Nutritional status of women referred to a gynaecological cancer centre for treatment of a pelvic mass

Thesis submitted for the degree of Doctor of Philosophy at University College London

By

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I, Nyaladzi Balogun 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.

Dedicated to Lizzie Ndebele.

Abstract

Background: Malnutrition is a major challenge for patients diagnosed with ovarian cancer and affects between 28% and 67% of women at some point in their cancer trajectory. It is strongly associated with poor health outcomes and decreased survival. Few studies have evaluated nutritional status in this population. The impact of nutritional intervention on outcomes such as body composition and survival is also not well understood. Characterising changes in nutritional status and understanding how women perceive a cancer diagnosis to affect their diet and nutritional needs is required.

Aim: This study characterises nutritional status of women diagnosed with ovarian cancer during the period of acute first-line treatment. It also explores the perceptions of women regarding their nutrition and dietary needs and their preferences for supportive intervention.

Methods: A mixed-method (quantitative/qualitative) study was conducted to prospectively assess nutritional status. 58 newly diagnosed women and 27 controls were recruited and anthropometric/body composition measures (weight, body fat, dry lean mass, lean mass total body water and extracellular water) and biochemical markers (prealbumin, albumin, C-reactive protein, CA125) assessed at baseline, during treatment and at the end of treatment. Women also completed a study specific questionnaire on their health and dietary intake as well as quality of life questionnaires. Data was analysed using SPSS. Two focus groups with 8 eight women were conducted and discussions centred on the importance of nutrition. The group sessions were recorded, transcribed verbatim and analysed using thematic analysis.

Results: The findings are that some women (43%) are malnourished by the time they attend a cancer centre for investigation or treatment of ovarian their cancer. They have lost weight, have decreased lean mass and a low prealbumin. Their quality of life is also affected. Women in the study consider their diet and nutrition to be important and do not feel adequately supported by their clinical team. Nutritional support based on current practice does not seem to improve nutrition outcomes.

Conclusion: Well-designed, targeted, randomised controlled trials with specific interventions aimed at early treatment and prevention of further nutritional complications in ovarian cancer patients are urgently required.

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Baseline assessment: Assessment of patients before they received any treatment.

During treatment assessment: Assessment of cancer patients on their first visit to the hospital following surgery, usually at 2-3 weeks. It also refers to the assessment carried out following 1 cycle of chemotherapy for women treated with neo-adjuvant chemotherapy.

End of treatment assessment: Assessment of patients following completion or stoppage of acute first-line treatment. It is also the assessment following surgery (the last treatment) for controls and women diagnosed with borderline malignancy and stage 1 & 2 ovarian cancer) and treated with surgery alone.

Cachexia   A multifactorial syndrome defined by an on-going loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Cachexia includes sarcopenia as a part of it pathology.

Dietary intake   An individual's food and nutrient intake.

Lifestyle   An individual's attitudes, values and way of life. It is used in this thesis to refer to an individual's particular way of living in aspects concerning their health such as diet, exercise and self-management of symptoms and treatment effects.

Malignant ascites   A build-up of fluid within the peritoneal cavity that contains cancer cells.

Borderline malignancy   Ovarian tumours of low malignant potential. They are different to ovarian cancer because they grow slowly and do not grow into the stroma.

Disease related malnutrition The point at which the severity or persistence of inflammation results in a decrease in lean body mass associated with functional impairment. In this thesis it refers to malnutrition arising from disease related factors such as malabsorption, inflammation, insulin resistance, and anorexia.

Nutritional intervention A specific aspect of nutritional support which involves manipulating dietary intake through counselling or additional nutrients.

Nutritional status The condition of the body in those respects influenced by diet or the levels of nutrients in the body and their ability to maintain normal metabolic integrity.

Nutritional support The management of patients' nutritional needs which includes counselling and provision of nutritional supplements.

Quality of life The general well-being of an individual.

Respondent Each woman who participated in the focus group discussions.

Sarcopenia The reduction in muscle tissue of more than 2 standard deviations below that typical of healthy adults. The reduction results in functional impairment and decreased survival.

Sarcopenic-obesity A condition where an obese individual (increased fat mass) has decreased muscle mass and function.

Self-efficacy An individual's belief in their capacity to execute behaviours necessary to produce desired goals.

Self-management A treatment that aims to maximise functioning of self-regulatory processes and often combines biological, psychological and social intervention techniques. The individuals manage their day-to-day tasks to minimise the impact of disease on health status.

Teachable moment   The window of opportunity when learning a particular topic becomes possible or easiest. A diagnosis of cancer is said to be such a moment for adoption of a healthier lifestyle.

Total Parenteral Nutrition (TPN) The delivery of nutrition intravenously.

Volunteer   Each woman who participated in the observational study.

Well-being   The general state of wellness.

List of abbreviations

APPR	Acute phase protein response
BCM	Body cell mass
BIA	Bioelectrical impedance analysis
BME	Black and ethnic minority
BMI	Body mass index
BW	Body weight
CNS	Clinical nurse specialist
CRF	Cancer related fatigue
CRP	C-reactive protein
CRUK	Cancer research UK
CT	Computerised tomography
DoH	Department of Health
DXA	Dual energy x-ray absorptiometry
EOC	Epithelial ovarian cancer
EORTC	European organisation for research and treatment of cancer
ERP	Enhanced recovery programme
FIGO	International Federation of Gynaecology and Obstetrics
GOG	Gynaecologic oncology group
GP	General Practitioner
HAPA	Health action process approach
LOA	Loss of appetite
MUST	Malnutrition universal screening tool
NCSI	National cancer survivorship initiative
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
OS	Overall survival
Qlq	Quality of life questionnaire
QoL/qol	Quality of life
UK	United Kingdom

1 Introduction

1.1 Overview

The incidence of malnutrition in women diagnosed with ovarian cancer varies between 28% and 67% (1, 2) and can be higher in women who also have bowel obstruction (3). The clinical endpoints of cachexia which are weight loss, anorexia, decreased quality of life, reduced physical activity and reduced overall survival, (4) are devastating for the patient. Up to 20% of patients with cancer die of the effects of malnutrition rather than of the malignancy (5). Only a few studies have evaluated nutritional status or how it changes over time in women with ovarian cancer (5). Clinically, investigations into malnutrition and its effects are often left too late when clinical signs become evident. The patient is unlikely to respond to interventions at this stage thus perpetrating the misconception that nothing but palliation of the worst effects of cachexia is all that can be achieved for malnourished/cachectic cancer patients (6). Furthermore, there is evidence that mechanisms that ultimately lead to the severe wasting of cachexia are operating early in the natural history of the disease (6) when the patient may be able to respond better to nutrition intervention. Although nutrition started to feature more in patient care in more recent years with consensus groups and health departments in Europe becoming more involved in making broad statements about nutrition, cancer patients' nutritional needs remain largely unmet (7). Therefore objectively identifying malnutrition, characterising nutritional status, and understanding the impact of an ovarian cancer diagnosis on women's diet and nutritional needs as well as their perceptions of the adequacy of nutritional support in practice is important. It provides an opportunity to increase knowledge about this complex syndrome as well as help to design patient informed interventions.

1.2   Main aim

The main aim of this thesis was to identify and characterise changes in the nutritional status of women with ovarian cancer from diagnosis to the end of primary treatment.

1.2.1 Study specific objectives

The observational study (Study A) aimed to utilise multiple nutritional assessment tools at baseline, during treatment and at the end of treatment to address the following:

- To compare the nutritional status of ovarian cancer cases with that of benign controls (at baseline and at the end of treatment)

- To compare changes in the nutritional status of women over time: at baseline, during treatment and at the end of treatment and at baseline and at the end of treatment for controls

- To assess how disease and well-being markers such as CA125, CRP and albumin are affected by ovarian cancer and to investigate the relationship between these markers and nutritional status

- To investigate the relationship between lifestyle factors such as smoking, alcohol intake and menopause and nutritional status in cases and controls

- To investigate the impact of some ovarian cancer symptoms such as pain, nausea, abdominal distension etc. on nutritional status, dietary intake and overall health status of cases

- To determine which nutritional assessment best evaluates nutritional status in ovarian cancer patients

The qualitative enquiry (Study B) complimented study A and aimed to;

- Explore patients' understanding of their nutritional status, and their information and support needs to meet nutritional challenges

- Explore the impact of the physiological (nutritional) changes on patients' eating habits and daily activities and discover some of their coping strategies and recommendations for a desired intervention.

- Explore how a health behaviour model, Health Action Process approach (HAPA), could be used to improve a potential future intervention package

- Consolidate evidence from study A with patients' perspectives of nutritional needs to make recommendations for future interventions

1.3 Research design

Assessing nutritional status is complex; no one method is universally approved or accepted for this purpose. Some of the major limitations in countering disease related malnutrition have been as a result of the lack of accepted, standardized criteria for defining and assessing malnutrition indices (8). The evolving challenge of malnutrition is also related to the increasing obesity epidemic, which can mask underlying lethal muscle wasting resulting in a combination of excess weight and reduced muscle mass and/or strength. Traditional methods of nutritional assessment based on weight assessment may no longer be relevant in many cases and may result in malnutrition being frequently undiagnosed. In addition, in its early stages cancer causes a series of metabolic and functional changes and malnutrition may only be later demonstrable by anthropometric changes (body shape, size and composition) (8). This means that body composition assessments may not always be sensitive enough to identify some of these early changes. Furthermore, the lethal nature of ovarian cancer and the quick relapse (median interval of 18-24 months) in 70% of patients with advanced stage disease (9) warrants intervention that targets a woman's entire life rather than just the acute phase. This requires patient involvement; their perceptions of their challenges are therefore invaluable.

To counter some of these challenges in assessing nutritional status and to also gain insight from patients, a multi-dimensional approach of using mixed methods and multiple tools for assessment was used.

1.4 Mixed-method approach

The research was divided into two separate but related studies. Study A involved the quantitative assessments of nutritional status and dietary analysis while Study B involved qualitative analysis of women's perceptions of their dietary and nutritional status to illuminate the quantitative assessments and preliminary findings. Study B also provided insight into women's nutritional concerns, their nutritional support needs and important clues for development of future interventions.

1.5 Thesis layout

This thesis is presented in 11 chapters. Chapter 1 is the introduction and outlines the overall purpose of the study, the research design and thesis structure. Chapter 2 is the literature review. This chapter examines existing literature on disease related malnutrition/cachexia, its pathophysiology, effects and current management. It also focuses on the nutritional issues specific to ovarian cancer patients, how these are different from other cancers and how they are currently managed. It highlights the knowledge gaps and uses the literature to formulate the research questions. Chapter 3, the first of 3 methods chapters, provides overall justification for the research and a rationale for its design. The research sites, patient pathways, and ethical and regulatory procedures are described. It also introduces the two studies, Study A, the observational study and study B, the patients' perspective study. Chapter 4, the second methods chapter, outlines the conduct of study A. It also describes the tools for assessment and the analytic methods used. It is followed by chapter 5, which outlines the findings from study A. Results are presented here in four sections. Section A presents findings on patient demographics, disease, treatment and symptoms for cases and controls where applicable. Sections B and C present findings on nutritional/body composition and biochemical statuses respectively for cases and controls at baseline, during treatment and at the end of treatment as appropriate. The last section of this chapter, section D, presents findings on diet and eating habit changes starting 3 months prior to baseline assessment to the end of treatment.

It also outlines associations between diet changes with nutritional status and overall health status as well as evaluate the impact of current nutritional interventions on nutritional status. Chapter 6, the second to present results from study A, outlines findings on the impact of ovarian cancer on quality of life, measured using the Euroqol EQ-5D questionnaire. Results are presented on the two aspects of the questionnaire. The first consists of 5 quality of life domains of mobility, self-care, usual activity, pain/discomfort and anxiety/depression. The second is the visual analogue scale representing the overall health status, a proxy for quality of life. The association between affected domains and overall health status with nutritional status is outlined. Chapter 7, the final of the methods chapters describes the conduct of the focus group discussions and how the data were analysed. The findings from analysis of patients' perspective on diet and nutrition are narrated in chapter 8. The final chapter, 9, provides an overall discussion of the results, highlights the strengths and weaknesses of the research and sets out suggestions for future work.

2 Literature Review

2.1 Summary of chapter

This chapter is dedicated to a review of the literature. The review focuses on the definition, classification, prevalence and pathophysiology of malnutrition/cachexia. The manifestations and impact of malnutrition are also reviewed. Particular attention is paid to current practice in nutritional support for cancer patients, strategies that have worked and those that have not. Finally, attention is paid to the nutritional challenges faced by women diagnosed with ovarian cancer, what has been achieved and what could be achieved in managing the challenges. Knowledge gaps are identified and the opportunities for research that lead to the overall research question are explored.

This thesis adopts use of both terms malnutrition and cachexia to refer to disease related malnutrition in cancer patients. The terms are frequently used non-exclusively in literature. Researchers tend to use the term 'cachexia', while clinicians most often refer to 'malnutrition'. Nutrition care literature usually refers to malnutrition indices rather than cachexia indices. For this reason the terms are used interchangeably in this thesis unless otherwise specified.

2.2 Cancer and malnutrition

The prevalence of malnutrition in cancer patients could be as high as 80% depending on cancer location and stage, treatment history, clinical setting and assessment criteria (10, 11). The problem is that a variety of definitions for malnutrition syndromes are found in the literature resulting in confusion (12) and there is a lack of a validated, universal classification system (13). The public health definitions generally describe a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome (6). These definitions imply that if the imbalance is

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corrected, then the problem of malnutrition will resolve. This is true in the absence of disease where malnutrition is caused by an inadequate or excessive consumption of nutrients. Although nutritional intake has been shown to be substantially reduced in most patients with cancer experiencing weight loss (14), it is not always diminished during the course of cancer (15). Recent evidence, suggests that this may be due to varying degrees of acute or chronic inflammation, which are contributing factors in the pathophysiology of malnutrition (12). There is also evidence to suggest that in some instances of cancer and HIV, nutrition supplementation fails to reverse malnutrition. This emphases the role of underlying abnormalities of host metabolism; with host tumour competition and tumour products interacting to affect both energy balance and metabolism of macronutrients (15).

A consensus definition of disease related malnutrition has been given as "The point at which the severity or persistence of inflammation results in a decrease in lean body mass associated with functional impairment", (Jenson et al., 2010; p. 157) (12). This form of malnutrition is partially attributable to a decrease in nutrient intake, but is also tightly linked to the effect of the inflammation. This definition is applicable in cancer patients where there is a complex interplay between underlying disease, disease-related metabolic alterations and, in some cases, the reduced availability of nutrients (because of reduced intake, impaired absorption and/or increased losses, or a combination of these) (6). 'Cachexia' is a preferential term to describe this form of malnutrition in cancer patients, although conceptually the states are along a continuum so that "not all malnourished patients are cachectic, but all cachectic patients are invariably malnourished" (16, 17).

2.3 Cachexia

Cachexia is a major problem associated with reduced physical functioning, tolerance to chemotherapy and survival (18). The word cachexia is derived from Greek words *Kakos (bad)* (12) and *héxis* (condition) (19). Its complexity has made it difficult for experts to agree a definition and the lack of a universal definition,

diagnostic criteria, and classification have impeded knowledge advancement for clinical trials and practice (20, 21). The consequences of this include delays in its identification, inadequate prevention and ineffective treatments (6) in clinical practice.

There has been progress in the understanding of cachexia over the past decade (22). In recent years, international groups have worked together to provide universally acceptable, clinically relevant definitions of key terms and consensus statements (6, 12). The Special Interest Group on cachexia-anorexia in chronic wasting diseases (6) adopted the definition of cachexia as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass" (Evans 2008) (23). Loss of muscle mass is important as it leads to frailty and loss of function. The important aspect of this definition is that it also recognised that weight change should be corrected for fluid retention. Fluid retention (24) is a common clinical symptom of some cancers. More is now understood and known about the cachexia/malnutrition processes since that definition was published leading to further adaptation of the definition to;

"*A multifactorial syndrome defined by an on-going loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Its pathophysiology is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism (22)".*

This later definition acknowledges that cachexia can occur before or without loss of fat mass, meaning that overweight and obese individuals can be cachectic. Therefore although weight loss is considered a signal event of the cachectic process depletion of other reserves such as muscle mass is important and should be considered. This later definition is more comprehensive and takes into account functional, metabolic and body composition disturbances (25) which are all

common in cancer patients undergoing treatment (15, 26). The consensus view is that cancer cachexia should be viewed as a continuum with three stages of clinical relevance: precachexia, cachexia, and refractory cachexia (27). Clinical and metabolic signs such as anorexia and glucose intolerance are ongoing and can precede involuntary weight loss in the precachexia phase. The risk of progression to the next phase, cachexia, varies and depends on such factors as cancer type, stage, lack of response to anticancer therapy. Patients in the cachexia phase have weight loss of more than 5% over the last 6 months, or a BMI less than 20 and on-going weight loss of more than 2% or sarcopenia and on-going weight loss of more than 2%.

The next phase is refractory cachexia where the cancer is very advanced or is progressive and unresponsive to treatment. This stage is characterised by catabolism, unmanageable weight loss, low performance status and a low life expectancy of less than 3 months. Therapeutic interventions at this stage tend to focus on symptom relief of for example pain and nausea and not to provide cure. This diagnostic framework although helpful needs sufficient validation (28). Blum et al., 2014 (17) attempted to validate the criteria and reported that the diagnostic criteria based on weight loss and BMI distinguish between cachectic and non-cachectic patients (concerning food intake, catabolism and function) and is associated with survival. Unfortunately others (18) have found the clinical relevance of pre-cachexia in patients with cancer to be limited as the present framework identifies very few patients. They suggest further refinement of the criteria to be able to identify more patients in the pre-cachexia phase, who have a greater chance of responding to nutrition interventions. This highlights that the current definition has its limitations and will possibly require revising in future.

Figure 1: below summarises what is currently understood about the relationship between cancer and cachexia.

Figure 1: A conceptual representation of the cachexia definition
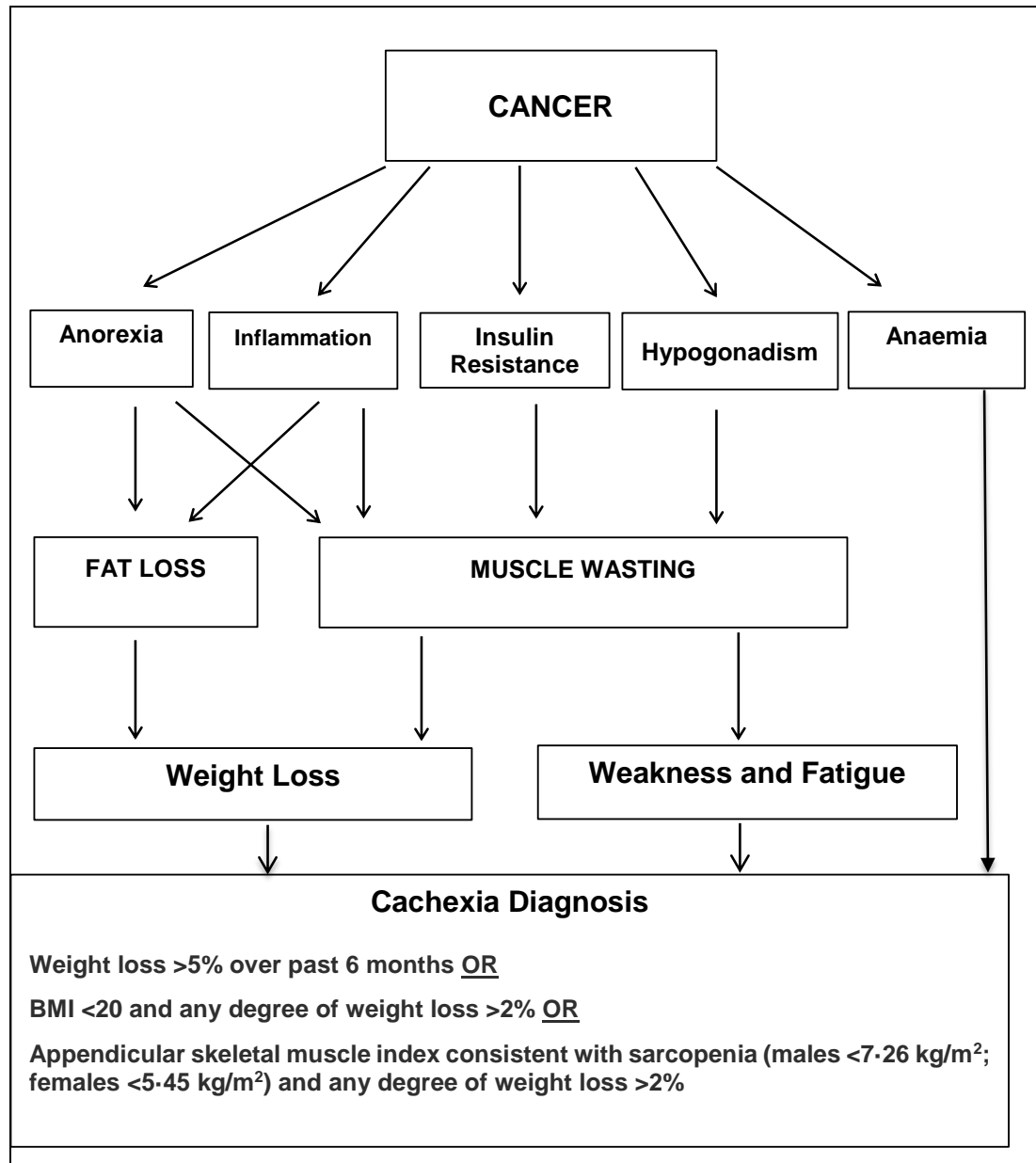
Reproduced with permission. Source: Evans (23)

Cachexia affects inflammatory, metabolic and other regulatory systems leading to fat or muscle loss or both. Whereas fat loss results in weight loss, muscle loss has more impact on function resulting in fatigue and ultimately decreased survival.

2.4 Overview of the pathophysiology of cachexia

Cachexia is characterized by a negative protein and energy balance driven by reduced food intake, low physical activity, systemic inflammation and abnormal metabolism mediated by cytokines, neuroendocrine hormones and tumour-specific factors (22). The dynamic changes in body composition and function observed in cachexia result from an imbalance between metabolisable energy content and the body's energy demands (29). Advanced stage of disease is the common cause for patients' nutritional deterioration (30). Inflammation plays a major role in the degree of weight loss and the severity of the underlying metabolic changes. Muller et al., (31) suggest that there are more complex pathways of 'fat–muscle crosstalk' (via myokines or cytokines) regulating development of cachexia and that the regulation of body weight is through the integrated control of individual body components such fat free mass and fat mass (29). They suggest that these components are interrelated and their proportions are stable despite weight changes. Their view is that changes in body weight are dependent on relationships between tissues and organs rather than on individual components or masses themselves. A detailed discussion of this concept is beyond the scope of this thesis.

2.4.1 Host-tumour interaction and inflammation

2.4.1.1 Tumour factors

Agents produced by the tumour directly, or produced systemically in response to the tumour, such as pro-inflammatory cytokines (IL-1, IL-6, TNF-α and IFN-γ) and hormones (insulin, cortisol and glucagon) are implicated in the pathogenesis of cachexia (15). Tumour cells are said to produce both pro-inflammatory and pro-cachectic factors, which then stimulate a host inflammatory response (32). These include the proteolysis-inducing (33) and lipid-mobilising factors (34) which are in turn involved in pathways that induce proteolysis in muscles and in hepatocytes, resulting in production of IL-6, IL-8 and C-reactive protein (CRP) (35).

2.4.1.2 Inflammation

It is thought that the cachexia process is driven by inflammatory cytokine production in response to tumour cells. Increased systemic inflammatory cytokine production, which correlates with the amount of weight loss have been shown in mice tumour models (36, 37). The TNF-alpha and the tumour factor proteolysis-inducing factor are thought to play an important role in skeletal muscle atrophy in cachectic patients. They increase protein degradation through the ubiquitin-proteasome pathway and depress protein synthesis through phosphorylation of eukaryotic initiation factor 2 alpha (38). High levels of IL-6 have been shown to correlate with high CRP values and concomitant body weight loss (6).

2.4.1.3 C-reactive protein (CRP) and Acute Phase Protein Response (APPR)

Acute phase response proteins are produced as a response to inflammation (39). It has been shown that up to 50% of patients with solid epithelial cancers may have an elevated acute phase protein response (APPR) (40). APPR is thought to be associated with increased metabolism. Some longitudinal studies have found a poorer prognosis in patients displaying this response, independent of weight loss (41). In clinical care, CRP is commonly used to assess inflammatory response. An elevated CRP concentration has been associated with a poor prognosis in colorectal, breast and ovarian cancer. Hypoalbuminaemia (which is often associated with elevated CRP levels) has been reported to be a good predictor of poor prognosis in many types of cancer (42). Despite the understanding of the role of individual factors the exact mechanisms linking cachexia, APPR, and poor outcomes is still not clearly understood.

2.4.1.4 Prealbumin (transthyretin)

Prealbumin is also called transthyretin and is produced by the liver. Serum prealbumin has been reported to reflect changes in the clinical status of certain cancer patients (43). It also remains a relevant nutritional marker because it is a good marker of visceral protein status and is affected earlier by acute variations in protein balance (44).

2.4.1.5 Albumin

Albumin is the most common protein found in the blood. Its main function is to regulate the osmotic pressure of blood. Normal albumin levels in adults range between 3.5 to 5 g/dL. Its levels are affected by impaired liver function, ascites and inflammation. Recently, serum albumin has been used to determine the severity of cancer, disease progression and prognosis (45, 46). The use of albumin as a nutritional marker is limited because non-nutritional factors, such as hydration and disease process can obscure the effects of actual nutrient deprivation (47). On the other hand it has a strong correlation with morbidity and mortality and is therefore often referred to as a marker of illness rather than of nutrition. The association between hypoalbuminemia and poor prognosis in patients with cancer is well documented (46).

2.4.1.6 Cancer/Carcinoma Antigen 125 (CA125)

CA125 belongs to the mucin glycoprotein family. It is a repeating peptide of the mucin MUC16. It was shown to be excreted by ovarian tumours more than 30 years ago (48). It promotes proliferation of cancer cells while inhibiting anti-cancer immune responses (49). The significance of CA125 in ovarian cancer management is three-fold; 1) As a biomarker where increase beyond 35U/l is generally associated with ovarian cancer (50). When used with imagining it helps to distinguish between benign and malignant disease in women who present with pelvic masses. Recently, this approach has helped to streamline diagnosis such that only women who need treatment in a specialised cancer centre do so, and not women with benign disease. 2) It is used to monitor response to therapy in women with ovarian cancer (51). Often in responders (women who respond to treatment) the CA125 level decreases or returns to baseline. In contrast an increase from a post-treatment level or baseline may indicate disease progression or recurrence. 3) It is a potential a screening test for the early detection of ovarian cancer. The probability of ovarian cancer is thought to be better predicted on longitudinal monitoring of CA125 through a method called Risk of Ovarian Cancer Algorithm (ROCA) (52).

2.4.1.7 Neuroendocrine factors

In recent years there has been an increase in the understanding of the role of hormones involved in the metabolism of nutrients and maintenance of homeostatic functions (53-61). They include insulin, leptin, ghrelin, neuropeptides and cortisol. Cancer appears to affect the regulation of most neuroendocrine factors resulting in insulin resistance, reduced anabolic activity, and elevated cortisol (62). Although insulin secretion is relatively normal in cancer, there tends to be reduced insulin sensitivity (peripheral insulin resistance). Insulin resistance results in a reduced action on tissue glucose uptake and suppression of hepatic glucose production resulting in inefficient metabolism and availability of carbohydrates to the body and also affects muscle protein anabolism (63). It has been suggested that the systemic inflammatory response associated with cancer plays a role in insulin resistance (64).

Other hormones and neuropeptides implicated in energy control, feeding behaviour and accretion of fat include 'ghrelin', (a 28 amino acid neuropeptide) released by endocrine cells of the stomach fundus in response to fasting and stimulating food intake. Its levels increase with weight and it is said that it can stimulate energy intake by 30% in patients with cancer anorexia without any side effects (55, 65). There is insufficient data at the moment to prove whether infusion of ghrelin changes body weight.

Other mechanisms thought to be active in cancer malnutrition/cachexia include increased circulating lactate secondary to anaerobic metabolism of cancer cells and exacerbated by hepatic impairment (66); testosterone or its derivatives as well as insulin-like growth factor 1. The contribution of these mechanisms is not fully understood and discussion of these factors in detail is beyond the scope of this thesis. However understanding the roles of the different factors presents research opportunities where manipulation of mechanisms to stimulate food intake, or prevent breakdown of body reserves hold potential for improved patient outcomes.

2.4.2 Metabolic dysregulation

Tumours escape all the normal mechanisms of metabolic control and causing increased levels of metabolic activity at the expense of the host (67). Terms such as 'host-tumour response', 'parasitic metabolism of the tumour at the expense of the host' and 'the impact of the tumour on the metabolism of the host' have all been used to describe this intriguing metabolic relationship between the tumour and host. Cancer cells interact with host cells to produce cytokines which lead to an acute phase response, neuro-endocrine activation and a chronic state in which catabolism dominates anabolism (28). Metabolic alterations have been studied extensively in animal models, and in various clinical settings. Interestingly in animal models, cachexia occurs only when tumour burden represents 10% to 40% of the animal's weight, when in clinical practice cachexia develops in patients whose tumours rarely exceed 1kg in weight and represent about 1% of body weight (15). This suggests that the type of tumour is more relevant in the development of cachexia than the size of the tumour. This could be important for identifying patients who may benefit from nutrition intervention. Malignant cells have been shown to have a high degree of anaerobic glycolysis and produce large amounts of lactate, and a net uptake of amino acids by human tumour tissue, suggesting an increase in metabolic demands by the tumour (68).

2.4.2.1 Carbohydrate metabolism

Nitenberg and Raynard (15, 69) suggest that tumours are 'glucose-traps' that produce lactates by anaerobic glycolysis, the lactate are then oxidised or recycled into glucose in the liver, resulting in an energy-wasting ('futile') metabolic pathway. In time neoglucogenesis seems to increase the use of the energy substrates in the cancer patient during the course of cancer and does not correspond to any usual mechanism of homeostatic regulation (70). Carbohydrate metabolism in cancer patients is also characterized by glucose intolerance, with a reduction in the sensitivity of peripheral tissues to insulin (54). The result is that even where there is sufficient consumption of carbohydrate the body may not be able to utilise it efficiently to provide energy. This has implications for intervention programmes where the underlying tumour is active.

2.4.2.2 Lipid metabolism

Increased mobilization of peripheral fat and excessive oxidation of fatty acids are consistent metabolic abnormalities in cancer patients (71) the result of which is eventual depletion of lipid stores. Cachectic patients have an increase in plasma concentrations of glycerol and free fatty acids as well as an increase in lipoprotein lipase activity (enzyme required for clearance of triglycerides) (15). This seems to be peculiar to cachectic patients as some studies have found no differences in the level of glycerol and free fatty acid metabolism between weight stable cancer patients and healthy volunteers compared to cachectic cancer patients who release glycerol and free fatty acids from the adiposities in the circulation more quickly than healthy subjects (72).

2.4.2.3 Protein metabolism

The debate on whether a reduction in protein synthesis, an increase in degradation or a combination of both is more relevant to the development of cachexia continues (73). In cancer there seems to be lack of the adaptive mechanism present in other conditions (such as fasting), that allows for slow protein catabolism and preservation of functional lean body mass (74). There is often an increase in protein turnover, a reduction in muscle protein synthesis, an increase in inflammatory ('acute phase') hepatic protein synthesis, a constantly negative nitrogen balance and various changes in the plasma amino acid profile (75). There are also suggestions that total protein turnover is accelerated as a result of increased hepatic protein synthesis coupled with an increase in muscle protein breakdown (76, 77). Regional changes in protein metabolism in cachectic states lead to marked hypoalbuminaemia. It is thought that this is due to a redistribution of peripheral proteins towards the visceral protein synthesis (acute phase protein synthesis) of the host and/or the tumour (78).

2.4.2.4 Energy Expenditure

There is controversy over whether cancer patients have elevated energy expenditure, relative to malnourished non-cancer patients. Some studies report that it was elevated and contributed to significant weight loss (79). These studies

were challenged for using non-specific methodologies and heterogeneous groups (80). Indirect calorimetric studies show no change, a minimal increase, or even lower EE in cancer patients than in weight-losing non-cancer patients or weight-stable cancer patients (81-83). The more accepted view is that energy expenditure should be interpreted as a function of the type and spread of the tumour, the patients nutritional status and the type of treatment where appropriate (15). That energy expenditure normalises after tumour resection, favours the hypothesis that any increases in energy expenditure are tumour driven (81). Intervention strategies at the time of aggressive tumour activity and heavy treatment therefore need to be carefully considered.

Figure 2 illustrates the multiple factors contributing to cachexia. These factors span across different categories of disrupted metabolism and nutritional intake. Causation of cancer cachexia is therefore multi-factorial. Different factors come into effect at various time points along the disease pathway.

Figure 2: Factors that cause and influence cachexia
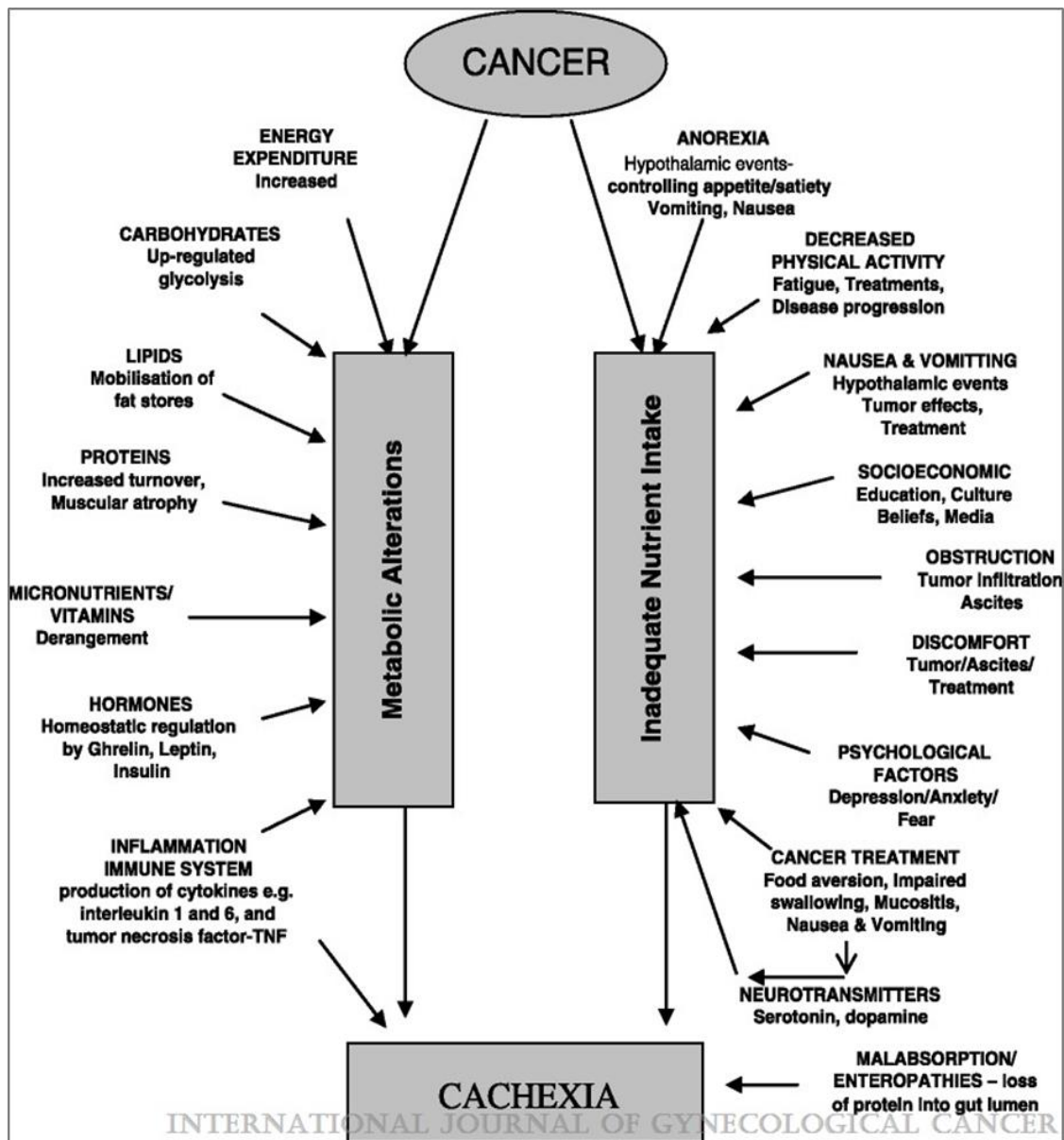
Reproduced with permission. source: Balogun et al., (5)

2.5   Clinical manifestations of cancer cachexia

The clinical manifestations of cachexia include weight loss, anorexia, reduced overall survival, decreased quality of life and reduced physical activity (4). Involuntary weight loss in cachexia, signals alteration of the normally precise controls that serve to maintain body weight and body composition throughout adulthood (29). Body composition changes at the chemical level result from imbalances between the macronutrients absorbed from the diet and the

metabolic fuels oxidized to meet energy requirements (29). Nutrition assessment tools measure directly or indirectly the adequacy of macronutrients in the body evidenced by anthropometric changes in body shape, size and composition.

2.5.1 Weight loss

Mechanisms other than reduced dietary intake and mechanical obstruction by the tumour are involved in the weight loss, including both tumour and host factors (32). Progressive weight loss in cancer cachexia is in excess of that explained by reduced food intake and therefore is unlikely to be effectively treated by satisfying any deficit in intake alone (84). Besides, evidence suggests that earlier in the cancer trajectory, patients are characterised by periods of loss, gain and stable behaviour of fat and muscle until very close to death when weight loss becomes predominant (85). Müller et al., suggest that cachexia is not an unmitigated trajectory of weight loss, but is instead characterised by opposing forces of catabolism driven by the cancer and treatment anabolism when treatment is effective. These opposing forces may result in periods of stability and regain, as well as loss (29). This is particularly significant when considering nutritional intervention and windows of opportunity for maximum benefit of patients.

Loss of body weight is a main identifying feature of cachexia and can be a major source of distress for cancer patients and their carers because it makes the disease visible and is usually taken as signifying the proximity of death (86). A recent systematic review showed a negative relationship between health-related quality of life and loss of weight, with weight loss at presentation being an independent prognostic variable (87). However ascites and oedema can lead to paradoxical weight gain (88). In advanced cachexia, water retention may occur as a consequence of severe hypo-albuminaemia and often accounts for an increase in body weight in spite of severe body wasting (6). These are common prior to treatment and can also be signs that the patient is progressing towards refractory cachexia. Single measures may therefore mask weight loss. However over time, changes in body weight can still be an informative indicator of

nutritional decline, where rapid weight loss may be indicative of more severe malnutrition (15, 89).

2.5.2 Fat loss/gain

Adipose tissue acts as an insulator and lipid reservoir, storing energy in the form of triglycerides during periods of excess energy intake, and releasing it in the form of non-esterified fatty acids (88) for other organs during fasting periods. Its role (in particular white adipose tissue) extends to neuroendocrine control of energy homeostasis, appetite and immune/inflammatory responses (90). Loss of fat has been shown to occur alongside increased circulating free fatty acids and decreased triglycerides in plasma of cachectic mice (90). Morphological changes observed in adipocytes appear to be more severe in cachectic compared to pair-fed (fed the same amount of food) animals, indicating that reduced food intake alone was not sufficient to account for the extent of fat depletion in cancer cachexia. Moreover there is evidence that even though patients may regain weight when using appetite stimulants this weight is from an increase in adipose tissue and not muscle mass (91). The same has also been observed in patients receiving parenteral nutritional supplementation (92) and those using insulin for treatment of cancer cachexia (93). This change in body composition may not be identified if inappropriate assessment tools are used. This loss of muscle mass or sarcopenia is a condition characterised by loss of muscle mass and strength which although primarily associated with aging, is also associated with malnutrition and cachexia (6). It is relevant in cancer cachexia in that even though the loss of adipose tissue accounts for the majority of the weight loss, the loss of muscle impacts most upon morbidity and mortality (22, 94). Patients with limited accretion of lean body mass show no significant improvement in quality of life (32).

2.5.3 Muscle mass loss

Muscle accounts for 60% of the body protein stores and its decrease is associated with functional impairment (6). In healthy adults, muscle mass remains fairly constant in the absence of stimuli such as exercise and thus protein

synthesis and degradation generally remain in balance. There is loss of muscle mass that conventionally occurs with aging (16). This loss of lean muscle mass occurs at the rate of approximately 1% per year after 30 years of age (95). In cachexia there is more protein breakdown and loss of skeletal muscle (96). This imbalance between anabolic and catabolic rates within muscle is responsible for accelerated muscle loss (6). Cancer cachexia produces a marked depletion of skeletal muscle with an estimated 75% fall in protein mass at 30% weight loss (97). Skeletal muscle loss is associated with significant increases in health risks and an impaired health state resulting in increased morbidity, mortality and hospital stay (98). Muscaritoli et al., 2010 suggested that the loss of skeletal muscle should be considered the most clinically relevant phenotype feature of cachexia.

Loss of muscle mass is not restricted to patients who appear thin nor is it limited to loss of skeletal muscle (6). It also incorporates depletion of visceral protein which can be estimated by serial measures of indicators of visceral protein status such as transthyretin (23), retinol-binding protein (RBP) and albumin (99). Both correlate with decreased survival. Frailty or illnesses often lead to sedentary behaviour which may worsen lean body mass loss by disuse-induced deconditioning and deterioration in skeletal muscle mass (100).

2.5.4 Inadequate food intake

Various events occur in cancer cachexia that result in reduced food intake (below 80% of the usual food intake (101). Reduced food intake is both a consequence of tumour effects and treatment-related side effects as well as a contributor to cachexia progression. The mechanisms by which tumour effects alter food intake include anorexia, nausea/vomiting, pain, taste/smell changes, fatigue, alterations in the central nervous system (CNS) which controls food intake, early satiety, decreased response to insulin, increased circulating lactate and the production of some cytokines (102-104). In addition the side effects of cancer treatment that can cause nausea and vomiting, abdominal cramps and bloating, mucositis, paralytic ileus and malabsorption (15, 105) may also result in decreased food

intake. Meanwhile local tumour effects such as pain (general or on swallowing), gastrointestinal obstruction, and malabsorption (103) also affect food intake. This is particularly common in tumours impinging on the gastrointestinal tract such as ovarian cancer. Oral feeding with regular food, which is preferred to enteral feeds or Total Parenteral Nutrition (TPN) (106), becomes complicated in cancer patients where ascites and/or mass compression of the gastrointestinal tract are common.

2.5.5 Socio-economic influence

Healthy behaviours following a cancer diagnosis are thought to contribute to increased survival rates (107). Culture and socioeconomic status can strongly influence these behaviours. Social and economic factors have been associated with cancer mortality and survival (69). Financial concerns constitute an obvious significant barrier to changes in health behaviours. A study of some ethnic minority in breast cancer survivors in America showed that women understood that they could have been making different choices about their diet, but could not afford to (108).

Social, cultural and symbolic understandings of the nature of food, mediate the effect of the changing physiology of illness, and are significant for patients, families and health professionals (109). The emotional meaning attributed to food may change with different life stages, however individuals are embedded in social and cultural organisations that affect decisions about what should be eaten and why at each stage (109). Furthermore diet and eating habits are a complex behavioural phenomenon that results from an interaction between where we live, what is available, what we can afford, how much time we have to dedicate to the process of procuring and preparing food, and even what we are allowed in terms of family traditions, societal, religious, and gender norms (110). Therefore research strategies focussing on both the preventative and the therapeutic impact of diet would benefit from sensitively factoring in cultural diversity groups (111). Interventions that ignore a patient's social situation are unlikely to succeed in the long term (111).

2.5.6 Ethnicity

Cancer research UK suggests that in the UK, there is evidence of lower cancer symptom awareness amongst those experiencing deprivation and those from Black and Minority Ethnic communities (BME) (112). They also state that there is evidence of inequalities based on ethnicity at each stage of the cancer patient pathway, starting from information provision through to palliative care. There is lack of evidence of documentation of ethnic variations in the nutritional status of cancer patients. A review of 82 physical activity trials by Speck et al., (2010) (113) concluded that 76% of reviewed studies did not properly describe the sample characteristics and race was the factor most commonly overlooked. However, it has been shown that African American women although at lower risk of being diagnosed with ovarian cancer, they tend to present with more aggressive disease and experience worse survival (114). Postmenopausal African American women with a BMI > 40, 1 year before diagnosis and those with weight gain since the age of 18 were reported to have a higher risk of ovarian cancer (115). There is also evidence that in breast cancer patients, being overweight or obese is associated with a higher risk of secondary tumours, recurrence, and mortality (116). Black breast cancer survivors have been shown to be 70% more likely to be obese than their white counterparts (117). The limited data so far suggests that black patients are more likely to gain weight after diagnosis (118) and are less likely to meet physical activity or nutrition recommendations (119) Others have suggested, based on findings from multi-centre trial of breast cancer survivors (N = 692; blacks = 71) that a behavioural intervention may support clinically meaningful weight loss (120).

2.5.7 Psycho-emotional impact

Psychological factors that occur frequently in cancer patients such as fear, depression and anxiety independently affect quality of life and performance status. They also negatively impact on appetite and food intake (89, 121, 122). The distress suffered is due to disease effect, the aggressive standard medical treatments (surgery, chemotherapy, and radiation therapy) and related side effects (123-125), and fears about disease recurrence and death (126).

Gynaecological cancers, including ovarian cancer entail additional consequences because the body parts involved are emotionally charged, being associated with femininity, sexuality, and childbearing (127). The damage to them threatens female identity often causing further psychological morbidity (128). A relatively high prevalence of anxiety and depression has been reported with up to 21% of all gynaecological cancer patients found to be clinically depressed while 29% were above the 75th percentile for anxiety (129). A separate study showed that 3 months following chemotherapy, 38% of ovarian cancer patients had clinical anxiety and another 33% were depressed (130).

Traditionally women have been predominantly responsible for the procurement, preparation and serving of food, and through the provision of healthy and tasty meals, maintain harmonious family relations that symbolize love and nurturing for family members (131). A cancer that often results in personal struggles not only with food but survival itself causes a direct conflict with what could be termed 'natural state of being'. Studies have shown in some cancer survivors that family can be both a motivator and a barrier to health behaviour changes (132). Family members tend to continue to view women as a wife and/or a mother and expect them to fulfil their household and child-rearing tasks (108). The expectations are unlikely to be different in ovarian cancer survivors, despite that most women would be beyond their childbearing years. The prevalence of the psycho-social impact compared to other populations is discussed further with the quality of life findings in section 9.3 page 253.

This section was used to demonstrate that factors that affect food intake are varied and are both internal (disease related or psychological) and external (socio-economic). They extend beyond the disease and its effects, to include family, financial and societal issues as illustrated in Figure 2. Decreased food intake contributes to the cancer cachexia/malnutrition conundrum and it is often a symptom of the underlying disease while on the flipside it will itself contribute to cachexia. Thus, the paradigm of mal/nutrition along the cancer trajectory is not static. Management of nutritional needs should therefore shift with the changing

needs. Life stage and its associated priorities will affect the emphasis that might be placed on each outcome of wellness and well-being (133). Moreover, the processes are intertwined such that clear lines cannot be drawn between reduced food intake, anorexia and cachexia. For example, tumour volume might cause early satiety resulting in reduced food intake, which may also be interpreted as anorexia (loss of appetite), which contributes to cachexia, which in turn will exacerbate the anorexia.

