researcher to discuss your concerns about the study. Every care will be taken to ensure your safety during the course of the study. University College London (UCL), the Research Governance Sponsor, has indemnity (insurance) arrangements in place for non-negligent harm, in the event that something does go wrong and you are harmed as a result of taking part in this study. If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation but you may have to pay your legal costs.

Will taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Only your UKCTOCS volunteer reference number is on the questionnaire, not your name or any other personal details. We will separately store the consent section from the rest of your questionnaire.

Occasionally the research documentation and results will be looked at by the people funding the research programme to check that the study is being carried out properly. Any information which is viewed by people not directly related to the research team will not have your name and address on it.

What will happen to the results of the research study?

The results of the research will be used in a PhD study of the symptoms of ovarian cancer. Additionally, the results will be reviewed by medical professionals and published in the medical press. Individuals will not be identified in any publications.

Who is organising and funding the research?

The research is part of a PhD study that is linked to the United Kingdom Collaborative Trial of Ovarian Cancer Screening. The Medical Research Council is funding the study.

Contact for further information

For further information please telephone Penny Allen in the Department of Gynaecological Oncology on 0207 380 6919 or 0789 733 7573. Alternatively, you can write to:

Penny Allen
Department of Gynaecological Oncology
UCL Institute for Women's Health
Level 1, Maple House
149 Tottenham Court Road
London
W1T 7DN

Thank you for taking the time to read this information.

Appendix XVI Pilot OCSq Consent Form

United Kingdom Collaborative Trial of Ovarian Cancer Screening

Prospective Study of Ovarian Cancer Symptoms

Consent Section for Questionnaire

		Please initial box
1.	I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected.	☐
3.	I understand that information collected by the UKCTOCS study may be looked at by the researcher where it is relevant to my taking part in the research. I give permission for the researcher to have access to my UKCTOCS records.	☐
5.	I agree to take part in the study.	☐

_____ _____ _____

Name of study volunteer Date Signature

Appendix XVII Pilot OCSq Retest Validation Invitation Letter

Department of Gynaecological Oncology
Level 1, Maple House
149 Tottenham Court Road
London
W1T 7DN

(Name)
(Address line 1)
(Address line 2)
(Address line 3)

Date Volunteer Ref:

Dear (name),

We are writing to you about a new study that is being conducted as part of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). The study is inviting a group of randomly selected women who are participating in UKCTOCS to complete a draft symptoms questionnaire and provide feedback on its content.

If you wish to take part please read the enclosed study information sheet, sign the consent section and complete questionnaire A. Two days later please complete questionnaire B. Please do not copy information from questionnaire A to questionnaire B as we wish to know about your symptoms on the two different dates. If you have any difficulties completing the questionnaire, or have any comments, please write these on the feedback sheet. Please return the completed questionnaires in the freepost envelope provided.

Please take care to complete both sides of the questionnaires as they are printed double-sided.

If you would like more information about the study please contact Penny Allen on 0207 380 6919 or 0789 733 7573.

Thank you for taking the time to read this information.

Yours sincerely
Penny Allen

Appendix XVIII Pilot OCSq Retest Validation Study Information Sheet

United Kingdom Collaborative Trial of Ovarian Cancer Screening

Prospective study of ovarian cancer symptoms

As a participant in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) you are being asked to take part in research to develop an ovarian cancer symptoms questionnaire. Before you decide to take part it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

Previous research has reported that the early symptoms of ovarian cancer are subtle or non-specific. Due to this the majority of women are diagnosed with ovarian cancer after it has spread from the ovaries. By then it is much more difficult to treat and as a consequence many women will die of the cancer. By contrast, treatment is more successful and the outlook can be good for women diagnosed before the cancer has spread. The purpose of this study is to develop a valid and reliable ovarian cancer symptoms questionnaire.

Why have I been chosen?

This study is a sub-study of the United Kingdom Collaborative Trial of Ovarian Cancer Screening and you are already participating in UKCTOCS. We are inviting a randomly selected group of women to take part in the questionnaire validation process.

Do I have to fulfil any other criteria to take part?

The only criteria you need to fulfil are:

- Already enrolled in the United Kingdom Collaborative Trial of Ovarian Cancer Screening.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign the consent section of the questionnaire and fill in the questionnaire and feedback form. The consent for this study is different to the original consent form that you signed to enrol in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. If you decide not to take part you do not have to give a reason. Deciding to participate or not will not affect any medical care you receive.

What will happen to me if I take part?

Symptoms Questionnaire

If you would like to take part in this study please complete the consent section then fill in questionnaire A. Please also fill in the questionnaire feedback form. Two days later please complete questionnaire B. We would like to know about your symptom experiences on the two separate dates so please don't copy from questionnaire A. Please return all forms in the freepost envelope provided. If you have any questions please contact the researcher, Penny Allen, on the telephone number at the end of this form, who will discuss the study in greater detail and will give you the opportunity to ask any questions.

What are the possible disadvantages of taking part?

- Participation in the questionnaires will take approximately 40 minutes of your time.
- Thinking about symptoms may create anxiety in some women.

What are the possible benefits of taking part?

- There are no direct benefits of taking part although being asked about symptoms may help some women to remember symptoms that should be discussed with their doctor.

What if I have experienced any of the symptoms in the questionnaire or am worried about symptoms?

Please keep in mind that you have been randomly selected to participate in the survey, not for any other reason. Many of the symptoms listed in the questionnaire are common in healthy people or may be related to other conditions. If you are worried about any symptoms please contact your GP or gynaecologist.

What if something goes wrong?

It is not anticipated that anything will go wrong in this study as it only involves you filling in the enclosed questionnaire. It does not involve any tests or other questions.

You will always be able to contact the researcher to discuss your concerns about the study. Every care will be taken to ensure your safety during the course of the study. University College London (UCL), the Research Governance Sponsor, has indemnity (insurance) arrangements in place for non-negligent harm, in the event that something does go wrong and you are harmed as a result of taking part in this study. If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation but you may have to pay your legal costs.

Will taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Only your UKCTOCS volunteer reference number is on the questionnaire, not your name or any other personal details. We will separately store the consent section from the rest of your questionnaire.

Occasionally the research documentation and results will be looked at by the people funding the research programme to check that the study is being carried out properly. Any information which is viewed by people not directly related to the research team will not have your name and address on it.

What will happen to the results of the research study?

The results of the research will be used in a PhD study of the symptoms of ovarian cancer. Additionally, the results will be reviewed by medical professionals and published in the medical press. Individuals will not be identified in any publications.

Who is organising and funding the research?

The research is part of a PhD study that is linked to the United Kingdom Collaborative Trial of Ovarian Cancer Screening. The Medical Research Council is funding the study.

Contact for further information

For further information please telephone Penny Allen in the Department of Gynaecological Oncology on 0207 380 6919 or 0789 733 7573. Alternatively, you can write to:

Penny Allen
Department of Gynaecological Oncology
UCL Institute for Women's Health
Level 1, Maple House
149 Tottenham Court Road
London
W1T 7DN

Thank you for taking the time to read this information.

Appendix XIX Pilot OCSq Feedback Form

United Kingdom Collaborative Trial of Ovarian Cancer Screening

Development of a Questionnaire for the Prospective Study of Ovarian Cancer Symptoms

Feedback questions

UKCTOCS Reference Number | | | | | | | | |

1. How long did it take you to complete the questionnaire? (please circle one option)

   1 = 10-15 mins
   2 = 16-20 mins
   3 = 21-30 mins
   4 = more than 30 mins

2. Did anyone help you to complete the questionnaire? (please circle yes or no)

   0 = No
   1 = Yes Who provided you with help? _____

If yes, which questions did you receive help with? (please tick all that apply):

Q1.		Q6.		Q11.		Q16.		Q21.		Q26.		Q31.		Q36.	
Q2.		Q7.		Q12.		Q17.		Q22.		Q27.		Q32.		Q37.	
Q3.		Q8.		Q13.		Q18.		Q23.		Q28.		Q33.			
Q4.		Q9.		Q14		Q19.		Q24		Q29.		Q34.			
Q5.		Q10.		Q15.		Q20.		Q25.		Q30		Q35			

Please explain about the type of help you received for each question ticked above:

3. Did you have difficulty answering any questions? (please circle yes or no)

0 = No
1 = Yes

If yes, which questions did you have difficulty answering? (please tick all that apply):

Q1.		Q6.		Q11.		Q16.		Q21.		Q26.		Q31.		Q36.	
Q2.		Q7.		Q12.		Q17.		Q22.		Q27.		Q32.		Q37.	
Q3.		Q8.		Q13.		Q18.		Q23.		Q28.		Q33.			
Q4.		Q9.		Q14		Q19.		Q24		Q29.		Q34.			
Q5.		Q10.		Q15.		Q20.		Q25.		Q30		Q35			

Please explain about the type of difficulty you had for each question ticked above:

4. Were there questions that you found upsetting? (please circle yes or no)

0 = No
1 = Yes

If yes, which questions did you find upsetting? (please tick all that apply):

Q1.		Q6.		Q11.		Q16.		Q21.		Q26.		Q31.		Q36.	
Q2.		Q7.		Q12.		Q17.		Q22.		Q27.		Q32.		Q37.	
Q3.		Q8.		Q13.		Q18.		Q23.		Q28.		Q33.			
Q4.		Q9.		Q14		Q19.		Q24		Q29.		Q34.			
Q5.		Q10.		Q15.		Q20.		Q25.		Q30		Q35			

For each question ticked above please explain how it was upsetting:

5. Were there any questions that you found irrelevant? (please circle yes or no)

0 = No
1 = Yes

If yes, which questions did you find irrelevant? (please tick all that apply):

Q1.		Q6.		Q11.		Q16.		Q21.		Q26.		Q31.		Q36.	
Q2.		Q7.		Q12.		Q17.		Q22.		Q27.		Q32.		Q37.	
Q3.		Q8.		Q13.		Q18.		Q23.		Q28.		Q33.	
Q4.		Q9.		Q14		Q19.		Q24		Q29.		Q34.	
Q5.		Q10.		Q15.		Q20.		Q25.		Q30		Q35	

For each question ticked above please explain why you found it irrelevant:

6. Please use the space below if you have other issues with the questionnaire or comments:

Thank you for completing the for m.

Appendix XX Pilot OCSq Spearman Correlations Table

		Pelv discom/pain	Abdom discom/pain	Indigh/heartburn	Naus/vom	Full quickly	Change appetite	Abdom bloat/full	Abdom pressure	Increased abdom size	Abdom lump	Pelv bloat/full	Pelv pressure	Pelv heaviness	Pain on open bowels
Pelv discom/pain	r_s	1.00													
	Signif.	.													
	n	776													
Abdom discom/pain	r_s	0.49	1.00												
	Signif.	0.000	.												
	n	762	764												
Indigh/heartburn	r_s	0.35	0.43	1.00											
	Signif.	0.000	0.000	.											
	n	763	756	778											
Naus/vom	r_s	0.38	0.35	0.30	1.00										
	Signif.	0.000	0.000	0.000	.										
	n	759	754	756	763										
Felt full quickly	r_s	0.31	0.36	0.33	0.36	1.00									
	Signif.	0.000	0.000	0.000	0.000	.									
	n	761	754	759	758	768									
Change appetite	r_s	0.23	0.24	0.23	0.28	0.44	1.00								
	Signif.	0.000	0.000	0.000	0.000	0.000	.								
	n	755	749	755	750	753	764								
Abdom bloat/full	r_s	0.35	0.49	0.45	0.30	0.50	0.25	1.00							
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	.							
	n	758	753	755	755	756	755	767							
Abdom pressure	r_s	0.32	0.49	0.28	0.30	0.36	0.19	0.53	1.00						
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	.						
	n	742	738	739	740	740	742	748	748						
Increased abdominal size	r_s	0.33	0.36	0.38	0.25	0.31	0.23	0.55	0.45	1.00					
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	.					
	n	752	745	751	746	748	750	754	743	763					
Abdom lump	r_s	0.17	0.25	0.15	0.19	0.15	0.07	0.17	0.22	0.14	1.00				
	Signif.	0.000	0.000	0.000	0.000	0.000	0.043	0.000	0.000	0.000	.				
	n	744	739	742	740	738	745	745	740	744	749				
Pelv bloat/full	r_s	0.54	0.38	0.29	0.29	0.35	0.16	0.40	0.33	0.41	0.17	1.00			
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	.			
	n	752	745	747	746	746	749	752	744	748	745	759			
Pelv pressure	r_s	0.59	0.44	0.30	0.36	0.31	0.18	0.34	0.38	0.36	0.24	0.55	1.00		
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	.		
	n	748	742	744	743	745	743	748	739	745	738	747	755		

		Pelv discom/pain	Abdom discom/pain	Indigh/eartb urn	Nausv/om	Full quickly	Change appetite	Abdom bloat/full	Abdom pressure	Increased abdom size	Abdom lump	Pelv bloat/full	Pelv pressure	Pelv heaviness	Pain open bowels
Pelv heaviness	r_s	0.54	0.37	0.22	0.37	0.34	0.21	0.33	0.37	0.36	0.21	0.56	0.64	1.00	
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	.	
	n	742	736	739	739	738	738	741	734	738	734	742	742	748	
Pain open bowels	r_s	0.45	0.36	0.30	0.27	0.22	0.20	0.24	0.20	0.24	0.12	0.33	0.34	0.40	1.00
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	.
	n	751	744	751	744	746	746	749	737	746	738	746	745	741	762
Diff empty bowels	r_s	0.27	0.25	0.22	0.25	0.28	0.18	0.21	0.22	0.20	0.15	0.30	0.27	0.28	0.42
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	n	756	750	758	752	752	752	756	743	752	746	753	752	746	756
Change bowel	r_s	0.28	0.22	0.19	0.24	0.25	0.17	0.26	0.20	0.29	0.10	0.30	0.29	0.24	0.29
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.006	0.000	0.000	0.000	0.000
	n	744	739	745	743	742	743	745	735	739	737	742	742	738	744
Excess flatulence	r_s	0.38	0.28	0.35	0.27	0.33	0.09	0.40	0.29	0.41	0.15	0.42	0.36	0.33	0.33
	Signif.	0.000	0.000	0.000	0.000	0.000	0.015	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	n	756	749	755	748	751	748	754	740	751	740	750	750	743	752
Urinary freq	r_s	0.24	0.18	0.16	0.21	0.21	0.19	0.18	0.21	0.30	0.09	0.21	0.22	0.21	0.20
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.018	0.000	0.000	0.000	0.000
	n	745	739	745	737	741	740	742	732	742	731	738	736	729	738
Urinary urgency	r_s	0.24	0.20	0.16	0.22	0.21	0.17	0.23	0.19	0.27	0.09	0.21	0.24	0.23	0.24
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.016	0.000	0.000	0.000	0.000
	n	752	745	751	745	749	745	751	736	747	734	744	743	737	747
Pressure bladder	r_s	0.32	0.31	0.22	0.29	0.23	0.15	0.29	0.30	0.25	0.10	0.30	0.38	0.34	0.28
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.006	0.000	0.000	0.000	0.000
	n	748	743	746	743	746	744	747	735	742	735	743	742	735	746
Diff empty bladder	r_s	0.17	0.17	0.12	0.15	0.17	0.14	0.13	0.13	0.21	0.07	0.19	0.27	0.19	0.10
	Signif.	0.000	0.000	0.002	0.000	0.000	0.000	0.001	0.000	0.000	0.071	0.000	0.000	0.000	0.005
	n	742	739	741	740	740	739	743	734	738	735	738	738	732	740
Pain pass urine	r_s	0.20	0.17	0.13	0.22	0.14	0.10	0.09	0.15	0.13	0.07	0.19	0.30	0.24	0.15
	Signif.	0.000	0.000	0.000	0.000	0.000	0.006	0.014	0.000	0.000	0.059	0.000	0.000	0.000	0.000
	n	745	741	743	741	742	742	744	736	742	738	742	742	735	743
Short breath	r_s	0.20	0.24	0.28	0.15	0.24	0.07	0.25	0.21	0.25	-0.02	0.16	0.20	0.14	0.16
	Signif.	0.000	0.000	0.000	0.000	0.000	0.056	0.000	0.000	0.000	0.580	0.000	0.000	0.000	0.000
	n	741	738	742	737	741	740	743	731	738	731	738	737	730	738
Back ache/pain	r_s	0.34	0.31	0.30	0.25	0.25	0.16	0.29	0.23	0.23	0.11	0.29	0.30	0.31	0.23
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.000	0.000	0.000	0.000
	n	748	740	749	741	744	742	747	730	741	731	739	740	732	744