2.5.8 Anorexia

Anorexia is one of the most significant contributors to reduced food intake, promoting skeletal muscle wasting and therefore cancer cachexia (15). Anorexia and reduced food intake are physiological responses prompted by the growing tumour (134) and are prevalent up to 40% at diagnosis and 70% in advanced disease (135). It is commonly the symptom which prompts individuals to consult their physicians in the first place, and its alleviation can be perceived as a sign of effective management of the disease (136). There are still difficulties in clearly defining and diagnosing anorexia because of the multifactorial pathogenesis related to disturbances of the central physiological mechanisms controlling food intake and its precise neurochemical mechanisms (136). It has been suggested that anorexia is the most frequent and most important contributory factor in nutritional deterioration among cancer patients (137). The onset of anorexia significantly affects the clinical course of the disease (134). Food aversions especially related to chemotherapy treatment can exacerbate the problem of anorexia. Around 33% of cancer patients experience changes in the recognition of some tastes resulting in aversion to some foods (138).

Various definitions of cachexia have been offered and include: a loss of appetite associated with the systemic effects of cancer (139); or a syndrome of patients with malignant diseases consisting of loss of appetite, aversion of food, disturbances of taste and smell and a decrease of nourishment below 80 % of the usual food intake (101). The expert group (6) added that its pathogenesis in the context of cancer "is complex and multifactorial and is believed to result from

inflammation-driven resistance of the hypothalamus to appropriately respond to orexigenic (i.e. appetite stimulating) and anorexigenic (i.e. satiety stimulating) signals". The question remains whether treating anorexia and improving energy intake will result in a long-term benefit for cancer patients with active disease (136). Despite this uncertainty improving anorexia and energy intake could have a positive impact on quality of life (140).

Anorexia exacerbates the detrimental effects of tumour-related alterations of metabolism and is an independent prognostic factor in terminally ill cancer patients (141). Despite its significance, anorexia is often neglected in the clinical management of cancer patients.

2.5.9 Weakness and fatigue

2.5.9.1 Weakness

The concept of cachexia and its impact has evolved to encompass functional components such as decreased exercise capacity and muscle strength which can result in adverse effects on quality of life, self-care and independence) (142). Impaired protein metabolism significantly impairs structure, function and wellbeing (143), manifesting in a number of clinical consequences, including reduced QoL, fitness, and the ability to sustain physiological function (143).

2.5.9.2 Fatigue

Cancer-related fatigue (CRF) is characterized by feelings of tiredness, weakness, and lack of energy. It may be an early symptom of malignant disease, reported by as many as 40% of patients at diagnosis increasing to 80% and 90% in those treated with chemotherapy and radiotherapy respectively (144). The exact reason for cancer fatigue is unknown, but it is thought to be related to both the disease process and treatments, including surgery, chemotherapy, and radiation therapy and high amounts of cytokines. Fatigue is also related to anaemia, which can be as a result of treatment. Other suggested mechanisms of action range from tumour-induced "hyper metabolic" state where tumour cells compete for nutrients

at the expense of the normal cell's growth and metabolism to medications used to treat side-effects such as nausea, pain, depression (145). A study of women with ovarian cancer found a positive correlation between fatigue and CA125, suggesting that fatigue was related to tumour burden (146). They did not find a significant relationship between fatigue and age, stage of disease, course of treatment, or depression. In a systematic review by Servaesa et al., (2002) (147), 6 of 7 studies that investigated anaemia and fatigue found no significant relationship between them. However they found several studies showed that the intensity of fatigue strongly correlated with indicators of psychological distress such as depression, somatisation and anxiety. Fatigue is a significant problem that can persist for months and even years following completion of cancer treatment.

2.6 The impact of malnutrition

2.6.1 Morbidity and mortality

Approximately half of cancer patients will have lost at least 5% of their pre-illness weight at presentation (148). The prevalence of cancer-related malnutrition ranges from 30% to 64% in inpatients and is related to an increased risk for adverse clinical outcome (149, 150). It is estimated that between 20% and 40% of patients with cancer die of the effects of malnutrition rather than of the malignancy itself (151),(152). For this reason there have been suggestions that malnutrition should be treated as a problem equal to the primary diagnosis (153). The risk of complications and death during the course of treatment is high for such patients (89). Some studies have shown mortality to depend both on the extent of weight loss and on baseline BMI. In a series of more than 1000 medical oncology patients, mortality among those with >20% loss of weight and a baseline BMI of <21 kg/m^2 was four times that of patients with <6% weight loss and a BMI above 27 (154). In a study of pancreatic cancer patients, cachexia was shown to be significantly associated with poorer survival despite the fact that cachectic and non-cachectic patients did not differ in tumour size or lymph node status (155). Malnourished patients are at risk of increased length of intensive care and hospital stay, total parenteral nutritional utilisation and a delay to resumption of

an oral diet and for those patients who are discharged there are more readmissions, general practitioner (GP) visits and consultations resulting in increased resource utilisation and cost compared to their well-nourished counterparts (156). Falls and fractures are common in patients with muscle weakness.

Each phase of the cancer survivorship continuum, that is, treatment and recovery; long-term disease-free living or living with stable disease or living with advanced cancer, is associated with different nutritional needs and challenges (157). However the evidence of the success of nutritional interventions to counteract the deleterious consequences of cancer cachexia in any of the phases is limited. Lack of scientific evidence to inform practice means that in general daily oncology practice nutrition is not often prioritised (158). Health care providers tend to prioritise the strength of evidence and are less likely to discuss diet with their patients if they perceive the evidence base as weak (159). There is a gap between practice and suggestions that to improve prognosis, nutrition intervention should be delivered as soon as the diagnosis is made and concomitantly with oncology treatment. This curative approach could potentially improve performance status (160), improve patients' tolerance to treatment (161), reduce postoperative complications (162), enhance immuno-metabolic host response (163), shorten length of hospital stay and control cancer-related symptoms (e.g. anorexia, nausea, among others) (103) and improve QoL (164).

2.6.2 Infections and wound healing

Malnutrition is associated with alterations in cellular physiology and organic function with implications for surgical outcome and postoperative morbidity and mortality respectively (165-167). Malnourished patients undergoing surgery are more likely to have complications such as increased blood loss, fatigue, poor wound healing, impaired immune competence, impaired inflammatory response in particular impaired T cell activity and admissions to intensive care units, (103, 168, 169). These undesirable outcomes decrease the quality of life for the patient, and are also costly to the health care provider. Serum albumin levels less than

51

35g/l significantly increase the risk of post-operative complications in patients with no co-morbidities or dehydration (165). Co-morbidities such as chest infections due to decreased immunity and electrolyte imbalance with implications for lung function and cardiac complications are also common.

2.6.3 Complications during cancer treatment

The feasibility of complete cytoreduction is related to tumour volume and location, as well as a patients' ability to withstand a long operation (age, performance status, nutritional status) (170). Survival in patients requiring chemotherapy directly correlates with dose and the timely completion of the prescribed chemotherapeutic regimen (171). Poorly nourished patients tend to have a suboptimum response to therapy and have an increased risk of treatment-related side effects and death during the course of treatment (89). It has been shown in patients with advanced breast cancer that response rates are lower among those who had lost weight before chemotherapy (28). In a prospective study of 100 Non-Small Cell Lung Cancer (NSCLC) patients undergoing chemotherapy, those who were malnourished and hypoalbuminaemic experienced major toxicities significantly more frequently than those who were not (172). A retrospective review of data gathered in 1555 consecutive chemotherapy patients with gastrointestinal cancer showed that patients who had self-reported weight loss before treatment experienced more frequent and severe toxicities (stomatitis, and plantar-palmar toxicity) despite being treated for a shorter period (shorter due to breaks in treatment being more often) (173). Failure to complete intended chemotherapy regime is also common and leads to increased mortality.

2.6.4 Decreased physical activity

Decreased physical activity can be due to fatigue caused by muscle wasting or other complications common in cancer such as anaemia. It can also be because of the cancer treatment. Cancer survivors particularly the elderly have been shown to experience a fundamental deterioration in physical functions because of the effect of surgical treatment, chemotherapy, and radiotherapy, and this is more prevalent in women than men (174). The relationship between fatigue and

physical activity has been demonstrated in a systematic review which concluded that this was associated with less daytime activity (147). Fatigue described earlier can affect all areas of life by making the patient too tired to take part in daily activities, relationships, social events, and community activities, with a profound effect on their quality of life.

2.6.5 Decreased quality of life (QoL)

The World Health Organisation (1995) (140) described QoL as reflecting a patient's subjective evaluation of all dimensions of their health experience, including physical health, psychological state, level of independence, social relationships, personal beliefs, and their relationship to salient features of the environment. It is a multidimensional concept that includes the impact of the disease together with therapeutic interventions, expectations and personal satisfaction (30). Various aspects of a cancer diagnosis and treatment including anorexia and reduced energy intake often impinge on QoL as does cancer related fatigue which affects physical functioning and the ability to perform activities of daily living. Quality of life has in recent years become a critical endpoint in the management of cancer patients as well as the design of clinical trials (123, 136, 175). Appropriate care of patients now requires an evolving response and measures to preserve and/or enhance the quality and quantity of life (123). This emphasis helps to shift mind-sets from goals of therapy that are focused only on tumour response and survival (126), to include lifestyle issues that may previously not have been considered as important.

It is difficult to quantify the interrelationship between QoL and nutrition. This is partly due to the fact that it is conceptually challenging to clearly define and clarify the definitions and indexes of quality of life in nutrition terms (176, 177). In a systematic review of studies that relate QoL with nutritional status in cancer patients (178), there was evidence of a correlation between nutritional status and quality of life. The lack of specific measures of the impact of nutritional status on QoL means that most studies used generic questionnaires such as the EORTC-QLQ-30. Using non-specific tools makes interpreting data difficult because the

influence of underlying disease on nutritional status cannot be isolated. Regardless, a study of gastric, pancreatic and colorectal cancer patients with weight loss at presentation showed them to have significantly lower mean quality of life scores than patients with no weight loss (173). The poorer QoL scores in patients with weight loss was thought to occur because they received significantly less chemotherapy and developed more toxicity rather than it being due to reduced tumour responsiveness to treatment. A recent systematic review of the effectiveness of interventions in malnutrition and cachexia found that there were significantly greater benefits to quality of life in cancer patients who received nutritional oral nutritional supplements compared with routine care (164).

The detrimental effects of malnutrition in cancer patients are unquestionable. Recent progress towards understanding its causation and progression and efforts to find consensus definitions of terms are to be applauded. This is crucial for future efforts to manage malnutrition. Also crucial to its management is comprehensive assessment of the patient's nutritional status and identification of clinically relevant limits. Malnutrition evolves during the course of the cancer and is a continuum, which will require periodic reassessment (15) to identify patients at risk of malnutrition and to see if they can benefit from nutritional intervention. At the other end of the spectrum those who are unlikely to benefit from interventions would be appropriately managed with symptom control. The next section introduces and reviews literature specific to ovarian cancer. The statistics, management and nutritional challenges faced by women diagnosed with the disease are considered.

2.7 Ovarian cancer

2.7.1 Statistics

Ovarian cancer has the highest mortality of all gynaecologic malignancies (179). It is the 5th commonest women's cancer in the UK, after breast, bowel and lung and endometrial or womb cancer. There were 7116 new cases of ovarian cancer diagnosed in the UK in 2011, and 4271 deaths from it in 2012 (180). It is mainly

a disease of the older post-menopausal woman, with almost 85% of cases being diagnosed in women over 50 years. A very small proportion of the cancers are detected at a localized stage when the disease can be cured successfully. About two-thirds of patients are diagnosed with advanced stage disease with regional or distant disease (181, 182). Despite aggressive surgery and chemotherapy, the prognosis for these women is poor, with an overall 5-year survival rate of around 30%. Survival of ovarian cancer patients has remained relatively unchanged for almost three decades (183). Table 1: shows the detailed 5-year survival rates of 2008 according to Cancer Research UK (CRUK). These figures suggest that around 46% of women diagnosed with ovarian cancer now survive beyond 5 years, in contrast to the previous 30%. It is however evident that that higher survival is due to women diagnosed with early stage disease (stage 1 & 2). The general poor outcome in late stage disease is due in part to the lack of effective prevention and early detection strategies. Significant research is underway to develop highly sensitive and specific early detection tests that are minimally invasive (184).

It is estimated that at diagnosis only 15% of ovarian cancer is localized to the ovary, 17% is regional, and the majority, 62% occurs as distant disease (185). Although ovarian cancer has historically been called the "silent killer" meaning that it does not normally manifest symptoms, in retrospect, many patients will note a several-month history of vague abdominal discomfort that is generally nonspecific (186). Recent evidence shows ovarian cancer does manifest with early symptoms of bloating, abdominal pain, feeling full after eating, frequent urination, and irregular menstrual bleeding but that these are variable between patients and often misdiagnosed as benign gastrointestinal and gynaecological issues and are consequently not believed to represent serious underlying pathology (187). As such, 75% of ovarian cancer is diagnosed late after the cancer has reached stage III or IV (188). Malignant ascites, a build-up of fluid in the peritoneal cavity secondary to cancer is common in women with advanced disease. It often makes women unwell and has been described as the worst experience of the cancer journey (189). Around 77% of all newly diagnosed

patients with ovarian cancer have ascites and another 31% develop ascites at first relapse (190).

Table 1: The Five-Year Stage-Specific relative survival rates of adults aged between 15 and 99 years in England and Wales for 2004-2008

Stage at diagnosis	Number of cases in each stage	% of all cases	5-year relative survival (%)
Stage I	424	29	92.0
Stage II	62	4	55.1
Stage III	652	45	21.9
Stage IV	216	15	5.6
Unstaged	89	6	27.6
All stages	**1 443**	**100***	**43.5**

*percentages may not add due to rounding

Source: Adapted from CRUK *http://www.cancerresearchuk.org/cancer-info/cancerstats* (Accessed April 2014)

Although the 5-year survival rates of ovarian cancer are predicted to increase to about 46%, they continue to fall beyond the 5 years to 35 % at 10 years as shown in Table 2.

Table 2: The One, five and ten-year net survival (%) predicted for patients diagnosed in 2010-2011 in England and Wales

	1yr survival (%)	5-yr survival (%)	10-yr survival %
Net survival	72.4	46.2	34.5
95% Lower Confidence Limit	72.4	45.9	33.8
95% Upper Confidence Limit	72.5	46.4	35.3

Adapted from CRUK (180), (accessed Aug 2015)

2.7.2 Causation

The cause of ovarian cancer continues to baffle scientists. Advances in research now point to ovarian cancer being a general term for a series of molecularly and etiologically distinct diseases that simply share an anatomical location (183).

Pathological and genomic findings indicate that many ovarian cancers are derived from non-ovarian tissues and that the different histological types share few molecular similarities (191). Although now generally accepted that the distal fallopian tube is the likely source of high-grade serous ovarian cancers, evidence persists that some high grade serous tumours originate from the epithelial surface of the ovary (186). There is a strong epidemiological link between clear cell and endometrioid cancers with endometriosis (192). The known types of histological subtypes of ovarian cancer are shown in Table 3.

Table 3: The known histological subtypes of epithelial ovarian cancer (EOC)

Histological subtype	Percentage of EOC cases (%)	Tissue of origin
Serous, high grade (type II)	70	Fallopian tube fimbria
Serous, low grade (type I)	<5	Fallopian tube fimbria
Clear cell (type I)	10	Endometrial/endometriosis
Endometrioid (low grade, type I; high grade, type II)	10	Endometrial/endometriosis
Mucinous (type I)	<5	-

Adapted from Engelberth et al., 2014 (186)

Advances in molecular biology and the emergence of new technologies means new strategies for prevention, early detection and treatment of the disease may be identified. These may involve the development of "personalized medicine," where prevention, detection and treatment are aimed at the specific molecular mechanisms of an individual tumour and its microenvironment, as well as at the specific genetic and biologic profile of the host (183). Some lifestyle factors including physical activity and obesity are thought to play a role in ovarian cancer risk and mortality (193).

2.7.3 Treatment

Treatment of ovarian cancer predominantly focuses on the primary diagnosis and has been said to neglect the concomitant malnutrition which portends an unfavourable postoperative risk of complications and poor recovery (194). Standard treatment includes cytoreductive (debulking) surgery, chemotherapy and/or radiotherapy. The specific combination depends on prognostic factors such as stage, tumour grade and histology (195). Studies dating back more than 30 years have consistently demonstrated an inverse correlation between the volume of tumour remaining at the completion of initial surgery and overall survival (OS) for patients with ovarian cancer (196). Therefore the goals of initial surgery in ovarian cancer are to diagnose and stage disease and to provide therapeutic benefit with cytoreduction. The terms "optimal" and "suboptimal" refer to the size of the largest residual tumour nodule that remains after debulking surgery: 1 cm or less is considered optimal, and greater than 1 cm suboptimal debulking (196). Patients with a high risk of major morbidity or mortality from primary debulking receive neo-adjuvant chemotherapy (197). This treatment pathway shows a decreased survival when compared to optimal or complete debulking (198, 199). The decision of which patients are best suited to undergo neo-adjuvant chemotherapy is not readily agreed upon. Despite progress in the use of imaging in recent years, there are still no objective criteria that enable gynaecological oncologists to determine this. Precise histologic diagnosis and accurate staging are required before chemotherapy treatment since chemotherapy regimens and prognosis are determined by the type and stage of the disease (198). Ovarian malignancies are surgically staged according to International Federation of Gynaecology and Obstetrics (FIGO) staging system (24) outlined in Table 4. Stage II disease is the least commonly diagnosed stage of ovarian cancer. This is likely because there is no anatomic boundary between the pelvis and upper abdomen. If disease has spread outside the ovary to pelvic structures, it is also likely to spread to the upper abdomen. Due to the observed higher recurrence rate seen for stage II disease, the Gynaecologic Oncology Group (GOG) is now including stage II in the category of advanced disease for trial purposes (200).

Table 4: FIGO staging and prognosis of ovarian cancer

FIGO Stage	Characteristics	Stage distribution	10-year survival rate
I	Disease confined to the ovaries	20%	73%
IA	One ovary, capsule intact, no ascites		
IB	Both ovaries, capsule intact, no ascites		
IC	Stage IA or IB plus ascites or washings, capsule ruptures, tumour on ovarian surface		
II	Disease spread confined to the pelvis	5%	45%
III	Disease confined to the abdominal cavity, including surface of the liver; pelvic, inguinal, or para-aortic lymph nodes; omentum or bowel	58%	21%
IIIA	Negative lymph nodes, plus microscopic seeding of peritoneal surface		
IIIB	Negative lymph nodes, peritoneal implants <2 cm		
IIIC	Positive lymph nodes and/or abdominal implants >2 cm		
IV	Spread to liver parenchyma, lung, pleura, or other extra-abdominal sites	17%	<5%

Reproduced with permission. Source: Jelovac et al., (188)

2.7.4 Prognosis

Biochemical and histological prognostic factors in ovarian cancer are known to include stage, tumour histology, grade, and cytology (201-203). Performance status, residual tumour volume and presence or absence of ascites have been

shown to be independent predictors of survival in patients with epithelial ovarian cancer (202, 204, 205). Change in body weight during primary chemotherapy (206) and malnutrition (207) have both been reported as potential prognostic factors. Patients diagnosed with ovarian cancer are 19 times more likely to present with a poor nutritional status before treatment compared to patients with benign conditions or endometrial cancer (208). Malnutrition has been reported to some extent in 67% in this patient group in retrospective studies (209). This is a problem that requires proactive management. Challenges to managing the disease remain and much is still unknown; for example why patients with the same ovarian tumour characteristics (histological type, stage, and grade), will experience variations in survival. This has previously driven extensive research efforts on molecular prognostic factors to enable more efficient and targeted therapeutic regimens (210). Lifestyle factors such as nutrition and physical activity are thought to contribute to prognosis, disease free survival and the response to complications from treatment (210).

2.7.5 Nutritional challenges

Cancer is a challenging disease. However gynaecological cancers, and ovarian cancer in particular entail additional consequences beyond those common to other cancer patients (211). The location of the ovarian tumour deep in the abdomen limits the possibility of a precise early diagnosis. Late diagnosis is associated with advanced disease, which in turn is associated with worsening nutritional and performance outcomes. Patients tend to have 1) a reduced ability to eat (feeling too full too quickly, nausea and vomiting), 2) bowel obstruction and sometimes 3) diarrhoea, the consequences of which may cause patients to stop eating. In addition to the systemic and metabolic disturbances and treatment effects discussed in earlier sections, the psychological impact of a disease arising in a reproductive organ consequently reduces appetite and nutritional intake (128).

A study by Fuchs-Tarlovsky et al., (2013) comparing nutritional status of 120 women (57 with ovarian cancer and 63 with benign tumours), showed

measurements of skin-fold thickness at four different sites and arm circumference to be statically lower in the cancer group ($p < .05$). Body fat and protein reserves appeared to be significantly lower when measured by the Siri equation but not when measured by Dual Energy X-Ray Absorptiometry (DXA) scan or Bio-Electrical Impedance (BIA). Biochemical parameters like albumin, transferrin, haemoglobin, lymphocytes levels were significantly lower in the cancer group $p < .05$) (212). This is one of a few studies where comprehensive nutritional assessment was performed in a homogenous ovarian cancer population. The findings support the school of thought that nutritional management should be implemented as soon as possible in patients diagnosed with ovarian cancer. Evidence suggests that nutritional deterioration in ovarian cancer patients continues as they enter into treatment. Six months post diagnosis ovarian cancer patients (including women who start off being overweight or obese), show weight loss and a significant decrease in their BMI and serum albumin levels (208). Another study by Gil et al., also prospectively assessed nutritional status in patients with ovarian cancer (213), using weight and body composition. They found that women lost weight following surgery but regained it slowly over the following year and did not lose muscle mass. As such they did not find any changes in Body Cell Mass (BCM) over the 12-month period following treatment. It must be noted that BCM is a nonspecific measure of body composition which includes all the metabolically active tissues such as muscle, organs, intracellular and extracellular water, and bone tissue. An increase in intra/extracellular water (hydration/ascites) for instance may mask a decrease in muscle mass.

Literature and advice on nutritional management of patients undergoing treatment for ovarian cancer is not clear and recommendations made by advisory bodies in Europe, America and Australia for cancer patients lack evidence and are largely based on expert opinion (214). For example it is still not clear which patients should be treated aggressively and what mode of therapy should be pursued in women with bowel obstruction (215). Lack of accurate information can disempower women and lead to erroneous beliefs or fears that may constitute barriers to effective management of disease and treatment related symptoms (216). Provision of factual information can counter misconceptions and help

patients to develop accurate expectations (216) and enhance feelings of control (217). An effective patient-clinician partnership will empower a woman to face the fight of her life (183).

Understanding the roles and goals of both the physician and patient, clear and honest communication and a balance of power are necessary tools for involving patients in the management of their nutritional care.

2.8　Nutrition care

Nutrition care refers to the management of patients' nutritional needs and includes nutrition screening, nutrition assessment and nutrition support/intervention. It encompasses formulation of a nutrition care plan, implementation of the plan, patient monitoring, evaluation of the plan, evaluation of the care setting, and reformulation of the plan or termination of therapy (218). These stages are discussed further in the following sections. Implementing nutrition care plans in cancer patients has proved very challenging for reasons discussed below.

2.8.1 The challenges

One of the challenges faced by oncology clinicians and researchers in the nutrition field has been that there are no universal accepted standardized criteria for assessing malnutrition indices (8). Historic definitions for malnutrition syndromes had many limitations including, poor specificity, sensitivity, and inter-observer reliability and lack of validated diagnostic criteria (219). Misdiagnosis of malnutrition is said to be frequent alongside confusion caused by the not so clear and overlapping definitions. Disease causes a series of metabolic and functional changes in earlier stages, and these changes are only later demonstrable by anthropometric changes (body shape, size and composition) (8). For this reason nutritional assessments should consider the physiological requirements and nutritional intake, functional status and body composition (148) and not just one of these.

Lack of validated, scientifically sound, standardised tools with sufficient sensitivity and specificity to identify various levels of malnutrition means that the impact of underlying disease, hydration state, inflammation etc. cannot always be separated from nutritional status. Unclear diagnostic criteria has compounded the problem and led to grouping together of different stages of malnutrition, instead of individualised assessments that take into consideration function and possible treatment options. Progress had previously been hampered by overlooking the nutritional state of patients in pre-surgical assessments (54) and the lack of training of healthcare practitioners in assessment and diagnosis of malnutrition.

The evolving challenge of malnutrition now also relates to the increasing obesity epidemic, which can mask the underlying lethal muscle wasting (16), resulting in a combination of excess weight and reduced muscle mass and/or strength (sarcopenic obesity). The picture of a cachectic patient is no longer just the classical underweight patient. This also challenges the traditional methods of assessment that largely rely on weight assessment.

This clinical picture was well painted by Baracos (220) who said,

"*We were surprised to record an average of fat mass in excess of 20kg, in a cohort of metastatic colorectal cancer patients at one month from death, in spite of preceding weight loss and large burden of metastatic disease*".

The complexity of the malnutrition/cachexia syndrome continues to draw attention from specialists. Expert groups have met to define terms and also set guidelines, criteria and frameworks for assessment. These definitions are based on the current scientific understanding of the effect of the disease on nutrient intake and body composition. Universally accepted definitions and parameters can potentially propel clinical practice forward and also provide a unified platform on which to carry out research. Unfortunately as knowledge increases these guidelines are bound to change.

2.8.2 Nutritional screening

Nutrition screening refers to a process to identify an individual who is malnourished or who is at risk for malnutrition to determine if a detailed nutrition assessment is indicated (218). An ideal screening tool should be easy to use, standardized, rapid, non-invasive, and cost-effective to identify cancer patients at nutritional risk in daily clinical practice (221). The Nutrition Screening Survey in the UK and Republic of Ireland (2011), reported that the 'Malnutrition Universal Screening Tool' ('MUST') was the most commonly used nutritional screening tool in all care settings (i.e. 85% hospitals and 92% care homes) (222). The survey also found that in a few centres no screening tools were being used and/or no training on nutritional screening provided.

Despite there being a variety of validated screening tools for nutritional screening in cancer patients (223-225), the guidelines issued by the National Institute for Health and Clinical Excellence (NICE) regarding nutritional screening, dietary requirements and care of people identified as at risk are often not followed (226). Some of the factors contributing to this include poor training, lack of time, competing tasks, and a perception that this basic care is less important than other duties or is the responsibility of others. Although the proportion of hospitals screening 76-100% patients on admission has increased significantly over the last few years (222), there is still limited information about the nutritional status in particular of cancer outpatients because the practice of nutritional screening is rarely performed in this setting (227). Where some screening has been carried out it is mainly to inform treatment plans such as chemotherapy dose calculation, rather than for the management of nutritional needs. Nutritional screening is particularly relevant in cancer patients as it could lead to timely management of weight loss, which if left untreated has undesirable consequences.

2.8.3 The importance of screening

Nutritional screening if appropriately used would 1) be carried out on all cancer patients in any setting (hospitals, outpatients, care homes, home) where patients are being cared for). 2) Identify patients including those who are well nourished,

malnourished, or at risk of malnutrition. 3) Be followed up with an appropriate referral to a specialist or for a complete nutritional assessment where appropriate. Nutritional screening might include: BMI, unintended weight loss, impaired food intake, treatment plan and disease severity (148). It can therefore be viewed as an instrument to determine whether additional information (via formal assessment) is required to warrant an intervention (218). The lack of routine screening procedures was shown to leave more than 50% of nutritionally at risk patients unidentified (228, 229). Identifying these patients provides an opportunity for early intervention associated benefits including improved response to treatments and quality of life (7).

Nutrition screening is a gateway for individualised patient management. A nutrition care algorithm is indicated in Figure 3. This algorithm shows how screening links with other aspects of the care of patients. Nutritional screening and assessment should continue beyond the instigation of nutritional support.

Figure 3: Nutritional care algorithm

Reproduced with permission. Source: Ukleja et al., (230)

Van Cutsem et al., suggested that nutritional management should be prophylactic rather than reactive and nutritional interventions should be an integral part of cancer therapy in order to improve clinical outcomes (103). In the UK, the

Department of Health (231) acknowledges that it is essential for management and regulatory structures of health and care providers to accept a wider responsibility which ensures that all professional staff, at all levels of the services, see issues around nutrition and help with eating and drinking as a core part of their responsibilities, for which they will be held to account (231). This raises the issue of expertise, training and experience amongst staff, which has long blighted this field. These challenges start high in the clinical hierarchy with physician practices, which often fall short, of addressing the nutrition aspects of cancer patients (232). This was demonstrated in a survey of all trainee oncologists (specialist registrars) in the UK. It showed 80% (n= 267) of trainee participants said a patient was malnourished compared to 14% of nutrition experts while only 59 % said the patient was at risk of malnutrition compared to 86% of the experts. The lack of standardised guidelines and necessary training among professionals is clearly an issue that cascades down to affect the management of patients.

2.8.3.1 Malnutrition Universal Screening Tool (MUST)

MUST is a five-step screening tool to identify adults who are malnourished, at risk of malnutrition (undernutrition), or obese. It is a tool that was developed by the Malnutrition Advisory Group, a standing committee of BAPEN (British Association for Parenteral and Enteral Nutrition) in 2003. It uses a BMI score, weight loss score as well as an acute disease score to calculate the malnutrition risk. Management guidelines are provided to manage patients who are identified as being at risk of malnutrition. Although widely used in the NHS to screen patients, it is not an appropriate instrument for use in this research as it does not assess or characterize malnutrition. It is only able to identify at risk patients.

2.8.4 Nutritional assessment

Patients identified as nutritionally at risk through screening should have a nutrition assessment. American Society for Parenteral and Enteral Nutrition (ASPEN) defined nutrition assessment as "a comprehensive approach to diagnosing nutrition problems that uses a combination of the following: medical, nutrition, and medication histories; physical examination; anthropometric measurements; and

laboratory data" (218). Dietary considerations should also be included and increasingly functional assessments are also being considered, as muscle wasting becomes better understood. Nutritional assessment is more rigorous and complex than screening since it is carried out to confirm the presence, extent, degree of severity, and type of malnutrition (148). This is done by documenting baseline nutrition parameters, identifying nutritional risk factors and specific nutrition deficits, establishing individual nutrition needs, and identifying medical, psychosocial, and socioeconomic factors that may influence the prescription and administration of nutrition support therapy (230). In summary the objectives of nutritional assessment should include 1) identifying patients who might benefit from dietary nutritional intervention, 2) determining the severity and cause(s) of malnutrition, 3) assessing risk of morbidity and mortality related to malnutrition 4) assessing the efficacy of an intervention (15).

Nutritional assessment is a measure of body composition. A change in body composition in turn reflects a change in the physiological reserves of energy and protein in the body (220). Methods that have been used to assess nutritional status include anthropometric and laboratory measurements (e.g. weight change, mid-arm muscle circumference, triceps skinfold thickness, serum albumin, transferrin assays and nitrogen balance studies, hydro densitometry and air displacements) (65, 148, 233-236). In more recent years, the use of other methods such as DXA, BIA, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) has increased, while the use of albumin has been questioned. Although some require specialised and highly skilled personnel to operate, and have high operational costs, they can differentiate a unit of body weight into specific amounts of lean or fat.

In efforts to achieve universal definitions and diagnostic criteria, the previously mentioned consensus group (22) suggested that cancer cachexia be viewed as continuum (with three stages of clinical relevance: precachexia, cachexia, and refractory cachexia) and that not all patients traverse the entire spectrum as outlined in Figure 4. Once patients enter the refractory cachexia phase, the

burden and risks of artificial nutritional support are likely to outweigh any potential benefit. Therefore potential intervention is most likely to benefit patients if administered in the first two stages of this classification.

Figure 4: The stages of cachexia

	Precachexia	Cachexia	Refractory cachexia
Normal			Death
	Weight loss ≤5% Anorexia and metabolic change	Weight loss >5% or BMI <20 and weight loss >2% or sarcopenia and weight loss >2% Often reduced food intake/ systemic inflammation	Variable degree of cachexia Cancer disease both procatabolic and not responsive to anticancer treatment Low performance score <3 months expected survival
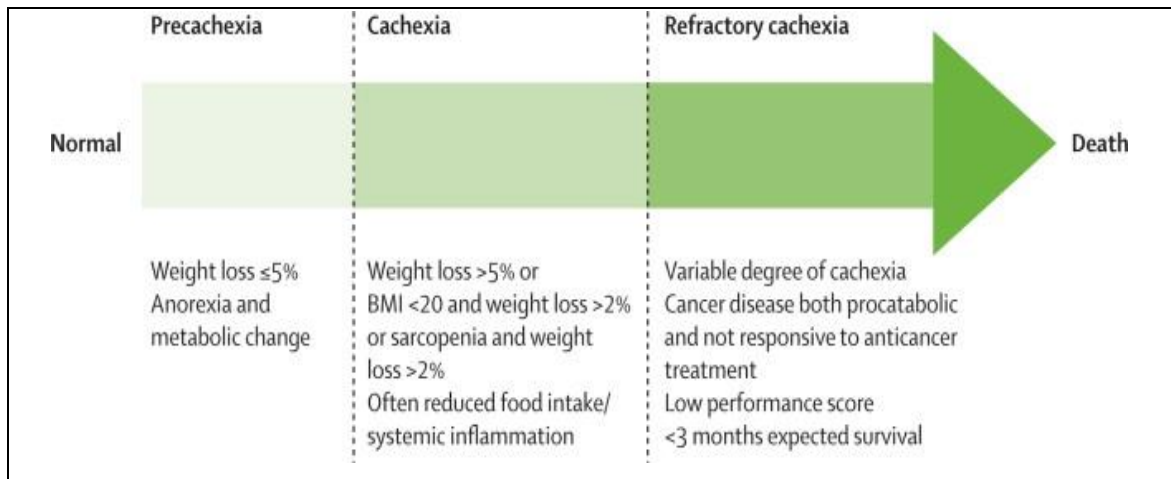
Reproduced with permission. Source: Fearon et al., (22)

A model of screening, assessment and management of cachexia based on the consensus definition and classification of cachexia is shown below in Figure 5. This model is similar in principle to the model of screening and assessment in Figure 3 except in this model, patients could be screened for cachexia, using the consensus suggested cut off points. A detailed multimodal management plan would then be implemented for those patients identified as being cachectic. The management plan would include for example monitoring, nutrition, exercise and anti-inflammatory strategies depending on the phase of cachexia the patients are at, but always alongside the routine optimum oncological and general medical management. Once patients have been assessed, their specific management identified then they would fit into the previous nutrition algorithm (230) with periodic reassessments and evaluation, but using the specific cachexia cut-off points.

Figure 5: Management algorithm for cancer cachexia
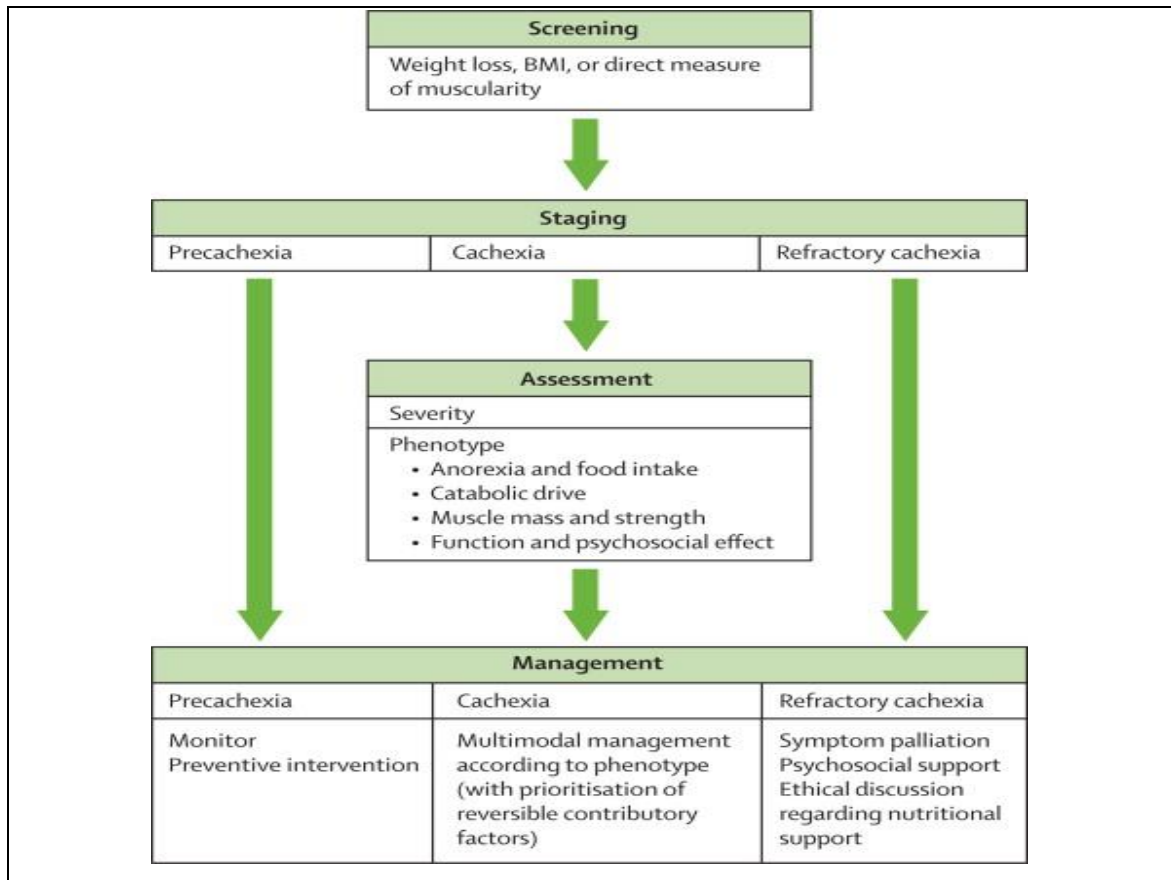
Reproduced with permission. Source: Fearon et al., (22)

If validated this classification and management model would help to address some of the previous challenges of identifying patients who might gain demonstrable clinical benefit from nutritional support. It would provide a rationale for intervention which has often relied more on inherent plausibility of the adverse effects of malnutrition and on individual opinion rather than scientific evidence (28). However as discussed earlier, this model already has limitations and some authors, Blauwhoff-Buskermolen et al., (2014) suggest that the diagnostic criteria should be revised to increase sensitivity. This proves how difficult it is to achieve universal acceptable criteria for such a complex syndrome.

2.8.5 Nutritional intervention

Nutrition intervention in this thesis refers to nutritional support (additional or alternative provision of nutrients (237) and or advice or counselling provided by a professional to patients identified as requiring it, based on screening or assessment. This excludes the use of nutrition formulas given routinely as in the 'Enhanced Recovery after Surgery' programmes (238), which became part of routine surgical management in the NHS (239). The aim of intervention is primarily to improve or maintain nutrient intake with the ultimate outcomes being to improve cure rates (including by enhancing adherence to treatment), lengthen survival time and to improve QoL in line with the three major goals in cancer treatment (123). The main interest of this thesis however is to assess interventions based on regular diet. These have the advantage of being able to be tailored to individual needs (164).

The negligible response of cachexia to available pharmacological and nutritional interventions has for a long time led to the misconception that the complex syndrome of cachexia is uniquely amenable to palliative care (6). However, recent clinical and experimental evidence indicates that those mechanisms ultimately leading to the severe wasting of cachexia are operating early during the natural history of disease, suggesting that appropriate interventions, if administered early, might be effective in preventing or delaying the onset of this syndrome (6). As such, some authors advocate for interventions be delivered as soon as possible after diagnosis and concomitantly with oncology treatment (103). The latest consensus definition and framework for classifying cachexia also support this approach. Prior to reaching its refractory phase, cachexia is not completely irreversible, treating symptoms that affect and reduce food intake and stimulating appetite can help. Treating some metabolic abnormalities such as insulin resistance could also help to offset or delay as long as possible, the stepwise decline that occurs in patients with progressive disease.

Nutritional intervention has in the past mainly focused on additional nutrients being provided and usually in the perioperative phase or towards the end of life

for palliation. Some of the arguments for supplementation/support in this phase include that optimal nutritional support provides the substrate to meet the increase in metabolic demand. This then limits catabolism, promotes wound healing, and musters a defence against infection (15). Adequate nutrition can limit nutritional deterioration of cancer patients and improve some metabolic and nutritional indices (89). Although the reasoning is sound, such short-term interventions have yielded short-term results associated with quick recovery from surgery and less infections but no long-term benefit. Moreover the selection criteria of patients requiring intervention have been controversial. Some researchers advocated for nutritional supplementation even in patients unlikely to show improvement (240) offering that simple dietary recommendations could significantly increase oral protein-energy intake in the course of treatment or in palliative care, regardless of whether there appears to be a beneficial effect. Others argued that not all patients are suitable for nutrition supplementation, and that it is indicated only when spontaneous oral protein-calorie intake is insufficient despite observance of dietary advice (15). Yet some other authors felt that in the case where the tumour was in situ, nutritional response is limited and is always lower than that observed in malnourished non cancer patients receiving equivalent artificial nutrition (241). Sadly the overall findings of a meta- analysis by Baldwin et al., 2011 (242) suggest that oral nutritional supplements have no overall effect on survival and that the effect on body weight and energy is inconsistent. The only improvements noted were in some aspects of quality of life and greater patient satisfaction. The weaknesses in the individual studies such as irregularities of the cut off points for entry into the studies provide an opportunity on which to build future research.

Nutritional intervention strategies such as counselling and guidance have been used and evaluated in systematic reviews in the last few years. Some studies have shown that intensive individualised nutritional counselling with regular foods, with or without supplements, can increase nutritional intake and prevent therapy-associated weight loss and treatment interruptions in cancer patients (188, 189). A study of head and neck patients undergoing radiotherapy was one of the first to show that dietary counselling could be more effective than adding oral

nutritional supplements to the diet. Patients receiving dietary counselling significantly improved all QoL function scores in association with an adequate dietary intake and nutritional throughout the entire assessment period (243). There have been similar reports including a systematic review and meta-analysis by Halfdanarson et al., 2008 (244) of the effect of diet counselling on quality of life in cancer patients showing that dietary counselling may provide positive impact on QoL. Although an improvement in survival due to nutritional interventions has not yet been demonstrated convincingly, evidence points to improving nutritional indices and QoL by addressing clinical and psychological factors that are affected by diminished response to oncology treatment or weight loss (245). The European Society for Clinical Nutrition and Metabolism guidelines recommend individualised counselling and the use of high-protein dietary supplements for gastrointestinal and head-neck cancer patients undergoing radiotherapy with or without chemotherapy (246). Researchers are now shifting the focus from nutritional endpoints such as change in food intake and their impact on nutritional status to nutritional end points and their impact on clinical outcomes and functional endpoints (164). These include outcomes such as survival, toxicity and quality of life. This shift in focus is partly because the overall effectiveness of nutritional interventions on nutritional, clinical and patient centred outcomes remains doubtful.

2.9 Nutritional Intervention in ovarian cancer

There is limited evidence and historical controversy over earlier published work regarding nutrition supplementation in ovarian cancer and other gynaecological cancers owing to serious methodological flaws such as variations in nutritional status before surgery, small sample sizes, inadequate randomization, use of unmatched control groups, retrospective data, heterogeneous populations and a failure to assess patients' nutritional status adequately (233, 247). As such it has been difficult to interpret studies that have looked at the effect of nutrition supplementation on patient outcome. Even the recent interest in 'Immunonutrition' (a nutritional therapy aiming to reinforce the immune system's defences) (234) failed to yield other benefits besides reducing infectious complications and

length of pre- and post-operative fasting (248, 249). Furthermore there are now suggestions that, as crucial as nutritional intervention may be, timing of the intervention is also crucial and that maybe the immediate pre-operative phase is not necessarily an appropriate window for urgent nutritional compensation (158). If patients can tolerate it, oral feeding with regular diet is a preferred to enteral feeding or Total Parenteral Nutrition (TPN) (106).

As long as there are no indisputable results on which to base rational nutritional support in malnourished surgical patients (250), malnutrition will continue to be a considerable problem for surgeons and patients undergoing major surgery and/or without chemotherapy (251-254). The lack of a universal agreement on a nutrition supplement consensus despite attempts is due to the problems highlighted earlier in this section but is also due to the fact that in most trials carried out so far, 1) malnutrition had been defined by a multitude of different scores and threshold values for weight loss and serum protein, 2) study designs are rarely dedicated to malnourished patients, 3) the quantity of calories are not sufficiently explained (i.e. no clarity of what was actually consumed in case of oral supplements) and 4) there is no clear rationale for the type and quantity of nutrients provided (255). These considerations make comparison among trial results difficult and the conclusions difficult to apply in clinical practice (250). There are logistical and cost challenges if nutritional support requires preoperative hospitalization for at least 7 to 10 days. Finally there remains the challenge that severe malnutrition is often an indirect sign of advanced cancer (unresectable tumour, metastatic spread) which usually makes patients unsuitable for a surgical approach (250).

In a previous publication (5) our research group found that there are no randomised control trials that evaluated the impact of additional oral nutrients or other interventions such as dietary counselling in the ovarian patient group. Gupta et al., (256) evaluated the impact of nutrition on survival in a cohort of women diagnosed with ovarian cancer.

The other seven studies evaluated the efficacy and safety of early postoperative feeding compared to delayed feeding. Even so, only one (257) was a site specific study of ovarian and peritoneal cancer patients, the other 6included all gynaecological cancers with one, Schilder et al., 1997 (258) including non-cancer patients. Health outcomes related to surgical protocols were the primary outcome for all the studies. They showed that early postoperative feeding was safe and well tolerated by patients and also that there was reduction in postoperative complications such as infection and length of stay. This evidence supports the post-operative Enhanced Recovery Programme (ERP) (oral intake as soon as possible after surgery) currently practiced in many surgical settings in the UK National Health Service (259-261). There was no strong evidence of an impact on long-term outcomes. Gupta et al., (256) found that patients who were well nourished at baseline or whose nutritional status improved at 3 months had significantly better survival than those whose nutritional status deteriorated. However their baseline assessment included patients who had as well as those who had not had any treatment, making it difficult to objectively determine the impact of the intervention from that of treatment.

The majority of patients treated for ovarian cancer in the UK do not receive a nutritional management package at the onset. There are exceptions where nutritional problems interfere with planned treatment and patients are referred to a dietician for intervention. Patients' weight and height are assessed at first contact and prior to treatment. Comprehensive nutritional screening is often only carried out at the time of admission to hospital. Even so, there are questions of how well applied the assessment outcomes are to daily patient care. Similar to nutritional supplementation trials, most included heterogeneous populations and the methods used to assess nutritional status varies by trial making comparisons between studies difficult. Nutritional support tends to be more robust where there are complications to treatment (based on observations made while recruiting patients), or in end stages where enteral and parental routes are preferred, and usually as part of palliation. There is no clear evidence of what type of nutrients could be used to slow down or reverse cachexia and what doses and conditions would enable this to happen. Researchers often focus on very specific and

usually short time periods (around treatment) for assessment and intervention, whereas the processes that lead to cachexia precede any signs or symptoms and continue where there is underlying disease.

The lethal nature of ovarian cancer and the quick relapse warrants interventions that target a woman's entire life rather than just the acute phase. Healthy weight management, diet, and a physically active lifestyle could prevent recurrence, second primary cancers, and other chronic diseases for cancer survivors (157). While intensive nutritional therapy may be suitable for patients who are severely nutritionally compromised, most patients could benefit from a more patient centred approach. Health behaviour modification approaches leading to the empowerment of women to self-manage their dietary and nutritional needs may benefit patients as they transition from the end of primary treatment to survivorship.

2.10 A behaviour change and self-management approach?

Cancer care occurs in a continuum that stretches from prevention to the end of life. The identified six major phases on the cancer-care continuum are: prevention, early detection, diagnosis, treatment, survivorship, and end-of-life care (262). This implies that care needs to be viewed as long term and extending beyond the acute phase, a concept that challenges the previous paternalistic paradigm where the expert prescribes care. Moreover nutritional experts suggest that healthy weight management, a healthful diet, and a physically active lifestyle aimed at preventing recurrence, second primary cancers, and other chronic diseases should be a priority (157) for cancer survivors. Therefore planning for long term care requires an on-going collaborative relationship between patients and providers instead of an acute, prescriptive relationship (262). As such, there is need for evidence to build a sound knowledge base to ensure best practice for all phases of the cancer continuum where patients can potentially actively participate in their own care. New patient care models must enable oncology

providers to form partnerships with patients and families, and other providers, such as primary care clinicians (262). Consensus groups and health departments in Europe have pressed for patient involved strategies of nutrition management in cancer patients. The European Partnership Action Against Cancer consensus group in their recent policy statement speculated that cancer care is undergoing a paradigm shift from disease-focused management to a patient-centred approach in which increasingly more attention is paid to psychosocial aspects, quality of life, patients' rights and empowerment and survivorship (263).

Understanding factors that influence behaviour change may help to improve the services offered in the area of dietary and nutritional support. Approaches that aim at changing behaviour by promoting self-efficacy and self-management of nutritional needs could complement clinician input and improve outcomes. Self-management strategies may benefit patients as they transition from the end of primary treatment to survivorship, a period in which cancer survivors express feelings of absolute abandonment (264). The demands of survivorship include regularly participating in routine but less frequent oncology visits, understanding the signs and symptoms of disease recurrence, adjusting to and managing the late-term effects of cancer and cancer-treatment, re-establishing normal routines and social roles, and dealing with residual psychological distress in order to minimize negative impact on QoL and relationships (262). Strategies that incorporate health behaviour change can encourage replacement of health-compromising behaviours by health-enhancing behaviours. Health behavioural change theories are designed to describe, predict, and explain such processes, theories or models and examine a set of psychological constructs that explain what motivates people to change and how they take preventive action (265).

These theories attempt to explain why behaviours change and cite environmental, personal, and behavioural characteristics as the major factors in determining behaviour. For instance 30-60% of cancer survivors report making healthy dietary changes, but these reports are not corroborated by evidence as many studies have shown that many survivors do not adhere to guidelines and their lifestyles

are not different from those of adults without cancer (266). Understanding why cancer survivors find it difficult to make changes that are sustainable over time is important. More so because survivors have been shown to be highly motivated to seek information about food choices, physical activity, and dietary supplements to improve their treatment outcomes, quality of life, and overall survival (157). Understanding behaviour change presents a window of opportunity to bridge the gap between patients seeking information and translating that desire into action. This opportunity, or 'teachable moment" when individuals might be more motivated to make changes that may reduce health risks (19, 267) can be capitalised on for delivery of strategic interventions. A healthy life lifestyle following a cancer diagnosis may improve long-term outcomes (268) especially because evidence suggests that cancer survivors are also at a greater risk than the general population of other conditions such as cardio-vascular diseases and diabetes (269).

Some health behaviour models identify threats or risks as important influences on behaviour while others are problem oriented. If an individual perceives the threat or problem to be real with a potential to impact on lifestyle or livelihood then they may be more willing to consider changing their behaviour. Interventions and new behaviours are likely to be effective/sustained if they target these 'real threats' – teachable moments. Schuz et al., 2009 (270) outlined that different behaviour change models emphasize different aspects of approaching the behaviour of individuals. A few stage theory models, shown in Table 5, emphasise the transitioning from preintentional, intentional and actional stages of change, which are most relevant for making individual diet related behaviour changes as well as incorporation into intervention studies.

Table 5: A summary of stage theories of behaviour change

Theory	Main constructs	Suggested use
Transtheoretical Model (TTM) (271) (Prochaska 1979 in Prochaska et al., 1992) (272)	This model subdivides individuals into 'levels of motivational readiness' along a continuum of behaviour change. The different stages are pre-contemplation, contemplation, preparation, action and maintenance. It assumes that individuals at the same stage of change face similar problems and barriers and can be helped by the same intervention. Self-efficacy and decisional balance drive the transition between stages.	For management of addictive behaviours such as smoking and often by practitioners more than researchers.
Precaution Adoption Process Model (PAPM) Weinstein 1998 (273) in Weinstein and Sandman 1992 (274),	This model suggests that factors that influence behaviour will be different depending on the threat or problem. The different stages are defined according to mental state. It identifies 7 stages along the path of awareness which are; unaware, unengaged, undecided, decided not to act, decided to act, action and maintenance. It explains how a person comes to take action.	It is useful for the development and evaluation of behaviour change interventions.

Theory	Main constructs	Suggested use
Health Action Process Approach (HAPA) Schwarzer 1992 in (275)	It is a framework of motivational and volitional constructs which distinguishes between pre-intentional motivation processes that lead to behavioural intention, post-intentional volition process and actual behaviour change. Perception of risk, consequences and competences (self-efficacy) are key to the pre-intention phase. Self-efficacy and planning are important for the post-intentional volition phase. Self-efficacy is important at all stages and includes pre-action, maintenance and recovery self-efficacies.	It is useful for predicting and explaining individual health behaviour changes This model is described in more detail in chapter 8
Model of Action Phases (MAP) Heckhausen et al., 1987 in (276)	This model describes successful goal pursuit in four stages of pre-decision, pre-action, action and post-action phases. It considers goal setting and self-regulation as necessary for successful behaviour change. It also extends to evaluation of thoughts once a successful behaviour has been adopted. The model deals explicitly with the sequence of intentions and the cognitive processes involved to transform intention into action.	It can be used to explain how people transform what they want to do into what they actually do. Its use extends beyond health, to education, relocation and other settings.

Theory	Main constructs	Suggested use
Integrated Change Model (I-Change model) de Vries et al., 2004 (277)	This model's assumption is that the stages of awareness of a problem, motivation and action (determined by self-efficacy, planning and goal setting) phases can be identified. These are influenced by behavioural, psychological, biological and socio-economic situations. Behaviour is the result of a person's intentions and abilities. The model integrates aspects of other models such as the Transtheoretical Model	It is useful in explaining types of health behaviour as it takes into account psychosocial and information effects.
Similarities between the models	The models assume that individual pass through an ordered set of qualitatively different stages on their way to adopting health behaviour. Stage transitions are shifts in perception and cognition, each requiring different information. There are different barriers to change at different stages. Different is information required for each stage. Self-efficacy is key for transitioning forward between stages. Individuals can relapse or progress and there is no prescribed minimum amount of time to be spent in a particular stage. Models can be used in experimental studies using matched or mismatched interventions. Individuals in a given stage should respond better to an intervention that is correctly matched to their stage.	

The basic principle of the stage models of behaviour change is that individuals pass through different mind-sets on their way to behaviour change (270). Thus, interventions may be most efficient when tailored to these particular mind-sets. For example, patients who have not decided on changing their behaviour (non-intenders) may benefit from confrontation with outcome expectancies and some level of risk communication (278). This could best be achieved by learning that the new behaviour has positive outcomes as opposed to the negative outcomes that accompany the current behaviour. In contrast, intenders will not benefit from such a treatment because they have already moved beyond this mind-set. They should benefit from planning to translate their intentions into action and actors will need intervention that prepared for particular high-risk situations such as disease relapse. Thus incorporating an appropriate health behaviour model supports individualisation of care.

Health behaviour change models assume qualitative differences between individuals who have not yet decided to change behaviour and those who are already decided. The if-then plans (implementation intentions) (279) are differentially effective depending on the presence of intentions being more effective in individuals who have already formed intentions to act than in those without such intentions (280). The differentiation between intention and action is characterized by overt changes in behaviour supported by cognitions such as self-efficacy. Self-efficacy is an individual's impression of their own ability to perform a demanding or challenging task based upon factors like the individual's prior success in the task or in related tasks, the individual's physiological state, and outside sources of persuasion, or the belief that one can achieve what one sets out to do (281). It is thought to be predictive of the amount of effort an individual will expend in initiating and maintaining a behavioural change. Self-efficacy is a powerful direct influence on individuals' health behaviour and supports differences between individuals who only intend to change and those who already act (282). It is also important for stage transitions across all stages of change (283). Ultimately individuals with high self-efficacy expectancies are thought to be healthier, more effective, and generally more successful than those with low self-efficacy expectancies.

Understanding the challenges of cancer related malnutrition and how this affects short and long term outcomes and that cancer survivors can benefit from being involved in their own care could lead to more structured administration of self-management strategies. Management of and by oneself and taking responsibility for one's own behaviour, self-management (SM) could optimise patients' care and experiences. Self-management in the context of cancer care was described by Foster et al., (284) as the

"Approaches used by the individual affected by cancer and its effects to optimise living with the illness and its effect" or more recently the "awareness and active participation by the person in their recovery, recuperation, and rehabilitation, to minimise the consequences of treatment, promote survival, health and well-being." (285).

Its aim is to keep wellness in one's psychological foreground (286). An important aspect in addition to the core tasks and skills of SM being that it is set within the context of the family (287). It is a lifelong dynamic process of self-monitoring and self-evaluation (288).

A model of self-management for cancer survivors was identified by the Expert Patient Programme (Department of Health 2001) as an appropriate approach to providing care in cancer survivors. Self-management support for cancer survivors is one of the five key shifts highlighted in the National Cancer Survivorship Initiative (NCSI) Vision Document (285). Incorporating these principles in care can enable and empower patients and families to care for themselves, in partnership with their providers, across the cancer-care continuum in the way they mutually determine (262).

In more lethal cancers like ovarian cancer, with a 40-50% rate of recurrence within 3 years in women who achieve a remission after first-line chemotherapy; an average duration of survival of 12 to 18 months after recurrence (289) and a

20% and 6% 5 year survival if diagnosed with stage III and IV respectively (290), it is important that oncology providers work in partnership with patients and their families a way they mutually determine (262). The patient-clinician contact is likely to be more frequent than in other chronic diseases, therefore a model of care that involves both clinicians and patients uniting to address the nutritional imperatives of care when appropriate seems most suited.

2.11 Summary

Surviving ovarian cancer mainly depends on patient characteristics, tumour biology (stage, grade etc.) and the quality of treatment (256, 291). Whereas the first two are non-modifiable, quality of treatment can be. Nutrition is or should be an important aspect of quality of treatment that could potentially impact on patient outcomes. Women with ovarian cancer may have co-existing excess weight or obesity. In addition many will also have ascites which adds additional weight. Appropriate screening and assessment methods that will be able to identify malnutrition in these circumstances are required so that treatment is provided (237). Gathering objective data on nutritional status and its evolution throughout the disease course is a necessary first step towards effectively managing nutritional deterioration (143). The current situation whereby nutritional support is not routinely provided can be summarised as being due to 1) lack of useful universally acceptable and practical criteria 2) the lack of reproducible nutritional data, 3) lack of publications in large cohorts and 4) complex guidelines (158). The focus of research should include all nutritional dimensions as well as patients' expectations and the impact of the disease (143). Although nutrition supplementation has been shown to be desirable in the perioperative period (15), clear evidence for its effects on recurrence rates, prognosis or long term benefits in quality of life has not been demonstrated. Questions that arise from this are whether there maybe prognostic value in focusing intervention effort at other phases and not just the perioperative phase in surgical patients (158) or whether it is time to attempt regular diet based types of interventions that provide structured support for women. These interventions could become part of the post diagnosis lifestyle of women rather than an acute intervention phase.

Placing a nutrition intervention package within the current treatment pathways requires more research evidence. Issues such as 1) When is the optimum time for intervention? Is it early in the pathway even prior to treatment or later when patients have had surgery or started chemotherapy? 2) What are the logistical considerations for early intervention? Is there a confirmed diagnosis (some patients only get diagnosed at or post-surgery), does stage, type of tumour matter or should all patients be treated the same 3) What nutritional package to use and what is the selection criteria for patients? 4) Are patients willing to allocate some of their time for nutritional issues or is their treatment priority? 5) Who decides that the patient needs intervention if it is not so severe as to affect the treatment plan; patient or clinician? 6) Who is best suited to deliver the intervention? and 7) What is the role of the patient in their management? These questions could be answered by well-designed randomised trials. An important preliminary step is to characterise the nutritional status of the relatively under researched population of ovarian cancer patients, to identify, quantify and understand the problem of malnutrition in this population.

The next chapter outlines the aim and objectives of the research and discusses the rationale behind the chosen methods of assessment and also describes the instruments used to carry out assessments.

3   Methods (background)

3.1 Introduction to chapter

The methods for this thesis are presented in three chapters. This first chapter provides an overview of the rationale, justification and design of the research. It also outlines the aims and objectives of the study. The research sites, patient pathways, and ethical and regulatory procedures are described. This chapter also introduces the two studies (Study A and Study B) that were undertaken for this thesis. Study A examined the nutritional status of women referred to two inner city gynaecological cancer centres for investigation and/or treatment of ovarian cancer. The nutritional status of women diagnosed with the cancer (cases) was compared to that of women diagnosed with a benign gynaecological condition (controls). The impact of an ovarian cancer diagnosis on well-being and eating habits was also investigated in study A. Study B explored women's perceptions of the importance of diet and nutrition and their satisfaction with current nutritional support following an ovarian cancer diagnosis. It also elicited women's views of what would constitute a suitable nutritional intervention. The conduct of study A, the tools used for assessment and analytic methods used are outlined in the study specific methods chapter 4. The conduct and analysis of study B are outlined in Chapter 7.

3.2 Justification and study design

In Chapter 2 (literature review) it was revealed that few studies have evaluated nutritional status in women diagnosed with ovarian cancer (5) and fewer still have measured nutritional status at multiple time points (204) despite evidence that malnutrition is a continuum which requires regular reassessment. Currently, there are no published Randomised Control Trials (RCTs) specifically addressing the treatment of malnutrition in women with ovarian cancer or investigating the use of nutrition assessment linked to preoperative nutritional interventions in this patient group (237). This is worrying considering that the incidence of malnutrition in women with ovarian cancer varies between 28% and 67% (1, 2) and is up to

75% where there is associated bowel obstruction (3). Evidence suggests that the mechanisms which ultimately lead to the severe wasting of cachexia are operating early in the natural history of disease (6). Investigation of nutritional changes in women undergoing diagnosis and treatment for ovarian cancer is an important prerequisite for future intervention research. Identifying if and when nutritional changes occur could inform strategies for improved timing and context of nutritional support and perhaps change the current conception that "nothing can be done, and palliation of the worst effects of cachexia is all that can be achieved" (6).

3.3   Aims & objectives

3.3.1 Aim

The main aim of this thesis was to identify and characterise changes in the nutritional status of women with ovarian cancer from diagnosis to the end of primary treatment and to make recommendations for a potential future intervention package.

3.3.2 Specific objectives

3.3.2.1 Study A specific objectives

The observational study (Study A) aimed to utilise multiple nutritional assessment methods at baseline, during treatment and at the end of treatment to address the following:

- To compare the nutritional status of ovarian cancer cases with that of benign controls (at baseline and at the end of treatment)

- To compare changes in the nutritional status of women over time: at baseline, during treatment and at the end of treatment for cases and at baseline and at the end of treatment for controls

- To assess how disease and well-being markers such as CA125, CRP and albumin are affected by ovarian cancer and to investigate the relationship between these markers and nutritional status

- To investigate the relationship between lifestyle factors such as smoking, alcohol intake and menopausal and nutritional status in cases and controls

- To investigate the impact of some ovarian cancer symptoms such as pain, nausea, abdominal distension etc. on nutritional status, dietary intake and overall health status of cases

- To determine which nutritional assessment best evaluates nutritional status in ovarian cancer patients

3.3.2.2 Study B specific objectives

The qualitative enquiry (Study B) complimented study A and aimed to;

- Explore patients' understanding of their nutritional status, and their information and support needs to meet nutritional challenges

- Explore the impact of the physiological (nutritional) changes on patients' eating habits and daily activities and discover some of their coping strategies and recommendations for a desired intervention.

- Explore how a health behaviour model, Health Action Process approach (HAPA), could be used to improve a potential future intervention package

- Consolidate evidence from study A with patients' perspectives of nutritional needs to make recommendations for future interventions

3.4 Research design

3.4.1 Mixed-method approach

Mixed methods research is a methodology for conducting research that involves collecting, analysing, and integrating (or mixing) quantitative and qualitative research (and data) in a single study or a longitudinal program of inquiry (292). It

was intended through this approach, to obtain and analyse objective nutritional data through study A. It was also the intention to partly interpret these findings analytically using statistical methods as well as interpret them through patients narratives' using the qualitative inquiry, study B. In this regard, qualitative and quantitative methods were felt to be commensurate means of generating knowledge (293), deriving their value from the aims of understanding all aspects of nutritional challenges. The study set out to characterise the nutritional status of women diagnosed with ovarian cancer and undergoing first line treatment. Women undergoing major surgical treatment for benign pelvic masses or uterine conditions were recruited as controls. The retrospective element of the study (collecting diet and weight data up to 3 months prior to assessment) provided an opportunity investigate the early onset of cachexia. The prospective aspect of the study provided an opportunity to gain knowledge of women's nutritional status and support needs from the point of diagnosis. Quantitative analysis was used to characterise within and between group changes in nutritional status. The qualitative enquiry of focus group discussions provided insight into women's nutritional concerns, their nutritional support needs and important clues for development of future interventions. More data sources and analytic perspectives were perceived to provide a more comprehensive insight into the challenges faced by women. The additional dimensions of patients own interpretation of events, health behaviours, emotions and personal circumstances were felt to be important and requiring assessment in this research.

The challenges of using mixed methods include that it is a relatively new phenomenon with many unknowns on how best to use the methodology. However the point of interface our two studies, i.e. presenting for focus group discussion, the preliminary findings from objectively collected was considered to be invaluable. It provided an opportunity to obtain a real expression (women's perspectives) of the complex interaction between disease, and its physiological impact (nutritional status) on women diagnosed with ovarian cancer. Thus the study would not only detect nutritional deficits using quantitative analysis, and but also extend the contextual understanding of the nutritional problem and support needs using women's views. This approach also means that deficiencies of any

one method could be overcome by the combined strengths of these two approaches (294). Ultimately this approach has potential to increase the relevance of our findings for translation into clinical care, and to be a sound a base for future research.

3.5   Research outline

Figure 6 illustrates the five major phases of the research. Phase I involved reviewing literature, refining the research question and formulating research aims and objectives. It also involved consulting with clinical teams, designing study documents, and applying for ethical regulatory approvals to conduct the study. The second phase involved identifying suitable places to approach, consent and assess patients as well as setting up at a secondary research site. A substantial amendment for the recruitment of women with benign disease from non-gynaecological cancer clinics was submitted to the ethical review committee in this phase. Recruitment of patients to the focus groups also took place in this phase. Data analysis and write up of the thesis followed. The final step, extending beyond this thesis was to disseminate the results to surviving participants. The research processes in each phase of the study were constantly reviewed and adapted in response to emerging challenges and needs. These steps are described in detail in subsequent sections.

Figure 6: Research outline
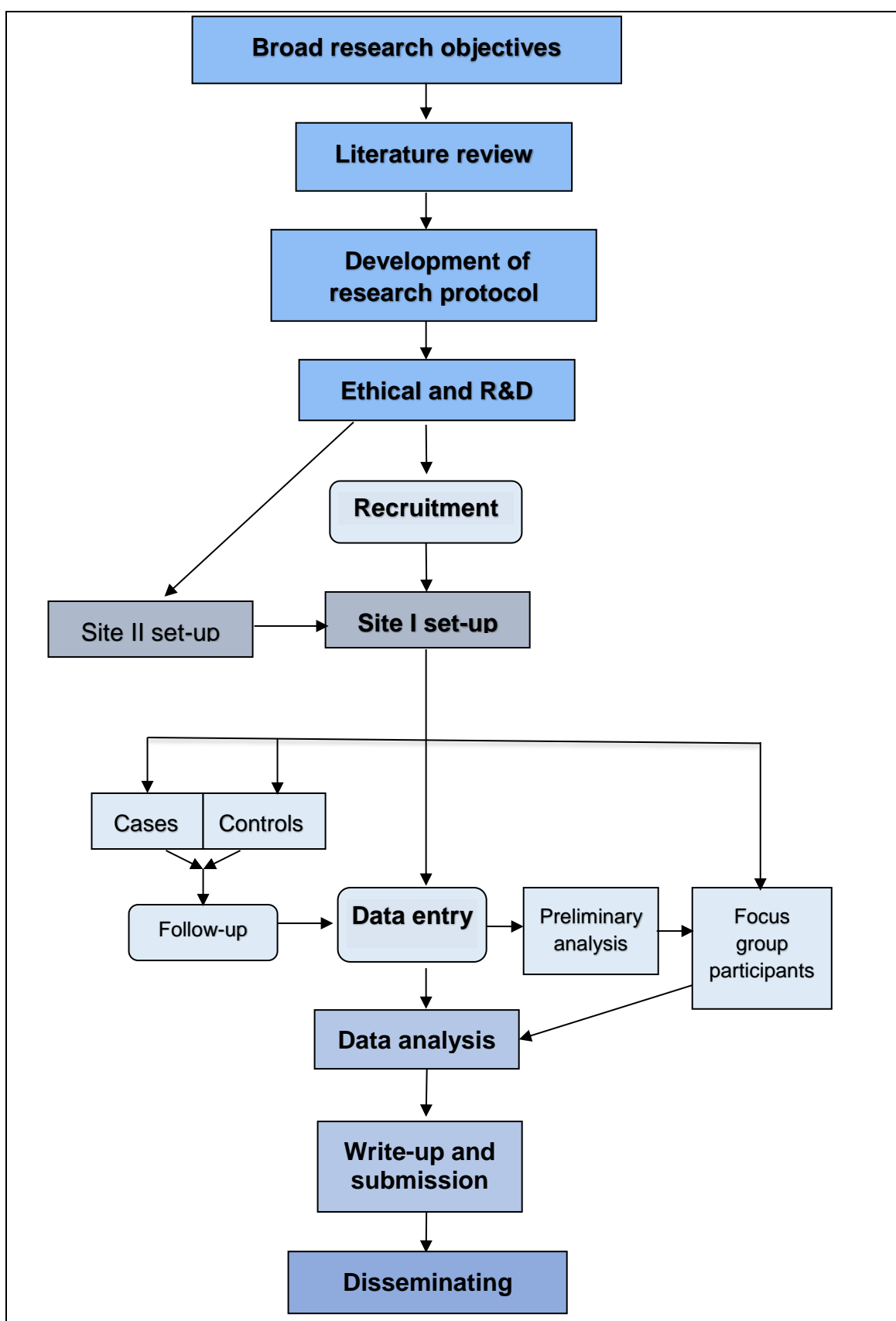
3.6   Research sites and patient pathways

3.6.1 Research sites

The main study site was a London inner city NHS Foundation Trust and teaching hospital. The Trust has a designated cancer centre, providing specialist care for women suffering from gynaecological cancer within a network of 6 Hospitals. It hosts outpatient and day care cancer services. The second research site was a different inner city hospital, with a gynaecological referral centre for a separate network of hospitals within London. Set up at the second site was initiated 6 months after commencement of enrolment to boost recruitment numbers. Additional controls were recruited from a women and babies specialist hospital associated with the primary study Trust. Participants for the focus group discussions were also recruited from the gynaecological oncology clinics at the primary study site. Additional participants were recruited via the Eve Appeal and Ovacome charities, utilising databases of patients. Patients approached via the ovarian cancer charities did not need to have been treated in either of the two trusts.

3.6.2 Patient pathway management

3.6.2.1 Cases /Women newly diagnosed with ovarian cancer

The network referral systems were managed centrally in each cancer centre. The coordinator received referral requests from unit hospitals and allocated appointments to patients to the appropriate consultant clinic and a slot for discussion in the Multi-Disciplinary Meeting (MDM). All new patients referred to the gynaecological centre were reviewed by the MDM. MDMs were held weekly in both cancer centres. While the primary study site ran a combined surgical and oncology clinic each week; the secondary site held separate oncology and individual surgeon clinics. All clinics were generally run on the same day and time each week.

Decisions about care and times to treat were originally outlined in a government document, The Cancer Reform Strategy (2007) part of The NHS Cancer Plan 2000. It was a long term national strategy to prevent, diagnose and treat cancer; and to reform the way cancer services are delivered aimed to improve patient experience and to invest in equipment and the cancer workforce (295). This document was superseded by *A Strategy for Cancer (296)).* The new document set out an ambitious vision for improving the delivery of information to cancer patients and their carers. Rather than setting targets the later focuses on improving certain cancer-related outcomes, such as one-year-survival rates. The Cancer-Networks continued to be the vehicle for delivery of the cancer strategy. Times to treat patients (Figure 7) also remained in place. Cancer centre treatment protocols were based on these strategic documents guidelines and were particularly relevant to study A as they dictated the short recruitment window prior to treatment.

Figure 7: The national cancer waiting times
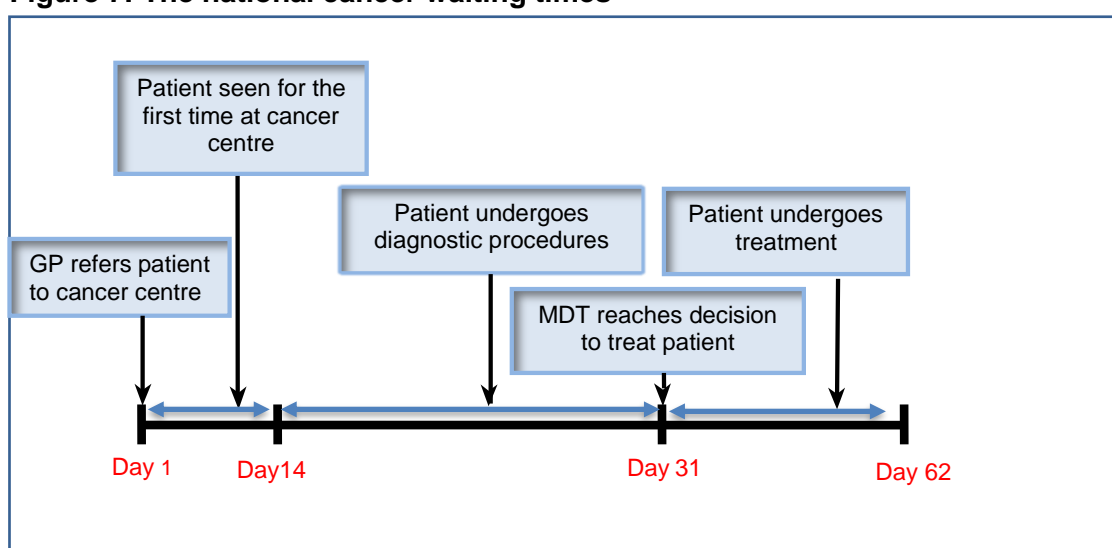
Adapted from UCLH Gynaecological Cancer Centre Audit; Jan - Dec 2009

3.7 Negotiating access to research sites

Study A was embedded within the clinical setting to benefit from consultant and other clinical team support as well as MDM meetings. This was informed by previous research (297) that showed that recruiting newly diagnosed ovarian

cancer patients or women suspected of having this cancer is particularly challenging. The presence of the researcher in the clinics acted as a prompt for consultants to identify eligible patients and alert the researcher.

In accordance with standard ethical practice, researcher access to clinics, identification of eligible patients relied on members of the clinical team. The researcher relied on clinicians to identify potential patients from clinic lists and alert her to when patients would attend the pre-assessment clinics. Missed opportunities to recruit patients occurred when some clinics at site 2 coincided with clinics at the primary site or when appointments were added to the list at the last minute.

3.8   Regulatory and ethical considerations

3.8.1 Ethical approval

Ethical approval to carry out the research was granted by The National Research Ethics Service North London Committee 3 in March 2011(REC reference number is 1/LO/0001). A substantial amendment for the change of inclusion criteria for controls was approved by the same ethical committee on 12 October 2011. The amendment allowed for recruitment of patients from general gynaecological clinics if they were having surgery to remove their uterus and or ovaries. Later in February 2012, the committee approved a Site Specific Assessment (SSA) authorization to recruit patients from a second study site.

The initial submission was rejected as a number of ethical issues were raised by the ethical committee. These related to recruiting patients who are newly diagnosed with cancer and could be potentially suffering from nutrition related issues. The specific issues included that;

- Participants were recruited at a stressful time therefore had to demonstrate suitability/sensitivity of materials used in recruitment including wording and phrasing in documents

- The appropriateness of raising nutritional concerns in this group of patients if there was no dietary advice, support or feedback offered

- Lack of clarity on confidentiality issues particularly to do with focus group discussions in study B, how data was to be recorded, stored and analysed

The above issues were carefully considered and addressed as described below for the second submission.

3.8.1.1 Recruiting patients at a stressful time

The time of a cancer diagnosis can be stressful and emotional for patients, such that recruiting patients at this stage requires sensitivity and empathy from researchers. Patients were reassured that their routine care was available to them throughout the study. This included dietetic referral if appropriate. Concerns raised by patients during any part of the study were referred to the relevant clinical team member with the patients' consent. The research team consisted of staff with experience recruiting ovarian cancer patients around the time of diagnosis. They would identify concerns and distress and act appropriately if it arose. The first supervisor and chief Investigator is an experienced cancer nurse and health care researcher well versed in the sensitive nature of observation and information collection at the time of a cancer diagnosis. Other supervisors were professors and consultants in gynaecology oncology and gastro-intestinal medicine and could provide guidance and support if issues arose.

3.8.1.2 Raising awareness without dietary support

The very sensitive nature of nutrition around the time of diagnosis in this population is one of the reasons this area is under researched. However to provide better care there is a need for scientific evidence acquired ethically and sensitively at this stage. We understood that the heightened awareness caused by the nutrition assessments could be a potential source of concern for some patients, especially those who associated weight change with disease progression. Measures were put in place to support patients appropriately with

an opportunity for referral to an appropriate member of their care team for management of their nutritional concerns if necessary.

3.8.1.3 Confidentiality

Patient confidentiality was a priority and was protected throughout the research. Patients in study A were assigned a study reference number at the time of consent and this was used to identify them subsequently. All their data was linked to the study reference number; only researchers could access patient identifiers. Information contributed by participants in study B was treated as confidential. All personal identifiers were removed from the data and participants were referred to as respondents one to eight. Data were stored in secure password protected computers or in files in a locked section of the research office. The research office is secure and can only be accessed through a code-only-entry door.

3.9   Informed consent

3.9.1 Study A

Written informed consent was taken when women indicated to the researcher that they had read the information leaflet and had sufficient time to consider participating in the study. Some women preferred to give written consent on the same day. They could do so provided the researcher was satisfied that they had read and understood the information leaflet. Other women preferred to take the information sheet home, to read in their own time. In this case permission was sought for the researcher to telephone them between 24 to 48 hours to find out whether they wanted to participate. If they did, an arrangement was made to meet with them when they next attended hospital/outpatient clinic to answer any questions they might have and to take consent.

Prior to signing the consent form, the researcher ensured that women understood what the study was about and their right to withdraw anytime. There was an option for a 'Language Line' telephone interpreter for patients whose first

language was not English. Patients could also use family and friends to translate/interpret if they chose to. Patients were asked to consent to current and future use of their data and samples; they could opt out of future studies if they chose to. Each patient was given a copy of their signed consent form and a copy placed in their medical notes. A third copy was filed with the research documents in the secure research office.

3.9.2 Study B

Women gave their written informed consent when they attended for the focus group the discussions. The study had already been explained to them when they attended clinic or were contacted via the cancer charities. The patient information leaflets had been given or sent in the post upon confirmation of interest to participate. Women were given further opportunity to ask questions about the study prior to signing their consent form and therefor participating in the group discussions. Women recruited via the ovarian cancer charities had to provide evidence in the form of a hospital letter confirming their diagnosis.

3.10   Doctors letters

Patients General Practitioners (GP) were sent a letter informing them that the patient was participating in the study and that there was no additional action required on their part. GP letters were not sent to women in the focus group discussions as it was a one off discussion and women did not have to reveal their GP details.

3.11   Advisory group

A dietician, a clinical psychologist and a clinical nurse specialist were involved in the development of the study protocol. They and a lay member from the administrative team of an ovarian cancer charity (Ovacome) were selected to form an advisory group for the study. It was intended that they would meet 3 times

during the recruitment period to provide guidance and to ensure maintenance of the multi-disciplinary and patient-focused approach.

3.12 Disseminating results

3.12.1 Publications

The results from the research are a core component of this doctoral thesis. Findings from this thesis will subsequently be written and submitted for publication in peer-reviewed journals.

3.12.2 Communicating findings to participants

Upon completion of the thesis surviving participants will be provided with their individual nutritional status results and the main findings of the study. Clinic lists and electronic records will be checked to ensure that patients are still alive, before mailing the results. Surviving cancer patients will also be telephoned in the event they wish to discuss the findings. In the case of controls, each participant will be sent their nutritional footprint as well as the main findings of the study. Participants will be provided with a telephone number should they wish to contact the researchers to discuss the results. Similarly, surviving participants who participated in focus group discussions will be sent a summary of the main findings of the study. They will be offered an opportunity of a telephone call to discuss the finding if they wish.

This chapter has identified the methodologies that guided the design and conduct of this research. The strengths of the complementary nature of quantitative and qualitative research approaches were reviewed. Issues relating to ethical considerations have been made explicit. The conducts of the two individual studies are outlined in chapters 4 and 7.

4 Methods (The Observational Study)

4.1 Introduction to chapter

This chapter provides a detailed description of the eligible participants, the outcomes of interest and the tools used for data collection. It also outlines how the study was conducted and the data analysed. The numbers of recruited patients, completed questionnaires and assessments are outlined in a flow diagram.

4.2 Participants/subjects

4.2.1 Cases

Cases were women who had a new diagnosis of ovarian cancer, primary peritoneal cancer or a fallopian tube cancer. These cancers are staged and managed similarly. Women were approached to participate in the study while they were having further investigations and awaiting treatment. At this point women were aware of the potential/confirmed malignant diagnosis. A confirmed diagnosis at recruitment was not necessary as women with benign disease were eligible to be controls for the study.

4.2.2 Women with borderline/low malignant potential tumours

These were women suspected of having ovarian cancer but were later diagnosed with borderline malignancy following surgery. Women with a diagnosis of borderline ovarian malignancy were a separate group because their tumours behave differently from invasive ovarian cancer or benign tumours. The growth of their tumours is more controlled as they do not usually invade other tissues although they can sometimes become cancer.

4.2.3 Controls

This group originally consisted of women suspected of having ovarian cancer but to be later diagnosed with benign ovarian disease. In a previous study that ended recruitment in 2009, 363 of 741 suspected ovarian cancer patients had in fact diagnosed with benign disease (297). However the number controls recruited this way was low. This was because improved diagnostic algorithms and more rigorous investigations since, (biomarkers, imaging, biopsy and cytology) led to more accurate identification of possible ovarian cancers prior to treatment. Therefore increase numbers, the inclusion criteria were amended to allow recruitment of women having major abdominal surgery to remove their ovaries and/or uterus for any benign gynaecological condition such as fibroids and endometriosis. The additional group of women were recruited from the primary study site general gynaecological preadmission assessment clinics.

4.3   Inclusion and exclusion criteria

4.3.1 Inclusion criteria

- Women aged 18 years and above being treated for the first time for a suspected or confirmed ovarian malignancy (including fallopian tube and primary peritoneal cancers)
- Women with a suspected benign adnexal mass
- Women undergoing a hysterectomy or removal of ovaries for a known benign condition

4.3.2 Exclusion criteria

- Patients under the age of 18 years
- Women with a history of treatment for ovarian malignancy
- Women with a history of treatment for endometrial cancer

4.4 Outcomes

The primary outcome for the study was the nutritional status of participants at different time points (baseline, during treatment and end of treatment). Nutritional status refers to the state of the body in those respects influenced by the diet, the levels of nutrients and the ability of those levels to support normal metabolic integrity. There is no single acceptable method of measuring this or a marker of nutritional status. A variety of nutritional status, body composition and well-being markers were selected for the study. Current clinical practice guidelines and/or consensus classifications were used to categorise participant's nutritional status. Where these were not available, a rationale for chosen criteria is provided. Each outcome and number of times it was measured throughout the study are outlined in Table 6.

Table 6: A description and frequency of assessment of the nutritional status, body composition, disease and wellbeing outcomes investigated by the study

Assessment	Definition/description	Frequency of assessment
Body weight	A measure of a person's mass or weight	Baseline, during treatment*, and end of treatment
Body Mass Index (BMI)	A measure of relative weight based on an individual's mass and height	Baseline, during treatment*, and end of treatment
Body fat (percentage)	Total mass of fat in the body. It includes essential and storage body fat	Baseline, during treatment*, and end of treatment
Lean body mass	A component of body composition, calculated by subtracting body fat weight from total body weight. The lean body mass determines the pharmacokinetic variability of several anticancer agents	Baseline, during treatment*, and end of treatment
Dry lean mass	A component of body composition calculated by deducting total body water from lean body mass less	Baseline, during treatment*, and end of treatment
Total body water	This is the total amount of fluid in a person's body. Water is important as the medium of the body's internal environment	Baseline, during treatment*, and end of treatment
Extracellular water	The 1/3 of total body water that is contained in areas outside of cells. Such as the interstitial (surrounds the cells) and intravascular fluids	Baseline, during treatment*, and end of treatment
Pre-albumin /Transthyretin	A hepatic protein that is decreased in malnutrition and in acute and chronic inflammation, and thus is also a 'negative acute phase protein'	Baseline and end of treatment
Disease/wellbeing		
CA125	Also known as mucin 16, it is a glycoprotein found in greater concentration in tumour cells. It is present in greater concentration in ovarian cancer cells hence considered a reliable tumour marker	Baseline and end of treatment
C-reactive protein (CRP)	An acute phase reactant protein produced in the liver. The levels rise in response to inflammation	Baseline and end of treatment
Serum albumin	The most abundant protein in human blood plasma. It is a negative acute-phase protein that is down-regulated in inflammatory states	Baseline and end of treatment

*During treatment is applicable for cases only

4.5   Data collection and tools of assessment

For this study, nutritional status was measured using weight and BMI and body composition measures of body fat, dry lean mass and lean mass. Body water was assessed to determine its link to the presence of ascites. Serum markers of nutritional status, well-being as well as disease burden prealbumin, albumin, CRP and CA125 and were also measured. A variety of other methods for assessing nutritional status that include anthropometry, volume displacement, and more recently, direct methods including magnetic resonance imaging (MRI), Computed Tomography (CT) and Dual Energy X ray Absorptiometry (DXA) amongst others are also used. Most are expensive to use and use radiation such that they are only suitable in patient populations that would otherwise require their use as part of their on-going treatment and monitoring. They also often require a specific skill set and expertise to perform and to interpret the results. In the following sections I outline the rationale for choosing our outcomes as well describe the methods used to assess them.

4.5.1 Body weight (BW)

Body weight represents the sum of protein, fat, water and bone mineral mass. Changes in weight often reflect a change in body composition. A change in weight must be measured against a usual/baseline to be meaningful. Weight and weight change were used to assess malnutrition relative to known cut off points for cachexia. BW was measured using Seca scales, which are validated for use in clinical settings. Participants were asked to remove heavy outer clothing and footwear and weight was measured to the nearest 0.1kg. It was also used with height to calculate Body Mass Index (BMI) and for determining body composition using Bioelectrical Electrical Impedance (BIA) through use of a Quadscan.

4.5.1.1 Weight change prior to baseline assessment

Weight change was assessed through self-reporting for the 3-month period preceding baseline assessment, and through periodic measurements thereafter. The three month period falls in the suggested 3 to 6 month time-frame for relevant

weight loss in cancer patients prior to diagnosis (23). Weight change was recorded in the questionnaire as a loss or gain. Participants were also asked to provide a value/estimate of the weight change. Although self-reporting can be affected by recall bias, there is evidence to support the reliability of self-reported weight and weight history (298, 299). The consensus classification of cachexia (27) was used to categorise participants by weight loss into no cachexia (weight stable), pre-cachexia and cachexia. The refractory cachexia stage did not apply for weight change prior to treatment since women had not received treatment at that point.

An additional category of 'weight gain' was identified as relevant for the identification of malnutrition in our study. Some women presented with a history of abdominal distension and weight gain. Since there are no guidelines/criteria for patients who gain weight in the classification of cachexia, a > 2% cut-off was chosen to represent significant weight gain. It corresponds with the 2% lower cut-off for pre-cachexia.

4.5.2 Height

Standing height was measured using a stadiometer. Patients were measured without footwear and stood facing forward. Measurements were recorded to the nearest 0.1cm. Height on its own is not a measure of nutritional wellbeing. It was used with weight to calculate BMI and inputted into the BIA to determine body composition. Height is a constant variable and was assessed once during the study.

4.5.3 Body Mass Index (BMI)

Body weight and height are used to calculate Body Mass Index (BMI or Quetelet's index). It is calculated by dividing weight (kg) by the square of the height (m) (h^2). The desirable range associated with optimum life expectancy is between 20 and 25 (300). Values less than 18.5 are associated with under nutrition and values above 27 are associated with increased risk of disease. BMI provides a useful

way of assessing weight in relation to height, but it can be less meaningful in cancer patients with ascites that masks actual weight change. Used with other measures/markers it can help to build a comprehensive picture of nutritional status.

Participants were classified using BMI categories adapted from WHO, 2004, and modified to fit with the cachexia classification by using the lower cut-off point of 20 instead of 18.5.

4.5.4 Body composition using bio electrical impedance analysis (BIA)

Body composition is a measure of the relative proportions of protein, fat, water, and mineral components in the body. The components of body composition selected for this study are;

- Body fat
- Dry lean mass
- Lean mass
- Total body water
- Extracellular water

The water components were of interest because of the presence of ascites in many ovarian cancer patients. The components are described earlier in this chapter see Table 6. Lean mass and dry lean do not currently have clinically relevant cut off limits and are used in this study to show trends.

A Bodystat Quadscan (4000), a multi-frequency Bioelectrical Impedance Analyser (BIA) was used to determine body composition. This method has been validated for use in cancer patients. Bioelectrical Impedance analysis is a quick, easy, economical, portable and non-invasive method of fluid assessment and body composition analysis (301). It was a method of choice for this study because of its ease of use and its ability to discriminate between malnourished and well-

nourished patients. It is based on the principle that in certain proportions an individual is considered to be within a normal range for their age, sex and height, and below the expected proportion maybe considered to be malnourished. It estimates alterations in fat-free mass (FFM) and Body Cell Mass (BCM- fat-free mass minus the bone mineral mass and extracellular water) as well as taking into account disease related fluid changes in the body (271). The latter is an important aspect in ovarian cancer where ascites is common.

Figure 8: Quadscan and position of electrodes on patient

Reproduced with permission. Http://www.bodystat.com/products/quadscan-4000/
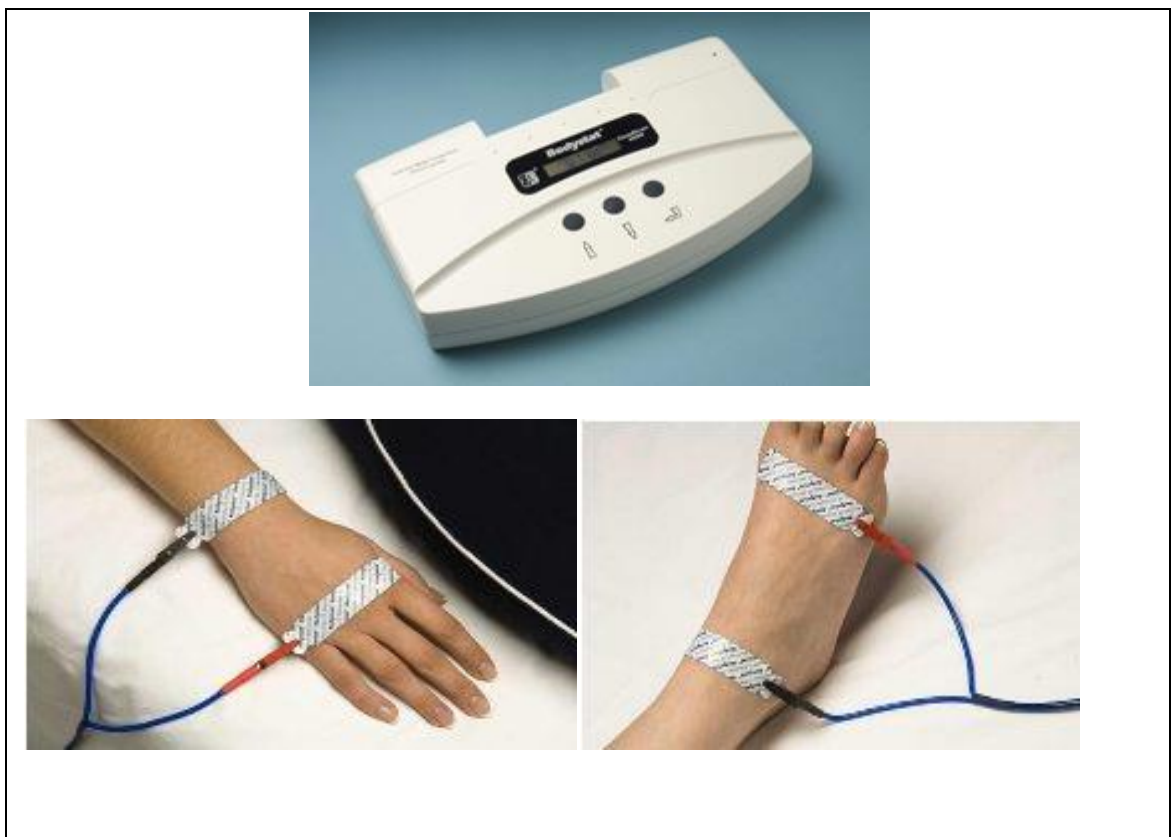
Measurement is done by attaching small stickers (electrodes) to a patient's wrists and ankles as shown in Figure 8. The patients is then connected via leads to the Quadscan. The machine passes a small non harmful electrical current through the body. The flow of this current (impedance) is dependent on the frequency applied. The current passes freely through the fluids contained in muscle tissue, but encounters relative resistance when it passes through fat tissue. At low

frequencies (5 kHz), the current cannot bridge the cellular membrane and will pass predominantly through the extra cellular space. At higher frequencies (200 kHz) it penetrates cell membranes and the current is conducted by both the extra-cellular water (ECW) and Intra-cellular water (ICW). By applying predictive equations, estimation of ECW and Total Body water and by deduction ICW can be made. Weight, height age and gender are required for the predictive equations (301). The resistance of the fat tissue to the electrical current is the 'bioelectrical impedance' measurement. The machine calculates and provides a summary of a variety of body composition measures.

Use of BIA has a potential to allow for identification of early lean mass depletion and therefore provide an opportunity to initiate intervention (302). BIA could also help to characterize the type of weight changes such as increase in fat mass instead of FFM. A draw-back of BIA analysis is that it is reliant on ideal testing conditions and can be easily affected by hydration, temperature and food intake. This was not always possible in this study due to the opportunistic approach to recruitment and timing of assessments to coincide with existing clinic visits.

4.5.5 Protein/Biochemical markers

Laboratory tests are often used to detect subclinical deficiency and also to confirm a clinical diagnosis. Measurement of serum and plasma proteins including pre-albumin and albumin can provide indirect information about the levels of visceral protein (303). The relevance of each marker including CRP and CA125 for this study are described below. It was designed that biochemical markers be analysed at baseline and at the end of treatment so that they were not influenced by surgery or chemotherapy.