		Pelv discom/pain	Abdom discom/pain	Indigh/eartb urn	Naus/vom	Full quickly	Change appetite	Abdom bloat/full	Abdom pressure	Increased abdom size	Abdom lump	Pelv bloat/full	Pelv pressure	Pelv heaviness	Pain open bowels
Leg ache/pain	r_s	0.26	0.28	0.26	0.23	0.28	0.20	0.28	0.19	0.27	0.10	0.20	0.29	0.19	0.25
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.007	0.000	0.000	0.000	0.000
	n	744	737	744	739	741	739	741	726	738	728	737	737	731	741
Leg swelling	r_s	0.20	0.21	0.20	0.17	0.21	0.19	0.20	0.11	0.23	0.02	0.19	0.27	0.23	0.21
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.003	0.000	0.552	0.000	0.000	0.000	0.000
	n	749	744	749	745	747	744	746	735	743	736	743	742	737	745
Tired/fatigue	r_s	0.33	0.32	0.33	0.32	0.36	0.28	0.36	0.28	0.37	0.12	0.34	0.31	0.34	0.30
	Signif.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.000
	n	747	741	751	741	746	741	746	729	743	730	738	737	730	743
Weight gain	r_s	0.23	0.23	0.24	0.14	0.19	0.10	0.28	0.26	0.50	0.04	0.23	0.27	0.28	0.20
	Signif.	0.000	0.000	0.000	0.000	0.000	0.009	0.000	0.000	0.000	0.249	0.000	0.000	0.000	0.000
	n	746	742	746	741	741	742	744	732	744	734	739	739	733	744
Weight loss	r_s	0.02	0.03	0.06	0.07	0.20	0.28	0.10	0.00	-0.01	0.00	0.01	0.02	0.03	0.04
	Signif.	0.613	0.492	0.128	0.048	0.000	0.000	0.008	0.927	0.794	0.981	0.782	0.663	0.358	0.233
	n	739	735	739	737	737	737	738	729	735	732	735	736	730	738
Abnor vag bleed	r_s	0.05	-0.02	0.02	0.03	0.03	0.04	0.04	0.06	0.05	-0.02	0.05	0.05	0.06	0.01
	Signif.	0.145	0.543	0.563	0.435	0.383	0.228	0.241	0.082	0.220	0.608	0.189	0.181	0.098	0.803
	n	743	740	741	740	739	740	741	732	740	735	739	737	732	740
Abnor vag discher	r_s	0.20	0.11	0.12	0.18	0.14	0.05	0.09	0.09	0.06	0.03	0.16	0.14	0.19	0.17
	Signif.	0.000	0.002	0.001	0.000	0.000	0.169	0.011	0.017	0.131	0.349	0.000	0.000	0.000	0.000
	n	744	740	742	741	742	741	742	733	740	734	739	738	733	741
Pain intercourse	r_s	0.26	0.28	0.16	0.24	0.16	0.22	0.06	0.16	0.11	0.06	0.12	0.25	0.10	0.12
	Signif.	0.000	0.000	0.013	0.000	0.015	0.000	0.325	0.015	0.089	0.394	0.067	0.000	0.120	0.075
	n	244	244	242	241	243	243	244	241	244	241	243	242	239	240

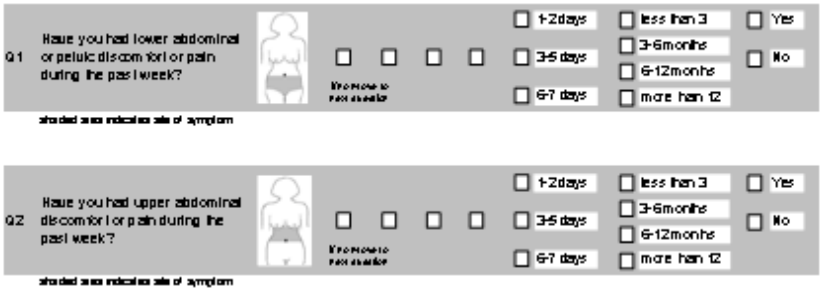
	Diff empty bowels	Change bowel	Excess flatulence	Urinary freq	Urinary urgency	Pressure bladder	Diff empty bladder	Pain pass urine	Short breath	Back ache/pain	Leg ache/pain	Leg swelling	Tired/fatigue	Weight gain	Weight loss	Abnor vag bleed
Pelv heaviness																
Pain open bowels																
Diff empty bowels	1.00															
	.															
	768															
Change bowel	0.36	1.00														
	0.000	.														
	752	755														
Excess flatulence	0.30	0.36	1.00													
	0.000	0.000	.													
	757	745	771													
Urinary freq	0.21	0.15	0.30	1.00												
	0.000	0.000	0.000	.												
	744	733	747	763												
Urinary urgency	0.23	0.11	0.29	0.63	1.00											
	0.000	0.004	0.000	0.000	.											
	752	739	753	754	772											
Pressure bladder	0.16	0.15	0.29	0.44	0.49	1.00										
	0.000	0.000	0.000	0.000	0.000	.										
	751	742	747	746	752	761										
Diff empty bladder	0.09	0.14	0.19	0.29	0.23	0.32	1.00									
	0.014	0.000	0.000	0.000	0.000	0.000	.									
	746	738	742	738	744	747	752									
Pain pass urine	0.14	0.09	0.17	0.19	0.17	0.29	0.28	1.00								
	0.000	0.010	0.000	0.000	0.000	0.000	0.000	.								
	749	739	744	741	746	749	749	754								
Short breath	0.19	0.15	0.27	0.15	0.17	0.20	0.11	0.14	1.00							
	0.000	0.000	0.000	0.000	0.000	0.000	0.003	0.000	.							
	745	735	743	738	744	746	744	745	752							
Back ache/pain	0.22	0.16	0.26	0.27	0.28	0.31	0.20	0.24	0.26	1.00						
	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	.						
	749	737	748	742	749	744	737	740	738	768						

	Diff empty bowels	Change bowel	Excess flatulence	Urinaryfreq	Urinary urgency	Pressure bladder	Diff empty bladder	Painpass urine	Short breath	Back ache/pain	Leg ache/pain	Legswelling	Tiredfatigue	Weight gain	Weight loss	Abnorvag bleed
Legache/pain	0.21	0.22	0.27	0.23	0.30	0.29	0.16	0.18	0.29	0.45	1.00					
	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	.					
	745	733	747	738	746	740	734	737	734	751	762					
Legswelling	0.20	0.22	0.22	0.23	0.26	0.27	0.22	0.19	0.25	0.24	0.43	1.00				
	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	.				
	749	740	752	743	749	746	742	745	740	748	747	762				
Tiredfatigue	0.30	0.24	0.36	0.32	0.34	0.31	0.21	0.19	0.40	0.40	0.40	0.31	1.00			
	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	.			
	749	736	754	743	749	745	737	739	739	750	750	752	768			
Weight gain	0.22	0.22	0.31	0.22	0.23	0.23	0.14	0.10	0.30	0.26	0.26	0.24	0.40	1.00		
	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.008	0.000	0.000	0.000	0.000	0.000	.		
	748	737	750	740	746	742	741	742	740	745	744	746	749	758		
Weight loss	0.06	0.08	0.04	0.01	0.03	0.06	0.05	0.05	0.08	0.06	0.07	0.09	0.09	-0.13	1.00	
	0.077	0.023	0.284	0.791	0.448	0.131	0.190	0.161	0.033	0.090	0.077	0.010	0.012	0.000	.	
	744	736	741	731	738	739	739	740	735	739	737	743	740	744	749	
Abnorvag bleed	0.07	-0.02	0.02	0.08	0.08	0.09	0.05	0.10	0.04	0.06	0.01	0.03	0.07	0.02	-0.03	1.00
	0.065	0.628	0.583	0.033	0.029	0.018	0.149	0.007	0.319	0.135	0.763	0.376	0.061	0.526	0.395	.
	746	736	742	734	740	739	740	742	735	736	734	740	735	741	738	751
Abnorvag dischar	0.15	0.12	0.14	0.14	0.14	0.17	0.10	0.21	0.07	0.23	0.12	0.14	0.15	0.09	0.01	0.20
	0.000	0.002	0.000	0.000	0.000	0.000	0.005	0.000	0.058	0.000	0.001	0.000	0.000	0.013	0.856	0.000
	745	735	743	737	743	741	742	742	737	738	735	741	737	742	738	746
Pain intercourse	0.16	0.07	0.09	0.18	0.22	0.23	0.16	0.29	0.20	0.14	0.19	0.07	0.23	0.11	0.02	0.17
	0.014	0.318	0.164	0.004	0.000	0.000	0.013	0.000	0.002	0.032	0.003	0.246	0.000	0.076	0.720	0.010
	244	238	243	240	243	242	242	244	241	244	243	242	241	243	241	245

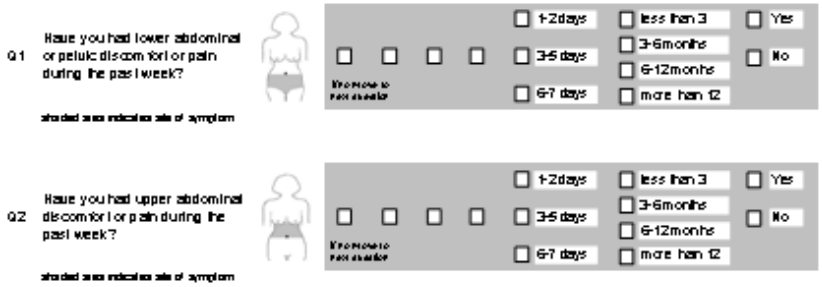
	Abnorvag dischar	Pain intercourse
Legache/pain		
Legswelling		
Tiredfatigue		
Weight gain		
Weight loss		
Abnorvagbleed		
Abnorvag dischar	1.00	
	.	
	753	
Pain intercourse	0.18	1.00
	0.005	.
	245	246

Appendix XXI Draft OCSq Shading Formats

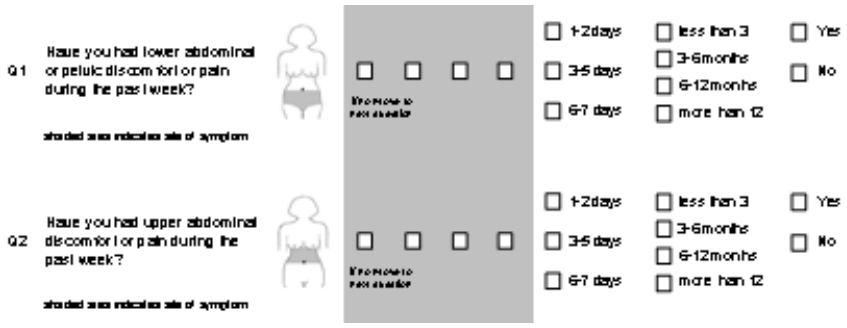
Shading Option A



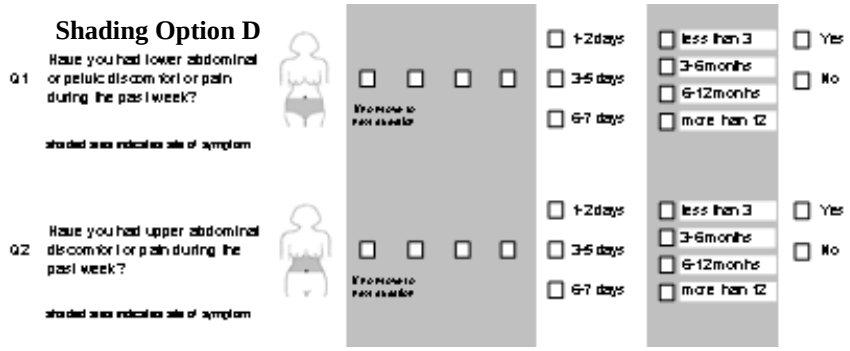
Shading Option B



Shading Option C



Shading Option D



Appendix XXII Final OCSq

Date ☐☐ ☐☐ ☐☐☐☐ Volunteer Ref ☐☐☐☐☐☐☐☐

For each question please tick the extent to which it has been experienced during the past week. If you have not experienced it, please tick the 'no' box and move onto the next question. If you have experienced it, please tick either the 'a little', 'quite a bit' or 'very much' box, tick the number of days in the past week you have experienced it, tick how many months since it first started and tick whether or not you have discussed it with a GP in the past three months.

		no	a little	quite a bit	very much	How many days during past week?	How many months have you had this?	Discussed with GP in past 3 months?
Q1	Have you had lower abdominal or pelvic discomfort or pain during the past week? shaded area indicates site of symptom	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q2	Have you had upper abdominal discomfort or pain during the past week? shaded area indicates site of symptom	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q3	Have you had indigestion or heartburn during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q4	Have you had nausea or vomiting during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q5	Have you felt full quickly when eating during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No

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Volunteer Ref ☐☐☐☐☐☐☐☐

		no	a little	quite a bit	very much	How many days during past week?	How many months have you had this?	Discussed with GP in past 3 months?
Q6	Have you had a change in appetite during the past week?	☐	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
	If no move to next question							
Q7	Have you had a feeling of upper abdominal bloating or fullness during the past week?  shaded area indicates site of symptom	☐	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
	If no move to next question							
Q8	Have you had a feeling of upper abdominal pressure during the past week?  shaded area indicates site of symptom	☐	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
	If no move to next question							
Q9	Have you had increased abdominal size or waistbands of clothes feeling too tight during the past week?	☐	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
	If no move to next question							
Q10	Were you able to feel an abdominal mass or lump during the past week?	☐	☐	☐	☐	N/A	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
	If no move to next question							
Q11	Have you had a feeling of lower abdominal or pelvic bloating or fullness during the past week?  shaded area indicates site of symptom	☐	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
	If no move to next question							

Finalised Version 1.15 Nov 2008

Volunteer Ref ☐☐☐☐☐☐☐☐

		no	a little	quite a bit	very much	How many days during past week?	How many months have you had this?	Discussed with GP in past 3 months?
Q12	Have you had a feeling of lower abdominal or pelvic pressure during the past week?  shaded area indicates site of symptom	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q13	Have you had a feeling of lower abdominal or pelvic heaviness during the past week?  shaded area indicates site of symptom	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q14	Have you had pain before, during or after opening your bowels during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q15	Have you had difficulty emptying your bowels during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q16	Have you had a change in bowel habit during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q17	Have you had excessive passing of wind or flatulence during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No