4.5.6 Prealbumin (transthyretin)

Prealbumin has a half-life of 2–3 days. It is a good marker of visceral protein status and is affected by acute variations in protein balance (303). It is therefore thought to be a sensitive marker of nutritional status. Its superiority over other

proteins such as albumin and transferrin in assessing nutritional status has been demonstrated in cancer patients undergoing radiotherapy (303).

4.5.7 Albumin

Serum albumin has a longer half-life of 21 days which makes it only minimally valuable as a nutritional marker because new steady levels can only be reached after 100 days (47). In conditions where malnutrition develops relatively quickly, its levels will not immediately reflect the effect, and recent protein intake has little effect on the albumin pool. Its levels are affected by impaired liver function, ascites and inflammation. Albumin has a strong correlation with morbidity and mortality (304) and is therefore often referred to as a marker of illness rather than of nutrition. It is used in this study as a prognostic marker of health and wellbeing. Albumin is routinely and regularly assessed in women diagnosed with ovarian cancer but not in general gynaecological patients undergoing surgery. Since the albumin values were extracted from patient records, controls therefore do not have this assessment. The study was not adequately funded to include additional analysis of albumin for controls.

4.5.8 C-reactive protein (CRP)

CRP is an acute phase protein synthesised by the liver to initiate or sustain the systemic inflammatory response. Its levels therefore rise in response to inflammation. It is commonly used in clinical settings to assess the extent of the systemic inflammatory response. Its rise can be caused by a number of conditions including infection and cancer (305). C-reactive protein is measured in mg/L. Normal levels are below 10 mg/dl or 3mg/dl in patients at high risk of cardiovascular disease. It was considered as a marker of inflammation in this study and its inclusion helped to further characterise the effect of the disease on women. Its association with nutritional status was also evaluated. The values of CRP were also extracted from patient records and matched for the dates of assessment.

4.5.9 CA125

CA 125 is a tumour marker recommended for clinical use in the diagnosis and management of ovarian cancer. The normal range for CA125 is 0-35 kU/L. CA125 is also often used to monitor the treatment of ovarian cancer or check for signs of recurrence. It is used in this study as a marker of ovarian cancer and a monitor of the effectiveness of treatment. Responders to treatment are women whose CA125 normalised following treatment while non-responders are those women whose CA125 remained above 35kU/L. CA125 levels were extracted from patient records.

4.5.10 Clinical assessment

Clinical assessment consists of a physical examination by treating clinician to detect signs which and a symptom report by patient, which were noted in medical records. It is most useful during the advanced stage of nutritional depletion when overt symptoms are present (306). For this study, the presence of obvious clinical symptoms such as wasting, subcutaneous fluid accumulation such as oedema and ascites were recorded by the researcher at each assessment. Medical records (electronic and case notes) and Multi-Disciplinary Team (MDT) reports were searched for clinical signs and symptoms that are relevant to nutrition and diet at each assessment time point. Medical records were also reviewed to confirm diagnosis, treatments, comorbidities and other relevant information including date of diagnosis, type of treatment(s), disease stage and grade, morphology, ascites drained, complications during treatment, residual tumour, nutritional intervention, referral to a dietician etc. This information helped to further characterize patients and identify other factors that could contribute to nutritional status.

4.6 Life style and quality of life

Life style and quality of life were assessed using questionnaires administered at baseline during treatment and at the end of treatment. A study specific questionnaire, and internationally validated EORTC QLQ-C30, FAACT A/CS-12

and EuroQol-5D (EQ-5D were used to collect diet, lifestyle, health and quality of life information. They are described below.

4.6.1 The study specific questionnaire

4.6.1.1 Design

The researcher designed the study specific questionnaire based on literature review and the objectives of the study. It aimed to collect demographic, symptom (including, the relevant symptoms of increased abdominal size and persistent bloating, persistent pelvic and abdominal pain, unexplained change in bowel habits, and difficulty eating and feeling full quickly, or feeling nauseous) life style, health and dietary information at each time point. Samples of the questionnaire are provided in appendix 3. The questionnaire was administered at three different time points (baseline, during treatment and at the end of treatment). The questionnaire maintained the same structure and numbering but asked questions that were relevant to the assessment time point. Different or additional questions at each time point had different numbers. For example question 1.9 in questionnaire 1 (baseline) asked for women's ethnicity. As people's ethnicities do not change, this question was not asked again in subsequent assessments. As such the question number 1.9, remained specific to that question and was not used again. On the other hand question 2.2 asking about change in eating habits is present was asked at subsequent assessments. The difference is the period of reference. In questionnaire 1, the change refers to three months prior to taking part in the study. In questionnaire 2, it refers to the period since diagnosis and in questionnaire 3 to the period since surgery or first cycle of chemotherapy. Maintaining the numbering in the questionnaire enabled easy data capture into the Access Database. The same template was used to capture data from all assessment time points. Each questionnaire being identified by the assessment period. Questionnaire 1 was completed at baseline, questionnaire 2 'during treatment' and questionnaire 3 at the end of treatment. Free text boxes were provided at the end of the questionnaire for women to provide additional information if they so wished. Relevant additional free text information was analysed and incorporated into the qualitative inquiry.

4.7 Validation

The questionnaire was validated for relevance and comprehension as follows. Ten clinical and research colleagues were asked to complete the baseline questionnaire and subsequently asked about the relevance of questions and if there were relevant questions that were missing. We also wanted to know if the questions were clear. We asked participants to identify questions that were difficult to answer, confusing, contained words difficult to understand, or wording that was potentially upsetting. We asked for suggestions for rewording questions. This feedback was incorporated into the next version of the questionnaire. The edited version was piloted in the first 10 women to participate in the study. Their feedback on the questionnaire was minimal and had to do with numbering and typing errors. This feedback was incorporated into the final version of the questionnaire which then was rolled out to all women.

4.7.1 EORTC QLQ-C30

The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) (307) has been used internationally as generic a questionnaire to assess quality of life. Version 3.0 of this questionnaire (QLQ-C30) was used in this study. The strength of QoL life assessment is that it rightly assumes patients to be the best source for identifying what is important to their well-being (207). This kind of patient involvement justifies its use against the negatives of the assessments being subjective and non-static. The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems (307). Even if low points are obtained in the functional and symptom sections and quality of life points are high, the quality of life is

indicated as low (308). This tool has been used as a malnutrition predictor in other cancers (238). Because this questionnaire is not validated in non-cancer patients, it was not analysed for this study.

4.7.2 Functional Assessment of Anorexia/Cachexia Therapy (FAACT A/CS-12)

The Functional Assessment of Anorexia/Cachexia Therapy (FAACT) is a validated and reliable QoL questionnaire for cancer and HIV-infected patients with anorexia/cachexia [18]. FAACT A/CS-12 measures specific anorexia/cachexia-related concerns. Anorexia or loss of appetite is a common symptom of malignancy and causes decreased nutrient intake. It has been said to be one of the common symptoms prompting women diagnosed with ovarian cancer to see their general practitioner. The extent and prevalence of anorexia can be determined using the FAACT A/CS-12 questionnaire. The A/CS-12 provides unique information relating only to anorexia and not captured by generic chronic illness questionnaires (135). Direct questioning using of the A/CS-12 helps to reveal the extent of anorexia in the population. Its main disadvantage is that it is only validated for use in patients with cancer and suffering from anorexia, and has not been validated for use in our control group. Data on the presence of anorexia was used in the symptom and nutritional status analysis.

4.7.3 EuroQol (EQ-5D)

This was the questionnaire of choice for measuring quality of life in the study as it is validated for use in cancer and non-cancer patients. EuroQol (EQ-5D) measure of health outcome is a widely used simple, generic instrument to measure health in a standardized way (309). It is a generic measure of health for clinical and economic appraisal. It is applicable to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for health status from which Quality Adjusted Life Years (QALY) can be calculated (310). The data from the dimensions can also be used to describe patients' problems.

It is a two part generic measure of quality of life. The first part has five domains or dimensions which are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the 5 dimensions of the scale records three levels of severity, which are indicated by numbers. No problems are coded 1, some or moderate problems are coded 2 and extreme problems coded 3. These dimensions are interpreted in line with the goals of each research project. An overall health state can also be described by with a five-digit number, for instance 12113 where each number represents no problems or some or severe problems on that dimension. The permutation above can be interpreted as no problems on the dimension of mobility, some problems on the dimension of self-care, no problems with respect to usual activities and pain/discomfort and severe problems on the dimension of anxiety/depression.

The second part of the questionnaire is the visual analogue scale (VAS) which measures overall self-rated health status. The status is measured on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'worst imaginable health state'. The VAS scale is from 0 to 100. The best health state score is 100 and the worst 0. This information can be used independently of the first part, as a quantitative measure of health outcome as judged by the individual respondents (310). This quantitative measure was useful in this study to provide an overall perception of health status and as a proxy for quality of life for cases and controls. EuroQol VAS has been used to assess health-related quality of life in other studies (311-313). The advantages of using this instrument are that it is cognitively undemanding (314), generic, can be used in the clinical and economic evaluation of health care as well as in population health. It is specifically designed for self-completion by respondents and is ideally suited for use in clinics, and in face-to-face interviews and is validated for non-cancer patients too.

4.8   Sample size

The plan was to recruit 100 women, 50 women with a cancer diagnosis and 50 with a benign diagnosis. It was calculated that this number would be statistically

sufficient to reveal differences in nutritional markers between cases and controls; assuming that up to 50 % of cases would suffer from some degree of malnutrition. The 50% was determined by averaging the lowest and highest estimates of malnutrition given in literature, i.e. between 28% (1) and 67% (2).

4.9   Identification and recruitment of patients

The researcher was responsible for the recruitment of patients at both research sites. Patients were identified from MDM lists, clinic lists, preadmission assessment lists, consultant clinics and theatre lists by a suitable member of the clinical team. Patients were identified to the researcher who approached them in the clinic/ward and introduced the study to them. Interested patients were given time to read the information leaflet and decide if they wanted to participate. Women who were admitted for treatment, or were transferred as inpatients from other hospitals, were approached to participate on the ward. Some women were approached in the preadmission/assessment clinics. In all cases the researcher ensured that patients were aware of their potential cancer diagnosis before approaching them. Those willing gave their written consent as described in chapter 3 section 10. NHS Protocols for admission of patients for surgery changed during the course of the research. More patients were admitted on the morning of their surgery instead of the traditional day or more before surgery. This reduced the potential for contact with patients prior to treatment.

Recruitment commenced in April 2011 and that of cases ended in June 2012 (1 year and 3 months after commencement) when the recruitment target of 50 women with a newly diagnosed cancer was reached. Women were followed up until the end of December 2012. Two patients were followed up in January and February 2013. Recruitment of controls continued until Dec 2013 due to slow uptake of the study. Follow-up was concluded in April 2014.

4.10 Assessments and data collection

Women who consented underwent relevant assessments, gave blood samples as well as completed the questionnaires. Where possible data collection and assessments were scheduled to coincide with the clinic appointments and hospital visits to avoid additional attendances for patients. Assessments were carried out in a lockable consultation room in the outpatient clinic or on patients' beds on the ward. Each assessment lasted approximately 15 minutes and included measurements of weight, height, and body composition using BIA as well as completing a questionnaire. At baseline and end of treatment patients donated samples of blood (2X10ml) for the assessment of pre-albumin and storage of whole blood for future research. In limited instances where there were no other scheduled clinic visits, assessments were carried out in patients' own homes (with patients' permission). Assessments were carried out at three specific time points as shown in Table 7.

Table 7: The assessment time points for cases and controls

Baseline	During treatment	End of treatment
After written informed consent but before the start of any treatment	2-4 weeks post-surgery or 3 weeks post 1st cycle of chemotherapy. (only applies to women treated with surgery and/or chemotherapy)	At completion of acute first line treatment of surgery $\pm$ chemotherapy or chemotherapy alone **Or** The last assessment for women treated with surgery alone and controls

4.10.1 Cases

Taking part in the study involved 2 or 3 assessments depending on a patient's diagnosis and treatment plan. Women who were treated with surgery alone only had two assessments, at baseline and at the end of treatment. They were considered as cured and needed no further treatment. Women who were treated with surgery with/or chemotherapy underwent three assessments; at baseline,

during treatment and at the end of treatment. Baseline assessment was the same for all women. It was done any time prior to commencement of treatment. The 'during treatment' assessment was done when patients attended clinic following surgery or when patients attended for their 2nd cycle of chemotherapy. No blood samples were required at either of these assessments. The 'end of treatment' assessment was the last, after completion/ or termination of neo/adjuvant chemotherapy treatment as shown in Table 8. The end of treatment assessment often occurred between 3 and 6 months after completion of the chemotherapy. This was the identified time for the study as it was the first visit to clinic for the woman for follow-up (that is assuming there were no complications). If there were complications or the woman required further treatment, this assessment was done any time prior to commencing that treatment. If not possible to carry out the assessment for whatever reason, the next opportunity was at 6 months women attended for their next follow-up. In general women with successful treatment are followed up every three months for the first 2 years and every 6months for the next 3 years.

4.10.2 Women with borderline malignancy

Tumours of borderline malignancy also called tumours of low-malignant potential are epithelial ovarian neoplasms that are intermediate between benign and malignant. They are characterised by epithelial proliferation without stromal invasion (315). Women diagnosed with tumours of borderline malignancy were assessed at baseline and at the end of treatment similar to controls. Although surgery for borderline tumours is considered curative, at the time of this study follow-up regimens were similar to those for continue to be followed up similar to women diagnosed with ovarian cancer.

4.10.3 Controls

Controls were assessed at baseline and at the end of treatment. These women required no further treatment. Controls are often discharged from care following surgery. Their follow-up was often scheduled between 6-8 weeks following surgery allowing them time to recuperate.

Table 8: Schedule of assessments for cases and controls

Assessment	Cases				Controls	Borderline malignancy
	Early stage (Stage 1 & II)	Late stage Stage (III & IV)				
	Surgery	Surgery	Surgery + chemotherapy	Chemotherapy $\pm$ surgery	Surgery	Surgery
Baseline	✓	✓	✓	✓	✓	✓
During treatment						
Post-surgery	-	✓	✓	-	-	-
Post cycle 1 of chemotherapy	-	-	-	✓	-	-
End of treatment	✓	-	✓	✓	✓	✓

4.11 Blood sample collection and processing

Participants donated a total of 40ml of blood, 20ml at baseline and another 20ml at the end of treatment. The blood was collected in 10ml standardised vacutainer tubes. One tube was for biochemical analysis of serum prealbumin and the other for whole blood sample collection and storage. The latter were processed and stored for use in future studies (with patient consent). Collection and processing procedures of blood samples were standardised to previous protocols within the research group. Upon collection, each tube was inverted 5 times to ensure blood mixed with the medium in the tube. The whole blood sample was placed in an upright position for one hour at room temperature. The serum sample was immediately placed on ice. Both samples could be processed after a minimum time of 1 hour or else the whole blood sample had to also be placed on ice. Both samples were to be processed within 3 hours of collection. Processing was done by spinning each sample in a centrifuge at 3000rpm. The supernatant from each sample was aliquoted into a secondary tube which was labelled with unique patient and sample ID numbers and frozen immediately at – 80 degrees. A cell pellet remaining after the extraction of plasma was also stored for potential future research.

In total, two hundred and sixty eight individual samples were taken, processed and frozen. Twenty were from women who became ineligible to participate post diagnosis. At the end of the study, 126 samples serum samples were thawed and 2ml of each sample pipetted into a separate tube. These were labelled and sent for analysis of prealbumin at Sheffield United Hospitals. The remainder of the serum was refrozen at -80 degrees Celsius. Prealbumin was analysed using nephelometry on a Siemens anti transthyretin reference number OUIF09 and Siemens Calibrator OQIM13 traceable to IRP DA470. UCLH did not offer an analysis service (for prealbumin) for research and the time. CA125, CRP and albumin values were extracted from patient records and matched for the date of assessment.

Venepuncture was performed by the researcher or phlebotomist if the patient was also having a routine blood test. The researcher also processed the samples except occasionally where the researcher was attending to patients. In this case an experienced laboratory technician assisted with sample processing in order to comply with the 3 hour window for processing.

4.12 Food intake and dietary habits

Data on eating habits was captured in Section 2 of the study specific questionnaires as well as the anorexia questionnaire. This data was used to show how an ovarian cancer diagnosis affects women's diet and eating habits. Factors that influenced their decisions on food choices were analysed. The study explored whether there were differences in nutritional outcomes between women who reported changing their diet and those who did not. Women's views on the nutritional intervention/support they received during treatment are explored and the relationship between such intervention and nutritional status examined. At the point of completing the questionnaire women had a suspected or recent diagnosis of ovarian cancer but had not commenced treatment. Since women were recruited early in their cancer journey, most had not received specific nutritional advice/counselling at the time, thus the study captured virgin information. The results of this analysis are presented in section D of chapter 5.

4.13 Data capture

Data from all original source documents collected were captured into the Microsoft Access Database. The researcher created in this database, templates of every form and questionnaire used to collect data. Data was manually captured from each document into the database. The database is safe and under the custodianship of UCL/UCLH data protection policies. For this reason, all data including patient identifiers were captured. The assigned unique volunteer ID was used to label every form, questionnaire or sample for each woman. Retrieving data from the database for analysis was done by running data queries. These allow the researcher to select required data, for the required time point for each

specific woman or groups of women. This data was then transferred into a spread sheet, Microsoft excel or IBM SPSS for analysis.

4.14 Analysis

Nutritional status was categorised using clinical and international consensus criteria for the classification of malnutrition and/or cachexia where applicable. Except in the case of unverifiable errors, all data were included in the analysis including some outliers (high and low weight and BMI). It was important that all data were represented in the study. Missing data were excluded from analysis. Data were missing due to patients being lost to follow-up, withdrawal of consent to continue in the study, declining specific assessments such as giving a blood sample if already given blood for routine tests, patients being too ill on the day of assessment and patients not returning questionnaires. Women who did not return outstanding questionnaires were telephoned and/or written to, to remind them to do so.

4.14.1 Statistical analysis

IBM SPSS Statistics 22 was used to analyse the data. Descriptive analysis was performed to characterise the study population. Within group differences between time-points were analysed using non parametric tests, the related sample Wilcoxon signed rank test. Differences between cases and controls were explored using the Mann-Whitney U test while the Kruskal-Wallis test was used to show associations between nutritional status and presence or absence of symptoms. The relationships between different variables and outcomes were explored using, Spearman's correlation and calculation of the Odds ratio. A $p <0.05$ was considered to be statistically significant.

4.14.2 Quality of life

The Euroqol EQ-5D questionnaire was analysed using SPSS to determine the proportions of women reporting problems with each dimension. The EQ-5D

scores were presented as a health profile, using frequencies of reported problems for each level of each dimension. Problems with relevant dimensions were correlated with nutritional outcomes. The VAS scale was analysed using the non-parametric related sample Wilcoxon signed rank test to compare heath statuses across time points and the Mann Whitney U test to compare cases and controls. The Kruskal Wallis test was used to determine association between health status with symptoms and type of treatment while Spearman's correlation was used to determine the relationship between quality of life and nutritional status. These findings are presented in Chapter 6.

4.15 Recruitment flow diagram

Participants were sub-grouped by diagnosis into cases, borderline malignancy, and controls. Those who, following surgery did not meet the inclusion criteria were excluded from analysis. Participants were lost to follow-up if they died (2 cases), relocated (2 cases) or withdrew consent (1 case). Some declined to be assessed or were no longer interested in further assessments (5 controls and one woman with a borderline malignancy). Some women did not respond to telephone contact or return the questionnaire. These all resulted in some missing data. Only four women were diagnosed with borderline ovarian malignancy and were therefore excluded from analysis due to the small sample size. A flow diagram showing the numbers of patients approached, recruited and the assessments undertaken are shown in the flow diagram in Figure 9. Further findings from this study are presented in the next chapter.

Figure 9: The recruitment flow diagram


```
                    ┌──────────────────────┐        ┌────────────────────────────┐
                    │ Approached (n=193)   │        │ Declined to participate    │
                    └──────────────────────┘        │ Too unwell (n=11)          │
                                │                    │ Prioritising treatment     │
                                │                    │ (n=21)                     │
                    ┌──────────────────────┐         │ Not interested (n=28)      │
                    │ Recruited (n=103)    │         │ Time constraints (n=30)    │
                    └──────────────────────┘         └────────────────────────────┘
                                │
                    ┌──────────────────────┐
                    │ Baseline assessment  │
                    │ (n=102)              │
                    │ 1 death              │
                    └──────────────────────┘
                                │
                    ┌──────────────────────┐        ┌────────────────────────────┐
                    │ Treatment and        │        │ Excluded: not              │
                    │ Diagnosis            │        │ meeting inclusion          │
                    └──────────────────────┘        │ criteria                   │
                            n=89                     │ (n=13)                     │
                                                     └────────────────────────────┘
```

Approached (n=193)

Declined to participate
Too unwell (n=11)
Prioritising treatment (n=21)
Not interested (n=28)
Time constraints (n=30)

Recruited (n=103)

Baseline assessment
(n=102)
1 death

Treatment and Diagnosis

Excluded: not meeting inclusion criteria (n=13)

n=89

Cases
(n=58)

Borderline malignancy
(n=4)

Controls
(n= 27)

Excluded from analysis:
(sample size too small)

Analysed

Baseline
Weight (n = 57)
BIA (n = 40)
Prealbumin (n = 46)
Albumin (n1 = 56)
CRP (n = 51)
CA125 (n = 55)
Questionnaires (n = 47)

During treatment
Weight (n = 48)
Questionnaires (n = 42)
BIA (n = 34)

End of treatment
Weight (n = 48)
BIA (n = 45)
Prealbumin (n = 42)
Albumin (n = 46)
CRP (n = 46)
CA125 (n = 45)
Questionnaires (n = 38)

Analysed

Baseline
Weight (n =27)
BIA (n = 24)
Prealbumin (n= 24)
Questionnaire (n=20)
Albumin (N/A)
CRP N/A
CA125 (N/A)

During treatment
N/A

End of treatment
Weight (n =19)
BIA (n = 16)
Prealbumin (n = 14)
Questionnaires (n = 15)
Albumin (N/A)
CRP N/A
CA125 (N/A)

5 The observational study results Part 1: (patient characteristics, lifestyle, nutritional and biochemical statuses)

5.1 Introduction to chapter

This is the first of two chapters that present findings from the observational study A. It is divided into 4 sections. Section A provides a description of the women who participated in the study based on age, ethnicity, menopausal status, diagnosis, stage of the disease, treatment and symptoms. Section B presents results on lifestyle, which includes smoking and alcohol intake. Nutritional and body composition outcomes of weight, BMI, body fat, dry lean mass, lean mass and total and extracellular body water are also presented. Findings on biochemical markers including prealbumin, albumin, C - reactive protein (CRP) and CA125 findings are presented in section C. Findings are presented for cases and controls at 'baseline', 'during treatment' and for the 'end of treatment' as applicable. A comparison is made between cases and controls where appropriate. Dietary changes captured using the study specific questionnaire are detailed in Section D. These changes relate to the period starting 3 months prior to baseline assessment, to assess the impact of the disease on diet and eating habits to the end of treatment assessment to assess the impact of treatment. Findings are presented on the specific diet changes, the reasons and rationale for the change in diet, the current practice on nutritional/dietary support as well as women's suggestions for an ideal future intervention. Findings from study A show outcomes that were affected, how they were affected and importantly, what that means for the woman involved. Quality of life results are presented in chapter 6.

5.2 Section A: General description, disease and treatment

5.2.1 Age and ethnicity

The median ages of cases, controls and women diagnosed with a borderline malignancy were 60, 49 and 35 respectively. The independent samples test showed that cases were significantly older that controls ($p < .01$). The majority of participants were Caucasian (white British, and white other) 52/58 (91%) and 20/27 (74%) of cases and controls respectively. There were 3/58 (5%) and 4/27 (14%) black African/Caribbean and 2/58 (3%) and 3/27 (11%) Asian/mixed Asian cases and controls respectively.

5.2.2 Menopausal status

Figure 10: Percentage of menopausal and non-menopausal cases and controls
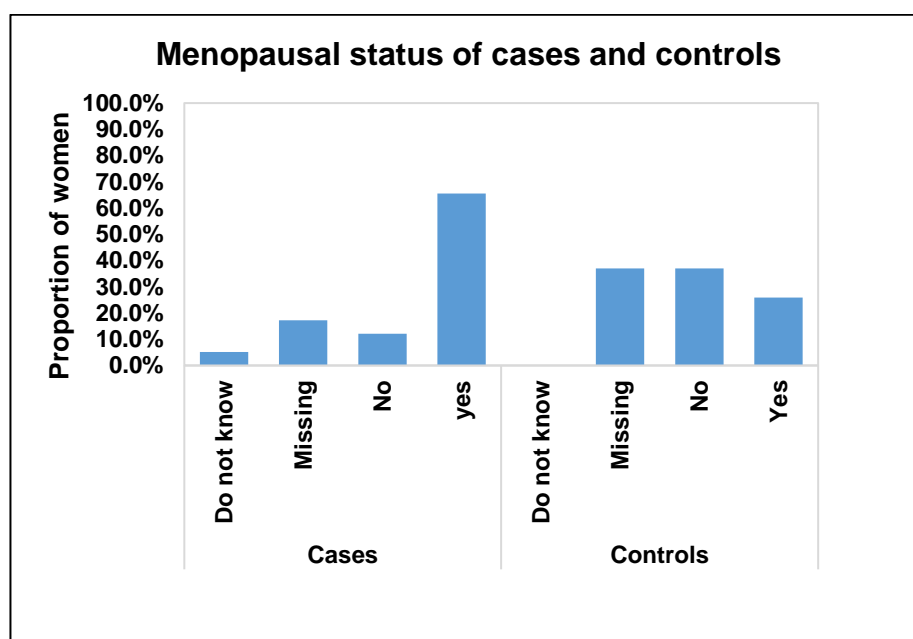
Figure 10 shows that the majority of cases were menopausal, 38/58 (66%). Only 7/58 (12%) were non-menopausal while 13/58 22% either did not know or did not provide their menopausal status information. Twenty six percent (7/27) of controls were menopausal while 10/27 (37%) were not. A further 37% did not provide

information on their menopausal status. It is expected that more controls in the missing group were non-menopausal due to the young median age. Increasing age in menopausal women is associated with a decline in metabolic rate and an increase in body fat. The median age of menopause in this study was 50. The average age of menopause in the United Kingdom is 51.

5.2.3 Diagnosis

The histological diagnoses of ovarian cancer and benign conditions of women in the study are shown in Table 9.

Table 9: The list of the histological diagnoses of cancer and benign conditions of cases and controls in the study

Cases		Controls	
Histology	**Total**	**Histology**	**Total**
Tubal Cancer	1	Endometriosis	5
Adenosquamous carcinoma	1	Serous cystadenoma	2
Transitional cell carcinoma	1	Ovarian fibrothecoma	2
Serous with clear cell elements	1	Benign ovary	3
Serous with mucinous adenocarcinoma	1	Mucinous cystadenoma	4
Clear cell and endometrioid carcinoma	1	Benign leiomyoma	7
Endometrioid adenocarcinoma	2	mature cystic teratoma	2
Mucinous adenocarcinoma	3	Brenner tumour	1
Primary peritoneal adenocarcinoma	4	Simple endometrial hyperplasia	1
Clear cell carcinoma	5		
Serous adenocarcinoma	38		
Total	**58**		**27**

5.2.4 Stage of disease and treatment

The classification of cases by stage of disease, treatment type, relevant symptoms and weight change at baseline are outlined in Table 10. Nineteen percent (11/58) cases were diagnosed with early stage disease (stage I and II) while 46/58 (79%) were diagnosed with advanced disease (stage III and IV). One woman could be not be staged due to complications during her surgery.

Women diagnosed with stage I & II disease were treated with surgery alone 5/11 (45%) or surgery with chemotherapy 6/11 (55%) if cancer was also found on the surface of the ovary or the cytology tested positive for cancer cells. Of the 26 women diagnosed with stage III disease, one woman was treated with surgery alone because she had a low-grade tumour that had been completely excised while 12/26 (46%) were treated with primary cytoreductive surgery followed by a course of chemotherapy. A further 9/26 (35%) were treated with interval debulking surgery, i.e. 3 cycles of chemotherapy followed by surgery and the remaining 3 cycles of chemotherapy given after surgery. The rest 4/26 (15%) were treated with chemotherapy alone. Twenty women were diagnosed with stage 4 disease. Only 2 women in this group were treated with primary cytoreductive surgery first. The majority, 15/20 (75%), were treated with interval debulking surgery. This is the recommended treatment for stage 4 patients with high metastatic tumour burden or for patients whose general condition is poor. Two women in this group were treated with chemotherapy alone while one woman died before receiving any treatment. Women treated with chemotherapy alone had either not shown satisfactory response to the chemotherapy, or their disease had progressed through treatment, which precluded successful debulking surgery.

Table 10 : The classification of cases by stage of disease, type of first treatment, relevant symptoms at baseline and death

Cases only	FIGO stage					Total (N)
	1	**2**	**3**	**4**	**Not staged**	**Total (N)**
Participants N (%)	10 (17%)	1 (1.7%)	26 (45%)	20 (34%)	1 (1.7%)	58
Median age (range)	56 (45-73)	46	62 (36-82)	68 (38-88)	56	-
Treatment type						
Surgery only	5 (50%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	5
Surgery then chemotherapy	5 (50%)	1 (1.7%)	12 (46%)	2 (10%)	1 (100%)	21
Chemotherapy then surgery	0 (0%)	0 (0%)	9 (35%)	15 (75%)	0 (0%)	24
Chemotherapy only	0 (0%)	0 (0%)	4 (15%)	2 (10%)	0 (0%)	6
No treatment	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	1
Relevant symptoms						
Distension/Swelling	4 (40%)	0 (0%)	13 (50%)	13 (65%)	1(100%)	31
Pain/Discomfort	5 (50%)	1 (100%)	15 (75%)	10 (50%)	1(100%)	32
Ascites**	3 (30%)	1 (100%)	21 (81%)	16 (80%)	0 (0%)	41
Nausea/vomiting/loss of appetite/bloating	4 (40%)	0 (0%)	10 (38%)	8 (40%)	0 (0%)	22
Fatigue	0 (0%)	1 (100%)	5 (19%)	4 (20%)	0 (0%)	10
Deaths @ $3^1/_2$ years post recruitment**	1 (10%)	0	13 (50%)	10 (50%)	0 (0%)	24

** Significant difference (Kruskal Wallis test) between early stage (I&II) and late stage (III&IV) ($p < .05$)

5.2.5 Symptoms

Relevant symptoms in cases included ascites, abdominal pain/discomfort, abdominal distension/swelling, nausea, vomiting, and loss of appetite (LOA), bloating and fatigue. The Kruskal Wallis test showed a statistical association between the prevalence of ascites and the stage of disease $p < .01$. There was also a significant association between abdominal distension and presence of ascites, $p = .05$ as expected. Pain and/discomfort were more prevalent in women with stage III than in those with stage IV disease (75% vs. 50%). The lower level of pain and discomfort may partly explain why women with stage IV disease had not presented earlier to their GP/hospital (pain and discomfort are analysed further in the quality of life, (chapter 6). Nausea, vomiting, loss of appetite and bloating were reported less frequently (there was a combined report of 22 for these symptoms). Fatigue was the least frequently reported symptom; only 10 women reported experiencing it

5.2.6 Deaths

Twenty-four women (41%) with cancer had died by 31 October 2014 three and a half years after commencement of recruitment. Of the 24 women who had died, 23 had been diagnosed with stage III or IV and one with stage I disease. Although a heart attack was the primary cause of the death of the woman with stage I disease, her post mortem report indicated her cancer had recurred with widespread deposits within the abdomen. One woman died in the control group within the same period. Her cause of death was complications arising from diabetes.

5.3 Section B: Life style, nutritional status and body composition

5.3.1 Lifestyle

Findings presented here on smoking and alcohol are from data collected using the study specific questionnaire.

5.3.1.1 Smoking

Figure 11: The percentages of cases and controls who ever smoked
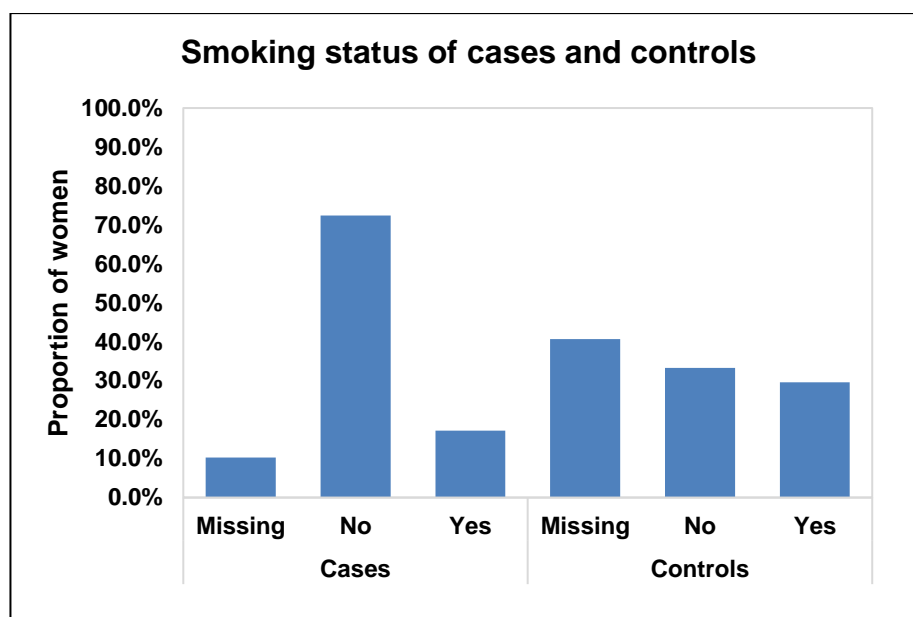
Only 10/58 (17%) of the cases ever/smoked, see Figure 11. Of these 5 gave up 5 or more years prior to participating in the study. Four gave up between 18 months and 4 years prior to their participation. Only one woman stated that she still smoked up to 15 cigarettes per day. Eight of twenty seven controls (30%) stated that they were or previously had been smokers. Of these, half had since stopped. The average number for those who still smoked was 11 cigarettes. These results align with Public Health England's (2016) figures and their report which concluded that smoking is least common amongst women aged 55 and over. Smoking may influence eating habits e.g. by decreasing snack frequency and energy intake. Although smoking has been linked to mucinous ovarian cancer (316), the small sample size and even smaller number of cases and controls who ever/smoked limits further analysis of the potential impact of smoking on diet and nutritional status.

5.3.1.2 Alcohol intake

Figure 12: The percentages of cases and controls who ever drank alcohol
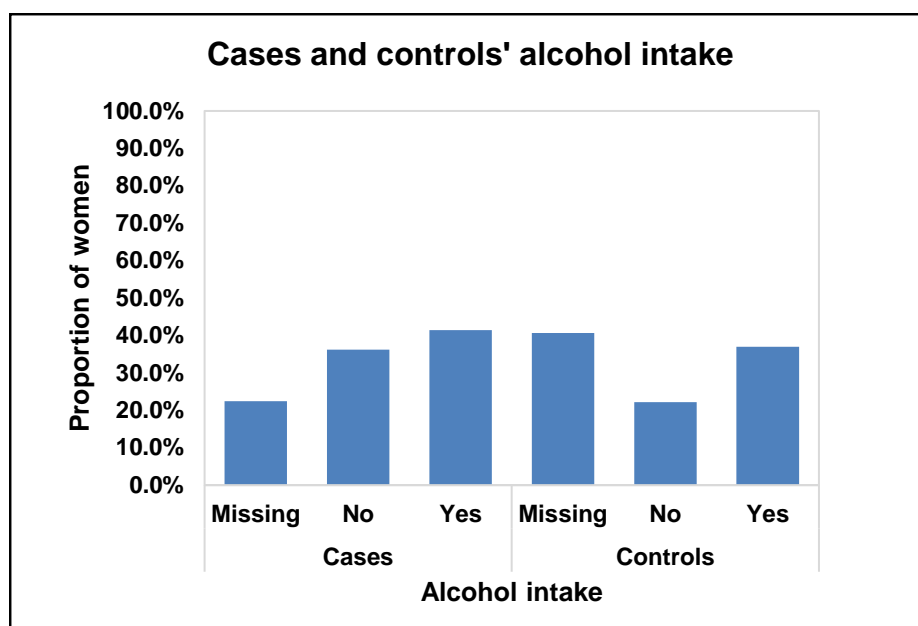
At baseline, 23/58 (40%) of cases had ever consumed alcohol as shown in Figure 12. Only 2 cases stated that they drank more than the recommended 14 units per week. The median number of drinks per woman per week was 3.2. Controls were found to drink a median of 4 units per/week. The relevance of alcohol to nutritional status is that, calories from its consumption tend to replace other desired nutrients. The recommendation in the UK is that men and women who drink regularly are safest not to drink more than 14 units/week. A potential or actual diagnosis of cancer does not seem to have influenced women's drinking habits as those women who drank, stated that they consumed similar amounts 3 months prior to their baseline assessment. The low average drinking within the groups limits scope for further analysis of a potential impact of drinking on nutritional status.

5.3.2 Nutritional status

Nutritional status and body composition were assessed using weight, BMI, percentage body fat, dry lean mass, lean mass. Total body water and extracellular water were also analysed to show if there was an association with

the presence of ascites. The median age of menopause for this study is 50. This age is used as a cut-off point for classifying pre-menopausal (50years ≤) and menopausal (> 50years). Findings for each outcome are presented below.

5.3.2.1 Weight

Weight change prior to recruitment

All but one of the 58 cases were weighed at baseline. Forty seven women completed the baseline questionnaire, and the numbers of those who retrospectively reported weight change prior to recruitment are stated in   Table 11. Twenty-three women reported losing weight in the three months preceding diagnosis. Weight loss ranged between 3.4% and 15.8 % of the baseline weight. Baseline body weight was used since prior weight could not be ascertained. Eight women reported that they gained weight in the same period. Self-reported weight change negatively correlated with abdominal swelling. This suggests that despite women presenting with abdominal distension, they reported overall weight loss. One woman with an overall weight loss reported that she had started to gain weight in more recent weeks. Similarly a woman with overall weight gain reported an initial weight loss followed by weight gain. Weight was therefore found to involuntarily fluctuate between gain and loss.

Table 11: The relationship between prior self-reported weight change and signs and symptoms at baseline for cases

Patients	Stable weight (change < 2%) N (%)	Wt. change unknown N (%)	Weight loss 2-4.9% (pre-cachexia) N (%)	Weight loss $\geq$ 5% (cachexia) N (%)	Weight gain $\geq$ 2% N (%)	Total (N)
Number of patients	19	15	5	10	8	47
Median age (range)	61 (43-82)	56 (42-75)	66 (53-71)	59 (37-76)	65 (40-88)	-
BMI < 20	0 (0%)	1 (6%)	1 (20%)	1 (10%)	0 (%)	3
Signs						
Prealbumin < 16mg/dl*	5 (26%)[3]	6 (40%)[3]	1 (20%)	4 (40%)[2]	3 (38%)[3]	19
Albumin < 36g/l	2 (11%)	3 (20%)[1]	1 (20%)	1 (10%)[1]	3 (38%)	10
Stage						
1	5 (26%)	3 (20%)	1 (20%)	0 (0%)	1 (12.5%)	10
2	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	1
3	9 (47%)	6 (40%)	3 (60%)	5 (50%)	3 (38%)	26
4	4 (21%)	6 (40%)	1 (20%)	4 (40%)	5 (63%)	20
Unstaged	1 (5%)	-	-	-	-	1
Symptoms						
Ascites	11 (58%)	11 (73%)	3 (60%)	9 (90%)	6 (75%)	40
Distension	7 (37%)	11 (73%)	3 (60%)	6 (60%)	3 (38%)	30
Pain/Discomfort	12 (63%)	8 (53%)	5 (100%)	8 (80%)	7 (88%)	40

Superscript refers to the number of missing values in that group
*Significant difference (Kruskal Wallis test) observed in the different categories of weight change (loss, gain) ($p < .05$)

Table 11 also shows that 5 of 19 women who reported a stable weight prior to recruitment had low prealbumin with 2 of those 5 also having a low albumin. This suggests that in some women the inflammatory processes that can contribute to cachexia were on-going without a manifest change in weight. The ten women who reported a weight loss > 5% of their baseline body weight warrant formal classification as cachectic. Four women in this group had correspondingly low prealbumin, one of whom also had low albumin. Weight change prior to treatment was negatively correlated with baseline prealbumin (r = -.340; p = .07). The correlations table is shown in appendix 6 because of its size.

Of the 8 women who gained at least 2% of their baseline body weight, 3 had low prealbumin and albumin and also had ascites and pain/discomfort at baseline. Five of the 8 women were diagnosed with stage IV disease. The combination of late stage disease, decreased prealbumin and or albumin suggests that weight gain in these women was likely to be related to their distension and ascites.

Weight change during the study

It was not possible to assess weight in 10 cases during and at the end of treatment due to poor health or death. An illustration of the difference in weight for each woman between baseline, during treatment and at the end of treatment is shown in Figure 13. This multiple line graph depicts the actual gain or loss in kg for each of the 43 cases whose weight was assessed at all three time points. The graphs show a general decrease in weight between baseline and during treatment, and an increase between the 'during treatment' and end of treatment for cases time points for cases.

Figure 13: Multiple line graph showing cases' weight change from baseline to during treatment to the end of treatment.
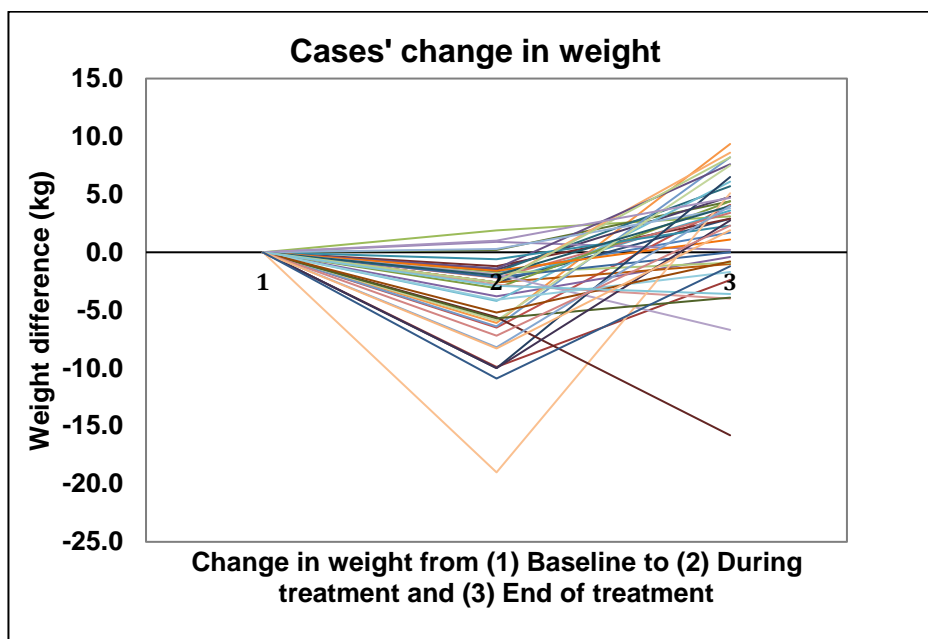
A descriptive summary of weight showing the median, standard deviations and Inter Quartile Ranges (IQR) is shown in Table 12. Further analysis of women's overall weight using box plots is shown in Figure 14.

Table 12: The descriptive analysis of weight at baseline, during treatment and at the end of treatment for cases and controls

		Baseline	During treatment	End of treatment
Cases				
N	Valid	57	48	48
	Missing	1	10	10
Mean		73.8	69.5	71.8
Median		69.2	66.2	66.2
Std. Deviation		18.84	17.74	17.69
Minimum		46.0	44.7	48.8
Maximum		143.2	132.3	131.1
Percentiles	25	59.8	56.4	60.7
	50	69.2	66.2	66.2
	75	84.9	76.5	78.1
Controls				
N	Valid	27		19
	Missing	0		8
Mean		74.6		72.1
Median		73.0		71.0
Std. Deviation		12.68	n/a	11.95
Minimum		51.0		50.0
Maximum		106.6		93.9
Percentiles	25	63.8		63.5
	50	73.0		71.0
	75	82.0		83.2

Figure 14: The box plots showing weight at baseline, during treatment and at end of treatment for cases and controls
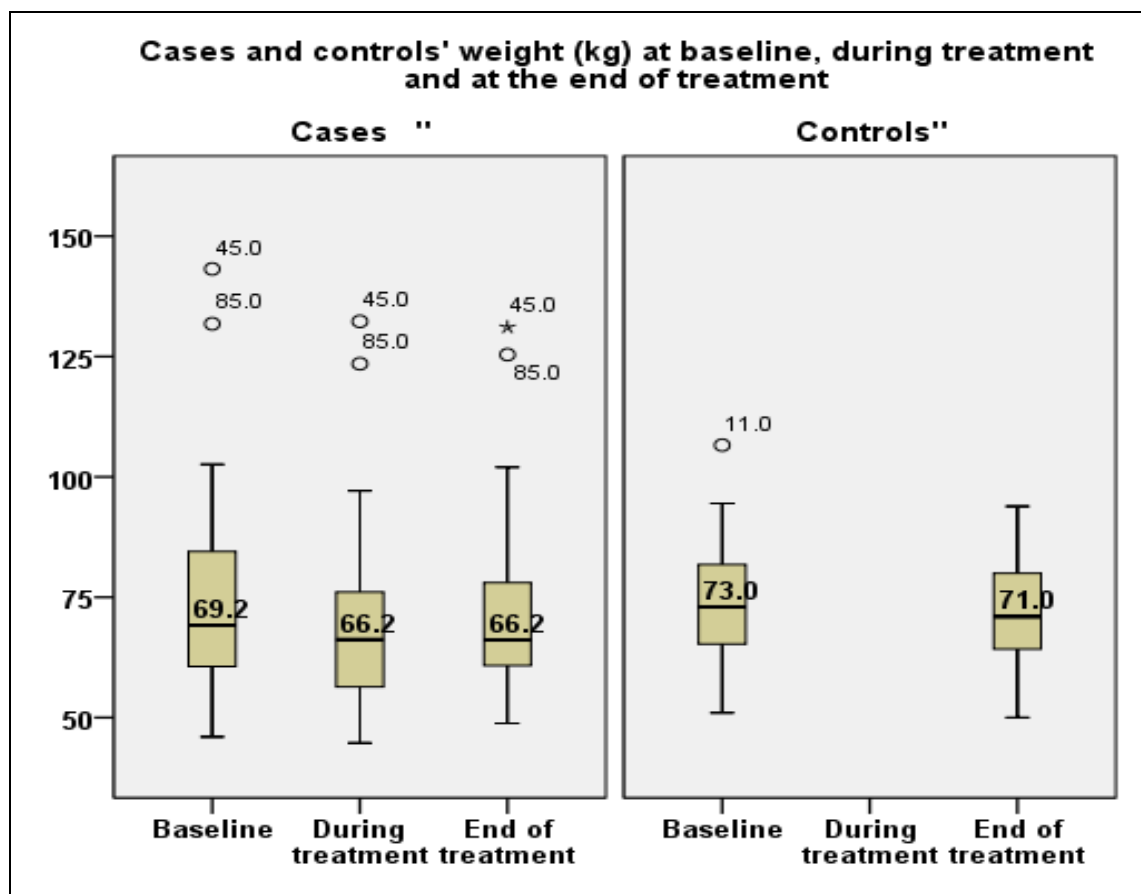
O, *: The floating numbers represent outliers

The box plots show a generally wide dispersion of weight in both cases and controls across all time points (long whiskers). Outliers are identified by 'O' and '*'. Outliers are all in the top end of the graph so they lie outside the expected upper ranges of weight. The cases were 50 and 55 years old. One had stage 3 and the other stage 4 disease. Both were treated with chemotherapy first, suggesting that they had other comorbidities. Both had normal levels of CA125 at the end of treatment implying that they had responded to treatment.