FineTuned Version 1, 15 Nov 2008

Volunteer Ref ☐☐☐☐☐☐☐☐

		no	a little	quite a bit	very much	How many days during past week?	How many months have you had this?	Discussed with GP in past 3 months?
Q18	Were you short of breath during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q19	Have you passed urine frequently during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q20	When you felt the urge to pass urine did you have to hurry to get to the toilet during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q21	Have you had a feeling of pressure on the bladder during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q22	Have you had difficulty emptying the bladder during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q23	Have you had pain when passing urine during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No

Finalised Version 1.15 Nov 2008

Volunteer Ref ☐☐☐☐☐☐☐☐

		no	a little	quite a bit	very much	How many days during past week?	How many months have you had this?	Discussed with GP in past 3 months?
Q24	Have you had ache or pain in your back during the past week?	☐	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
		If no move to next question						
Q25	Have you had an ache or pain in one or both legs during the past week?	☐	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
		If no move to next question						
Q26	Have you had swelling in one or both legs during the past week?	☐	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
		If no move to next question						
Q27	Have you had a feeling of tiredness, fatigue or lack of energy during the past week?	☐	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
		If no move to next question						
Q28	Have you gained weight without trying during the past year?	☐	☐	☐	☐	N/A	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
		If no move to next question						
Q29	Have you lost weight without trying during the past year?	☐	☐	☐	☐	N/A	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
		If no move to next question						

Volunteer Ref ☐☐☐☐☐☐☐☐

		no	a little	quite a bit	very much	How many days during past week?	How many months have you had this?	Discussed with GP in past 3 months?
Q30	Have you had abnormal vaginal bleeding during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No
Q31	Have you had abnormal vaginal discharge during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No

Please answer this question only if you have been sexually active during the past week:

Q32	Have you had pain during or after sexual intercourse during the past week?	☐ If no move to next question	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No

During the past week have you experienced any other symptoms? If so, please make a note of the symptom in the space below .

Q33	_____	☐	☐	☐	☐ 1-2 days ☐ 3-5 days ☐ 6-7 days	☐ less than 3 ☐ 3-6 months ☐ 6-12 months ☐ more than 12	☐ Yes ☐ No

Q34 Are you currently taking hormone replacement therapy (HRT)?

Please tick yes or no

☐ Yes
☐ No

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Q35 **Have you ever been diagnosed by a doctor with any of the following conditions?**

Please tick all that apply:

Heart failure	☐	Chronic bronchitis	☐	Hiatus hernia	☐
Irritable Bowel Disease (IBS)	☐	Emphysema	☐	Arthritis	☐
Inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis)	☐	Endometriosis	☐	Depression	☐
Diverticulitis	☐	Cancer ☐	Please specify type of cancer: _____		
None of the above	☐				

Q36 During the past month have you often been bothered by feeling down, depressed or hopeless?

Please tick yes or no

☐ Yes
☐ No

Q37 During the past month have you often been bothered by little interest or pleasure doing things?

Please tick yes or no

☐ Yes
☐ No

If there is any other information which you feel is relevant to this questionnaire please write it in the box below.

Thank you for taking the time to complete this questionnaire

Please remember this is only a survey, if you have any symptoms that are worrying or persistent please discuss them with your GP.

Appendix XXIII Symptoms Associated with CA125 Level

Level 2-3 severity	n	CA125≥30 U/mL n (%)	CA125 < 30 U/mL n (%)	OR (95% CI)	p-value
Difficulty emptying the bladder	276	2 (6.5)	1 (0.4)	16.83 (1.48-191.36)	0.03
≥12 days & <12 months					
Urinary frequency	254	7 (25.9)	21 (9.3)	3.43 (1.30-9.06)	0.02
Shortness of breath	268	4 (13.8)	8 (3.3)	4.62 (1.30-16.44)	0.03
≥12 days, <12 months & level 2-3 severity					
Change in appetite	271	3 (9.1)	4 (1.7)	5.85 (1.25-27.41)	0.04
Urinary frequency	254	5 (18.5)	11 (4.8)	4.46 (1.42-14.02)	0.02
Shortness of breath	268	3 (10.3)	4 (1.7)	6.78 (1.44-31.96)	0.03
Back ache or pain	278	4 (13.8)	8 (3.2)	4.68 (1.32-16.65)	0.03

Note: There were no associations between symptoms reported at any level of severity and CA125 level

Appendix XXIV Symptoms Associated with ROC Score

Symptom reported	n	Elevated ROC n (%)	Normal ROC n (%)	OR (95% CI)	p-value
At any level					
Indigestion or heartburn	303	39 (54.2)	91 (39.4)	1.82 (1.07-3.10)	0.03
Increased abdominal size	291	28 (41.8)	59 (26.3)	2.01 (1.14-3.55)	0.02
Weight gain	290	31 (45.6)	64 (28.8)	2.07 (1.18-3.61)	0.01
Level 2-3 severity					
Increased abdominal size	289	15 (22.4)	18 (8.1)	3.27 (1.54-6.92)	<0.0001
Pelvic bloating or fullness	286	11 (16.9)	13 (5.9)	3.26 (1.38-7.68)	0.005
Tiredness, fatigue or lack of energy	294	27 (40.3)	60 (26.4)	1.88 (1.06-3.32)	0.03
Weight gain	288	17 (25.4)	27 (12.2)	2.44 (1.24-4.83)	0.009
≥12 days & <12 months					
Indigestion or heartburn	295	7 (10.0)	6 (2.7)	4.06 (1.32-12.50)	0.02

Symptom reported	n	Elevated ROC n (%)	Normal ROC n (%)	OR (95% CI)	p-value
≥12 days & <12 months					
Urinary frequency	259	13 (20.6)	15 (7.7)	3.14 (1.40-7.02)	0.004
Urinary urgency	261	11 (18.0)	13 (6.5)	3.16 (1.34-7.49)	0.006
Shortness of breath	273	6 (9.5%)	6 (2.9%)	3.58 (1.11-11.52)	0.04
Weight gain	279	17 (26.6%)	33 (15.3%)	1.99 (1.02-3.89)	0.04
≥12 days, <12 months & level 2-3 severity					
Increased abdominal size	272	9 (14.1)	7 (3.4)	4.70 (1.67-13.18)	0.004

Appendix XXV Symptoms Associated with Complex Ovarian Morphology

At any level	n	Complex Morphology n (%)	Normal Morphology n (%)*	OR (95% CI)	p-value
Pelvic pressure	455	36 (23.4)	42 (14.0)	1.88 (1.15-3.09)	0.012
Level 2-3 severity					
Change in bowel habit	451	16 (10.4)	14 (4.7)	2.34 (1.11-4.94)	0.022

Note: there were no associations between complex ovarian morphology and symptoms reported at ≥12 days frequency and <12 months duration or level 2-3 severity, ≥12 days frequency and <12 months duration

**Includes normal ovaries as well as simple cysts below <60cc and non-visualised ovaries*

Appendix XXVI 100,000 Women Study Invitation Letter

United Kingdom Collaborative Trial of Ovarian Cancer Screening

Department of Gynaecological Oncology
Level 1, Maple House
149 Tottenham Court Road
London
W1T 7DN

(Name)
(Address line 1)
(Address line 2)
(Address line 3)

Date Volunteer Ref:

Dear (name),

We are writing to you about a new study that is being conducted as part of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). The study is inviting a group of randomly selected women who are participating in UKCTOCS to complete a symptoms questionnaire.

Participation in the research is voluntary and only includes a questionnaire. If you wish to take part please read the enclosed study information sheet first, then complete the questionnaire. We are interested to find out the symptoms post-menopausal women commonly experience. Even if you think your symptoms may be related to another condition we are still interested to know about them.