The Wilcoxon Signed Ranks Test showed a significant weight difference in cases between baseline and during treatment ($p < .01$). The median weight decreased from 69 (IQR: 58.1 - 83.5) to 65.6 (IQR: 56.4 - 76.8) during this period. There was also a significant increase ($p < .01$) in weight (kg) from during treatment to the

end of treatment 66.7 (IQR: 60.6-77.9). There was an overall borderline significant decrease between baseline and end of treatment weight, $p = .06$. The average weight loss between baseline and end of treatment was 2.3 kg. There was no significant difference in weight at baseline and at the end of treatment for controls, $p > .05$. The Independent Samples Median test showed no significant weight differences between cases and controls at baseline and end of treatment weights, $p > .05$ in both instances.

Cases' weight was further analysed by subgrouping women into those with ascites and those without, at baseline. The median weight for women without ascites was (69.4) and that of women with ascites was (68.8). The Independent Samples test showed no significant difference between them, $p > .05$. Five women who lost more than 5% body weight prior to baseline assessment continued to lose weight to the end of treatment. One woman lost more than 40% of her original weight by the end of treatment. Her weight decreased from 82.4 kg at baseline to 61kg at the end of treatment. She reported that she had already lost 13kg (15%) of her original body weight at baseline assessment. Others lost between 10 and 13%. None of these women had a BMI less than 20 despite the weight loss. Three of the 5 women had elevated CA125 at the end of treatment meaning that they had residual or progressive disease.

Overall findings from the analysis of weight are; 1) That prior to treatment, weight change (fluctuations between gain and loss) is a continuum affected by dietary change, malnutrition/cachexia and the presence of ascites and large tumours; 2) Weight tends to decrease during the early stages of treatment but increase thereafter such that it is only marginally lower at the end of treatment than at baseline; 3) Women with advanced disease ultimately lose more weight than that added by ascites; and 4) Weight does not separately account for ascites which is highly prevalent in this patient group. This is a limitation for its use as a measure of nutritional status in this patient group.

5.3.2.2 Body Mass Index (BMI)

Weight and BMI are closely related. The latter is a measure of one's weight for their height. For this reason BMI is presented here to show findings not already revealed by analysing weight. Participants were classified using categories adapted WHO 2004 and modified to fit cachexia classification by using the lower cut-off point of 20 instead of 18.5 as shown in Table 13. Only four cases were found to have a BMI less than 20 and would have been considered at risk of cachexia at baseline. A third (29.3%) of cases were of normal weight while 17% were varying degrees of obese (BMI > 30). There were no underweight controls. Forty four percent of controls were overweight while 30% were obese.

Table 13: The classification of cases and controls' BMI at baseline using cachexia classification cut-off points

Participants	Un-classified	Underweight <20	Normal weight (20-24.9)	Overweight (25-29.9)	Class I obesity (30-34.9)	Class II obesity (35.0-39.9)	Class III obesity≥ 40	Total (N)
Cases N (%)	1 (1.7%)	4 (6.9%)	19 (32.8%)	17 (29.3%)	9 (15.5%)	6 (10.3%)	2 (3.4%)	58
Controls N (%)	0 (0%)	0 (0%)	7 (25.9%)	12 (44.4%)	5 (18.5%)	3 (11.1%)	0 (0%)	27

A descriptive summary of BMI at the three assessment time points is shown in Table 14. Further analysis using box plots and subdividing women by age of menopause is shown in Figure 15.

Table 14: The descriptive analysis of BMI at baseline, during treatment and at the end of treatment for cases and controls.

		Baseline BMI	During treatment BMI	End of treatment BMI
Cases				
N	Valid	40	36	46
	Missing	18	22	12
Median		27.5	24.1	25.8
Minimum		18.8	17.5	18.1
Maximum		51.3	47.1	47.8
Percentiles	25	23.1	22.3	23.2
	50	27.5	24.2	25.8
	75	33.2	28.5	31.8
Controls				
N	Valid	24		16
	Missing	3		11
Median		26.5		26.3
Minimum		21.8	n/a	21.4
Maximum		37.9		32.8
Percentiles	25	24.1		23.3
	50	26.5		26.3
	75	29.9		28.0

The median BMI for all assessed cases was 27.5, 24.1 and 25.8 at baseline, during treatment and at the end of treatment respectively. Median BMI for controls was 26.5 and 26.3 at baseline and at the end of treatment respectively. The Related Samples Wilcoxon Signed Rank Test showed a significant difference between baseline and during treatment BMI for cases, p < .01, between during treatment and end of treatment, p < .01 and a borderline significance between baseline and end of treatment, p = .06. No significant

difference between baseline and end of treatment was observed in controls *p* > .05.

Cases and controls were sub-divided by the median age of menopause to identify differences that are due to age. The box plots showing this analysis are shown in Figure 15.

Figure 15: The box plots showing BMI at baseline, during treatment and end of treatment by age of menopause for cases and controls
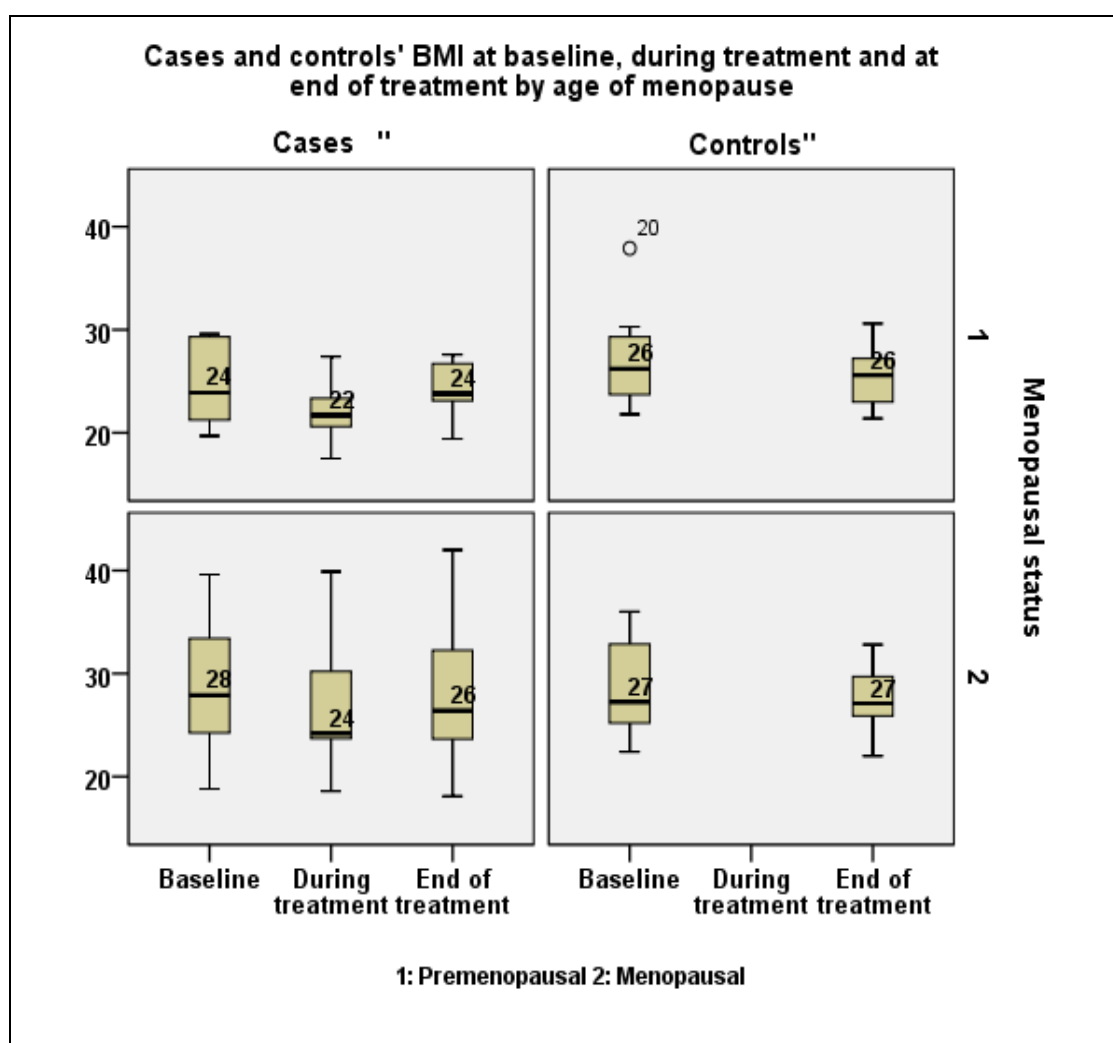
O, *: The floating numbers represent outliers

The relatively short box plots and whiskers for premenopausal cases and controls compared to menopausal cases and controls suggests that BMI is less dispersed in younger women than it is in older women. Premenopausal cases have the lowest BMI of any other group across all time points. The BMI of premenopausal cases fell by 2 units during treatment, but these units were regained by the end of treatment. On the contrary menopausal cases lost 4 units of BMI from baseline to during treatment, and regained only 2 of those by the end of treatment, thus not reaching their baseline BMI. Controls BMI was stable between baseline and end of treatment remaining at 26 for premenopausal women and 27 for menopausal women.

The Mann-Whitney U test showed a significant difference between the BMI of menopausal versus that of non-menopausal cases during treatment $p < .05$. The small sample sizes for premenopausal cases (8, 7 and 10 at baseline, during treatment and end of treatment respectively) and menopausal controls (8 at baseline and 7at the end of treatment) may not have allowed for subtle changes to be identified at other time points. Overall, controls and menopausal cases have a high BMI. Even with a loss of 2 units during treatment, menopausal cases' median BMI, at 24 is on the upper end of normal/healthy.

The main findings from the analysis of BMI are; 1) Loss of significant weight (>2% of body weight) does not result in a corresponding critical level fall in BMI; 2) Older cases who are also more likely to be diagnosed with advanced disease tend to have a higher BMI than younger cases; and 3) Weight lost by menopausal women is not fully gained back by the end of treatment indicating that this group may benefit from targeted nutritional intervention.

5.3.3 Body composition

Body composition was assessed using BIA. Findings on five components of body composition, body fat, lean mass, dry lean mass, extracellular water and total body water (TBW) are presented here. Clinical criteria for dry lean mass

and lean mass are either not available or have not been empirically validated. Data is presented here to show trends, rather than clinically relevant cut-off limits. Although there are no cancer cachexia consensus references or clinically relevant or agreed cut off points for body fat, the general classification by Heymsfield, Heo et al., (317) as shown in Figure 16, is used to characterise women. The descriptive analysis of body fat, dry lean mass and lean mass is outline in Table 15.

Table 15: The descriptive analysis of body fat, dry lean mass and lean mass at baseline, during treatment and at the end of treatment for cases and controls'

		Body fat (%)			Dry lean mass (kg)			Lean mass (%)		
		Baseline	During treatment	End of treatment	Baseline	During treatment	End of treatment	Baseline	During treatment	End of treatment
Cases										
N	Valid	40	36	46	40	37	45	40	35	44
	Missing	18	22	12	18	21	13	19	24	15
Mean		40.7	37.8	39.1	9.4	8.8	9.1	59.3	62.5	60.9
Median		41.0	38.6	38.9	9.9	9.6	9.7	59.0	62.1	61.1
Std. Deviation		8.47	7.99	7.96	2.70	2.91	2.95	8.47	7.84	8.11
Minimum		21	21	23	4.1	2.6	2.6	38.5	46.2	43.5
Maximum		62	54	57	14.9	14.5	14.5	79.3	79.2	77.0
Percentiles	25	34.2	31.1	32.6	7.3	7.0	6.8	54.5	56.6	55.4
	50	41.0	38.6	38.9	9.9	9.6	9.7	59.0	62.1	61.1
	75	45.5	44.1	44.2	11.4	10.8	11.2	65.8	69.2	67.6
Controls										
N	Valid	24		16	24		16	24		16
	Missing	3		11	3		11	3		11
Mean		37.8		37.1				62.2		62.9
Median		39.3		36.7	11.4		10.5	60.8		63.4
Std. Deviation		5.99	n/a	6.29		n/a		5.99	n/a	6.3
Minimum		27		23	3.5		3.7	50		55
Maximum		50		45	16.4		15.5	73		77
Percentiles	25	32.5		33.5	8.8		7.3	58.3		57.2
	50	39.3		36.7	11.4		10.5	60.8		63.4
	75	41.7		42.8	14.0		13.3	67.5		66.5

5.3.3.1 Body fat

Cases and controls were classified by body fat categories as shown in Figure 16.

Figure 16: The categories of body fat at baseline, during treatment and at the end of treatment for cases and controls
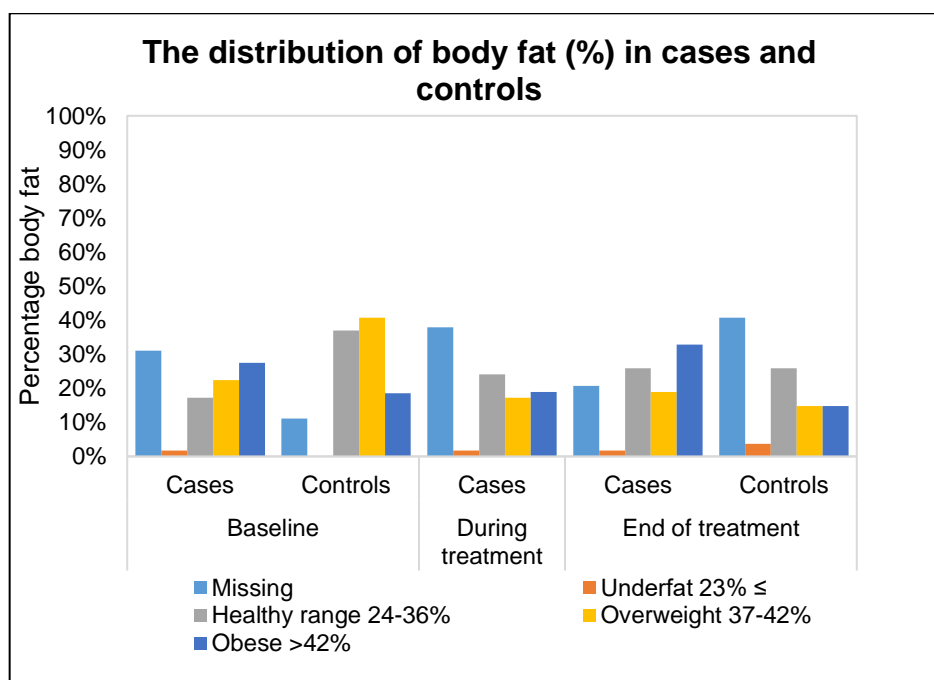
Only one case had less body fat than the recommended minimum of 24% at baseline and during treatment. A different woman was in this category at the end of treatment. More women may have been classified in this category at the end of treatment since some of those not assessed at this point were too poorly (n = 10) and may have lost weight and body fat.

The changes in body fat from baseline to during treatment and end of treatment are illustrated by the line in Figure 17. There was an increase in the percentage of cases within the healthy range from 17% at baseline to 24% during treatment and 26% at the end of treatment. The proportion of obese women increased to 33% at the end of treatment. None in the control group were below recommended body fat at baseline and only one was at the end of treatment.

There were proportionately less obese controls than cases at baseline and end of treatment.

Figure 17: Multiple line graph showing changes in body fat (%) between baseline, during treatment and the end of treatment for cases
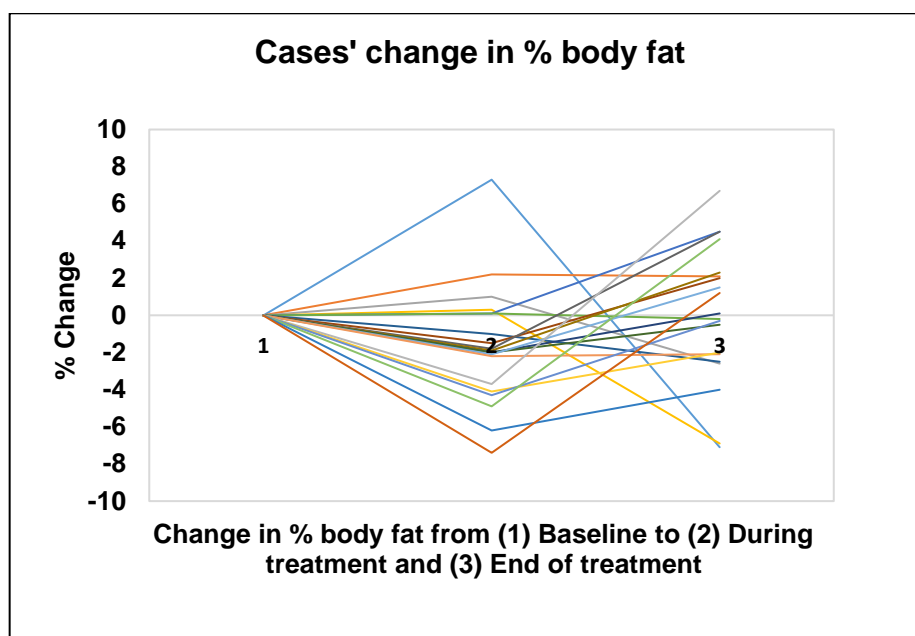
Box plots showing overall distribution of body fat for cases and controls across all assessment time points are shown in Figure 18 A. The Wilcoxon Signed Rank Test showed a significant difference between baseline and during treatment body fat, $p < .05$. There was a borderline significance $p = .083$ between baseline and end of treatment body fat an overall decline of 3.8%. No significant differences were observed between treatment and end of treatment, $p = .91$. Controls' body fat also declined by 2.6% from 39.3% at baseline to 36.7% by the end of treatment. This change was not statistically significant, $p > .05$. The Independent samples median test showed no significant difference, $p > .05$ between cases and controls at baseline and at the end of treatment.

Figure 18: The box plots showing body fat at baseline, during treatment and at the end of treatment for cases and controls
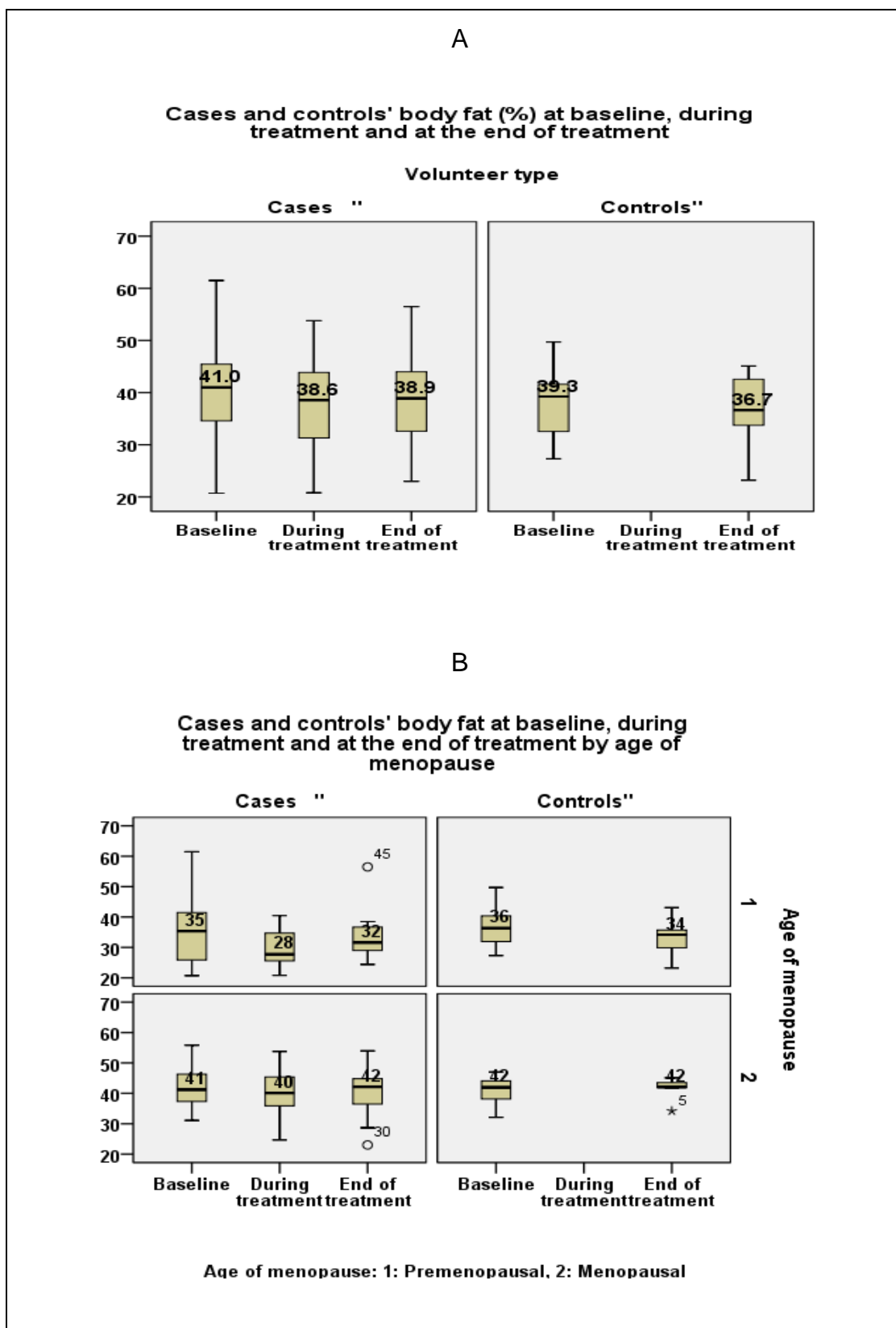
O, *: The floating numbers represent outliers

Further analysis by subdividing cases by the study median age of menopause showed that premenopausal cases have the lowest while menopausal controls have the highest percentage body fat. Premenopausal cases lost body fat during treatment and had not regained it to baseline levels at the end of treatment. Menopausal cases however, gained body fat to a higher percentage that they were at baseline. The Kruskal Wallis test showed significant differences between premenopausal and menopausal cases' body fat during treatment ($p < .01$) and end of treatment ($p < .05$). There was a borderline difference, $p = .06$ at baseline. There were significant differences between premenopausal and menopausal controls' body fat at baseline $p < .05$ and at the end of treatment $p < .05$. As in the general population, older women in this study have more body fat than younger women.

These findings show that; 1) Premenopausal cases lose more body fat; 2) Older women do not regain body fat to baseline levels; 2) The majority of cases are overweight or obese at all three time points indicating that malnutrition in the early part of the ovarian cancer trajectory is not represented by the standard thin and macro-nutrient deficient patient; 3) In menopausal cases, weight gained during the course of treatment is likely to be in the form of body fat.

5.3.3.2 Dry lean mass

The changes in dry lean mass across the three assessment time points are illustrated by line graphs in Figure 19. The graph shows a general trend of a fall in dry lean mass during treatment and a subsequent increase at the end of treatment.

Figure 19: Multiple line graph showing changes in dry lean mass between baseline, during treatment and the end of treatment for cases
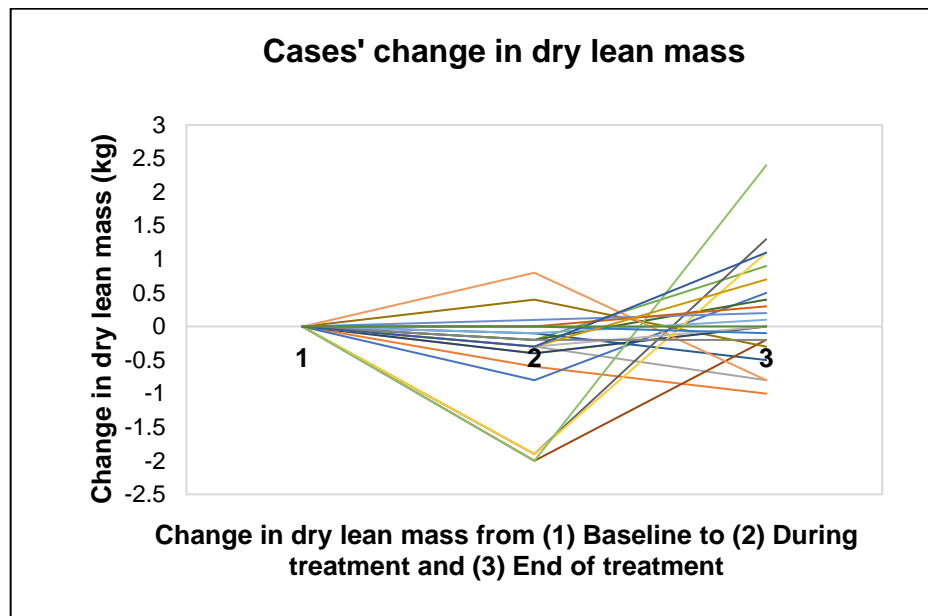
Box plots showing the distribution of dry lean mass are shown in Figure 20. The lower median dry lean mass for premenopausal cases compared to same age controls suggests that premenopausal cases may already have lost dry lean mass at baseline and continued to do so during treatment to the end of treatment. This loss between baseline and during treatment may partly be explained by the younger women's treatment plan. They are more likely to have had surgery, involving removal of their female reproductive organs and tumours leading to consequent loss of dry lean mass. There is an unexplainable gain in dry lean mass in menopausal cases from 9.1 to 9.7.

Figure 20: The box plots showing dry lean mass (kg) at baseline, during treatment and at the end of treatment for cases and controls
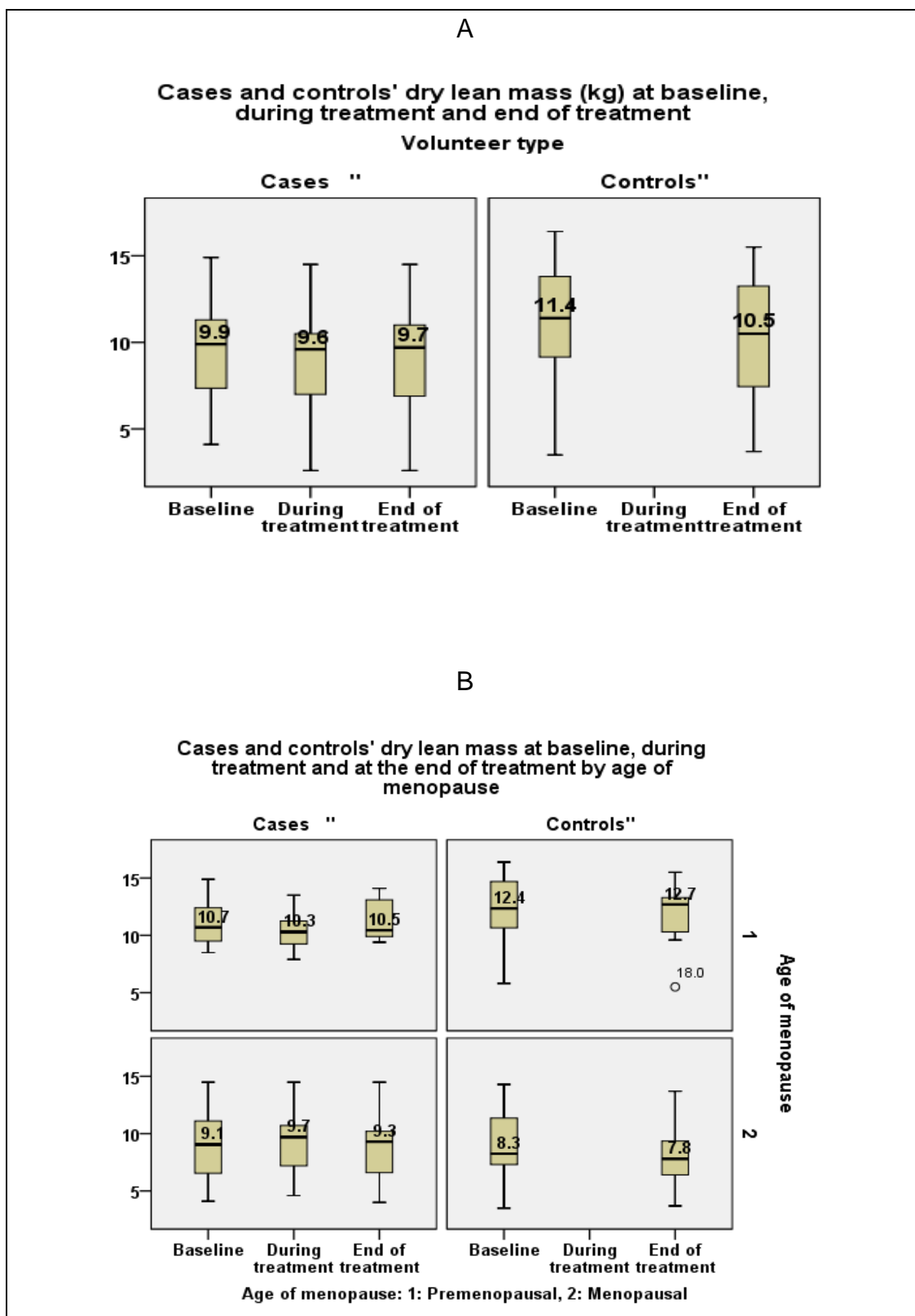
O, *: The floating numbers represent outliers

The Wilcoxon Signed Ranks Test showed an overall significant decrease ($p <$ .05) in dry lean mass between baseline and during treatment for cases and baseline and end of treatment for controls. Sub group analysis by age of menopause revealed that for cases, this difference was due to premenopausal cases losing dry lean mass during treatment. Age was significantly and negatively correlated with dry lean mass, $p < .05$. These findings are expected as dry lean mass is a sum of total protein and bone mineral mass. Both are expected to be lower in older women due to sarcopenia, a natural aging process.

The main findings here are that 1) Being older and having persistent disease at the end of treatment are associated with a lower dry lean mass and 2) Premenopausal cases may have lost dry lean mass at the baseline assessment and do not seem to regain it.

5.3.3.3 Lean mass

Lean mass is the proportion of the body mass that is not fat and is highly related to whole body resting energy expenditure. Table 15 shows that the median lean mass percentage was 59 at baseline, decreasing to 62 during treatment and further to 61 by the end of treatment. These changes are illustrated by the multiple line graph in Figure 21. The graph shows gains and losses in lean mass at each time point.

Figure 21: Multiple line graph showing changes in lean mass between baseline, during treatment and the end of treatment for cases
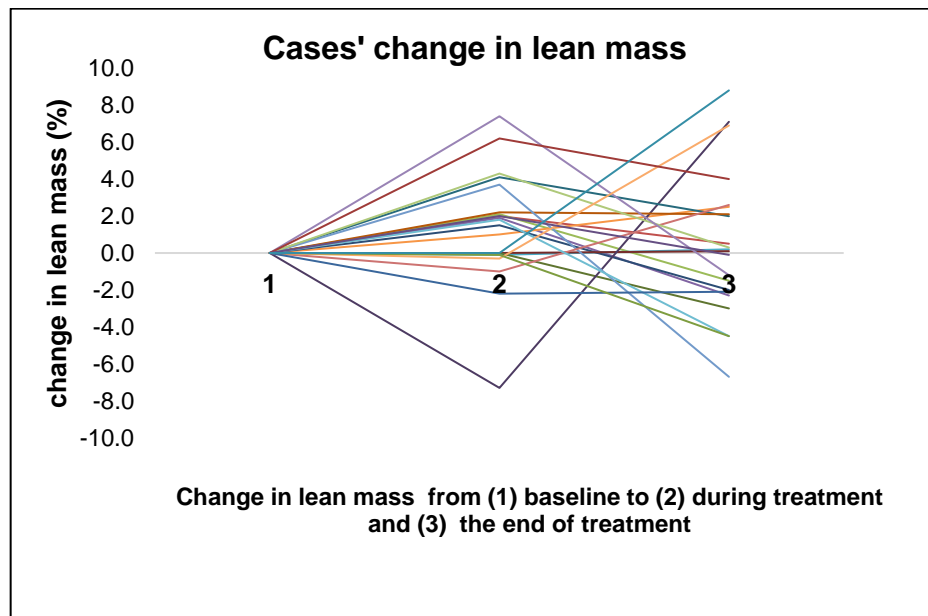
There was a significant difference between baseline and during treatment and baseline and end of treatment lean mass ($p < .05$) in cases. No significant differences were observed between baseline and end of treatment for controls and the Independent median test showed no significant differences between baseline and end of treatment lean mass between cases and controls ($p > .05$).

Figure 22: The box plots showing lean mass at baseline, during treatment and at the end of treatment for cases and controls
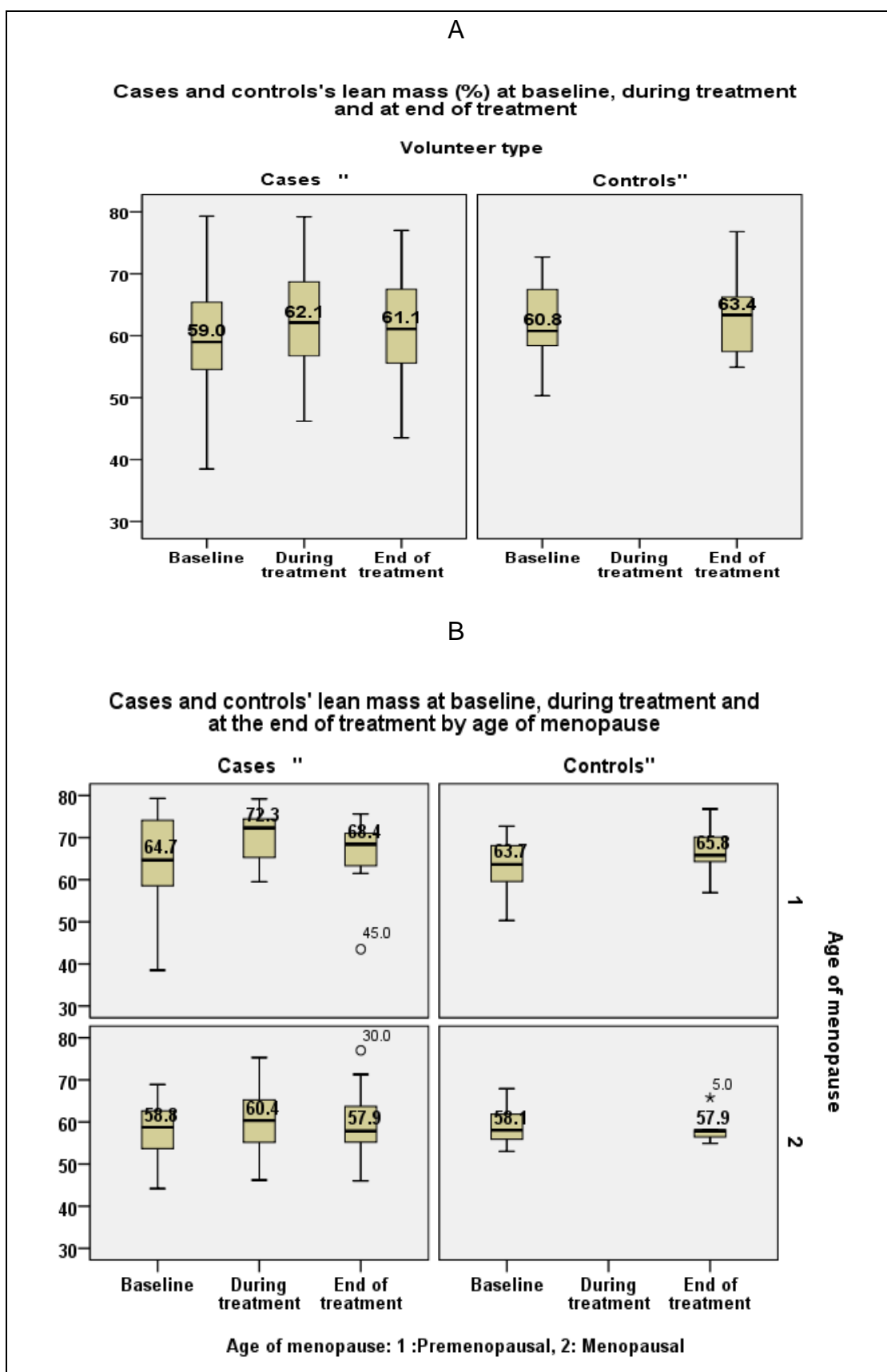
O, *: The floating numbers represent outliers

Subgroup analysis by age of menopause showed premenopausal cases to have the highest percentage of lean mass of all groups followed by premenopausal controls, shown in Figure 22. Lean mass also seemed to increase in all cases during treatment cases. This is difficult to explain except perhaps that it is linked with increase in body fluid related to intravenous infusions during surgery and chemotherapy. The differences according to age are expected as fat free mass is known to vary with some biological factors such as age and adiposity. Lean mass increased from baseline to 'during treatment' in both premenopausal and menopausal cases and then marginally decreased by end of treatment. These changes are in contrast to what was observed with body fat, which decreased during treatment and then increased by the end of treatment. The main finding is that the overall decrease in weight observed in cases may be due to loss of body fat rather than lean or dry lean mass.

5.3.3.4 Total body water (TBW %)

Total body water and extracellular water were analysed for cases to identify if ascites had an identifiable impact on them. The normal range for total body water for women is between 45 and 60% of their weight. The descriptive analysis for total body water is shown in Table 16.

Table 16: The descriptive analysis of % total body water at baseline, during treatment and at the end of treatment for cases

		Baseline	During Treatment	End of treatment
N	Valid	40	35	43
	Missing	18	23	15
Mean		47.5	49.5	48.8
Median		47.7	49.4	48.6
Std. Deviation		4.92	4.39	5.08
Minimum		35.4	40.40	37.60
Maximum		58.8	59.8	58.4
Percentiles	25	44.7	46.2	45.5
	50	47.7	49.4	48.6
	75	50.6	52.1	52.8

The Wilcoxon Signed rank test showed baseline total body water to be significantly lower than during treatment, $p < .05$. No significant differences were observed at other time points. This seems to confirm the increase in lean mass outlined in the previous section during this time. The Kruskal Wallis test showed no significant association between total body water and the presence of ascites at baseline, $p > .05$. The independent samples test showed no significant differences between baseline and end of treatment total body water between cases and controls $p > .05$ either. A borderline association, $p = .06$ was shown between pain/discomfort and total body, in chapter 6, section 6.1.3.

These findings show that despite documented clinical evidence of ascites, cases were generally at the lower end of expected total body water with a median of 47.7% (IQR: 44.7-50.6) at baseline. Although this improved significantly during treatment, $p < .01$, the measures remained on the low end of normal hydration at 49.4% during treatment and 48.6% at the end of treatment. The relationship between total body water and pain may be a factor in the link between ascites and pain/discomfort. When the build-up of ascites is severe it can cause abdominal distention which in turn causes discomfort or pain.

5.3.3.5 Extracellular water (ECW %)

Extracellular body water accounts for a third of total body water and is that fluid outside of the cells such as interstitial fluid. The descriptive analysis of extracellular water is shown in Table 17.

Table 17: The descriptive analysis of % extracellular water at baseline, during treatment and at the end of treatment for cases

		Baseline	During treatment	End of treatment
N	Valid	40	35	43
	Missing	18	22	14
Mean		22.7	23.7	23.9
Median		22.7	23.6	23.0
Std. Deviation		4.26	3.44	5.70
Minimum		14.1	17.7	16.6
Maximum		36.7	32.2	56.1
Percentiles	25	20.3	21.4	21.1
	50	22.7	23.6	23.0
	75	24.9	25.3	25.4

The Wilcoxon Signed rank test showed no significant differences between baseline and during treatment, during treatment and end of treatment and baseline and end of treatment, ($p > .05$) extracellular water. The Kruskal Wallis test showed no significant association between baseline extracellular water and the presence of ascites. The independent median test showed no significant differences, ($p > .05$) between cases and controls extracellular water at baseline and at the end of treatment. A significant association was found between pain/discomfort and extracellular water, $p = .03$ when using pain data from a quality of life questionnaire, section 6.1.3.

The findings on body water are unexpected. An association between extracellular body water and ascites were expected particularly at baseline, when 71% of cases were documented to have ascites.

5.4 Section C: Biochemical/protein markers

Results on the biochemical markers of nutrition (prealbumin), wellbeing (albumin), inflammation (CRP) and disease CA125 are presented here.

5.4.1 Pre-albumin (normal range 0.16 - 0.4 g/L)

The lower cut-off point of 16mg/dl in line with local clinical guidelines is adopted for this study. Descriptive analysis of prealbumin showing median, standard deviation and interquartile range is shown on Table 18. The classification of cases and controls by the level of prealbumin in shown in Table 19.

Table 18: The descriptive analysis of prealbumin at baseline and at the end of treatment for cases and controls

		Baseline	End of treatment
Cases			
N	Valid	44	42
	Missing	14	16
Mean		0.19	0.24
Median		0.17	0.23
Std. Deviation		0.07	0.07
Minimum		0.08	0.09
Maximum		0.37	0.41
Percentiles	25	0.14	0.20
	50	0.17	0.23
	75	0.24	0.29
Controls			
N	Valid	24	13
	Missing	3	14
Mean		0.23	0.27
Median		0.23	0.27
Std. Deviation		0.07	0.08
Minimum		0.13	0.14
Maximum		0.36	0.42
Percentiles	25	0.18	0.23
	50	0.23	0.27
	75	0.28	0.30

Table 19: The classification of cases and controls by the level of prealbumin at baseline and end of treatment.

Prealbumin (g/L)	Baseline N (%)		End of treatment N (%)	
	Cases	Controls	Cases	Controls
Missing	14 (24%)	4 (15%)	16 (28%)	14 (52%)
Low (0.16 <)	18 (32%)	4 (15%)	5 (9%)	1 (4%)
Low normal (0.17 - 0.20)	10 (17%)	5 (19%)	7 (12%)	0 (0%)
Normal (> 0.20)	16 (28%)	14 (52%)	30 (52%)	12 (44%)
Total (N)	**58**	**27**	**58**	**27**

Thirty two percent of cases had clinically low prealbumin (<16/L) at baseline compared to 9% at the end of treatment, shown in Table 19. A further 17% had borderline prealbumin of below 0.20g/L. All cases with a clinically low prealbumin at baseline had advanced disease (stage III or IV). The Kruskal Wallis test showed a significant association between prealbumin and stage of disease at baseline ($p < .01$) and a borderline association at the end of treatment, $p < .06$. Some controls, 15%, had low prealbumin at baseline compared to only 4% at the end of treatment. Women in the control group had longstanding issues such as fibroids and endometriosis which may have had an impact on their prealbumin. A bar graph illustration of cases and controls prealbumin is shown on Figure 23.

Figure 23: The bar chart showing prealbumin levels (g/L) at baseline and at the end of treatment for cases and controls
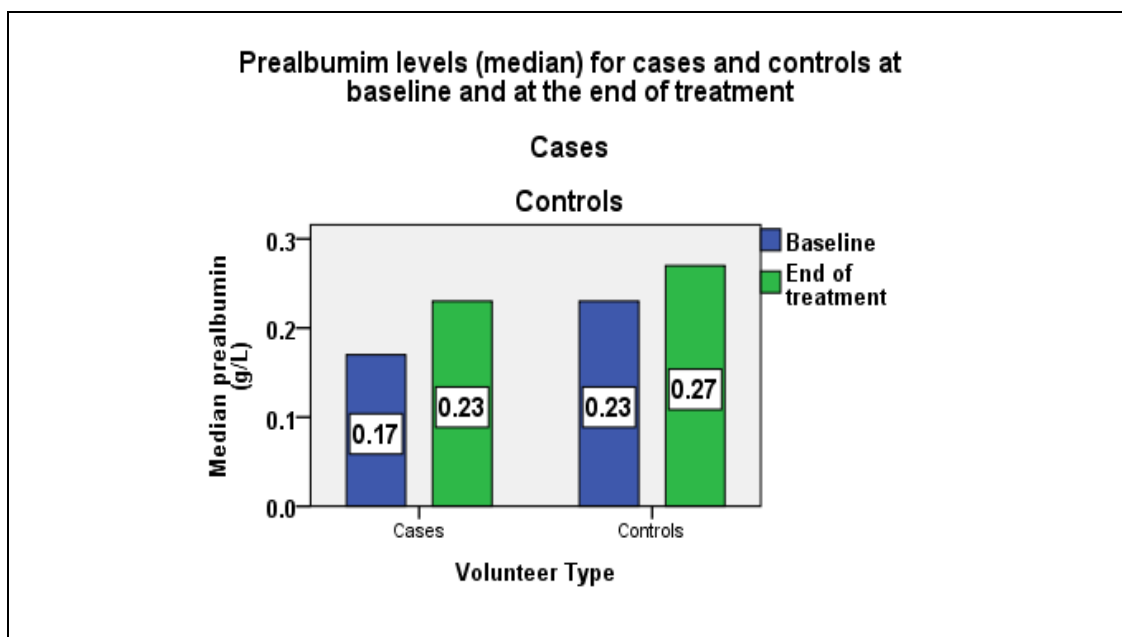
The median prealbumin for cases at baseline was 0.17 (IQR: 0.14-.-0.24), shown in Table 18. The related samples Wilcoxon Signed Rant Test showed a significant increase, ($p < .01$) between baseline and end of treatment to 0.23 (IQR: 0.20-.029). The Independent samples test also showed a significant difference between baseline cases and controls' prealbumin, $p < .05$. No significant differences were found between case and controls at the end of treatment, $p > .05$. The Kruskal Wallis test showed prealbumin to be associated with the stage of disease, presence of ascites and swelling/distension at baseline, $p < .01$ in all instances. A change in eating habits prior to treatment was associated with a low prealbumin Table 29. There was no correlation between prealbumin and eating habits at the end of treatment.

These findings suggest a direct and linear relationship between diet and prealbumin at baseline when women reported that their eating habits had changed the most. That pre-albumin was already affected by the time women presented to the hospital and had returned to normal in most cases by the end

of treatment despite residual disease in some women suggests that prealbumin reflects short-term nutritional changes.

5.4.2 Albumin

Albumin was not routinely assessed in patients undergoing surgery where cancer was not suspected. Albumin values for this study were extracted from electronic patient records and are therefore not available for controls. A cut-off point of 36g/L in line with local clinical guidelines was adopted. The descriptive analysis for albumin is shown on Table 20 and the classification in Table 21.

Table 20: The descriptive analysis of albumin at baseline and at the end of treatment for cases

		Baseline	End of treatment
N	Valid	56	46
	Missing	2	12
Mean		40.7	44.2
Median		42.0	45.0
Std. Deviation		6.71	5.49
Minimum		21.0	27.0
Maximum		53.0	61.0
Percentiles	25	36.0	41.0
	50	42.0	45.0
	75	46.8	48.0

Table 21: The classification of cases by the level of albumin at baseline and end of treatment

	Baseline N (%)	End of treatment N (%)
Missing	2 (3%)	12 (21%)
Low (< 36g/L)	11 (19%)	2 (3%)
Low Normal (36-39 g/L)	14 (24%)	5 (9%)
Normal (> 40g/L)	31 (53%)	39 (67%)
Total (N)	**58**	**58**

The median albumin at baseline was within the normal range, 42 (IQR: 36-47), shown in Table 20. However, nineteen percent of cases had a clinically low albumin while 14% had borderline normal albumin, as shown in Table 21. There was a strong association (Kruskal Wallis test) between presence of ascites and low albumin, $p < .01$, with all 19% of cases with low albumin having ascites. Only 3% of cases had a low albumin at the end of treatment despite residual disease in some women. The majority of cases 67% had a normal albumin at the end of treatment. The Wilcoxon Signed Rank Test showed a significant difference between baseline and end of treatment albumin, $p < .01$.

A bar graph illustrating the level of albumin by type of first treatment for cases is shown in Figure 24. This graph shows that albumin was lower at baseline and at the end of treatment in cases treated with chemotherapy alone or followed by surgery compared to those who were treated with surgery alone or followed by chemotherapy.

Figure 24: The bar chart showing albumin levels (g/L) for cases by type of first treatment at baseline and at the end of treatment
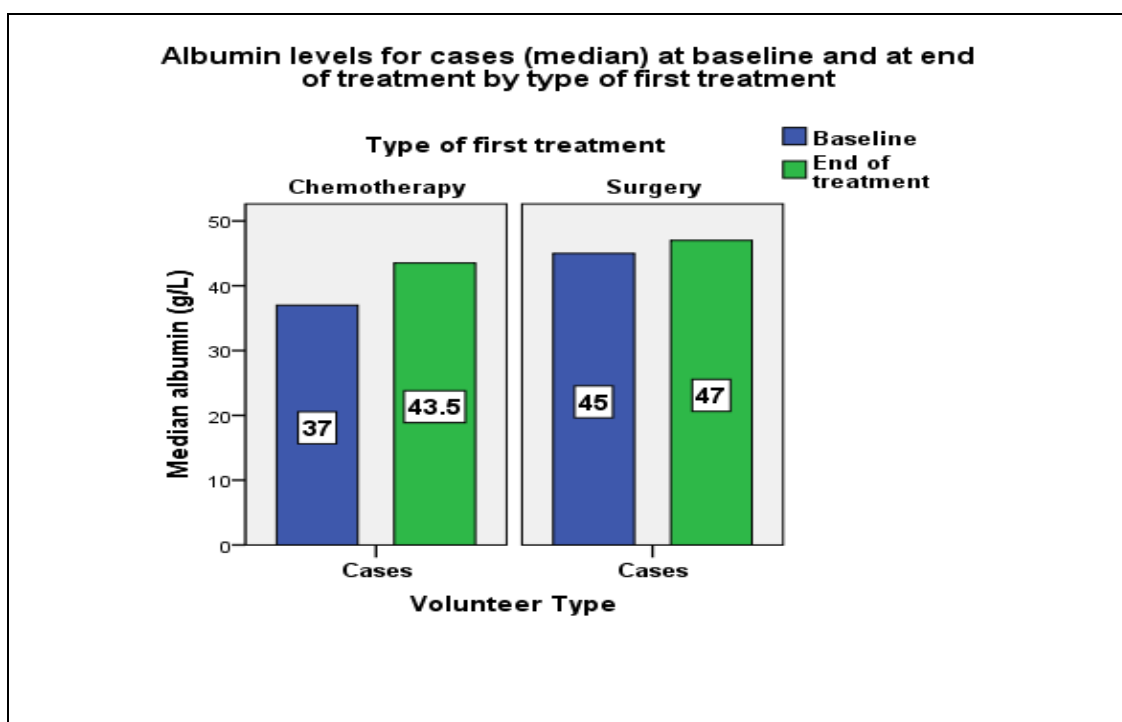
Ascites, swelling and changes in eating habits were associated with low albumin at baseline, as was shown in Table 10. A calculation of odds ratios showed that women who gained weight during treatment were 3.3 times more likely to have increased albumin compared to those who lost weight. Spearman's correlations showed that albumin positively correlated with health status (r = 0.440; $p < .01$) shown in Table 35.

The findings about albumin, ascites and swelling were expected since albumin is a measure of well-being. However additional findings that changes in eating habits are associated with a low albumin show that food intake correlates with biochemical changes in the body. Loss of weight shown by a decrease in BMI is associated with being unwell and low overall health status.

5.4.3 C - reactive protein (CRP) with normal range <10mg/L

Normal concentration levels of CRP in healthy human serum is between 5 and 10 mg/L. The descriptive analysis of cases' CRP at baseline and at the end of treatment is shown in Table 22 and the classification of cases by CRP level is shown in Table 23.

Table 22: The descriptive analysis of C-reactive protein (CRP) at baseline and at the end of treatment for cases

		Baseline	End of treatment
N	Valid	51	46
	Missing	8	13
Mean		57.9	35.8
Median		47.5	12.6
Std. Deviation		61.47	53.59
Minimum		0.60	0.60
Maximum		347.1	188.5
Percentiles	25	10.2	1.38
	50	47.5	12.6
	75	86.5	49.8

Table 23: The classification of cases by the level of C-reactive protein (CRP) at baseline and at the end of treatment.

	Baseline (%)	End of treatment (%)
Missing	7 (12%)	12 (21%)
Normal	12 (21%)	22 (38%)
Elevated	39 (67%)	24 (41%)
Total (N)	**58**	**58**

Sixty seven percent of cases had elevated CRP at baseline compared to only 21% who had a normal CRP as shown in Table 23. The percentage of women with normal CRP increased to 38 by the end of treatment. CRP decreased from a median of 47.5 (IQR: 10.2-86.5) at baseline decreased to 12.6 (IQR: 1.38 - 49.8) at the end of treatment. The Wilcoxon Signed Rank test showed these differences to be statistically significant, $p < .05$.

The bar graphs showing the levels of CRP in cases are shown in Figure 25. CRP was more elevated in cases with advanced disease (Stages 3 & 4) that in women with early stage disease (one woman with stage 2 disease was included with those with stage I disease). CRP was also elevated in cases that were treated with chemotherapy first.

Figure 25: The bar graph showing C-reactive protein (CRP) by stage of disease and type of first treatment at baseline and at the end of treatment for cases
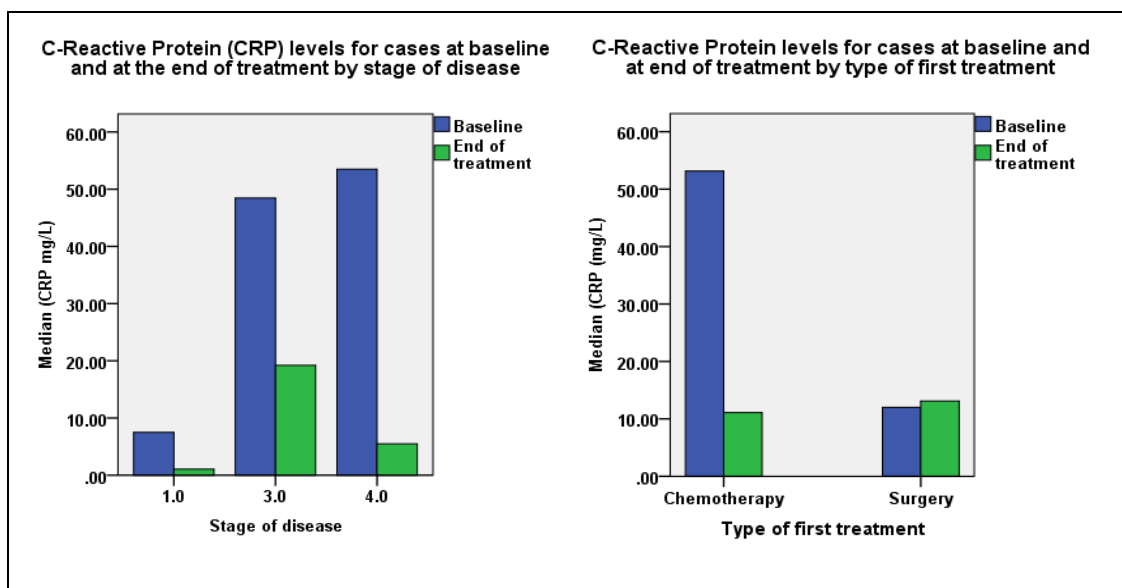
No significant associtaions were found between CRP and symptoms at baseline, or any correlation with other outcomes. This suggests that an elevated CRP, an indicatior of inflammation reflects the presence of cancer and is not dependent of stage, or presence of other symptions.

5.4.4 CA-125

CA125 is a useful tool for detecting ovarian cancer following an onset of symptoms. But it is also important for monitoring the response to treatment and for predicting a patient's prognosis after treatment. The clinical cut off points are 35u/L. It is used in this study to differentiate between women with no clinical evidence of disease and those with residual or progressing disease at the end of treatment.

Figure 26: The bar chart showing CA125 at baseline, during treatment   and at the end of treatment for cases
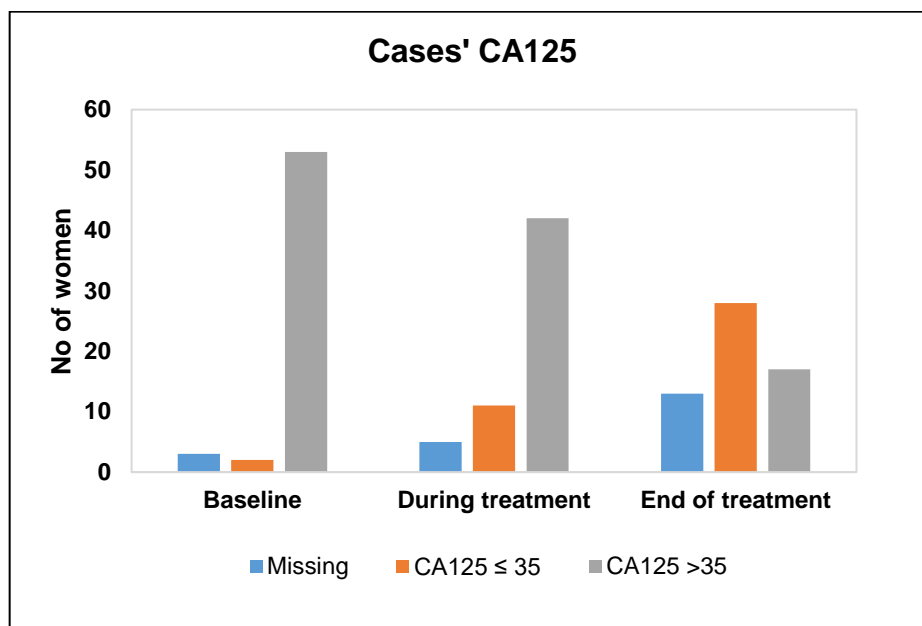
The above graph shows that 53/58 (91%) of all cases had an elevated CA125 at baseline. Seventeen women had elevated CA125 at the end of treatment. This implies that they had residual or recurrent disease. CA125 was shown to be associated the stage of disease, $p < .05$, the presence of ascites, $p < .05$ shown as shown in Table 25. Baseline CA125 also significantly but negatively correlated with prealbumin, $p < .01$ and albumin, $p < .05$. There was a borderline positive correlation with extracellular body water, $p = .07$, confirming the link between ascites and CA125, shown in Table 26. Women with an elevated CA125 at the end of primary treatment should be targeted for nutritional intervention as they are likely to require further treatment in the near future.

Table 24: Odds ratios (cases only)

Variable/ Outcome	Weight Gain/loss	BMI Gain/Loss	Body Fat Gain/Loss	Prealbumin Gain/Loss	Albumin Gain/Loss	Dry lean mass Gain/Loss
Weight	OR= 0.505 pv= 0.1 CI=[0.221 - 1.132]	OR= 0.423 pv= 0.049 CI=[0.176 - 0.985]	OR= 1.091 pv= 0.863 CI=[0.404 - 2.95]	OR= 0.846 pv= 0.773 CI=[0.269 - 2.659]	OR= 0.711 pv= 0.45 CI=[0.291 - 1.721]	OR= 0.283 pv= 0.021 CI=[0.093 - 0.802]
BMI	OR= 0.574 pv= 0.181 CI=[0.252 - 1.289]		OR= 0.462 pv= 0.134 CI=[0.163 - 1.251]	OR= 0.958 pv= 0.941 CI=[0.304 - 3.02]	OR= 0.895 pv= 0.814 CI=[0.353 - 2.257]	OR= 0.251 pv= 0.012 CI=[0.082 - 0.716]
Body fat	OR= 0.545 pv= 0.181 CI=[0.221 - 1.317]	OR= 0.429 pv= 0.07 CI=[0.168 - 1.06]		OR= 1.768 pv= 0.382 CI=[0.501 - 6.745]	OR= 1.236 pv= 0.676 CI=[0.458 - 3.38]	OR= 0.446 pv= 0.125 CI=[0.155 - 1.236]
Dry lean	OR= 0.28 pv= 0.008 CI=[0.107 - 0.699]	OR= 0.421 pv= 0.067 CI=[0.163 - 1.051]	OR= 0.48 pv= 0.156 CI=[0.169 - 1.305]	OR= 0.814 pv= 0.749 CI=[0.224 - 2.884]	OR= 1.243 pv= 0.673 CI=[0.454 - 3.475]	
Prealbumin	OR= 1.941 pv= 0.146 CI=[0.799 - 4.821]	OR= 2.186 pv= 0.106 CI=[0.854 - 5.741]	OR= 1.54 pv= 0.434 CI=[0.522 - 4.622]		OR= 0.915 pv= 0.863 CI=[0.332 - 2.553]	OR= 1.189 pv= 0.762 CI=[0.385 - 3.679]
Albumin	OR= 3.294 pv= 0.008 CI=[1.387 - 8.128]	OR= 2.987 pv= 0.017 CI=[1.232 - 7.506]	OR= 0.983 pv= 0.974 CI=[0.346 - 2.753]	OR= 1.4 pv= 0.601 CI=[0.403 - 5.254]		OR= 1.417 pv= 0.514 CI=[0.498 - 4.091]
Health status	OR= 2.485 pv= 0.069 CI=[0.942 - 6.796]	OR= 2.864 pv= 0.046 CI=[1.037 - 8.275]	OR= 1.371 pv= 0.613 CI=[0.402 - 4.779]	OR= 2.596 pv= 0.179 CI=[0.674 - 11.485]	OR= 0.54 pv= 0.272 CI=[0.174 - 1.603]	OR= 1.083 pv= 0.894 CI=[0.332 - 3.551]

Variable /Outcome >median =1, median < =0
Change: Gain = 1, Loss = 0
Grey is significant, Blue is borderline significant

Table 25: The Kruskal Wallis test of association between nutritional, well-being and cancer outcomes with symptoms at baseline for cases

	Weight	BMI	Body fat	Lean mass	Dry lean mass	Extracellular water	Total body water	Prealbumin	Albumin	CRP	CA125
Stage (grouped into early (1) and late (2)											
Chi-Square	2.055	1.239	.008	.008	3.864	.983	.350	10.013	2.885	1.327	5.771
df	1	1	1	1	1	1	1	1	1	1	1
Asymp. Sig.	.152	.266	.931	.931	**.049**	.321	.554	**.002**	.089	.249	**.016**
Pain/discomfort (grouped into no (0) and yes (1)											
Chi-Square	.749	.590	1.616	1.616	.239	.508	1.345	.117	.010	.223	.222
df	1	1	1	1	1	1	1	1	1	1	1
Asymp. Sig.	.387	.442	.204	.204	.625	.476	.246	.733	.921	.637	.637
Swelling and distension (grouped into no (0) and yes (1)											
Chi-Square	1.068	.208	.005	.005	.101	.261	.069	15.567	5.866	1.468	.327
df	1	1	1	1	1	1	1	1	1	1	1
Asymp. Sig.	.301	.649	.945	.945	.751	.609	.793	**.000**	**.015**	.226	.568
Ascites (grouped into no (0) and yes (1)											
Chi-Square	1.151	.903	.016	.016	.158	.136	.010	15.724	21.309	1.422	4.520
df	1	1	1	1	1	1	1	1	1	1	1
Asymp. Sig.	.283	.342	.898	.898	.691	.712	.921	**.000**	**.000**	.233	**.033**

Table 26: Spearman's correlations between all baseline outcomes in cases.

			AGE	Baseline weight	Baseline body fat	Baseline Lean mass	Baseline dry lean mass	Baseline BMI	Baseline extracellular water	Baseline Total body water	Baseline CA125	Baseline prealbumin	Baseline albumin	Baseline CRP
Spearman's rho	AGE	Correlation Coefficient	1.000	.143	.371*	-.371*	-.540**	.297	-.100	-.162	-.172	-.007	-.054	.072
		Sig. (1-tailed)	.	.243	**.031**	**.031**	**.002**	**.070**	.314	.214	.200	.487	.396	.364
	Baseline weight	Correlation Coefficient	.143	1.000	.814**	-.814**	.592**	.925**	-.834**	-.883**	-.273	.062	-.057	-.028
		Sig. (1-tailed)	.243	.	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.088**	.382	.392	.447
	Baseline body fat	Correlation Coefficient	.371*	.814**	1.000	-1.000**	.146	.897**	-.848**	-.928**	-.228	-.126	-.123	.175
		Sig. (1-tailed)	**.031**	**.000**	.	.	.239	**.000**	**.000**	**.000**	.132	.270	.274	.196
	Baseline lean mass	Correlation Coefficient	-.371*	-.814**	-1.000**	1.000	-.146	-.897**	.848**	.928**	.228	.126	.123	-.175
		Sig. (1-tailed)	**.031**	**.000**	.	.	.239	**.000**	**.000**	**.000**	.132	.270	.274	.196

			AGE	Baseline weight	Baseline body fat	Baseline Lean mass	Baseline dry lean mass	Baseline BMI	Baseline extracellular water	Baseline Total body water	Baseline CA125	Baseline prealbumin	Baseline albumin	Baseline CRP
Baseline dry lean mass	Correlation Coefficient		-.540**	.592**	.146	-.146	1.000	.305	-.442*	-.402*	-.084	.150	-.022	-.286
	Sig. (1-tailed)		**.002**	**.001**	.239	.239	.	**.065**	**.012**	**.021**	.341	.233	.457	**.079**
Baseline BMI	Correlation Coefficient		.297	.925**	.897**	-.897**	.305	1.000	-.807**	-.875**	-.290	-.005	-.033	.070
	Sig. (1-tailed)		**.070**	**.000**	**.000**	**.000**	**.065**	.	**.000**	**.000**	**.075**	.491	.436	.366
Baseline extracellular water	Correlation Coefficient		-.100	-.834**	-.848**	.848**	-.442*	-.807**	1.000	.959**	.294	.028	.126	-.042
	Sig. (1-tailed)		.314	**.000**	**.000**	**.000**	**.012**	**.000**	.	**.000**	**.072**	.446	.270	.419
Baseline total body water	Correlation Coefficient		-.162	-.883**	-.928**	.928**	-.402*	-.875**	.959**	1.000	.212	.060	.146	-.086
	Sig. (1-tailed)		.214	**.000**	**.000**	**.000**	**.021**	**.000**	**.000**	.	.149	.385	.238	.339
Baseline CA125	Correlation Coefficient		-.172	-.273	-.228	.228	-.084	-.290	.294	.212	1.000	-.446*	-.338*	-.021
	Sig. (1-tailed)		.200	.088	.132	.132	.341	**.075**	**.072**	.149	.	**.011**	**.046**	.459

		AGE	Baseline weight	Baseline body fat	Baseline Lean mass	Baseline dry lean mass	Baseline BMI	Baseline extracellular water	Baseline Total body water	Baseline CA125	Baseline prealbumin	Baseline albumin	Baseline CRP
Baseline prealbumin	Correlation Coefficient	-.007	.062	-.126	.126	.150	-.005	.028	.060	-.446*	1.000	.727**	-.248
	Sig. (1-tailed)	.487	.382	.270	.270	.233	.491	.446	.385	**.011**	.	**.000**	.111
Baseline albumin	Correlation Coefficient	-.054	-.057	-.123	.123	-.022	-.033	.126	.146	-.338*	.727**	1.000	-.182
	Sig. (1-tailed)	.396	.392	.274	.274	.457	.436	.270	.238	**.046**	**.000**	.	.187
Baseline CRP	Correlation Coefficient	.072	-.028	.175	-.175	-.286	.070	-.042	-.086	-.021	-.248	-.182	1.000
	Sig. (1-tailed)	.364	.447	.196	.196	**.079**	.366	.419	.339	.459	.111	.187	.

*. Correlation is significant at the .05 level (1-tailed).
**. Correlation is significant at the 0.01 level (1-tailed).

5.5 Section D: Dietary analysis

This section presents findings on changes to diet and food intake habits of women diagnosed with ovarian cancer. These changes relate to the period starting 3 months prior to baseline assessment to the end of treatment. The results are presented for two periods, baseline and from baseline to the end of treatment. Findings are presented on the specific diet changes, the reasons and rationale for the change, current practice on nutritional/dietary support as well as women's suggestions for an ideal future intervention. Associations between changes in diet and nutritional status are also presented. The relationship between current intervention/support and nutritional status is outlined. Suggestions for a potential future intervention package are also presented.

5.5.1 The specific changes made to diet

The majority of women, 32/47 (68%), who completed the baseline study questionnaire indicated that they changed their diet prior to treatment and/or confirmed diagnosis. Eighteen of 38 (47%) women who completed the end of treatment questionnaire said they had never received any nutritional advice/intervention from the clinical team. Five of 38 women at the end of treatment did not answer the question on diet change. The specific diet changes and the number of women who made those changes are shown in Table 27.

Table 27: The specific dietary changes made prior to treatment and during the period of treatment

Foods that were preferred	Baseline N (%)	End of treatment N (%)	Foods that were avoided	Baseline N (%)	End of treatment N (%)
Fruit and vegetables	8	1	Sweet foods	7	4
Small amounts of everything	8	1	Red meat	7	4
White meat/fish	4	2	Processed food	2	4
Flax seed Diet/Budwig	2	0	Alcohol	1	0
More of everything	1	2	Hard to swallow food	1	0
Green tea	1	0	Peanuts	1	0
Strong flavoured food	1	0	Acidy food	1	0
Became vegetarian	1	2	Heavy foods e.g. pies and steak	1	0
Soft food	1	1	Raw foods/nuts	0	1
Sweet foods	0	2	Bland foods	0	1
Full fat milk, cheese	0	3	Spicy food	1	0
Dried fruit	0	1	Tea/coffee	0	3
Fried food	0	1	Dairy	0	1
Orange juice	0	1	Poultry	0	1
Brown/whole meal bread	1	0	Salt	0	1
Not stated	4	6	Packed juice	0	1
			Not stated	3	6
Women who made diet changes	**32**	**19**		**32**	**19**

The sums of the columns may not add up to the total number of women who made changes because some women did not provide information on the changes made while some made more than one change

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Of those women who made changes between baseline and end of treatment, 8/38 (21%) reported only being able to tolerate small amounts of food at a time. A similar number said they ate more fresh fruit and vegetables. Eating only white meat and fish and following the Budwig or Flax seed diet were also some of the changes made. The flaxseed oil and cottage cheese based diet is designed to correct the Deoxyribonucleic Acid (DNA) so that it starts to produce healthy cells (318). No obvious food preferences stood out during the treatment period. Women reported eating more of everything, full fat foods, vegetarian diets and sometimes more sweets. Sweet or sugary foods, red meat and processed foods were more likely to be avoided at both time points. The tendency to prefer eating healthy foods that women reported before treatment could be true of be affected by an "intention to please", with participants reluctant to report consumption of foods known to be unhealthy (319). Self-reported dietary studies have been shown to under-report true habitual food intake with people changing their diet during the period of the survey (320). Women may have intended to 'eat healthy' in the face a cancer diagnosis but the intention to consume a healthy diet is not always a proxy for intake (321). It is not possible to verify or counter women's statements from our data, however, the qualitative data from focus group discussions (chapter 8, Theme 2) revealed a similar trend. Women revealed that they had greater determination to 'eat healthy' earlier in their cancer journey. Their best intentions were often hampered by the difficulty in sustaining the motivation to continue with diets faced with negative effects of chemotherapy, the need to satisfy cravings and an increased appetite said to be due to the chemotherapy. The latter led them to consume sweet and rich foods even against their better judgement.

5.5.2 The reasons and rationale given by women for changing their diet

The reasons and rationale given by women for changing their diet are outlined in Table 28. The most common reason given for changing diet prior to treatment was loss of appetite 10/47 (21%). Anxiety about a possible/confirmed cancer diagnosis was the second most common reason 7/47 (15%) that affected eating

habits at baseline. Other reasons included swelling of the abdomen making eating uncomfortable, bloating or feeling full too quickly. Some of these reasons such as swelling of the abdomen explain why many women reported being able to eat only small amounts of food at a time. They also indicate why maintaining sufficient food intake is often a problem for some women.

Table 28: The reasons given by women for changing their diet at baseline and during the treatment period

	No of patients	
	Baseline N (%)	**End of treatment N (%)**
No of women who completed questionnaire out of the total of 58	47 (81%)	38 (65%)
No of women who changed their diet	32 (68%)	21 (55%)
Reasons for change in diet		
Loss of appetite	10 (21%)	5 (13%)
Anxiety about a cancer diagnosis	7 (15%)	1 (3%)
Swelling of abdomen	6 (13%)	0 (0%)
Bloating/feeling full quickly	5 (11%)	0 (0%)
Too unwell	3 (6%)	1 (3%)
Change in taste	2 (4%)	16 (42%)
Pain	2 (4%)	0 (0%)
Difficulty swallowing	1 (257)	0 (0%)
Nausea/vomiting	1 (257)	0 (0%)
To put on weight	1 (257)	1 (3%)
Increased appetite	0 (0%)	2 (5%)
Change in sense of smell	0 (0%)	2 (5%)
To increase platelet count	0 (0%)	1 (3%)
To boost immune system	0 (0%)	1 (3%)
Want to eat healthy	0 (0%)	1 (3%)
Women who gave more than one reason	5 (11%)	7 (18%)
Women who did not give a reason	2 (4%)	0 (0%)

The sum of the responses does not correspond to the number of women because some gave more than one reason and some no reason

The reasons given for changing diet during treatment appeared to be different from those given prior to treatment. The most common reason, given by 16/38 (42%) of women who changed their diet during the treatment period was a change in the taste of food. Women attributed this change in test to the effect of chemotherapy treatment. Therapeutic reasons such as eating foods that could raise platelet count or build the immune system or to gain weight were also reported. The cancer trajectory seemed to influence the rationale for modifying diet. These results suggest that changes to diet were made in response to symptoms, treatment side effects and perceived physiological need.

Although change in taste was reported by 17/47 (36%) at baseline, only 2 attributed their diet choices to it as shown in Table 28. Similarly 8 and 11 women reported changes in smell prior to and during treatment respectively, yet only 2 reported that it affected their diet choices. This implies that the impact of some symptoms may vary by time point, i.e. prior to treatment versus during the treatment. The reporting of the impact seems to depend on whether the symptom is caused by the disease or by treatment or whether there are other more distressing symptoms or side effects at the time. Symptoms such as abdominal swelling, anxiety about a cancer diagnosis and bloating were no longer reported by the end of treatment. During this time change in taste was reported as affecting diet choices the most.

Although few women reported positive diet changes such as eating to put on weight and to be healthy etc., the reasons given for diet and eating habit change largely indicate that a diagnosis of ovarian cancer has a negative impact on food intake. Food intake was affected prior to presentation to the hospital and this continued throughout treatment for some women. The major drivers of diet change prior to treatment were symptoms such as loss of appetite, anxiety about a cancer diagnosis, discomfort due to abdominal distension or swelling and bloating or feeling full too quickly. Pain was rarely mentioned as a contributor. Women often made independent decisions on food choices particularly before treatment when most had not received any advice or treatment. Increased fruit

and vegetable intake and elimination of sweet and sugary foods were the most common choices. Changes in diet were not attributed to a change in sense of smell, even though the latter was common prior to and during treatment. The effect of positive eating is difficult to assess because of the small number of women who reported it.

5.5.3 The relationship between dietary changes and nutritional and well-being outcomes

5.5.3.1 Baseline

Table 29 shows the characteristics of women who reported making changes to their diet versus those who did not in the phase prior to treatment. The Kruskal-Wallis test was used to analyse differences between groups. No significant association was observed with the level of education between who reported making dietary changes and those who did not ($p > .05$). There was a significant difference ($p < .01$) by stage of disease, (early stage I & II versus late stage III & IV). Eighty five percent of women who made dietary changes had late stage disease. Significantly more women in the group that changed their diet experienced a change in taste ($p < .05$). No significant differences were observed in the change in smell, $p > .05$. Diet change was not attributed to either change in smell or taste prior to treatment. Significantly more women ($p < .01$) with ascites at baseline were in the group that changed their diet. Dietary changes were not associated with abdominal swelling, pain and nausea/vomiting were not different between the groups. There was significant association between changes in diet at baseline with treatment with neo-adjuvant chemotherapy, $p < .05$.

Table 29: The characteristics of women who made dietary changes prior to treatment versus those who did not

Characteristics	Made changes to diet	
	Yes N (%)	No N (%)
N (%) of a total of 58 cases	32 (55%)	15 (26%)
Median age (range)	61 (36-88)	57 (40-82)
Education		
Below O level	5 16%)	3 (20%)
O level	4 (13%)	5 (33%)
A level/professional qualification	8 (25%)	3 (20%)
University degree	9 (28%)	4 (27%)
Education unknown	5 (16%)	0 (0%)
Treatment**		
Surgery $\pm$ chemotherapy	11 (34%)	12 (80%)
Chemotherapy $\pm$ surgery	20 (63)	3 (20%)
Other (no treatment)	1 (3%)	-
Change in taste and smell		
Change in taste**	14 (44%)	3 (20%)
Change in smell	7 (22%)	1 7%)
Stage**		
1	2 (6%)	6 (40%)
2	1 (3%	0 (0%)
3	13 (41%)	6 (40%)
4	14 (44%)	2 (13%)
Not staged	0 (0%)	1 (7%)
Weight loss prior to baseline assessment		
Self-reported wt. loss	13 (41%)	4 (27%)
Self-reported wt. gain	6 (19%)	1 (7%)
Signs and symptoms at baseline		
Pain	17 (53%)	10 (67%)
Swelling	18 (56%)	5 (33%)
Ascites**	26 (81%)	6 (40%)
Nausea	12 (38%)	5 (33%)
Prealbumin (16mg/dl <)**	14 (44%)	1 (7%)
Albumin (36g/l <) **	7 (22%)	0 (%)
Median health status (range)**	50 (10 - 82)	80 (40 - 100)

**Significant difference observed between those who reported a change in eating habits and those who did not (Kruskal Wallis test) ($p < .05$)

Table 29 above shows that low prealbumin and albumin were significantly associated with reporting making changes to diet at baseline ($p < .01$) and ($p < .05$) respectively. Women who reported not making changes to their diet had significantly higher health status scores at baseline, $p < .01$. This association is important as it shows that those who felt the need to change their diet also felt that they had a lower quality of life. Weight, BMI, body fat, dry lean mass and lean mass were not significantly different between the two groups. It is possible that the non-significant difference in weight is due to a cancelling effect as some women gained and others lost weight. The weight gained would not have been healthy weight but ascites. This is supported by that women who reported weight gain and those who reported weight loss at baseline both reported making changes to their diet.

5.5.3.2 During treatment

Twenty on of 38 women (55%) who completed the end of treatment questionnaire reported making changes to their diet during the treatment period. The comparison of nutritional and well-being outcomes between those who made changes and those who did not are shown in Table 30. The Kruskal Wallis test showed no significant differences between making changes and age, stage of disease, education and marital status. Changes in the taste and smell of food were both significantly different between the groups ($p < .01$ and $p < .01$) respectively. However only changes in taste were reported to affect diet/food intake (all sixteen women). Only 2 women reported that their diet was affected by changes in the smell of food. Four women expressed that they thought the changes in taste were due to chemotherapy.

Table 30: The characteristics of women who made dietary changes during the treatment period versus those who did not

Characteristics	Reported of a change in eating habits	
	Yes	No
N (%) of a total of 58 cases	21 (36%)	12 (21%)
Median age (range)	62 (50 - 81)	56 (38 - 82)
Education		
Below O Level	3 (14%)	1 (8%)
O Level	2 (9%)	5 (42%)
A level/professional qualification	5 (23%)	0 (0%)
University degree	7 (32%)	4 (33%)
Education not stated	5 (0%)	2 (17%)
Symptoms		
Change in taste	16 (73%)	2 (17%)
Change in smell	11 (50%)	0 (0%)
Weight **		
Stable	2 (9%)	0 (0%)
Loss $\geq$ 2%	12 (55%)	2 (17%)
Gain $\geq$ 2%	8 (36%)	10 (83%)
Dry lean mass**		
Stable	3 (14%)	1 (8%)
Gain $\leq$ 2%	4 (18%)	5 (42%)
Loss $\geq$ 2%	10 (45%)	2 (17%)
Missing values	5 (18%)	4 (33%)
Signs		
Prealbumin <16mg/l	3 (14%)	0 (0%)
Albumin < 36g/l	1 (5%)	0 (0%)
Median health status (range)	65 (20-100)	80 (50-100)
Death @ $3^1/_2$ years	8 (36%)	2 (17%)

**Significant difference observed between those who reported a change in eating habits and those who did not (Kruskal Wallis test) ($p < .05$)

Changing diet during the treatment period treatment was associated with a significant loss of weight ($p < .01$) and dry lean mass ($p < .05$). No significant associations were found with prealbumin, albumin and health status. However all women who had low prealbumin and or albumin at the end of treatment were in the group that changed their diet in the same phase. The decrease in dry lean mass and the fact that we found no correlation between dry lean and responders/non-responders to treatment (using CA125) supports its possible association with diet.

5.5.4 Women's experiences with nutritional support offered by the clinical team

Table 31 shows the responses given by women when they were asked, in questions 2.17 to 2.26 of the study specific questionnaire, if they had received nutritional intervention (information/advice, referral to a dietician, supplements); the adequacy of this and what if support anything women would have liked support throughout treatment. Fifteen of 38 (39%) of those who completed the end of treatment questionnaire had received some form of nutritional intervention. Four women had been referred to a dietician, 2 were counselled/advised, 1 was prescribed oral nutritional supplements prior to treatment while another received intravenous (230) nutrition following surgery. The other 11 remaining women had been given nutritional information/advice. A nurse, dietician, pharmacist or doctor delivered the intervention. All but one woman who received intervention found it to be helpful or somewhat helpful. It served to support, reassure, encourage and create awareness of suitable foods to eat or avoid. Three women said that although the advice was helpful, it was not specific enough to meet all their needs. One woman felt that the intervention was not helpful as she was only given a generic Macmillan cancer support leaflet. Some women (7) went on to seek further information on their own initiative.

Table 31: A summary of the nutritional support provided by the clinical team throughout the course of the study

	Received nutrition information from clinical team		
	Yes **15**		**No** **17**
Who was information provided by	Ward sister, Macmillan nurse, pharmacist, doctor, dietician, chemotherapy nurse		N/A
Was the information helpful	**Yes** 14	**No** 1	N/A
How was information helpful/not helpful	• Provided support with eating appropriately to build strength for surgery • Created awareness of what to eat to help cope with treatment • Reassured patients that they were eating appropriately • Managed expectations of side effects of treatment • Helped to eat appropriately to maintain weight and to continue with chemotherapy • Encouraged to eat small amounts when there was loss of appetite • Helped with what foods to avoid • Provided with prescription for shakes and Ensure© (nutritional supplements) • Anchoring during a period of changing food habits	Given a Macmillan leaflet (leaflet not specified)	N/A

Nearly half of women, 18/38 (47%) who completed the questionnaire reported that they did not receive any nutritional intervention from the clinical team. Eight of these women went on to seek information on their own initiative. A Kruskal-Wallis test showed no significant difference ($p > .05$) in the ages of women who received or did not receive information and also those who sought or did not seek information on their own initiative. Those who sought further information, did so from the internet, Macmillan booklet, support group, family, a doctor and from other patients.

Reasons for seeking diet and nutrition information included wanting to know more about their condition, pressure from family to eat well, wanting to be healthy,

wanting to know if some foods make the cancer and wanting to cope with chemotherapy effects. One woman wanted reassurance that her diet was not contraindicated for her diagnosis. Some women did not seek further information because they felt reasonably well, or were eating well and felt confident that their routine diet met their needs. However, some women were disinclined to seek information independently because they were confused about their situation, were worried about treatment or simply just too caught up with their illness.

5.5.5 The impact of current practice on nutritional and well-being outcomes

The study explored whether women who received nutritional intervention or support had better nutrition outcomes. The Kruskal Wallis test showed no significant differences or associations in the baseline characteristics of women who received nutrition intervention and those who did not in terms of age, stage (early versus late), symptoms, albumin and prealbumin. Nor were any differences observed in weight, BMI, dry lean mass, lean mass, prealbumin, or health state at baseline and at the end of treatment. Table 32 below shows that a significant difference was observed only in the change in albumin, $p < .05$. Women who received intervention had a larger median increase (difference between baseline and end of treatment albumin level) compared to the group that did not.

Table 32: The relationship between current practice and nutritional status and well-being at the end of treatment

Characteristics	Reported that they received nutritional intervention	
	Yes	**No**
N (%) of a total of 58 cases	15 (26%)	18 (31%)
Median Age (range)	60 (46 - 75)	62 (38 - 82)
Stage		
1	4 (27%)	1 (5%)
2	1 (7%)	0 (0%)
3	7 (47%)	7 (37%)
4	3 (20%)	9 (47%)
Not staged	0 (0%)	1 (5%)
Nutritional and health status at the end of treatment		
Weight		
Stable	1 (7%)	1 (6%)
Weight loss $\geq$ 2%	6 (40%)	8 (44%)
Weight gain > 2%)	8 (53%)	10 (56%)
Prealbumin 16mg/l<	2 (13%)	1 (6%)
Albumin 36g/l <**	0 (0%)	1 (6%)
Health status median (range)	70 (33-100)	78 (20-100)
Death @ 31/2 years	5 (33%)	5 (28%)

**Significant difference observed between those who receiving intervention and those who did not (Kruskal Wallis test) ($p < .05$)

The results show that women were not routinely offered support by their clinical team. If offered, support was on an ad hoc basis and delivered by different members of the team. It is unclear who initiated discussion about nutrition (patient or clinician) or if any criteria were used to determine which women were to receive this intervention or what the desired outcomes were. Moreover the samples involved here are mall and may not have allowed subtle changes to be observed. These also become some of the reasons why a well desired clinical trial is needed.

5.5.6 Women's perspectives of an ideal nutritional intervention

Seventeen of 38 women (45%) who completed the end of treatment questionnaire gave their views of the type of support they would have like or if they received support whether this was adequate or not. Eight women were from

the group that received some intervention/support and nine from the group that did not. Table 33 the views of women on the intervention they received or would have liked to receive. Suggestions that were made for improvement of nutritional support included routine use of hand-outs as a basis for discussion, opportunities to talk over issues and not be told to eat anything, advice on diet to address specific needs such as a low platelet count. There were also suggestions to model the support on what patients have found helpful in other NHS requests to be referred to a dietician. These suggestions point to that some women are aware of services that could be available to them.

Table 33: The views of women of the support they received or would have liked to have received during the course of investigations and treatment

Women who did not receive information	Women who received information/support
Advice to improve platelets instead of niece seeking information	A simple pamphlet clearly marked out reasons why / why not certain foods are good / bad for people on chemotherapy. Clearly marked not vague
Suggestions on foods that help to combat cancer	The support provided was adequate (X3)
Information on foods to assist in recovery from treatment and nutrients to get energy levels back	Advice on which foods that are least likely to cause nausea during chemotherapy
Leaflets of examples of what one should 'try' and eat daily	Support provided was adequate, the main people supporting you always give time despite pressure of work
Referral to a dietician to made easy	I had a lot more information from the specialist nurse after a heart attack. They actually give patients a talk and leaflets, it's a model you may want to follow.
Talk over issues and not be constantly told eat 'anything' and all food is good at this time	I would have liked more information on specific foods that are useful to those recovering from ovarian cancer. Possibly a personal diet plan to improve my recovery
Recommend best diet, where to go for information and if there are any support groups within my area	
Give more information about diet, nutrition	
Give out information and discuss the issues and changes and advise what to eat.	

This chapter showed that women make changes to their diet even before they come into hospital for investigation/treatment of their cancer. The changes are largely based on symptom burden. Women continue to make changes throughout the course of treatment based on disease symptoms, treatment side effects and a desire to eat healthily. Changes to diet are associated with poor nutritional status (low pre-albumin), poor well-being (low albumin) and an overall lower quality of life (low health status) at baseline. Nutritional support is not offered routinely despite that women wish for it to be. There was no observable association between nutritional intervention with nutritional and well-being outcomes except for albumin. It is possible that a low albumin was the reason women were provided with nutritional intervention in the first instance. The suggestions for a future intervention are considered together with suggestions that emerged from focus group discussions in the next study, B. They are assimilated to make recommendations for a potential future intervention trial.

6 The observational study results Part 2 (Quality of life and summary of findings)

6.1 Introduction to chapter

This is the second of the observational study results chapters. Section A presents findings on the analysis of the Euroqol EQ-5D quality of life instrument. Results are presented on the two components of the instrument. The first, the EQ-5D consists of 5 domains/dimensions which are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The responses to the three levels of each dimension, (no problem, some/moderate problem and unable to/extreme problem) were reclassified into two categories of 'no problems' and 'problems', due to there being too few extreme problems. Cases are sub grouped by the median age of menopause for this study, 50. Comparisons of the prevalence of problems are made between cases and controls. The problems are analysed for association with nutritional status. The second component, the Visual Analogue Scale (EQ-VAS) provides a global assessment of each woman's perception of her health on a scale of 0-100 (worst imaginable health to best imaginable health). This is independent measure is used as a proxy for the overall quality of life. Correlations and associations between overall health status (quality of life) and nutritional status are reported for each time-point for cases and controls. Section B provides an overall summary of the findings from the observational study.

6.2 Section A: Quality of life findings

6.2.1 The proportion of cases reporting problems

The proportion of cases reporting problems for the EQ-5D dimensions at baseline, during treatment, and at the end of treatment are shown in Sub-grouping women by the age of menopause enabled identification of intergroup differences since ovarian cancer is predominantly a disease of menopausal women. A summary of the frequencies for each dimension and level is included in appendix 7

Figure 27: The bar chart showing the proportion of cases reporting problems for the EQ-5D dimensions at baseline, during treatment and at the end of treatment

Cases EQ-5D reported problems at baseline, during treatment and at the end of treatment

Legend:
- Baseline Premenopausal
- Baseline Menopausal
- During treatment Premenopausal
- During treatment Menopausal
- End of treatment Premenopausal
- End of treatment Menopausal
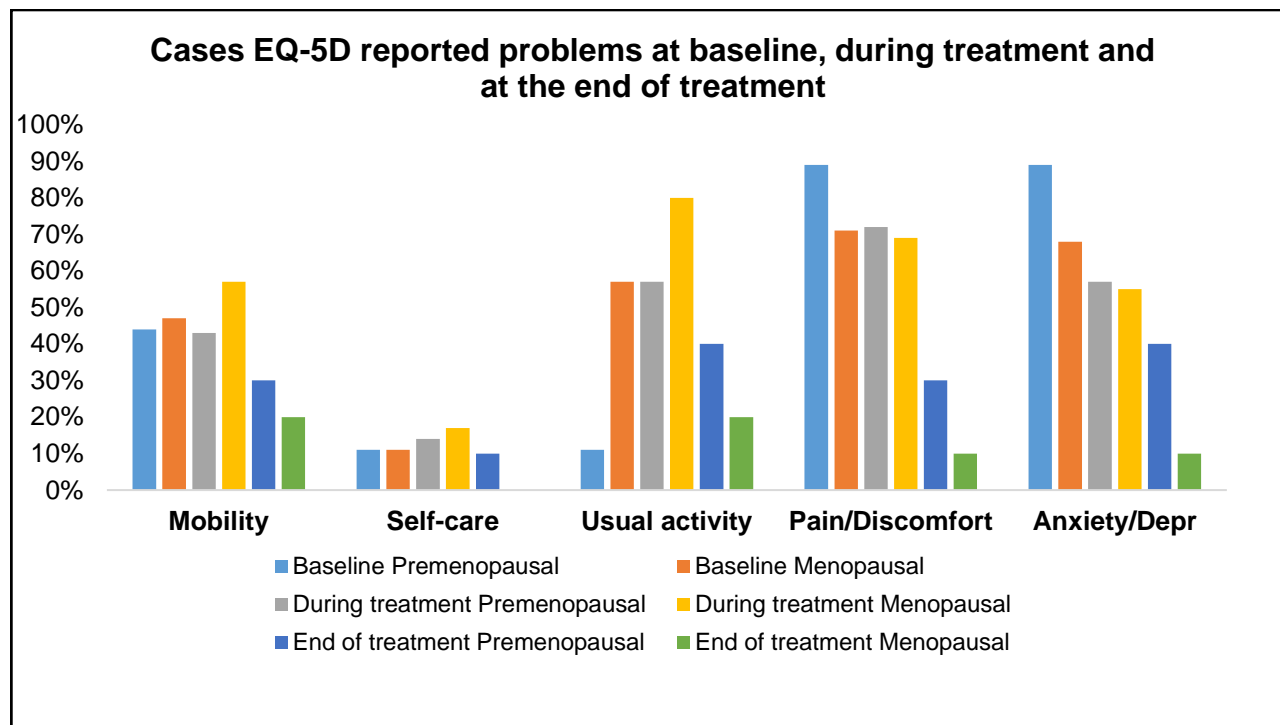
The above graph shows that self-care was the least reported problem in cases across all three time points. Between 40/58 (70%) and 52/58 (90%) of all women reported that they had no problem with their self-care at any given time. Mobility was reported as a problem by 3/7 (43%) of non-menopausal women and 18/38 (47%) of menopausal women at baseline. The frequency increased to 57% in menopausal cases during treatment, but decreased in both groups at end of treatment. Usual activity was a problem for older women particularly during treatment. They reported it at 57% at baseline, 80% during treatment and 47% at the end of treatment. Premenopausal women reported less of this problem rising only to rising 57% during treatment. The increase in mobility and self-care problems during treatment is likely to reflect the complex recovery process following major surgery and complications arising from the side-effects of chemotherapy treatment. Pain/discomfort and anxiety/depression were the most reported problems at baseline, and at the end of treatment. Premenopausal cases reported more problems with both dimensions than older women. They reported a pain/discomfort prevalence of between 60% and 89% across the three time points while older women reported between 50% and 71%. They also reported an anxiety/depression prevalence of 89%, 57% and 80% at baseline, during treatment and at the end of treatment respectively compared to 69%, 55% and 30% for menopausal women.

These findings suggest that a diagnosis of ovarian cancer affects all but one dimension of quality of life when measured using the EQ-5D instrument. Overall, the problems of self-care, pain/discomfort and anxiety/depression persisted to the end of treatment. Pain/ discomfort and anxiety/depression are known to negatively impact food intake and therefore nutritional status.

6.2.2 The proportion of controls reporting problems

The proportion of controls reporting problems for EQ-5D dimensions at baseline and end of treatment are shown in Figure 28. The proportions of controls in each dimension are outlined in appendix 7. Controls were not sub grouped due to the small sample size and an even smaller a number of menopausal women.