Please take care to complete both sides of the questionnaire as it is printed double-sided. A freepost envelope is enclosed for you to send your questionnaire back to us.

If you would like more information about the study please contact Penny Allen on 0207 380 6919 or 0207 380 6925.

Thank you for taking the time to read this information.

Yours sincerely

The UKCTOCS Team

Frequently asked questions

1. I am already in UKCTOCS, is this the same study?
2. This study is part of UKCTOCS but is a sub-study of the main screening trial.

Q) Has this questionnaire been sent to me before?
A) Approximately 1,000 UKCTOCS volunteers were sent a pilot version of this questionnaire so you may be one of these women who are asked to complete the questionnaire again. This questionnaire is, however, different to the UKCTOCS follow-up questionnaire and menopausal symptoms study.

Q) Can you give me my results on the above telephone number?
A) Sorry, no. We do not have direct access to your results. If you have any questions regarding results please telephone your local UKCTOCS centre on the telephone number given on your appointment letter.

Q) Do I have to do the questionnaire?
A) No, it is entirely up to you whether to take part or not.

Appendix XXVII 100,000 Women Study Invitation Letter

United Kingdom Collaborative Trial of Ovarian Cancer Screening

Ovarian Cancer Symptoms Study Information Sheet

As a participant in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) you are being asked to take part in research about symptoms. Before you decide to take part it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?
Previous research has reported that the early symptoms of ovarian cancer are subtle or non-specific. Due to this the majority of women are diagnosed with ovarian cancer after it has spread from the ovaries. By then it is much more difficult to treat and as a consequence many women will die of the cancer. By contrast, treatment is more successful and the outlook can be good for women diagnosed before the cancer has spread. The purpose of this study is to identify symptoms that precede a diagnosis of ovarian cancer in post-menopausal women.

Why have I been chosen?
This study is a sub-study of the United Kingdom Collaborative Trial of Ovarian Cancer Screening and you are already participating in UKCTOCS. We are inviting a randomly selected group of women to take part in a symptoms questionnaire.

Do I have to fulfil any other criteria to take part?
The only criteria you need to fulfil are:
1. Already enrolled in the United Kingdom Collaborative Trial of Ovarian Cancer Screening.

Do I have to take part?
No. It is up to you to decide whether or not to take part. If you do decide to take part please fill in the questionnaire. If you decide not to take part you do not have to give a reason. Deciding to participate or not will not affect any medical care you receive.

What will happen to me if I take part?

Symptoms Questionnaire
If you would like to take part in this study please complete the questionnaire then return it in the freepost envelope provided. If you have any questions please contact Penny Allen (telephone number at the end of this form), who will discuss the study in greater detail and will give you the opportunity to ask any questions.

What are the possible disadvantages of taking part?
2. Participation in the questionnaires will take approximately 10-15 minutes of your time.
3. Thinking about symptoms may create anxiety in some women.

What are the possible benefits of taking part?
- There are no direct benefits of taking part, although being asked about symptoms may help some women to remember symptoms that should be discussed with their doctor.

What if I have experienced any of the symptoms in the questionnaire or am worried about symptoms?
Please keep in mind that you have been randomly selected to participate in the survey, not for any other reason. Many of the symptoms listed in the questionnaire are common in healthy people, or may be related to other conditions. If you are worried about any symptoms please contact your GP or gynaecologist.

What if something goes wrong?
It is not anticipated that anything will go wrong in this study as it only involves you filling in the enclosed questionnaire. It does not involve any tests or other questions.

You will always be able to contact the researcher to discuss your concerns about the study. Every care will be taken to ensure your safety during the course of the study. University College London (UCL), the Research Governance Sponsor, has indemnity (insurance) arrangements in place for non-negligent harm, in the event that something does go wrong and you are harmed as a result of taking part in this study. If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation but you may have to pay your legal costs.

Will taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Only your UKCTOCS volunteer reference number is on the questionnaire, not your name or any other personal details.

Occasionally the research documentation and results will be looked at by the people funding the research programme to check that the study is being carried out properly. Any information which is viewed by people not directly related to the research team will not have your name and address on it.

What will happen to the results of the research study?
The results of the research will be used in a PhD study of the symptoms of ovarian cancer. Additionally, the results will be reviewed by medical professionals and published in the medical press. Individuals will not be identified in any publications.

Who is organising and funding the research?
The research is part of a PhD study that is linked to the United Kingdom Collaborative Trial of Ovarian Cancer Screening. The Medical Research Council is funding the study.

Contact for further information

For further information please telephone Penny Allen in the Department of Gynaecological Oncology on 0207 380 6919 or 0207 380 6925. Alternatively, you can write to:

Penny Allen
Department of Gynaecological Oncology
UCL Institute for Women's Health
Level 1, Maple House
149 Tottenham Court Road
London
W1T 7DN

Thank you for taking the time to read this information.

Appendix XXVIII 100,000 Women Study OCSq Instruction Page

United Kingdom Collaborative Trial of Ovarian Cancer Screening

How to complete the questionnaire

1. Please read the enclosed information sheet.

2. We are interested to find out the symptoms post-menopausal women commonly experience. Even if you think your symptoms may be related to another condition we are still interested to know about them.

3. For each question please tick the extent to which it has been experienced during the past week. If you have not experienced it, please tick the 'no' box and move onto the next question. If you have experienced it, please tick either the 'a little', 'quite a bit' or 'very much' box, tick the number of days in the past week it has been experienced, tick how many months since it first started and tick whether or not you have discussed it with a GP in the past three months.

Below is an example of how to fill in the questionnaire. This shows that the woman had hot flushes 'a little' for six to seven days during the past week, has been having hot flushes for six to 12 months and has not discussed her hot flushes with a GP during the past three months.

	no	a little	quite a bit	very much	How many days during past week?	How many months have you had this?	Discussed with GP in past 3 months?
E.g. Have you had hot flushes during the past week?	☐ if no move to next question	☑	☐	☐	☐ 1-2 days ☐ 3-5 days ☑ 6-7 days	☐ less than 3 ☐ 3-6 months ☑ 6-12 months ☐ more than 12	☐ Yes ☑ No

Please feel free to leave out any question if you feel uncomfortable replying to it, or for any other reason.

The questionnaire has 7 pages and takes approximately 10-15 minutes to complete.

If you have any questions or need help completing the questionnaire please telephone Penny Allen on 0207 380 6919 or 0207 380 6925.

Thank you for taking the time to complete this questionnaire

Appendix XXIX Symptoms Associated with Depression Screening Status in 100,000 Women Study

At any level	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
Pelvic discomfort or pain	41,682	47,88 (36.4)	4,872 (17.1)	4.63 (4.03-5.33)	<0.0001
Abdominal discomfort or pain	41,484	3,916 (30.0)	3,346 (11.8)	3.23 (3.06-3.40)	<0.0001
Indigestion or heartburn	41,854	6,431 (48.5)	9,149 (32.0)	2.00 (1.92-2.09)	<0.0001
Nausea or vomiting	41,729	5,032 (38.1)	4, 479 (15.7)	3.31 (3.16-3.47)	<0.0001
Feeling full quickly	41,782	4,264 (32.2)	3,754 (13.2)	3.14 (2.99-3.30)	<0.0001
Change in appetite	40,687	2,426 (19.0)	985 (3.5)	3.28 (2.86-3.77)	<0.0001
Abdominal bloating or fullness	40,861	5,077 (39.4)	5,034 (18.0)	2.96 (2.83-3.10)	<0.0001
Abdominal pressure	40,574	2,776 (21.9)	1,815 (6.5)	4.02 (3.77-4.28)	<0.0001
Increased abdominal size	40,805	4,666 (36.3)	4,282 (5.3)	3.15 (3.00-3.30)	<0.0001
Abdominal mass or lump	40,441	970 (7.7)	288 (1.0)	8.00 (7.00-9.14)	<0.0001