Figure 28: The bar chart showing the proportion of controls reporting problem for the EQ-5D dimensions at baseline and at the end of treatment
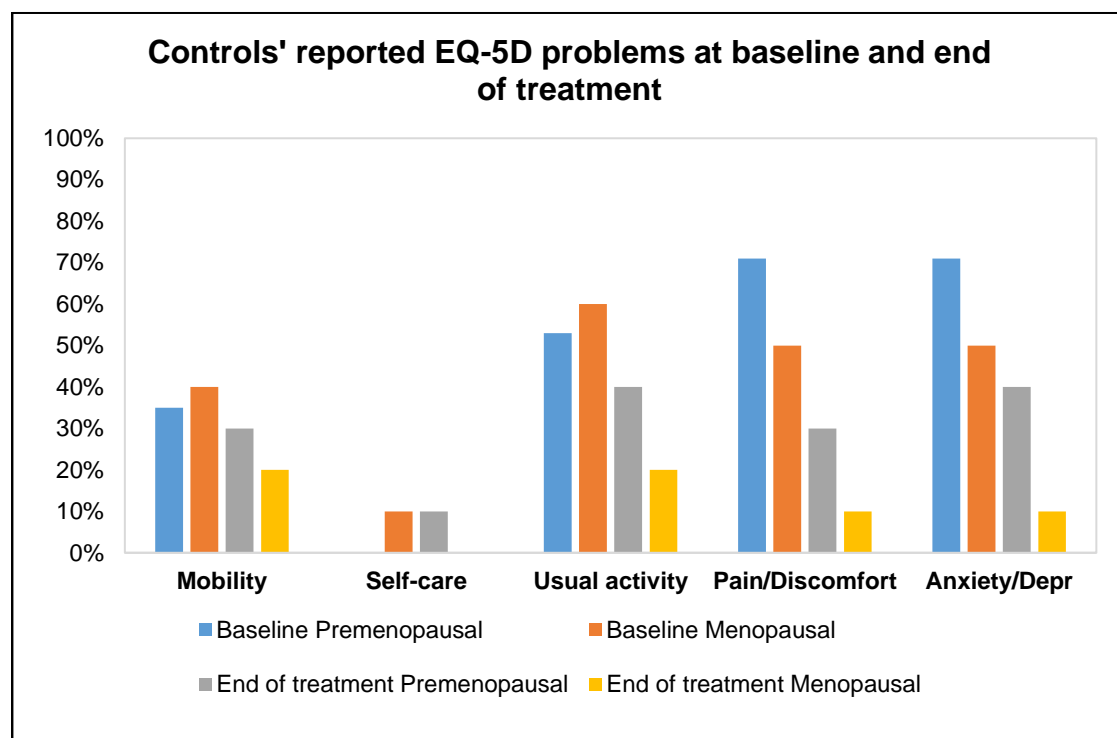
Self-care was again the least reported problem. It was not reported at baseline and was reported at 10% at the end of treatment. Mobility was a problem for 35% of women at baseline and 40% at the end of treatment. The most reported problems at baseline were usual activity at 53%, pain/discomfort at 71% and anxiety/depression at 71%. These problems persisted to the end of treatment, with usual activity reported at 60%, pain/discomfort at 50% and anxiety/depression at 50%. These findings suggest that women diagnosed with benign gynaecological diseases perceive the various domains of their quality of life to be affected similarly to women diagnosed with ovarian cancer. This would be expected pre-diagnosis.

6.2.3 The relationship between EQ-5D dimensions and nutritional status

The problematic dimensions of usual activity, pain/discomfort and anxiety/depression were analysed for association with nutritional and biochemical

outcomes at baseline using the Kruskal Wallis test. No association was found, $p > .05$ in all instances between all 5 dimensions with weight, BMI, body fat, lean mass, dry lean mass, albumin, CRP and CA125 for cases. There was a significant association between pain/discomfort and extracellular water, $p < .05$ and a borderline significance, $p = .06$ between pain/discomfort and total body water at baseline. Prealbumin was the only outcome to be significantly associated with difficulties with usual activity, $p < .05$ at baseline for cases. No significant associations were found with all dimensions and outcomes for controls. These findings suggest that women who had ascites were more likely to suffer from pain and discomfort. They also suggest that problems with various quality of life dimensions are independent of nutritional status with the exception of prealbumin which is associated with challenges in carrying out usual activities in cases.

6.2.4 Visual Analogue Scale (VAS)

A descriptive analysis of the perception of women's own health status using the Visual Analogue Scale (EQ VAS) is provided in Table 34. A wide range of scores were observed ranging from 0 (worst possible health) to 100 (best possible health) for cases and 3 – 95 for controls.

Table 34: The descriptive analysis of EQ VAS at baseline, during treatment and at the end of treatment for cases and controls

All Cases health status				
		Baseline	**During treatment**	**End of treatment**
N	Valid	46	37	25
	Missing	12	21	33
Median		50	57	70
Range		90	100	80
Minimum		10	0	20
Maximum		100	100	100
Cases treated with surgery ± chemotherapy				
N		20	20	10
Median		72.5	65	85
Range		70	100	55
Minimum		30	0	45
Maximum		100	100	100
Cases treated with chemotherapy ± surgery				
N		25	17	15
Median		50	60	70
Range		90	80	75
Minimum		10	20	20
Maximum		100	100	95
Menopausal cases				
N		37	30	20
Median		59	58	69
Range		90	100	80
Minimum		10	0	20
Maximum		100	100	100
Premenopausal cases				
N		9	7	5
Median		57	69	69
Range		85	45	20
Minimum		10	50	60
Maximum		95	95	80
All controls				
N	Valid	17	n/a	10
	Missing	10	n/a	17
Median		45	n/a	66
Range		92	n/a	85
Minimum		3	n/a	8
Maximum		95	n/a	93

6.3 Cases

The EQ-VAS frequencies at baseline, during treatment and end of treatment are also illustrated in graphs A, B and C of Figure 29. In graphs A and B, women are sub-grouped by the age of menopause. Only 5 non-menopausal women completed the end of treatment VAS. Sub-grouping could not be performed on this small sample size, hence only menopausal women are included in graph C.

Figure 29: The bar charts showing EQ VAS at baseline, during treatment and at the end of treatment by age of menopause for cases
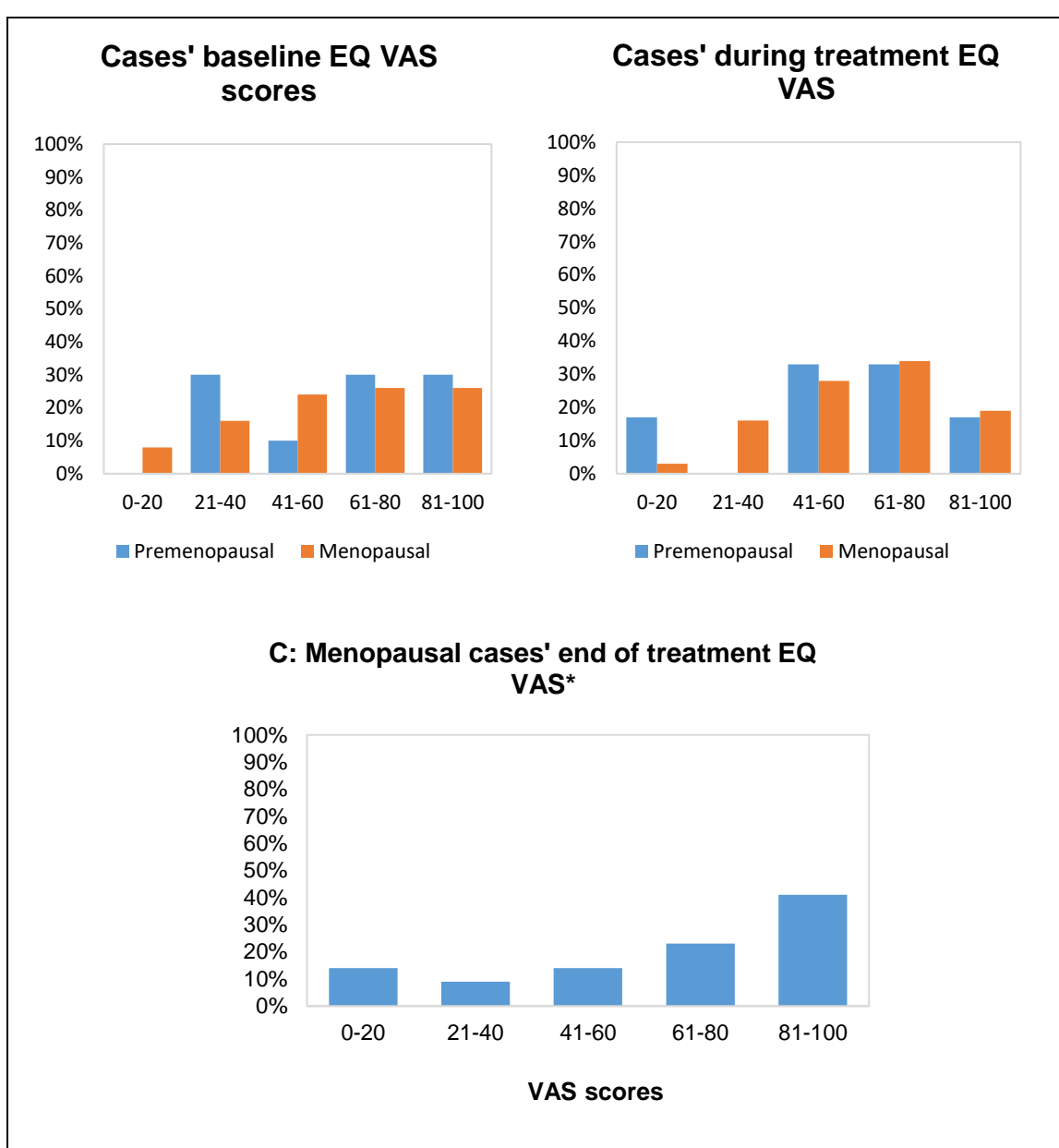
*Only 5 premenopausal cases completed the questionnaire; subgrouping therefore not possible

The median health status score improved progressively from 50 at baseline to 57 during treatment and 70 at the end of treatment. The Related-Samples Wilcoxon Signed Rank test showed no significant difference between baseline and the during treatment scores, $p > .05$. There was a significant increase between treatment and end of treatment, $p < .01$. There was also a significant overall increase from baseline to end of treatment, $p < .05$. These findings suggest that women did not perceive their overall health to improve immediately following surgery or their first chemotherapy cycle. This is probably due to that both treatments can have significant side effects and/or a difficult recovery phase. Although the end of treatment score of 70 suggests overall improvement in health status from baseline, some women did not complete the final questionnaire due to poor health and death. Thus the healthy volunteer effect may apply here.

The change in cases' VAS scores overtime, by age of menopause and type of first treatment are illustrated in Figure 30. This graph shows that younger women recorded the highest health status during treatment. Women treated with chemotherapy first had a constant increase in their health status from baseline to the end of treatment. The Kruskal Wallis test was used to further examine the relationship between baseline health status and stage of disease, type of first treatment and the presence of ascites at baseline treatment. There was no significant association between health status and the stage of disease $p > .05$. There was significant association between health status and the presence of ascites at baseline, $p < .05$. There was also a significant association between health status and type of first treatment, $p < .01$.

Figure 30: Multiple line graphs showing changes in EQ VAS median scores between baseline, during treatment and the end of treatment by menopausal status and type of first treatment for cases
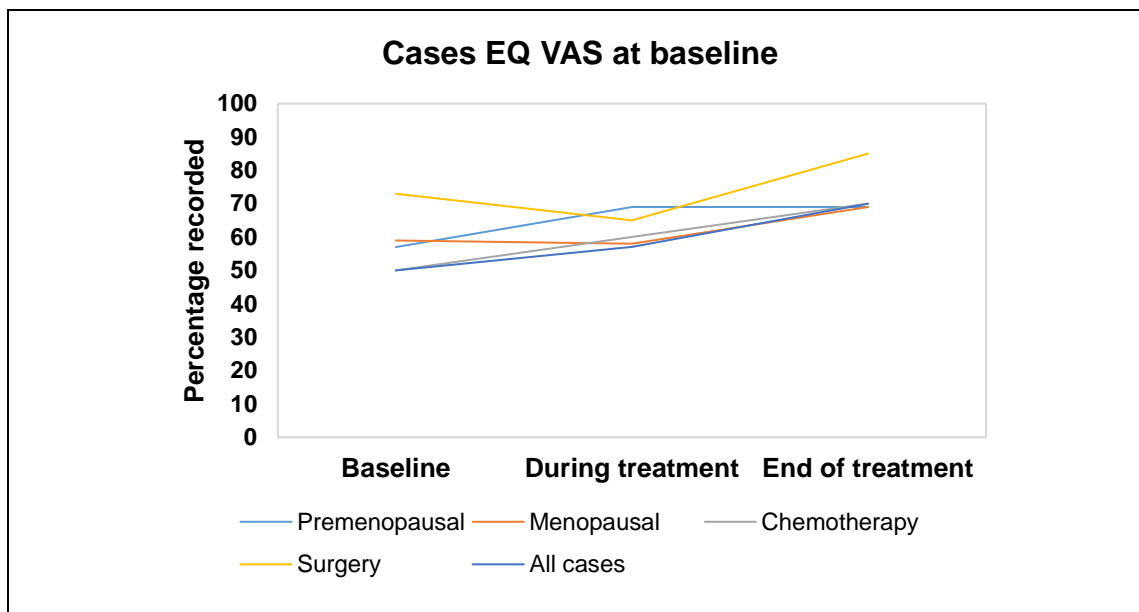
Spearman's correlational analysis showed a negative relationship between health status and age during treatment ((r = -316, *p* = .05), Table 35). This suggests that older women recorded lower health status scores during this time. There was also a significant negative relationship between health status and having chemotherapy as a first treatment at baseline. (r = -390, *p* < .01). This is unsurprising as women diagnosed with early stage disease (I & II) are generally younger (as was shown in Table 10) and treatment with surgery first followed by chemotherapy is the choice treatment for women with operable disease and less comorbidities.

6.4 Controls

The distribution and slope of the VAS scores in the controls are shown by graphs D and E in Figure 31. Subgroup analysis by age of menopause was not possible because of the small sample size. Only 10 women were assessed at the end of treatment so that frequencies from such a small sample would not provide meaningful results. As such the end of treatment distribution is not included in graph D.

Figure 31: The bar and line graphs showing the proportion of controls reporting problem for the EQ-5D dimensions at baseline and end of treatment
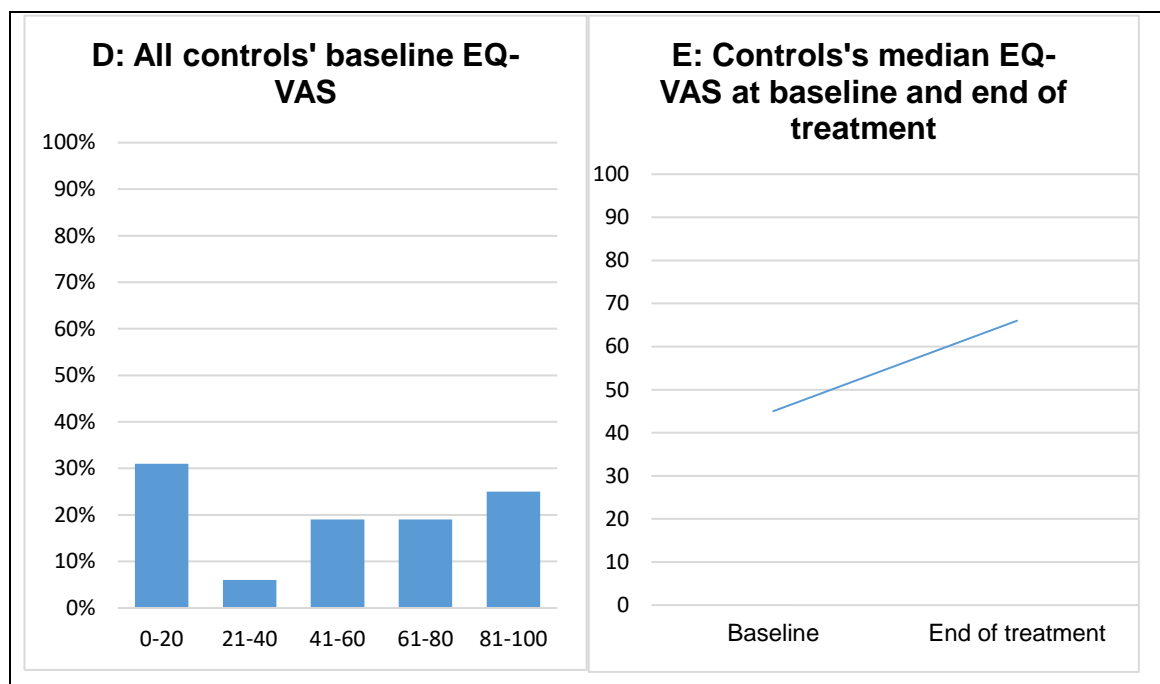
Thirty one percent of controls recoded a health status below 20 at baseline, Figure 31. The related sample Wilcoxon Signed Rank Test showed a borderline significant difference between baseline and end of treatment health status (p = .06). A larger sample size particularly at the end of treatment may have yielded a significant result. Health status was not significantly different between baseline and end of treatment between cases and controls although controls had lower scores in both instances. These results suggest that women diagnosed with benign disease perceive their health status to be similar or worse than that of women diagnosed with ovarian cancer.

The relationship between nutritional status and quality of life (using overall health status) is explored below. Correlations were computed among nutritional status and biochemical indicators for cases and the findings are shown in Table 35.

Table 35: The Spearman's correlations between health status and nutritional, body composition and biochemical outcomes for cases

			AGE	Weight	BMI	Body fat	Lean mass	Dry lean mass	Extracellular water	Total body water	Prealbumin	Albumin	CRP	CA125
Spearman's rho	**Baseline health status**	Correlation Coefficient	.060	-.004	.083	.017	-.017	.252	-.047	-.079	.478**	.440**	-.178	-.264
		Sig. (2-tailed)	.691	.978	.653	.928	.928	.164	.799	.666	**.003**	**.002**	.258	.079
		N	46	45	32	32	32	32	32	32	36	45	42	45
	During treatment health status	Correlation Coefficient	-.316*	-.010	-.089	-.277	.224	.288	.046	-.022	n/a	n/a	n/a	n/a
		Sig. (2-tailed)	**.057**	.956	.665	.171	.283	.153	.825	.916				
		N	37	34	26	26	25	26	26	26				
	End of treatment health status	Correlation Coefficient	-.039	-.010	-.094	-.192	.192	-.001	.021	-.006	.214	.135	-.328	-.106
		Sig. (2-tailed)	.854	.961	.670	.381	.381	.995	.925	.977	.338	.530	.136	.629
		N	25	25	23	23	23	23	23	23	22	24	22	23

**. Correlation is significant at the 0.01 level (2-tailed)

*. Correlation is significant at the 0.05 level (2-tailed)

Three correlations were statistically significant. Albumin and prealbumin positively and significantly correlated with quality of life at baseline (r = .42, *p* < .05) and (r = .478, *p* < .01) two tailed, respectively. No significant correlations were shown at the end of treatment, largely because both markers had returned to normal levels despite that some women had residual disease. Quality of life did not significantly correlate with BMI, body fat, lean mass or dry lean mass at any time point. Prealbumin was the only outcome to have a borderline significant correlation with quality of life in controls, (r = .494, *p* = .07) at baseline.

These results suggest that albumin, a well-known indicator of well-being, is confirmed to be such in this study of women newly diagnosed with ovarian cancer. Significantly, the results also show a strong relationship between nutritional status and quality of life, revealed by the correlation between prealbumin and overall health status in cases. Prealbumin is considered an objective marker of nutritional status.

6.5 Section B: Summary and discussion (observational study)

6.5.1 Diagrammatic representation of main findings

Figure 32: Summary of findings
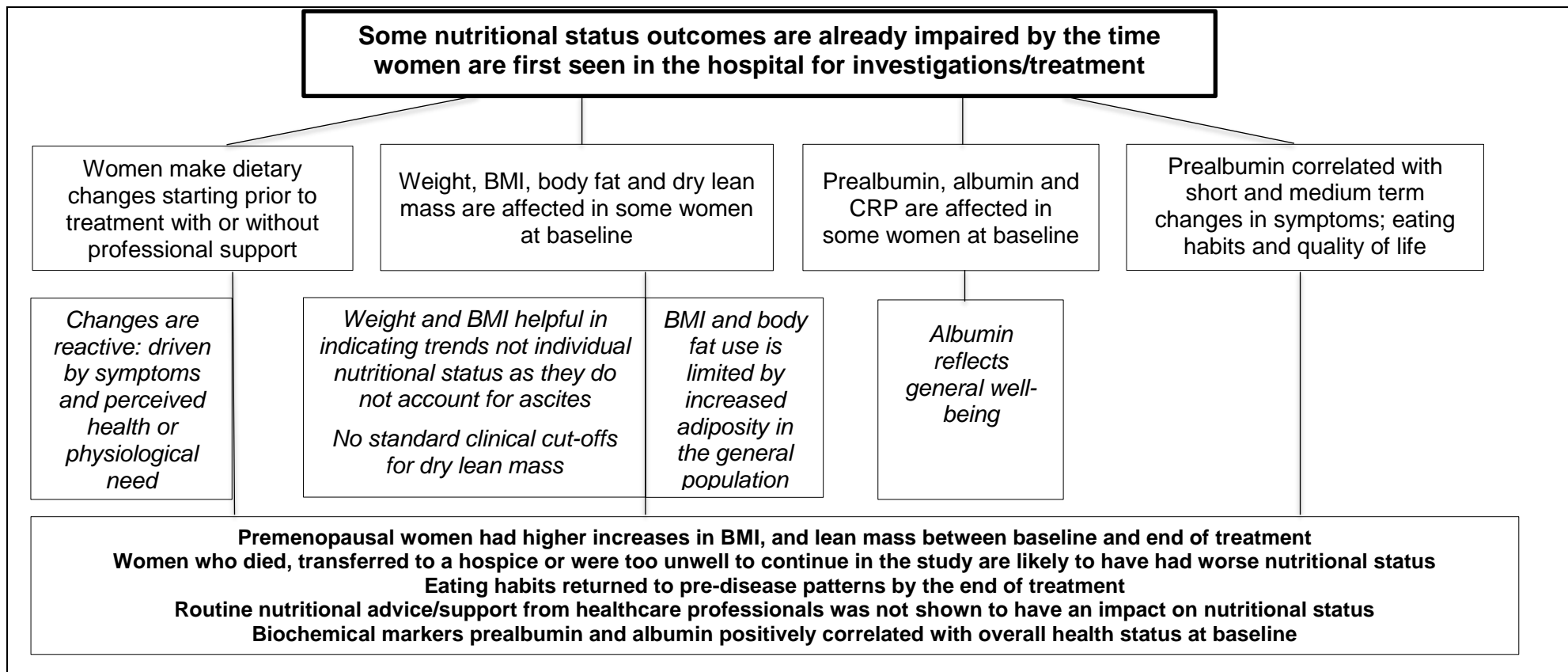
6.5.2 Summary and discussion

The results show that in some women nutritional status measures of weight, BMI, body fat and dry lean mass as well as biochemical markers; prealbumin, albumin and CRP were already impaired by the time women presented to the hospital for investigations and treatment of ovarian cancer. There was no association between total body water, extracellular water with the presence of ascites. In general women were on the lower spectrum of hydration, which may partly explain the lack of association. Both were however associated with pain and discomfort at baseline. We also found that an additional category of 'weight gain' was necessary for the classification of cachexia in our study population. This was because more than half of the women had ascites and distension when they presented to the hospital/clinic. Some women who reported gaining weight prior to treatment were shown to be clinically similar or worse off compared to women who lost weight. They had advanced disease, low prealbumin and albumin as well as ascites. A higher BMI correlated positively with increased albumin levels. A higher BMI and increased albumin were both associated with higher health status scores (quality of life). Younger women were more likely to have increased BMI by the end of treatment. Others have also found age and advanced disease to be associated with an increased risk of being malnourished (2) and impaired survival and greater risk of death among patients with ovarian cancer (322). A literature review by Cress et al., 2015 confirmed that age had a great effect on overall survival in epithelial ovarian cancer and that long-term survivors were more likely to be younger than 50 years of age. They suggest that a better performance status may mean that younger women tolerate more aggressive surgery and chemotherapy better. Ten women were lost to follow-up. Some had died, some relocated to hospices or moved to be close to family for end of life care while others were too ill to continue with the study. Most of these women are likely to have been classed as being in the refractory phase of cachexia. Nutrition intervention is unlikely to make any difference at this stage.

A diagnosis of ovarian cancer has a negative impact on 'food intake', one of the key contributors to cachexia. Food intake is affected prior to presentation to the hospital and continues through treatment for some women. The major drivers of

diet change are symptoms, treatment effect and perceived physiological need. These often result in women making independent decisions on food intake. Choices included increased fruit and vegetable intake; the elimination of sweet and sugary foods as well as red meat; and eating small amounts at a time. Change in taste, a common side effect of chemotherapy affects food intake the most during treatment. There were no longer specific 'healthy eating' related dietary changes observed by the end of treatment, raising the suspicion that women had either not implemented the intended changes stated prior to diagnosis or they had abandoned them during the course of treatment. Women who made changes to their diet prior to baseline were shown to have significantly lower prealbumin and albumin as well as health status scores at baseline. Similarly women whose diet changed during treatment lost more weight and dry lean mass than women whose diet did not change. A decrease in dry lean mass in women whose diet changed during treatment highlights the potential link between nutritional status and diet. Prealbumin correlated with change in eating habits further suggesting that there may be a direct and linear relationship between dietary intake and prealbumin at baseline when women reported that their eating habits had changed the most.

Significantly more women with ascites ($p < .01$) reported having changed their diet at baseline. That women who reported that their diet had changed at baseline were more likely to be treated with neo-adjuvant chemotherapy ($p < .05$), suggests that these women had more advanced disease and therefore complications associated. The relationship between the speed of onset of disease and the development of symptoms probably has a bearing on their impact on diet. Unfortunately little is known about the natural history of ovarian cancers before they become clinically apparent. Work by Brown and Palmer (2009) (185) investigating the preclinical natural history of serous ovarian cancer estimated that on average serous ovarian cancers have already progressed to a late stage nearly 1 year prior to their discovery. Serous ovarian cancers constitute 70% of all cancers that present at stage III or IV (323) and account for the majority of deaths.

There was an overall sense of lack of nutritional support of women by clinicians treating them. However there were no significant associations between receiving nutritional intervention and improvement in nutritional status. There was however and association with well-being (albumin). The significant differences in albumin are likely due to helpful nutritional support/advice that improved patients eating habits and therefore wellbeing. The advice may also have helped women to eat well and continue with treatment, which improved their underlying health status.

Quality of life results showed that cases and controls experienced problems with mobility, usual activity, pain/discomfort and anxiety/depression across all time points. These findings are not surprising (at baseline), since the benign conditions were severe enough to warrant surgical intervention. Premenopausal cases and controls reported more problems at the end of treatment than menopausal women. That controls were still reporting problems 6-8 weeks post-surgery is perplexing. As such our findings on anxiety and depression contradict what Yang et al., (2013) (324) showed from a meta-analysis, that the overall prevalence of anxiety in individuals with a cancer diagnosis was higher than that in non-cancer controls. They however concur with others that among ovarian cancer patients, younger age groups are disproportionately affected (325). The anxiety/depression was found to persist, with almost half of individuals experiencing anxiety symptoms at three months post-treatment. Prealbumin was the only nutritional outcome to be associated with difficulties with usual activities at baseline in cases. In this case, prealbumin may have reflected general wellness. Our study also found albumin and prealbumin to correlate with quality of life (EQ-VAS), confirming albumin to be a measure of well-being. More importantly, they show nutritional status (prealbumin) to be correlated with quality of life.

The next chapter describes the methods that were followed to elicit women's perspectives on diet and nutrition issues through focus group discussions and free text data from the study specific questionnaires.

7   Methods (Qualitative enquiry)

7.1   Introduction of chapter

This chapter outlines the research approach and justification for the inclusion of a qualitative analytic component in the study. The data collection method of choice was focus group discussions complemented by free text data from questionnaires. A description of the patients that took part in this research as well as the description of the conduct of the inquiry is provided here. The chapter also describes how a health behaviour model is used to interpret dietary and nutritional behaviours. A health behaviour change model can in future be incorporated in intervention strategies to support adoption and maintenance of healthier nutritional intake and lifestyle.

7.2   Research approach and justification

To provide a comprehensive understanding of the nutritional challenge it was important to have a component of the research that sought to understand the challenges from the patients' point of view. The qualitative approach was used to address the research objectives of 'developing an understanding of patients' perspectives of their nutritional challenges, nutritional information and support needs and exploring how a health behaviour model, Health Action Process approach (HAPA), could be used to improve a potential future intervention package'

A qualitative approach is useful in that it situates the research and locates the researcher in the world of the research participant to better understand their experiences (326). This positioning of the researcher allows for collecting of contextual material derived from speech or observation. It also attempts to understand the phenomenon of interest in terms of the meanings people bring to them (327). Patients' reactions to their disease and treatment are only partially related to objective parameters; they are also influenced by expectations

surrounding their functional level, and perceptions about themselves and the treatment environment (135). It was therefore felt that this component was invaluable in facilitating the study of issues in depth. Although qualitative methods are often criticised for their subjectivity due to hypotheses generated during data collection and analysis, patients' own perspectives add depth to understanding the challenge.

7.3 Focus group discussions

Focus group discussions were chosen ahead of other qualitative inquiries because their primary aim is to describe and understand meanings and interpretations of a select group of people to gain an understanding of a specific issue (328). This was what the study hoped to achieve with regards to diet and nutrition, experiences of nutritional support in the clinical setting as well as ideas for an ideal nutrition intervention. Another advantage of focus group discussions is that they can provide results quickly. They can generate complex information with the minimum amount of time as well as be used with a wide range of people and groups in different settings (329). In addition they provide the researchers with a great opportunity to appreciate the way people see their own reality and hence 'to get closer to the data' (330). An additional unique feature of focus group discussions is that they explicitly use group interaction as part of the method. Group processes assist people to explore and clarify their points of view (331). Researchers can obtain more insight of a wide range of views; they also have the opportunity to clarify issues or to obtain more views on an aspect they consider important. Another important aspect of focus group discussions is that they can help researchers understand the meanings people assign to social phenomena and to elucidate the mental processes underlying behaviours (5). These behaviours are often explained through the study of behavioural change theories. The theories attempt to identify and explain the major factors that determine behaviour.

The discussions were used to explore women's' views on nutrition in their journey with ovarian cancer as well as capturing the context, meaning and complexity of

managing their situation. Focus group discussions also probed participant health behaviours and choices based on some aspects of preliminary results from Study A. Some information relating to nutritional support packages was solicited and ideas of a future nutritional intervention package explored. The enquiries were semi-structured but also followed the naturalistic and emergent design flexibility to allow for new concepts to emerge from during the discussion.

7.4 Free text entries (study specific questionnaire)

Data provided by patients as free text in the study specific questionnaire was used as an additional component of the patient perspective study. This ensured that diverse women's perceptions of the nutritional challenges including those recruited in study A were captured.

7.5 Topic guide for the focus groups

Data from baseline and end of acute treatment questionnaires were preliminarily evaluated and used alongside the initial objectives to define the direction of the inquiry. A draft topic guide for the focus group discussions was developed based on review of the literature, the research aims and the researchers' experience of working with women diagnosed with ovarian cancer. The topic guide included open-ended prompts about nutrition, areas of diverse beliefs or practices, and what participants saw as important for their nutritional support. It covered issues such as whether patients were aware of nutrition as being important to their treatment and recovery, and what issues they believed should be considered when making decisions about their nutrition. A sample is provided in appendix 8.

7.6 Focus group participants

These are women who had an ovarian cancer diagnoses and were at any stage of their cancer journey. Some were undergoing first-line treatment, others were in remission and yet others were awaiting treatment for recurrent disease.

Patients who have been diagnosed and treated for ovarian have regular follow-up enabling clinicians to monitor women for side effects, recurrence and overall heath. Follow-up of ovarian cancer generally includes a physical examination, blood tests to check for tumour markers that may indicate recurrence if raised, Computerised Tomography (CT) scans and chest X-Rays are also used to monitor patients. Examinations are usually every 2-4 months for the first two years after treatment, every six months for the following three years and yearly thereafter (180). Women could participate in focus group discussions at any stage of their ovarian cancer journey, provided they had had/started treatment for the disease. The ideal size of a focus group for most non-commercial topics is between five and eight participants. Larger groups can be difficult to control and may limit individual's opportunity to share insights and observations (326). Two focus group discussions of 4 people each were conducted.

7.7 Inclusion and exclusion criteria

7.7.1 Inclusion criteria

- Women aged 18 years and above who had previously had treatment or were on treatment for ovarian malignancy (including fallopian tube and primary peritoneal cancer)
- Women who had not already taken part in study A

7.7.2 Exclusion criteria

- Women who had not received treatment for their cancer

7.8 Recruitment and patient characteristics

Eligible patients were identified from the weekly gynaecological oncology clinic at the primary research site. Recruitment took place over a 2 month period. For 3 successive weeks, gynaecology oncology outpatient clinic lists were screened for eligible patients. The researcher approached identified women and explained the

study to them. Women who expressed interest were given a package containing a patient information leaflet, a reply slip confirming their un/willingness to participate in the group discussion and a prepaid envelope to send their response to the research centre in. Where the researcher could not personally meet with the woman, their consultant was asked to pass the information package to them. All women who returned the slip were telephoned to acknowledge receipt of their response. The telephone call was also used to arrange a suitable date and time for the group discussion for those women who wanted to participate. Four possible dates and times were suggested and women chose the date that best suited them. A total of 62 women were approached in clinic, 27 expressed an interest to participate and 16 confirmed their willingness to take part by returning their reply slip. Only six women from those recruited in clinic eventually participated in the discussions. The majority of women could not attend on any suggested dates or other dates that other women could attend in.

7.9   Ovarian cancer charities

We planned to run the groups with eight participants in each group. However while trying to organize a date and time for the first group discussion it became apparent that we had insufficient numbers of women. Matching participants to dates proved difficult. Moreover women's treatment plans and health challenges made it difficult for them to commit to a date and time. After deliberation it was felt that more women should be approached. Since women in the oncology clinic had either been approached or declined or were already participating in Study A, two gynaecological cancer charities (The Eve Appeal and Ovacome) assisted with recruitment. The charities keep registers of women who express a willingness to participate in research if opportunity arises. The Eve appeal administrator identified 10 women who lived in London (for ease of travel) and emailed them the study information package. Women were asked to respond directly to the researchers using the reply slip. Ovacome on the other hand, asked the researcher to provide a summary of the invitation shown in to post on their website. Interested women responded by contacting the researcher directly. These women were sent the information package and asked to confirm their

willingness to participate through the reply slip. A self-addressed-prepaid envelope in which to return the slip was provided.

Eight women from both charities returned the slip confirming their willingness to participate. Upon receipt of the reply slip women were telephoned and offered possible appointments dates. Three women from Ovacome lived too far to travel into London for the discussions including one who lived in Scotland. The available dates for the discussion were not suitable for most women. Only two women approached via the charities eventually participated in the group discussions. Although some others were willing to participate, the dates and times offered were unsuitable or they lived too far away (Scotland) to attend the discussions in London.

Recruiting patients through the charities could have potentially introduced bias to the data through the healthy volunteer effect (332). This is a phenomenon where generally healthier individuals offer to participate in research compared to the less healthy counterparts. Also, women who are signed up to charities to help with research may not be representative of the overall population of ovarian cancer patients. They are probably more interested in health and nutrition issues than their counterparts who are not. However the small numbers of women recruited this way (only two) means the healthy volunteer effect may not have had as big an impact than if more women had been recruited in this manner. The characteristics of women who took part in this research are outlined in described in Table 36.

7.10 Conduct of the focus group discussions

Participants were involved in a structured and recorded group discussion. The recordings were which was later transcribed for analysis. Two discussions with 4 women each were held a month apart. The discussions took place in a small meeting room at a university affiliated with the primary NHS Trust research site. One meeting was facilitated by an MSc student, and the other by this researcher. Both were observed by the students' research supervisor who also acted as a moderator. Facilitators worked together to recruit participants, set-up dates and to review their interview guides. The group discussions were carried out in a similar format, albeit with a different emphasis on the endpoints. Everyone sat around a table with the audio-recorder placed in the middle. The discussions lasted 90 minutes each. Refreshments were provided half way through the discussion.

The facilitators opened the discussions by clarifying the purpose of the study and highlighting that the opinions of the participants were valued. Although the discussions were semi-structured participants were encouraged to express themselves and to interact with each other. The discussions were directed using a semi structured interview guide prepared beforehand. This helped to ensure important issues were discussed. This topic guide included some preliminary findings about diet and change in eating habits from study A. The moderator was skilled in the interview techniques and strategically asked both steering and testing questions during the discussions.

7.11 Data transcription

Audiotapes from the two focus groups were transcribed verbatim. Participant identifiers were removed; women are identified in the text as Respondents one to eight. The facilitators are identified as JS and NB and the moderator as AL. The Group one audiotape was transcribed using Express Scribe followed by double-checking to ensure accuracy. The Group 2 recording was transcribed manually to allow the researcher to relive the discussion and to be intimately

connected with the data (333). The data from the two groups and used in this thesis were wholly analysed by the research as described below.

7.11.1 Data quality assurance

Multiple coding of the focus group data was used to ensure rigour and counter concerns about the address the subjectivity sometimes levelled at the process of qualitative data analysis (334). In order to establish consistency of coding for the focus group and free text data, the researcher independently coded all the transcripts. Discussions of any incongruence took place in supervisory meetings. Differences were resolved by discussing the differing interpretations, identifying any misunderstandings, and refining code definitions as necessary. The researcher would put forward their rational for perceiving a particular meaning from the text. The supervisor could probe further or suggest a different perspective. A discussion would ensue, until there was consensus or middle ground was found. This ensured that a systematic process was followed and maintained transparency. Supervisory meetings facilitated reflexivity and safeguarded against individual bias by providing opportunities to make assumptions explicit and open to challenge (335). These meetings formed a kind of auditing that was "built into the research process to repeat and affirm (researcher's) observations" (336).

7.12 Data analysis

A thematic analysis approach was adopted for evaluating the data. The themes were arrived at inductively by using content analysis to generate codes and categories (337) and deductively because a set of pre-determined questions were posed to the participants to cover important areas.

A systematic and verifiable trail of the analytic process began with reading and re-reading of the Group 2 manuscript to discover and understand meaning from the data (338). Data was coded to generate an indexed copy of the first transcript. The track changes feature in 'Microsoft Word' was used to generate the codes.

The 'Add Comment' command was used to tag each topic (labelling it by meaning) throughout the text. This option suited the purpose because Microsoft Word automatically and sequentially numbers each additional comment. Equal attention was paid to all aspects of the data (339), which is an important aspect of the analysis. One hundred and sixty codes (NB1-NB160) and corresponding topics were systematically identified. The topics ranged from unclear professional advice, reading labels when buying or before eating food, not being ill during treatment, putting on weight during or after chemotherapy treatment to being obsessive about diet and not wanting to die and many more. The codes and the corresponding topics (the index) were copied onto a spread sheet. These were then reviewed to ensure that all data had been indexed. Supervision sessions were used to have another person cast an eye over segments of data or emergent coding frameworks. This was part of quality control of the analytic process.

When all data was accounted for, the codes were distilled to generate a revised code list. This involved grouping codes recognised as having the same or similar meaning. Individual codes and topics were maintained for cross-referencing. The next stage from this involved revising the topics and summarising them to be more specific and concise for example grouping them by those related to disease and symptoms, good food, bad food, and emotions of fear of returning disease etc. The initial 160 topics were reduced to 24 and re-coded 1-24, each code representing a revised topic. An in-depth review of the codes against topic was performed to ensure that text was appropriately located and the meaning not overshadowed or lost. The 24 codes and topics were then reviewed against the transcript and modified as necessary, to ensure all texts were appropriately located. The next step was to group them by contextual similarity into categories. Some codes, relating to disease, treatment and group dynamics, were discarded. They were deemed to not be relevant for the objectives of this thesis. The relevant codes were contextualised and summarised into 9 categories. Each step of the analysis was discussed and verified by a second person to maintain integrity of data. The 9 categories were felt to represent all data from the group discussions that were relevant to the objectives of the research. The 9 categories were

therefore used to code the second transcript. In addition, there was an opportunity for participants in study A to provide further free text written responses in a comments section of the study specific baseline and end of treatment questionnaires. These data were also coded using the same 9 categories generated from the Group 1 transcript analysis. The final data check and grouping revealed five distinct topics or themes that emerged and were relevant for this thesis. These are presented with the results in chapter 8.

7.13 Interpreting dietary and nutritional behaviours

Identifying how women's behaviour (regarding managing their diet and nutritional needs) changed after a cancer diagnosis could provide new opportunities for research. Targeted interventions could exploit this understanding of behaviour change. The flexible qualitative inquiry in this research allowed for some exploration of behaviours around food and diet in the context of known health behaviour change models. This thread was interpreted in the context of how these findings add to knowledge as well as their potential for incorporation into future interventions. The application of behaviour change theories in the areas of health has seen increased interest in recent years. The hope is that understanding behaviour change can help to improve how services/nutrition and intervention are offered. Exploring the issues around diet and nutrition with women was therefore also important to explain the underlying processes and behaviours women reported to have adopted or discarded following their diagnosis with cancer.

The Health Action Process Approach (HAPA) model (340) was found to best predict and explain some of the behaviours identified in our study. This behaviour change model was not selected a priori; rather it emerged from the evidence. It helps to understand and explain the behaviours that were narrated by women more objectively. A schematic representation of the model is shown in Figure 33.

This model proposes that health behaviour change is a process consisting of two phases, the motivational and volitional phases (341). Successful behaviour change would therefore hinge on the formation of an intention in the pre-

intentional motivational phase and the translation of that intention into action in the post-intentional volitional. An intention is usually to adopt certain health behaviour or to change a risky one in favour of another behaviour. Intention formation depends on three motivational factors: (1) risk perception – the belief that one is at risk, (257) outcome expectancies – the belief that behavioural change will reduce a health risk, and (3) perceived self-efficacy – the belief that one is sufficiently capable of exercising control over a demanding behaviour (342), (343). Individuals will ultimately fall into two groups, pre-intenders and intenders. Studies could capitalise on that pre intenders require risk and resource communication about the target behaviour while intenders require planning and support to translate intension to behaviour (344). An appropriate intervention could ensure that both groups are well equipped to move to the next phase.

In the volition phase, individuals initiate action and focus on maintaining the changes made despite the obstacles or failures that may occur along the process (341). This phase is subdivided into planning, initiation, maintenance, and relapse management. Self-efficacy plays an important role in the adoption of target health behaviours helping to reorganise intention into an action plan with specific goals of when where and how the action should take place. Maintaining the initiated action (action control) is on-going; self-regulated and involves focusing attention on the task and ignoring distracting stimuli, resisting temptations, and managing unpleasant emotions. Self-efficacy moderates the degree to which individuals can overcome barriers that arise in the maintenance period. Individuals with high coping self-efficacy invest more effort and have a higher probability of developing new routines turn them into healthy habits (341). Individuals with a low self-efficacy could easily relapse unless well supported.

This chapter has outlined the research approach and justification for the importance of including patients' perspectives in trying to understand nutritional challenges. The findings from this study and the interpretation of women's behaviours using the HAPA model are presented in chapter 8.

Figure 33: The schematic model underlying the Health Action Process Approach (HAPA)
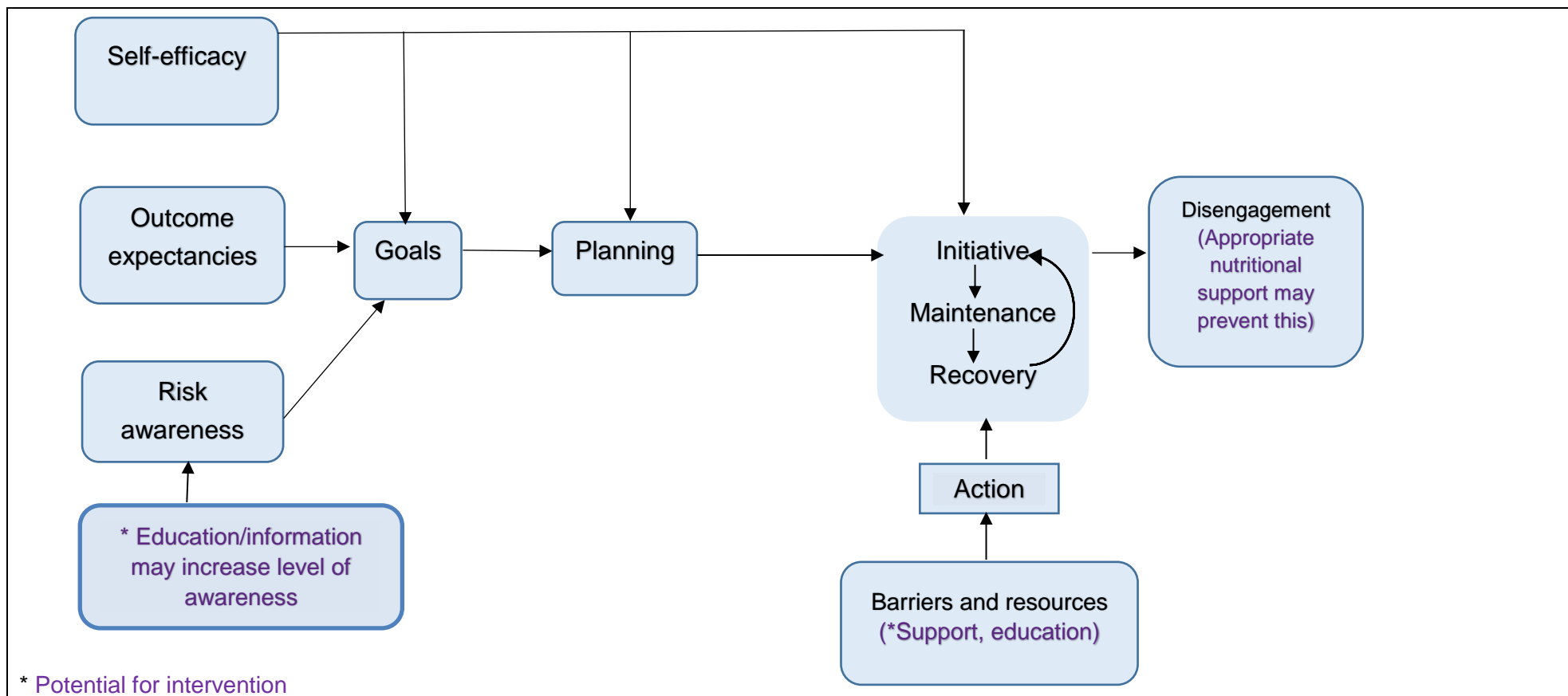
Adapted from Krutulyte et al., (341)

8 The patients' perspectives study results (qualitative enquiry)

8.1 Introduction

This chapter presents a patient perspective on the nutritional needs of women diagnosed with ovarian cancer. While chapters 5 and 6 focused on determining the quantitative impact of the disease and its treatment on the physiology, 'nutritional status', here I aim to reveal the human side of the nutritional conundrum. By exploring women's perspectives of the nutritional challenges they face, I probe deeper into how women diagnosed and living with an ovarian cancer perceive diet and nutrition, and manage their nutritional needs. I also examine what women consider would improve self-management of their nutritional needs. My aim is to build a patient informed platform on which to make recommendations for the future design of nutrition support packages.

Findings are presented in themes. The themes that were identified are 1: the perceptions of women of the importance of diet and nutrition from the time of diagnosis, 2: the changes that women made to diet and eating habits, 3: the availability of nutritional support and advise in clinical settings, 4: the physical and emotive impact of disease, symptoms and treatment on diet and nutrition and 5: how to meet diet and nutritional needs more efficiently. The themes represented common threads and ideas that emerged from the discussions and from the free text responses in the study specific questionnaires. They all relate to diet and nutrition.

The two focus groups are identified in the text as groups 1 and 2. Participants are identified as respondents 1 to 4 in group one and respondents 5 to 8 in group two. Individual contributions from the study A participants are identified by the participant's unique study reference number (50xxx).