At any level	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
Pelvic bloating or fullness	40,795	4,177 (32.5)	3,980 (14.2)	2.90 (2.76-3.04)	<0.0001
Pelvic pressure	41,323	2,720 (21.0)	2,049 (7.2)	3.42 (3.22-3.64)	<0.0001
Pelvic heaviness	41,302	2,943 (22.7)	1,969 (6.9)	3.94 (3.70-4.19)	<0.0001
Pain before, during or after opening bowels	41,454	3,920 (30.1)	3,536 (12.4)	3.02 (2.87-3.18)	<0.0001
Difficulty emptying bowels	41,564	4,619 (35.2)	5,327 (18.7)	2.36 (2.26-2.48)	<0.0001
Change in bowel habit	41,388	3,288 (25.3)	2,584 (9.1)	3.38 (3.19-3.58)	<0.0001
Excessive flatulence	41,764	6,761 (51.0)	8,200 (28.8)	2.58 (2.47-2.69)	<0.0001
Shortness of breath	40,540	5,133 (40.1)	4,437 (16.0)	3.52 (3.36-3.70)	<0.0001
Urinary frequency	40,505	6,028 (47.0)	6,966 (25.2)	2.63 (2.52-2.75)	<0.0001
Urinary urgency	40,767	6,617 (51.3)	9,098 (32.7)	2.17 (2.08-2.26)	<0.0001
Pressure on the bladder	40,364	3,228 (25.5)	3,104 (11.2)	2.72 (2.57-2.87)	<0.0001
Difficulty emptying the bladder	40,270	1,015 (8.1)	855 (3.1)	2.77 (2.52-3.04)	<0.0001

At any level	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
Pain when passing urine	40,304	1,650 (13.1)	379 (1.4)	10.84 (9.67-12.14)	<0.0001
Back ache or pain	41,863	8,522 (63.8)	11,182 (39.2)	2.74 (2.62-2.86)	<0.0001
Leg ache or pain	41,728	7,317 (55.1)	9,222 (32.4)	2.71 (2.48-2.97)	<0.0001
Leg swelling	41,373	4,058 (31.1)	3,113 (11.0)	3.66 (3.48-3.86)	<0.0001
Tiredness, fatigue or lack of energy	41,918	11,171 (82.9)	11,668 (41.0)	6.95 (6.61-7.31)	<0.0001
Weight gain	41,600	6,462 (49.1)	8,635 (30.4)	2.21 (2.12-2.31)	<0.0001
Weight loss	41,078	1,602 (12.5)	1,519 (5.4)	2.52 (2.34-2.71)	<0.0001
Abnormal vaginal bleeding	40,340	311 (2.5)	161 (0.6)	4.36 (3.60-5.28)	<0.0001
Abnormal vaginal discharge	38,649	790 (7.3)	672 (2.4)	3.16 (2.85-3.51)	<0.0001
Pain during or after sexual intercourse	18,735	853 (13.2)	942 (7.7)	1.82 (1.65-2.01)	<0.0001

Level 2-3 severity	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
Pelvic discomfort or pain	37,852	1,556 (13.9)	1,070 (4.0)	3.88 (3.57-4.20)	<0.0001
Abdominal discomfort or pain	37,414	1,135 (10.5)	710 (2.7)	4.26 (3.87-4.69)	<0.0001
Indigestion or heartburn	37,903	2,064 (18.3)	1,962 (7.4)	2.81 (2.63-3.00)	<0.0001
Nausea or vomiting	37,209	386 (3.6)	198 (0.7)	3.31 (3.16-3.47)	<0.0001
Feeling full quickly	37,664	1,547 (14.0)	926 (3.5)	4.54 (4.17-4.94)	<0.0001
Change in appetite	36,742	566 (5.4)	184 (0.7)	3.28 (2.86-3.77)	<0.0001
Abdominal bloating or fullness	37,244	1,935 (17.6)	1,179 (4.5)	4.56 (4.22-4.92)	<0.0001
Abdominal pressure	36,656	805 (7.7)	420 (1.6)	5.10 (4.52-5.75)	<0.0001
Increased abdominal size	37,072	1,798 (16.6)	981 (3.7)	5.12 (4.72-5.55)	<0.0001
Abdominal mass or lump	36,353	144 (1.4)	101 (0.4)	3.71 (2.87-4.79)	<0.0001
Pelvic bloating or fullness	37,065	1,489 (13.8)	940 (3.6)	4.30 (3.95-4.68)	<0.0001
Pelvic pressure	37,396	924 (8.6)	492 (1.8)	4.99 (4.46-5.58)	<0.0001

Level 2-3 severity	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
Pelvic heaviness	37,308	913 (8.5)	431 (1.6)	5.65 (5.03-6.35)	<0.0001
Pain before, during or after opening bowels	37,486	1,047 (9.6)	693 (2.6)	4.00 (3.62-4.41)	<0.0001
Difficulty emptying bowels	37,731	1,556 (14.1)	1,255 (4.7)	3.31 (3.06-3.58)	<0.0001
Change in bowel habit	37,340	724 (6.7)	458 (1.7)	4.12 (3.66-4.65)	<0.0001
Excessive flatulence	38,088	3,208 (28.2)	2,985 (11.2)	3.12 (2.95-3.30)	<0.0001
Shortness of breath	36,944	1,513 (14.0)	857 (3.3)	4.80 (4.40-5.23)	<0.0001
Urinary frequency	36,905	3,258 (29.9)	3,282 (12.6)	2.96 (2.80-3.12)	<0.0001
Urinary urgency	37,220	3,329 (30.2)	3,394 (13.0)	2.91 (2.76-3.07)	<0.0001
Pressure on the bladder	36,617	1,340 (12.7)	883 (3.4)	4.15 (3.80-4.54)	<0.0001
Difficulty emptying the bladder	36,350	354 (3.5)	215 (0.8)	4.30 (3.63-5.11)	<0.0001
Pain when passing urine	36,233	159 (1.6)	114 (0.4)	3.61 (2.84-4.60)	<0.0001
Back ache or pain	38,434	4,083 (35.1)	3,953 (14.8)	3.13 (2.97-3.29)	<0.0001

Level 2-3 severity	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
Leg ache or pain	38,112	3,734 (32.7)	3,552 (13.3)	3.17 (3.00-3.34)	<0.0001
Leg swelling	37,283	1,203 (11.2)	998 (3.8)	3.24 (2.97-3.54)	<0.0001
Tiredness, fatigue or lack of energy	38,610	6,172 (51.7)	3,186 (11.9)	7.90 (7.51-8.32)	<0.0001
Weight gain	38,055	3,240 (28.6)	2,676 (10.0)	3.60 (3.40-3.81)	<0.0001
Weight loss	37,099	550 (5.2)	319 (1.2)	4.52 (3.93-5.20)	<0.0001
Abnormal vaginal bleeding	36,363	28 (0.3)	11 (0.04)	6.55 (3.26-13.16)	ns
Abnormal vaginal discharge	36,461	178 (1.7)	81 (0.3)	5.67 (4.36-7.38)	<0.0001
Pain during or after sexual intercourse	15,331	257 (6.3)	262 (2.3)	2.81 (2.36-3.35)	<0.0001

≥12 days & <12 months	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
Pelvic discomfort or pain	41,682	1,001 (7.6)	889 (3.1)	2.56 (2.33-2.81)	<0.0001
Abdominal discomfort or pain	41,484	638 (0.9)	509 (1.8)	2.82 (2.51-3.18)	<0.0001
Indigestion or heartburn	41,854	816 (6.2)	694 (2.4)	2.64 (2.38-2.92)	<0.0001
Nausea or vomiting	41,729	300 (2.3)	146 (0.5)	4.52 (3.71-5.52)	<0.0001
Feeling full quickly	41,782	885 (6.7)	696 (2.4)	4.54 (4.17-4.94)	<0.0001
Change in appetite	40,687	560 (4.4)	312 (1.1)	3.28 (2.86-3.77)	<0.0001
Abdominal bloating or fullness	40,861	976 (7.6)	751 (2.7)	2.97 (2.69-3.28)	<0.0001
Abdominal pressure	40,574	473 (3.7)	287 (1.0)	3.72 (3.21-4.31)	<0.0001
Increased abdominal size	40,805	1,128 (8.8)	892 (3.2)	2.91 (2.66-3.19)	<0.0001
Abdominal mass or lump*	40,441	152 (1.2)	124 (0.4)	2.73 (2.16-3.47)	<0.0001
Pelvic bloating or fullness	40,795	832 (6.5)	635 (2.3)	2.97 (2.68-3.31)	<0.0001
Pelvic pressure	41,323	624 (4.8)	395 (1.4)	3.59 (3.16-4.08)	<0.0001

≥12 days & <12 months	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
Pelvic heaviness	41,302	577 (4.5)	373 (1.3)	3.54 (3.06-3.99)	<0.0001
Pain before, during or after opening bowels	41,454	567 (4.3)	390 (1.4)	3.27 (3.87-3.72)	<0.0001
Difficulty emptying bowels	41,564	706 (5.4)	584 (2.1)	2.72 (2.43-3.04)	<0.0001
Change in bowel habit	41,388	559 (4.3)	443 (1.6)	2.83 (2.50-3.21)	<0.0001
Excessive flatulence	41,764	1,357 (10.2)	1,499 5.3%	2.06 (1.91-2.22)	<0.0001
Shortness of breath	40,540	920 (7.2)	586 (2.1)	3.59 (3.23-3.99)	<0.0001
Urinary frequency	40,505	1,243 (9.7)	1,296 (4.7)	2.18 (2.01-2.37)	<0.0001
Urinary urgency	40,767	1,223 (9.5)	1,336 (4.8)	2.08 (1.92-2.25)	<0.0001
Pressure on the bladder	40,364	676 (5.3)	534 (1.9)	2.87 (2.56-3.22)	<0.0001
Difficulty emptying the bladder	40,270	212 (1.7)	181 (0.7)	2.62 (2.14-3.19)	<0.0001
Pain when passing urine	40,304	110 (0.9)	99 (0.4)	2.45 (1.87-3.22)	<0.0001
Back ache or pain	41,863	1,712 (12.8)	1,867 (6.5)	2.10 (1.96-2.25)	<0.0001

≥12 days & <12 months	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
Leg ache or pain	41,728	1,760 (13.3)	1,915 (6.7)	2.12 (1.98-2.27)	<0.0001
Leg swelling	41,373	643 (4.9)	518 (1.8)	2.79 (2.48-3.13)	<0.0001
Tiredness, fatigue or lack of energy	41,918	3,038 (22.5)	2,460 (8.7)	3.07 (2.90-3.26)	<0.0001
Weight gain*	41,600	2,961 (22.5)	4,125 (14.5)	1.71 (1.62-1.80)	<0.0001
Weight loss*	41,078	990 (7.7)	926 (3.3)	2.48 (2.26-2.72)	<0.0001
Abnormal vaginal bleeding	40,340	34 (0.3)	18 (0.1)	4.19 (2.36-7.42)	<0.0001
Abnormal vaginal discharge	38,649	230 (2.1)	167 (0.6)	3.57 (2.92-4.37)	<0.0001
Pain during or after sexual intercourse	18,735	28 (0.4)	16 (0.1)	3.33 (1.80-6.15)	<0.0001

≥12 days, <12 months & level 2-3 severity	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
Pelvic discomfort or pain	41,682	529 (4.0)	377 (1.3)	2.56 (2.33-2.81)	<0.0001
Abdominal discomfort or pain	41,484	353 (2.7)	220 (0.8)	3.57 (3.01-4.23)	<0.0001
Indigestion or heartburn	41,854	486 (3.7)	400 (1.4)	2.68 (3.35-3.07)	<0.0001
Nausea or vomiting	41,729	134 (1.0)	58 (0.2)	5.04 (3.70-6.86)	<0.0001
Feeling full quickly	41,782	514 (3.9)	347 (1.2)	3.28 (2.86-3.77)	<0.0001
Change in appetite	40,687	239 (1.9)	103 (0.4)	5.15 (4.09-6.50)	<0.0001
Abdominal bloating or fullness	40,861	581 (4.5)	365 (1.3)	3.57 (3.13-4.08)	<0.0001
Abdominal pressure	40,574	243 (1.9)	127 (0.5)	3.72 (3.21-4.31)	<0.0001
Increased abdominal size	40,805	574 (4.5)	319 (1.1)	4.04 (3.52-4.65)	<0.0001
Abdominal mass or lump*	40,441	65 (0.5)	32 (0.1)	4.52 (2.96-6.90)	<0.0001
Pelvic bloating or fullness	40,795	428 (3.3)	266 (1.0)	3.58 (3.06-4.18)	<0.0001
Pelvic pressure	41,323	306 (2.4)	161 (0.6)	4.25 (3.51-5.15)	<0.0001

≥12 days, <12 months & level 2-3 severity	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
Pelvic heaviness	41,302	274 (2.1)	146 (0.5)	4.17 (3.41-5.11)	<0.0001
Pain before, during or after opening bowels	41,454	264 (2.0)	163 (0.6)	3.58 (2.94-4.36)	<0.0001
Difficulty emptying bowels	41,564	369 (2.8)	272 (1.0)	3.00 (2.56-3.52)	<0.0001
Change in bowel habit	41,388	241 (1.9)	175 (0.6)	3.04 (2.50-3.70)	<0.0001
Excessive flatulence	41,764	825 (6.2)	846 (3.0)	2.17 (1.97-2.40)	<0.0001
Shortness of breath	40,540	427 (3.3)	186 (0.7)	5.12 (4.30-6.09)	<0.0001
Urinary frequency	40,505	794 (6.2)	705 (2.5)	2.52 (2.28-2.80)	<0.0001
Urinary urgency	40,767	762 (5.9)	688 (2.5)	2.48 (2.23-2.75)	<0.0001
Pressure on the bladder	40,364	348 (2.8)	200 (0.7)	3.89 (3.27-4.64)	<0.0001
Difficulty emptying the bladder	40,270	89 (0.7)	47 (0.2)	4.21 (2.95-6.00)	<0.0001
Pain when passing urine	40,304	48 (0.4)	41 (0.1)	2.57 (1.70-3.91)	<0.0001
Back ache or pain	41,863	1,090 (8.2)	906 (3.2)	2.71 (2.48-2.97)	<0.0001

≥12 days, <12 months & level 2-3 severity	n	Depression screen positive n (%)	Depression screen negative n (%)	OR (95% CI)	p-value
Leg ache or pain	41,728	1,064 (8.0)	1,039 (3.7)	2.30 (2.10-2.51)	<0.0001
Leg swelling	41,373	312 (2.4)	199 (0.7)	3.47 (2.90-4.15)	<0.0001
Tiredness, fatigue or lack of energy	41,918	2,046 (15.2)	1,110 (3.9)	4.41 (4.08-4.75)	<0.0001
Weight gain*	41,600	1,304 (9.9)	1,178 (4.1)	2.54 (2.35-2.76)	<0.0001
Weight loss*	41,078	308 (2.4)	192 (0.7)	3.61 (3.01-4.32)	<0.0001
Abnormal vaginal bleeding	40,340	6 (0.5)	7 (0.03)	ns	ns
Abnormal vaginal discharge	38,649	56 (0.5)	28 (0.1)	5.13 (3.26-8.08)	<0.0001
Pain during or after sexual intercourse	18,735	13 (0.2)	8 (0.1)	3.08 (1.28-7.44)	0.008

** Reported at <12 months duration only as frequency data not collected*

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