8.2 Participants

8.2.1 Focus groups

The characteristics of the participants are outlined in Table 36. Their ages ranged from 51 to 74 years. All stages of the disease were represented. Five women had advanced disease (stages III and IV), one had stage 2 and two had stage 1. The length of time women had lived with the disease, varied from less than six months to ten years. Women were at various points on the cancer pathway; some were undergoing primary treatment, others were in remission or either undergoing or waiting to start treatment for recurrent disease.

Table 36: The characteristics of focus group discussion participants

Respondent	Group	Age	Ethnicity	Education	Disease stage	Time since diagnosis	Disease state at discussion	Treatment status at discussion
1*	1	65	White British	O-Level	IV	6 months	Disease progression while on treatment	Neo-adjuvant chemotherapy cycle 4
2	1	51	White British	Degree	IIc	12 months	Responding to treatment	Surgery then chemotherapy, currently on cycle 5
3	1	62	British-Indian	O-Level	IIIc	36 months	Progressing disease	6 months post 3rd line chemotherapy
4	1	52	Filipino	O-Level	IV	6 months	Responding to treatment	Surgery then chemotherapy. On cycle 4
5*	2	65	White German	Not stated	Ic	120 months	Recurred 48 months ago	Awaiting 6th line treatment with chemotherapy
6	2	52	White British	Degree	III	24 months	In remission	Completed first line treatment of surgery +chemotherapy 18 months ago
7	2	74	White British	Diploma	III	108 months	Recurred 24 months ago	Currently on 3rd line treatment with oral Tamoxifen
8	2	64	White British	Not stated	1a	18 months	In remission	Completed 1st line treatment with surgery and chemotherapy one year ago

*Deceased on 31/12/14

8.2.2 Women who provided additional free text data

Participants in study A provided further free text written responses in a comments section of the study specific baseline and end of treatment questionnaires. Thirteen women entered text at baseline and 23 at the end of treatment. Five additional codes were generated which are 1) Information on medicines for treatment of comorbidities 2) Impact of non-cancer related pain e.g. related to knee replacement or arthritis 3) The impact of the cancer and its treatment on social life e.g. not being able to work or exercise 4) Other reasons for avoiding certain foods such as allergies and 5) Cancer related pain and/or complications such as pain from blood clots; hot sweats post-hysterectomy. Data under these codes were excluded from presentation in the thesis, as they did not shed light on the research question. Relevant data was included under the existing themes.

8.3 Conduct of the discussions

The subject of nutrition was of considerable interest to the self-selected group of women such that a call for a break was ignored in both groups with women preferring to continue the discussion. Although guided, the discussion did expand beyond nutrition to other aspects of living with the cancer, which the participants were keen to share in the group. These data are only presented here where they provide an instructive context for the women's views on nutrition.

Participants seemed to draw from each other's experiences. Occasionally there was palpable empathy between the women, expressed simply in 'Ums and Ahs'. Suggestions were made of therapies and diet tips that had been helpful. The mood, although often light was punctuated by a difficult moment in group1 when respondent four was distressed talking about her isolated social circumstance. There were occasional strained moments when two speakers held opposing views but tensions were easily diffused with a return to amicably discussion.

Participants were generally forthcoming concerning their current health status, and the treatments they had undergone. They discussed how they had been first diagnosed and the impact living with the disease was having on their diet and

lifestyle. Sensitive and personal information was divulged including discussions about struggles with alcohol abuse and unfaithful spouses. Humour was used to describe or discuss potentially difficult issues, but there was tacit acknowledgment of the gravity of their diagnosis which respondent five expressed as being '*Pretty angry at our body'*.

8.4   Thematic analysis

This part of the study explores patient's perceptions of their nutrition. I felt that sustainable long-term benefits could be better achieved if women's experiences, perspectives and opinions informed the development of future nutritional intervention packages.

8.4.1 Theme 1: Perceptions of the importance of diet and nutrition from the time of diagnosis

My primary interest was to find out whether nutrition was perceived to be important to participants. If so, when it became important and what behaviours and actions women adopted to maintain or improve it. I wanted to explore the question in the context of the participants' views of the role of nutrition in their life. I also wanted to find out what women used as indicators of changing nutritional status. A preliminary analysis of diet and eating habits data from the study specific questionnaire indicated that women altered their diets in response to a suspected cancer diagnosis or symptoms.

Three different perspectives on the importance of nutrition were evident. There were women (or loved ones) who from the point of diagnosis perceived nutrition and diet to be important and set out implementing dietary changes. A second group of women said they were too unwell at the beginning to worry about aspects of their diet beyond the bare minimum they could tolerate at the time. The third group for a variety of reasons did not feel compelled to make changes to their diet and continued as they were prior to diagnosis.

Respondent six who felt that nutrition was important from the onset and felt compelled to change her diet said,

"When I was first diagnosed ….I did wonder if there were things I could do with my diet which could help me respond to treatment…"

She seemed to have embraced her situation and then set about acting on her needs. She outlined being driven by a desperate desire to be in control of some aspect of her life. She felt obligated to find ways to ensure her body was in the best state for treatment to work effectively.

The second group of women, because of being unwell due to disease or following surgery felt that recovery was their priority. The overwhelming symptoms and/or treatment effects preoccupied these women such that they were forthright in saying that nutrition information would not have been welcomed at this time. Health challenges and the need to recover outweighed nutritional concerns at that time for some of these women.

*"I was so ill after my operation. ….If you are lying there, and you have tubes down there to bits you didn't even know you had, food is the last thing on your mind and the thing is when you come home, you think you want to eat something; you know to keep your energy levels up; then fine, but actually what you should or shouldn't be eating I really didn't have any recollection at all" (*Respondent eight)

Respondent two struggled to keep food down post-surgery, and confirmed that at this stage *"nutritional information would have been sort of overkill".*

Ovarian cancer is often diagnosed late and women can be considerably unwell. Tumour spread and symptoms such as ascites, distension and bloating can profoundly affect appetite and sometimes cause digestion problems. The priority for these women is similar to those with surgical complications; to get better. Respondent one articulated sad relief that diagnosis meant that treatment could begin and there was hope for symptom relief.

"I was relieved that I had been going through such pain and discomfort and then I found out what it was and once I knew what it was it was going to be dealt with and it was a sheer relief".

Some of her major symptoms had been that she "*couldn't eat at all*"; she "*had a lot of fluid in her abdomen*" and "*felt full all the time*".

The third group of women felt no need to change their dietary habits. These women were at different stages of their cancer journey; respondent four had recently been diagnosed while respondents three and seven had been living with cancer for 3 and 10 years respectively. Their reasons for not changing their diets were different and based on good appetite and culture.

"I am eating just like normal, everyday is normal. I have an appetite to eat anything (sic)." (Respondent four).

She added that because she had a good appetite, she ate her traditional diet that consisted mainly of rice and fish. Respondent seven attributed her lack of diet and nutritional concerns to previous unsuccessful dieting experiences:

"I have done that before. I have tried the diet for my arthritis. ..I did it for 18 months and in the end I couldn't stand it".

She was a retired registered nurse who admitted to being a 'pernickety eater' all her life preferring fruit and vegetables over meaty or sweet foods.

Respondent three, despite the fact that she had presented with abdominal distension and been referred to a dietician seemed unfamiliar with the constant worry about food. She confronted respondent two saying;

"Can I just ask you... instead of thinking, can't you just eat what you feel like eating…?"

Respondent two interrupted her questioning by clarifying that after her surgery she had not felt like eating at all. This conflict demonstrated that nutritional challenges and management approaches are unique to each woman.

Though a woman did not change her diet, it was not necessarily the case that she considered her nutrition of little importance. Respondent three above referred to eating what you feel like eating, suggesting that keeping it simple, familiar and about what you want to eat was important and perhaps more sustainable. There was also a sense of confidence in some that they were eating healthily and that their diet met their needs. 57-year-old volunteer 50014 in her free text response implied that there was no need for her to change her diet habits.

"I was always conscious of health issues, studied & practised aromatherapy & nutrition".

The overall sense from the two small groups of women as well free text data was that nutrition and diet were important and for some this was a priority right from the point of diagnosis. Others battled with symptoms or treatment side effects. During this time they ate the little they could tolerate and focused on getting better. Women who reported not changing their diet indicated a satisfaction that their diet was sufficient. The variety of perspectives and ensuing behaviours around diet and nutrition and indeed other aspects of well-being after diagnosis and treatment for ovarian cancer are revealed here as highly individualistic. Furthermore they are driven by personal goals and modified by both internal and external influences (133) unique to the woman as outlined below.

Internal influences impact the emotional and rational aspects while external influences are those that one feels they have very limited control over. The internal influences were demonstrated in the following comment,

"My framework for it; I think my way of sort of trying to get my head around the idea that I had this thing to deal with, what I latched onto was the idea of my immune system and that was very powerful for me. … I started to really look at everything as is this good for my immune system or is this bad for my immune

system? That was everything from nutrition to stress to emotional reactions to things…" (Respondent six)

The above insight suggests underlying machination and a rationalisation process that precedes action. This internal process is often riddled with conflict and anxiety because of lack of certainty surrounding nutritional advice in cancer. The lack of clear nutrition guidelines and the impact of the cancer diagnosis and treatment on diet and food intake are further outlined in themes three and four of this chapter.

The external influences also play an important role. There was a sense of helplessness as women succumbed to the overwhelming symptoms or treatment effects. Respondent two conceded that she had altered her diet, commenting;

"Actually it's the chemo not the cancer. ...it's the chemo that has changed taste also. So there are certain things, like coffee has no taste, or for most of the time things taste metallic, which is all chemo, related. So there are certainly foods I don't eat because they don't taste. It's like having lots of colours but no pallet"

These challenges often resolve at the end of treatment particularly if it is successful. Women's nutritional needs and diet are constantly changing in the context of multiple treatments and over short periods of remission.

The paradigm of mal/nutrition and cancer is therefore not static. As the underlying disease and treatment effects resolved, women who had not prioritised nutrition did so as they became able to act on their needs. Respondent 2 gave insight into this dynamism.

"Somebody said to me you know are you very purist about your food. And I said well actually at one stage it was just getting something down"
This shows that women are able to identify different life stages in their cancer journey. Different stages have associated priorities which affect the emphasis that might be placed on each outcome of wellness and well-being (133). The significance and associated actions shift and change as the journey progresses.

Newly diagnosed women battling treatment side effects have different priorities and objectives from survivors who have lived with the disease for a while. Similarly women whose disease has recurred may have different objectives from women who are in remission as pointed out by respondent six who said *"..Things are all right at the moment. If they were not I suspect I would become obsessive about it again"*.

Women's behaviour and actions appeared to be associated with their treatment trajectory and the point they had reached on this. Internal and external influences determined some of the behaviours around nutrition management.

I was interested to find out what the defining points were for women in terms of nutritional status and body composition. What changes if any alarmed them and caused them to take action? It emerged that weight was the main index used. Weight change was an issue across the different stages of the cancer trajectory. Women associated their nutritional well-being with being a particular weight and also how they looked with this weight. Fifty-year-old volunteer 50083 said;

"I was putting on extreme weight on the stomach but lost a lot of weight from face, arms and breast. I looked gaunt but very fat"

While loss of weight can be stressful because it makes the cancer visible, physical change in appearance changes sense of self, which can lead to puzzlement and confusion (345), and even challenges identity (346).

Weight falling off during treatment presented its own challenges and distress about not being able to complete treatment. Respondent two said about it; *"I did actually get worried as I thought unless I can stop the weight going down I'm not going to be able to tolerate chemo…"* Respondent two.

On the contrary weight gain above a woman's usual weight particularly during remission caused frustration. Respondent five who felt quite well after her chemotherapy treatment said,

"…I put on a lot of weight. 'I think it was the steroids, they make you put on a lot of weight'...It was absolutely awful. And so I had to go on a diet..."

Nutrition was important to maintain desired weight. Loss of weight was immediately associated with complications and poor outcomes. On the other hand weight gain beyond that acceptable to a woman, was an 'awful' experience for some. These views represented two ends of the spectrum in the cancer trajectory. Weight loss during treatment was perceived as a cause for alarm. Post successful treatment, weight gain beyond a personal healthy weight was also cause for alarm because women believed that their best chance to prevent the disease from returning or to fight it better if it does return is when their body is at its best health and not overweight.

"You think you're doing the right things. …you know; that you are going to avoid hopefully it ever returning and if it does at least your body is going to be that much fitter. If at any stage it comes back, back you'd like to think your body is that much stronger to deal with whatever else is thrown at it".

The assiduous quest for information and/or guidelines on how to cope with disease/treatment and what to/not to eat was another indicator of the importance of nutrition.

"… my niece was looking on the website and I meant to bring it today I totally forgot, a book on what to eat and what not to eat for cancer patients" (Respondent three)

Women sought information to help them make better choices about their diet and therefore become healthier as well as to be sure that their diet choices were not contraindicated for their cancer and or treatment. Nutrition was a part of the whole cancer diagnosis and treatment, rather than a separate piece; for many it was affected by disease, symptoms and treatment. A summary of the foods that women preferred to or not to eat changes that women made to their diet is provided in   Table 37.

Table 37: The reasons given by women for changing their diet after the diagnosis of ovarian cancer

Respondent	Main reasons for changing diet	Preferred food	Foods avoided
1	Distension, ascites	Little more frequently	Pasta, no longer likes the taste
2	Treatment effects	Coconut milk, oil or coconut chips, spinach, rocket, smoked salmon, fish pie, dark green dark red vegetables, beetroot, avocados tomatoes, blueberries	Starchy foods because they do not digest well and cause constipation. Raw fish
	To prevent infection	Yoghurt, almonds, honey	
3	To prevent infection	No change	Live bacteria, takeaways (during treatment)
4	None	Eating normal. Good appetite to eat anything.	Reduced junk food (Kentucky Fried Chicken (KFC) and MacDonald's)
5	To boost immune system	Occasional glass of wine, homeopathic supplements, steamed vegetables	Red meat
6	Boost Immune system	Organic food only, strong immune supplements, grass fed organic meat, olive oil	Refined sugars, fruits and vegetables sprayed with chemicals, processed oils or saturated fats
	During treatment to shrink tumour	Budwig protocol i.e. flaxseed oil amalgamated with dairy products	Non organic food
7	Not clearly stated	Fruit and vegetables	Fatty food, oil and butter and full-cream or milk
8	Build the body to be strong to fight	Organic food fruits and vegetables, some white meat and some fish	Alcohol, sugar, sweets

8.4.2 Theme 2: Dietary and eating habit changes

The continuum of cancer survivorship includes treatment and recovery; long-term disease-free living or living with stable disease; and, for some, living with advanced cancer. Each phase has different needs and challenges. Few if any studies have evaluated the association between diet and ovarian cancer survival, in particular the impact of diet change after diagnosis (347). Thus the role of diet in survival from ovarian cancer remains unclear. Despite this lack of scientific clarity, diet was one aspect of lifestyle that women they paid concerted attention to. In theme 1, women discussed changing or modifying their diet and lifestyle following diagnosis. In this theme I look into what practical actions were taken by women in an effort to maximize their nutritional wellbeing.

A cancer diagnosis changed everything for participants.
"You come home and you have to start to learn how to live, lead another life …be totally different" (Respondent eight).

This other life encompassed more than diet and nutrition changes and included exercise, emotional and psychological wellbeing, sexuality and spirituality as mentioned by women during the discussions. Some women acknowledged that a total lifestyle change was needed to face up to the cancer illness. With regards to dietary changes, refined sugar was one of the food groups that some women reduced, or eliminated from their diet because they believed that *'…cancer cells love sugar'* as respondent five voiced. Respondent six, a vegetarian who ate only organic food and followed the Budwig protocol adopted a more scientific approach to her sugar intake. She elaborated;

"I do actually feel that one of the things I've successfully done is change my diet to be much more aware of the glycaemic index of things to relative amounts of sugar"

The Glycaemic Index (GI) is a ranking of carbohydrate-containing foods based on the overall effect on blood glucose levels. Slowly absorbed foods have a low GI rating, while foods that are more quickly absorbed have a higher rating (348).

Foods with a low glycaemic index can help even out blood glucose levels and are therefore recommended.

Symptoms and effects of treatment also determined what women ate. Respondent one who stated that she ate very little but frequently due to her ascites commented;

"Well from my point of view it's the symptoms that cause the nutritional problems for me. I've had breast cancer that was over 20 years ago. ..I had a lumpectomy and I had radiotherapy and I had no ill effects apart from the effects of the radiotherapy and post-surgical effects. So the ovarian cancer is definitely a bigger issue".

On the opposite end of the spectrum respondent eight reported that she had increased appetite during treatment that lead her to eat more sweets and subsequently she struggled to maintain a healthy weight.

"Minded by the chemotherapy longing for the sweet stuff. I was waking up in the middle of the night hungry and munching on biscuits. You know what I mean? This real punter of sweet things and taste!"

Weight management was one of the reasons mentioned for changing diet or eating habits. This was experienced at both end of the spectrum with some women wanting to eat more to curtail weight loss and to continue with treatment, *"..Just try and eat anything you can.., whereas before it was maybe two, three meals a day now it's just little and often"* (respondent one),

While on the other hand some women tried to lose the weight gained during chemotherapy,

'…Well I joined a slimming group and it worked' (respondent seven).

The final reason identified for changing diet and eating habits was a desire to be healthy. This was in the hope that the body would be strong enough to cope in

case the cancer returned. Respondent eight whose diet consisted of some organic food, white meat and fish with sweets and alcohol avoidance said;

"You think you're doing the right things. …you know; that you are going to avoid hopefully it ever returning and if it does at least your body is going to be that much fitter. If at any stage it comes back, you'd like to think your body is that much stronger to deal with whatever else is thrown at it".

Women made dietary changes for therapeutic reasons, due to the impact of disease and symptoms, to gain or maintain weight, and also to be healthy. The changes tended to follow the cancer journey. Women on first line treatment focused on eating to gain or maintain weight or to be able to continue with treatment. Women in the post treatment phase focussed more on healthy eating, exercise and other lifestyle issues such as mental well-being and involvement with social activities. These strategies are important factors in establishing and maintaining a sense of well-being and enhancing quality of life(157).

Most women were specific about the foods they preferred to or not to eat. Some opted for organic foods, others avoided fatty foods; one participant followed the Budwig diet with curative/therapeutic intent. Most eliminated sugar and sweets from their diet despite there being no undisputable evidence to support their actions. Although there are some dietary constituents and related lifestyle factors and characteristics that influence risk and progression of cancer high sugar intake has not been shown to increase the risk or progression of cancer (157).

Foods rich in protein were thought of as being good.
"The CNS said to me, it's really good you are eating a lot of protein that's really good because it helps prevent muscle wastage". Respondent two

Changing diet and lifestyle was not without challenges. Women stated that there was information overload particularly on the Internet, a lack of clarity and coherent guidelines and protocols for nutrition and diet.
"There so many books, you know. I mean, (names an American author) published several books and one of them is a book of 8 survivors of cancer and the title is,

'They Have Done it So Can You'. And they tell you exactly their diet and what they were taking and they're all completely different so you think, well what do you do? Where do you start or where do you stop?" (Respondent five)*.*

Women chose daily what they believed was best for them and even if they were sometimes ambivalent about the efficacy of their dietary strategies they tried to adhere to them, and keep motivated to sustain diet and lifestyle changes.

"Yes, it becomes, very, very difficult to make decisions and what goes with what and what doesn't go with what and what should you do when you are having chemo" (respondent six)

Particular difficulties with eating also had to do with the fear of jeopardising treatment if one was not well nourished. Respondent two articulated this while highlighting the role her friends and neighbours played by providing her with prepared and freezable meals;

"And I do have friends I have very good friends and good neighbours who have been fantastic. But I wouldn't be in the state I am as sane and therefore tolerating the chemo I suspect if I hadn't had all of that. ……I would have delays and reductions in dose, which would have had all sorts of knock on medical consequences".

Women had to eat well to be strong and to continue with treatment, yet making sure that they ate nothing that was contra indicated for the treatment.
"But ready meals do contain additives and things which may not be you know, sympathetic to …the to the treatment your receiving" (Respondent three).

In addition, being overly obsessive about what one ate or did not eat could also cause stress, which women felt was not conducive to their recovery.
"I must admit, I buy organic some of it. Some I don't. It's an expensive scenario really, and I think if you can't afford organic stuff that you think is going to make you feel better then you start to get anxious" .

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The evidence from our study suggests that most women self-managed their nutritional needs, sometimes with help from family and friends. The concept of self-management relies on the individual's ability to manage their symptoms, treatment, physical and psychosocial consequences and life style changes inherent in living with a chronic condition (349). Some of the practical changes and reasons for changing diet are individualistic and based on each woman's needs, and to an extent demonstrating each woman's perception of the role of nutrition in their life after a diagnosis of ovarian cancer.

8.4.3 Theme 3: Availability of diet and nutritional support and advice in clinical settings

Results from study A show that women whose eating habits had changed by the time investigations for their cancer begun also had worse nutritional status. Furthermore questionnaire results show that more than half of women reported not systematically receiving information and support from health care professionals during treatment. The information sought from the public domains about foods they should eat or avoid was thought to be often contradictory. Results from the focus groups elaborate the dietary and nutritional support women received.

Two women had been referred to a dietician from the onset. They had first presented with advanced disease characterised by distended abdomen and severe loss of appetite. One reported that her weight had been 'falling off'. They were counselled and one had nutritional supplements prescribed. Both considered the support sufficient for their short term needs. This support had not continued beyond the acute phase.

"I did (receive nutritional support), but only because I just was not eating at all. I had a lot of fluid in my abdomen and I just could not eat. I felt full up all the time so they got the dietician to come and see me" (Respondent one)

Respondent two had received some nutritional information from her CNS. This had come later in her cancer journey when eating was no longer a problem. She

said "*I found that I could eat, but she (CNS) did ask me about the food, I presume actually had she you know been there earlier…*". She was implying that had the CNS been involved earlier, she might have been helped when she needed it.

Other women had not received any nutritional support. They recalled that there had been nothing asked about their diet. "

"*Doctors themselves are no help at all. They just say eat what you like. That's what they say to you and if you talk about a special diet like I was on … I'm laughed at you know. Not loud but kind of say well, you know but if it makes you happy then of course carry on*" (Respondent five).

The chasm between patient need and clinical support was further revealed by respondent six who thought, "*The doctors are slightly cranky about considering your nutrition*". The expressed lack of support is particularly disconcerting considering that physicians and other health care providers have a unique opportunity to guide cancer patients toward optimal lifestyle choices, to optimise the survivorship trajectory regardless of the individual's survivorship phase (157).

There was possible breach of moral and ethical codes around the management of patient's nutritional needs where weight was monitored and the patient informed that it was dropping each time yet there was no follow-up or a management plan for it.

"*I remember being weighed and being told the weight had dropped but I don't think that was followed up by a question*" (Respondent three).

Women emphasised that "*diet is important very important in any kind of illness and even more so in the cancer patient*". However they also felt let down that doctors in particular did not '*have time*' to discuss these important aspects of their lives.

"*They told me the plan and I thought yes, that has to be the right road to go. Medically they did, but diet wise it wasn't considered*" (Respondent one).

Nutritional information if/when received was found to be helpful. Respondent three although admitting that she was over the worst when she discussed nutrition issues with her CNS said of the information given to her regarding eating foods high in protein;

"I was spending a lot of time in bed, ...that was a really good point which I didn't know before …..that was helpful because obviously ….if you are in bed if there are things you can eat which actually might help slow down the muscle wastage when you actually are so petit you can't do a lot of exercise that's a good thing".

Most women voiced a lack of coordinated support from clinicians to help them manage diet and lifestyle changes they believed would aid their recovery. They also expressed that the information they were given in the form of leaflets or that which they found in the public domain was often confusing.

"..*The booklets that you pick up while you're sitting and waiting to see the doctor, you can pick every booklet that's there and obviously with time progressing you want to focus on getting better. You know, so then you think I want to do something now that's going to get me better. You know, be as positive as you can about these things but information that's fed to you, I feel, is contradictory in some areas.*" (Respondent eight)

Women self-managed their nutritional needs. Most stated that family and friends had helped them through some of the difficult times. The next theme explores the challenges women faced regarding their food and dietary intake because of the cancer.

8.4.4 Theme 4: The physical and emotive impact of disease, symptoms and effects of treatment on diet and nutrition

An ovarian cancer diagnosis can have a strong psychological impact on the survivor, due in part to the high mortality and often advanced stage of disease at diagnosis (350). Our results in study A show that women identified worry/anxiety about a possible/confirmed ovarian cancer diagnosis as one of the reasons they

had changed their diet. The emotional and psychological impact of the diagnosis and treatment can affect all aspects of a woman's life including decisions over diet and nutrition.

Women experienced a range of emotions; the pendulum swung from the very negative emotions such as frustration, being angry with their bodies, grief, shock, sadness, isolation, and anxiety to joy of still being alive. Sixty seven year old volunteer 50039 expressed frustrations of the restrictions to lifestyle and dietary intake saying;

"The pain on either side of stomach is really bothering me. I am restricted by pain and pressure in stomach, getting fed up".

Feelings of guilt and blame arose from suspicions that one's previous lifestyle may have contributed to causing their cancer,

"I know one of the questions that I ask for sure is why me? What have I done? …drinking; been doing that since about 18, I'm now 64. Whoops, could that have caused it? Then you look at the things you're eating. Then you think you shouldn't have been eating that. Could that have caused it? And you do question that. What you've done in your life to induce these things" (Respondent eight).

Acceptance and adaption followed the period of questioning and blame. The same respondent emphasised that it was a "*huge effort*" to accept that one was "*never going to get the same life because it's not the same any more. You can't do the same things that you did, you know. And it is different and I think mentally, dealing with that, to me, was very hard. I found that really hard*".

She was emphasizing how difficult it was amongst other things, to go to a restaurant with her sister and not be able to order her favourite food because she believed it to be contraindicated for her diagnosis.

Difficulties were compounded by feelings of isolation on the cancer journey

"You're completely alone with this thing… You know, you're anxious all the time. I am about what I am eating or not…" (Respondent five).

Women described their vulnerabilities and uncertainty about implementing dietary changes. Respondent two revealed how some of the uncertainties were rooted in the fear of derailing treatment;

"….my goodness maybe if I have that one additive you know I'm jeopardising my whole recovery. 'So I found that whole what I call the extreme healthy stuff quite terrifying".

There was perpetual weighing up of whether foods or certain types of nutrients were contra-indicated or might interfere with treatment. It was an additional anxiety alongside battling treatment effects, fear of disease relapse or living with relapsed and untreatable disease.

The difficulties of the burden of the cancer diagnosis and symptom management were detailed in the focus group. However, loss of function, hobbies and control were sometimes as frustrating especially if they affected the role of the woman as a food maker in her home. 82-year-old volunteer 50077 in free text lamented; *"I've lived a very healthy life. ….diet always lots of fresh fruit & vegetables. Home cooked meals. Not too much red meat. …..Large garden and grow my own vegetables until this year".*

The stress and lack of motivation to continue making choices that were believed to be ideal could be overwhelming even for the more determined woman.

"..Things that are very difficult to do, I actually think you get to a point where you just think it just isn't working" .

Respondent six was referring here to the difficult choices she had to make trying to avoid "*fruits and vegetables that are sprayed with chemicals*", and then trying to eat organic foods as much as possible, which was "*expensive and had implications*". She stated that she had relaxed somewhat because '*things are*

alright at the moment. If they were not I suspect I would become obsessive about it again".

Sometimes the challenges were about seemingly simply issues. Respondent five found it difficult to adjust to the healthier but "*boring*" food options. She conceded that people who were vegetarian by choice would not necessarily hold the same view. She felt that it was

"*Difficult when you are a meat eater and have to become more vegetarian*".

In the midst of the difficult challenges, women adopted some coping strategies which included acceptance, taking control, positive thinking and action, and reliance on religious beliefs.

Acceptance was important, and it helped to ground participants to their new normal. Psychological resilience has been suggested to represent a process of adapting well in the face of adversity (351). Patients who employ positive framing are thought to be better able to initiate active coping behaviours and tend to experience better QOL (352). Respondent two, a lawyer, felt that for her it was important that treatment or nutrition intervention programmes made her feel as if she was in control and had a choice,

"*It was very important that I felt I had a choice I knew I didn't really but yes I wanted to be guided but not told...*"

Positive thinking and spirituality have been said to help discern meaning from a cancer experience and to maintain hope (353). Respondent 4 who had reported she had no family in the UK, showed how her faith kept her positive and demonstrated psychological resilience saying;

"*.. I don't depress about it. I have my faith about what is happening to me…. I have to be strong I cried for that time when they told me…..*"(Respondent 4)

The same woman reported that she had not changed her diet, had a good appetite and ate her regular food.

Women outlined some of the positive actions that helped them. Often it was things that in health can be taken for granted, such as walking or gardening. Growing one's vegetables and herbs helped (Respondent two),

"…I've been planting herbs. …therapeutically it has been a fantastic joy… But I look at this little Belfast sink with some cut and come again lettuce and I think well and that's my lettuce. I have grown that and I go and pick it so it becomes a positive focus in an environment where there are a lot of things you can't do at some stage"

The daily dietary concerns of women diagnosed with this disease were clear and many. Women tried everything they could to "*help their bodies to heal themselves*" to "shrink *whatever was going on*" etc. In the process they experienced a range of emotional and psychological difficulties following their diagnosis. Their stories told of resilience and determination. Individuals prepared to fight, not just for quality of life, but also for survival. Fear of death was frequently on the background.

'……Nobody wants to die so that's very important' (Respondent five)

The emotional and psychological burden of an ovarian cancer diagnosis is unavoidable. However effective support systems can help ease some of the weight. The next theme explores some of women's views on how their nutritional management could be better managed.

8.4.5 Theme 5: Meeting diet and nutritional needs more efficiently

Study A showed that more than half of recruited patients reported not routinely receiving nutritional intervention throughout their treatment. This was despite the fact that the majority of women reported that their diet and food intake was already affected prior to treatment. The evidence suggested discrepancies between nutritional challenges and the endeavours taken to counter them in the clinical settings.

Women had ideas about what would constitute effective diet and nutritional help. It had less to do with actual nutrient supplements, and more about suitable guidelines for navigating the difficult journey of eating well in the face a cancer diagnosis and its treatment.

*"I'm saying if it (leaflet/booklet) gives you a guideline. …Whereas if you've got no idea. Myself, I really didn't have a great idea …You know, you're not always aware… and I think you need to be made more aware personally" (*Respondent eight)

For respondent one it was about any intervention being an integral part of the treatment process.

"I remember very, very clearly reading the side effects of the treatment of the chemo that I was having, Taxol in particular... It could be that there is a paragraph making it clear that that it could affect your eating habits..."

Respondent two who suffered from severe constipation, resulting intense headaches which she interpreted as possible spread of the cancer to her brain, said she would have welcomed information that clearly stated "*with the chemo you may find digesting these foods difficult because ….it's affecting your gut".* She emphasised that *"how it's phrased"* would be important.

Phrasing was repeatedly highlighted as an important aspect of any information/advice provided. Respondent three suggested that a leaflet needed to include "*clearly marked out reasons why/why not certain foods are good/bad for people on chemotherapy. ..Not vague".* Respondent six also thought that a leaflet should be "*broad, clearly outlining potential challenges and counter measures" so* that women could apply them if they suited their need. That way you would *"take what you need when you need it"*

Some participants suggested that there should be a consultation with a member of the clinical team in the first instance, to discuss and hand out nutrition information/leaflet. A clinical nurse specialist (Macmillan nurse) or dietician were

suggested as being best placed to provide this support. Respondent two felt that it would *"in fact probably be useful not to have yet another person"* added to the long list of specialists that women already see during the initial stages of diagnosis and treatment. *"Simplicity would be really helpful,"* she added.

Respondent eight felt that discussing individual nutritional needs with a health care professional, even as a one-off event would be more informative and *"better than someone saying go away and read this".* Respondent seven concurred and eagerly anticipated a time when diet could be a subject between members of the clinical team and patients.

"It could be an appointment to see the Macmillan nurse to discuss diet, our nutritional intake. …It's lovely to feel that it could be possible".

Further suggestions were made of the leaflet having a contact number in case women needed further clarification,

"..and you could have a contact …if you would like to discuss this further with somebody." Respondent two

The premise that nutritional support should be provided as soon as possible once a diagnosis is confirmed to prevent nutritional deterioration and possibly delay or offset onset of cachexia is widely accepted. Indeed this work shows that women whose diet has been affected by the cancer and its effects before diagnosis had worse baseline nutritional status. Women's views on the timing of dietary/nutritional advice are therefore important.

Three participants rejected the idea of nutritional intervention from the onset.
"I don't think I would have been very receptive (around the time of diagnosis)" (Respondent seven)

She had been unwell and presented with large ascites. Respondent eight concurred, elaborating that a diagnosis of ovarian cancer comes with many psychological challenges that take precedence over issues of nutrition;

"When you are diagnosed with it, your brain is concentrating on being diagnosed and the thought to think, I've got to worry about food and this and that. That wouldn't have helped me one little bit I'm afraid".

Respondent 2 who had primary surgery and was opposed to very early intervention thought that *"to have been able to go and have a chat with somebody at the pre-chemotherapy assessment"* would have been more *"helpful".* This point is usually 2-3 weeks after surgery and 1-2 weeks before the start of chemotherapy. She felt that at this point the consultation could be best tailored to support women who have post-operative complications but also prepare them for the possible challenges of chemotherapy treatment.

On the contrary, Respondent six was one of two women who felt that they "*would have been receptive from day one".* She had proactively sought to eat to boost her immune system from the onset. She also strictly followed the Budwig diet throughout her treatment in the hope that it would repair her DNA to start producing normal cells. These contrasting views suggest that interventions would need to be well thought out and take into account the individual needs of women. The diverse views support the need for a face-to-face consultation with a health care professional during the treatment phase.

Two out of 8 women who forthrightly rejected the idea of early intervention had post-surgical complications and would have been more receptive upon recovery but prior to the start of their chemotherapy. Three participants who had surgery as first treatment but did not have severe symptoms/complications would have been more receptive to immediate intervention. Two of three women who received chemotherapy as first treatment had also received nutrition intervention on the onset. All three women suggested that non-acute intervention would have been well received around the start of chemotherapy. This time point coincides with that suggested by the two women who had surgery and were opposed to earlier intervention. These findings suggest that women who have acute nutritional needs when they first present such that their treatment may be compromised were identified and provided with professional intervention. Women who developed acute nutritional challenges after surgery would not have been

receptive to intervention during that time. The women who had no complications and tolerated food intake well would have been more receptive from the beginning. This apparent paradox may prove challenging for the design and delivery of an effective intervention.

Women acknowledged that incorporating a nutrition programme would not be easy. It is "*quite difficult to generalize about what is good for individual people",* Respondent six stated adding that *"nutrition in cancer care, it's just so much more complicated because ultimately you have to also look at the psychological expectations. What feeds your positive bits? What feeds your negativity?"*

Developing an effective intervention is beyond the scope of this thesis. However women's views and suggestions provide a basis for making recommendations for the development of such an intervention. This qualitative study has demonstrated that nutritional needs evolve depending on the impact of the underlying disease and symptoms and also women's own perception of the importance of diet and nutrition.

8.5   Summary and discussion of patients' perspective study

This chapter presented women's perspectives on the importance of nutrition to a woman who is diagnosed with ovarian cancer starting right at the beginning of their cancer journey. Most women felt that nutrition was very important to them. Although it is possible that the self-selected women participated in focus group discussions were more nutritionally aware, evidence suggests that women diagnosed with ovarian cancer are motivated more than other cancers, to seek information about food choices (157). Many women stated that making daily choices of what to or not to eat particularly during treatment was often accompanied with anxiety. The anxiety was due to a lack of structured support by the clinical team, from conflicting evidence in literature, the fear of compromising treatment, and the difficulty of sustaining motivation. Women made specific changes to their diet and eating habits based on the effect of the disease

its symptoms and treatments, perceived physiological need and also the time point in their journey with the cancer. The HAPA model suggests that women who successfully implement and sustain desired dietary and nutritional changes are those who have higher self-efficacy. They believe that they are sufficiently capable of exercising control over the difficult behaviour.

The emotional and psychological burden of an ovarian cancer diagnosis was worsened by perceived lack of support in an area of care women considered central to their well-being. Feelings of being alone, unsupported and sometimes patronised by clinicians dedicated to supporting them in their lifestyle choices were common. Women had converging views on an ideal support package being a leaflet or booklet. It would cover a wide range of nutritional issues but be well summarised. This leaflet/booklet would be given following face-to-face consultation with a designated member of the clinical team. The context of the intervention would be to highlight potential negative side effects of treatment, such as constipation but mainly focus on the positive things that women could do if they faced difficulties. Women wished for this guidance but not to be told how to self-manage their nutritional needs. The suggestion of guidance and not being told implies a flexible relationship between the patient and the clinician. This flexible relationship would then consider the complex phenomena of where people live, what is available, what they can afford, how much time they have to dedicate to the process of procuring and preparing food, and even what we is allowed in terms of family traditions, societal, religious, and gender norms (110). This all add more dimension and possible complications that need to be considered when planning intervention.

The nutritional challenges and possible interventions presented here focus on the diagnostic and first line treatment phase. This was by design, to reinforce our understanding from the women's perspective of the challenges and possible intervention for this very difficult time in a woman's life. This qualitative study complements study A, which assessed nutritional status of women during the same period. The presence of women who had been living with the disease for

longer in the group discussions served to highlight that nutritional challenges are not limited to this specific period, but extend throughout the survivorship phase. The challenges and needs are different depending on the life stage of each woman. The current American, nutrition and physical activity guidelines for cancer survivors (157) acknowledge these differences and suggest that during active treatment, some of the overall goals of nutrition intervention should be to prevent or resolve nutrient deficiencies, maintain a healthy weight and preserve lean body mass. These change to lifelong goals such as weight management, healthy diet and an active lifestyle after successful treatment.

The approaches of individual women's management of their diet and nutritional needs were as varied as the women themselves. However the underlying processes were often not random. Closer scrutiny of the reasons given for wanting to or making dietary changes and navigating the challenges following their diagnosis revealed that the behaviours can largely be explained through the HAPA health change behaviour model. This self-regulatory framework appropriately makes a distinction between setting goals and pursuing them. Some women articulated setting and pursuing goals, such as when one expressed successfully changing her diet to be more aware of the glycaemic index of things relative to the amounts of sugar. In the observational study A, women were found to have the intention to act on their diet by eating healthily (avoiding sugary and fatty foods while increasing their fruit and vegetable intake). However these behaviours were not evident by the end of treatment, suggesting that they had either not pursued/engaged or had failed to maintain intended behaviours. Part of the reason is that maintaining the chosen actions (dietary changes) was outlined as being very difficult, an aspect clearly identified by the model. Women expressed that it was difficult to pursue desired eating habits and that they often felt like giving up. Risk assessment was also evident in some women who articulated being "terrified" of jeopardising their recovery by incorporating certain diets or nutritional supplements and rather preferred to take instruction from their physicians. It was evident from some women that they implemented coping planning, based on their individual circumstances by just trying to eat anything they could no matter how small.

Not all women reported that they changed their diet in both studies. Some perceived that their diet was sufficient for their needs; others would have liked support and guidance in making the changes. It is known that nutrition knowledge has a profound influence on food choice and nutrient intake (354) and thus individuals' awareness or assumptions about food are key determinant of food choices (355). The individual differences between women who reported changing their diet and those who did not have not been analysed here, but the two women in the focus groups, who were most vocal and reported a methodologically approach to managing their diet with specific intentions of cure or maintaining muscle mass and treatment were a sociologist and a lawyer. They seem to exhibit high levels of self-efficacy, which may have helped them to sustain the changes overtime.

9   General discussion

9.1   Nutritional and biochemical statuses

Our study is the first that we know of, to prospectively assess serial markers of nutritional status in a homogenous ovarian cancer population with a control group. Our population specific study enables us to make recommendations for tailored future interventions. Assessments were carried out prior to the commencement of treatment (baseline); during treatment and at the follow-up outpatient visit after completion of the acute first-line treatment of surgery and/or chemotherapy. This enabled us to identify that weight, BMI and dry lean mass and well as biochemical markers; prealbumin, albumin and CRP were already impaired in some women by the time they presented to the hospital for investigation and treatment for ovarian cancer. Also that some markers did not return to normal by the end of treatment.

The self-reported weight change for the 3-month period prior to treatment provided valuable information. Three types of weight change were identified; 1) weight loss; 2) weight loss then gain; and 3) weight gain (page 130). The relevance of these findings is in that significant weight loss (>2%), the threshold for identifying the risk of cachexia may already have been reached by the time women present at the hospital. Forty three percent of cases reported significant weight loss while 17% gained weight in this time. Weight loss at presentation has been associated with poor survival, reduced response to treatment, and poorer quality of life (QoL) in gastrointestinal and lung cancer patients (173, 356, 357). The two main mechanisms of weight loss relate to depletion of body fat, a condition that reflects a prolonged, severe, negative energy balance and skeletal muscle wasting due to a fall in skeletal muscle protein mass (sarcopenia), a situation that reflects the clinical condition of the patient (358). Sarcopenia can be fatal as it is characterised by progressive weakness and fatigue and is not responsive to nutritional intervention towards the end of life. This reinforces the need for early intervention in patients with ovarian cancer which has spread into the peritoneum, most of whom have advanced disease (75%) at the time of initial

diagnosis (359). Moreover evidence suggests that serous tumours, which are rarely detected before they reach an advanced stage and are associated with most deaths, would already have progressed to a late stage nearly 1 year prior to their discovery (185). Table 3 showed that about 75% of ovarian cancers are of a serous type. Weight gain prior to treatment is likely to be due to large tumours and accumulation of ascites which is associated with advanced disease. Weight gain during treatment can be due to; 1) less activity due to chemotherapy side effects; 2) eating more for comfort of due to some medications which may increase appetite; 3) fluid retention such as ascites or oedema; and 4) chemotherapy treatment e.g. which sometimes contains steroids that can cause fat deposits to develop.

Abdominal distension was recorded in 56%, and ascites in 80% of women with stage III and IV in our study. These provide a confounding effect for non-discriminate markers of nutritional status such as weight and BMI. However our results also showed that despite the presence of ascites, some women exhibit overall weight loss. Therefore weight change remains the simplest way to indicate changes nutritional status. Women diagnosed with ovarian cancer viewed gaining weight as positively impacting their quality of life (OR = 2.485; p = .06) while women in the control group, as might women in the general population, associated it with negative well-being (weight: r= -0.52; p < .05) (Table 24). Hess et al., (206) also found weight gain during chemotherapy treatment for ovarian cancer was associated with improved overall survival. Weight decreases of >5% and 0-5% led to survival of 48.0 and 49.3 months respectively and weight increases of 0-5% and >5% resulted in survival of 61.1 and 68.2 months respectively. Like us they found no evidence of an association between change in body weight and disease progression. In our study, 55% of cases with stable weight and 50% who gained weight by the end of treatment had residual disease seen on end of treatment CT scan. The United States National Institute of Health includes weight loss as one of the key common Terminology Criteria for Adverse Events (CTCAE) in clinical Trials (360).

These findings are interesting in relation to contradictory reports in other cancer sites. Higher BMI has been associated with recurrence and decreased survival in breast (361) and prostate (362) cancers. Hess at al suggest that there may be a hormone related explanation for this. Nearly 80% of breast cancers are oestrogen receptor (ER) positive (363), and increased or prolonged circulating oestrogen promotes the initiation and progression of breast cancer. Excess adipose tissue enhances circulating oestrogens, which in turn contributes to the increased risk. Ovarian cancer, on the other hand, has not been shown to be hormone-dependent; with less than 40% of the cancers demonstrating ER positivity (364). Weight gain during treatment therefore seems to have a protective effect in women diagnosed with ovarian cancer.

A median BMI of 28 (IQR: 23-27) for menopausal cases suggests that women in our study were generally overweight or obese despite reports of recent weight loss, changes in dietary patterns, depleted biochemical (prealbumin and prealbumin (19%) and presence of inflammation (increased CRP (67%)). High levels of obesity in menopausal women are in line with population trends that indicate a rise in the prevalence of obesity among older adults (365, 366). There is concern that existence of excess fat could mask decreased muscle mass resulting in 'sarcopenic obesity' (367). Sarcopenic obesity occurs with the aging process but can be exacerbated by disease and malnutrition or cachexia. Increasing obesity trends can render the lower cut off of BMI<20 to identify cachexia impractical. This point is highlighted by the participant who lost >40% of her baseline body weight by the end of treatment yet her BMI remained within the healthy range. A BMI >20 is not indicative of health in ovarian cancer patients as it reveals nothing of the underlying body composition, the contribution of excess ascetic fluid and inflammatory processes. The association between BMI and adverse outcome in ovarian cancer patients is not clear although a meta-analysis by Protani et al., 2012 (368) found overall evidence that the risk of survival among obese women is 15-20% less than in women with a healthy BMI regardless of whether BMI was measured before diagnosis, at diagnosis, or at the commencement of chemotherapy. Potential confounders such as ascites that may have increased the risk of death were not accounted for. The practice of

'dose capping' chemotherapy drugs based on body surface area in some centres may also account for decreased survival in women with a high BMI (369). A more recent study (193) of pre-diagnosis BMI categorized into underweight, (BMI <18.5kg/m^2), normal (BMI between 18.5 and 25kg/m^2), overweight (BMI between 25 and 30kg/m^2) and obese (BM>30 kg/m^2) failed to show an association of BMI with all-cause or ovarian cancer specific mortality.

We also found, as expected that menopausal cases and controls had the highest body fat across all time points (Figure 18); premenopausal cases had the least. Premenopausal cases lost more body fat during treatment and had a lower body fat % at the end of treatment than at baseline. Menopausal cases gained body fat during this period. This was in contrast to lean mass which increased overall (baseline to end of treatment) in premenopausal cases (65%, 72% and 68%) compared to (59%, 60%, and 58%) in menopausal cases at baseline, during treatment and at the end of treatment respectively. We speculate that the increase in lean mass during treatment is linked to intravenous infusions during surgery or chemotherapy sessions. These findings show that overall younger women gain lean mass while older women gain body fat. Lean mass's importance is as a determinant of the pharmacokinetic variability of chemotherapy treatments (370-372). Patients with a low lean mass demonstrate a low drug metabolism/clearance. They tend to be relatively overdosed and have higher rates of chemotherapy-induced toxicity (373). The role of body fat in cancer survival has also been examined. Torres et al., (179) investigated the role of pre-operative body composition measures using CT images to predict outcomes in patients with ovarian cancer. In their retrospective study of 82 patients with stage IIIC/IV disease, fat composition was the strongest independent predictor of poor survival with a greater risk of death at lower levels of subcutaneous and muscular fat or total fat. BIA is not able to predict the different types of body fat. Further research is required in this area.

Our findings on the lean mass of menopausal women concur with those of Gil et al (374) who assessed Body Cellular Mass (BCM), a component of lean mass,

and found that women do not re/gain significant BCM during the short term, up to 12 months from the start of treatment. They also found that changes in body composition over the short term are restricted to alterations in body fat. Our results contradict these findings for premenopausal cases. We also found that in our cases changes to dry lean mass (another component of lean mass) had already occurred at baseline assessment. This was evidenced by the significantly lower dry lean mass of premenopausal cases compared to premenopausal controls ($p < .05$), (Figure 20). As expected menopausal cases and controls had the lowest dry lean mass, which decreases with age. Sub-group analysis by the study median age of menopause enabled us to show meaningful differences in BMI and body composition of younger versus older women. These findings shed light on who might benefit from targeted intervention. For instance menopausal women gain body fat, but may be at risk of sarcopenic obesity. If sarcopenia is identified those women could benefit from nutritional intervention. Some of our subgroup samples sizes were small and the results therefore need to be interpreted with caution.

Our study found that at baseline, the biochemical markers prealbumin and albumin were depleted in 32% and 19% of cases respectively. More had borderline levels hovering 1-3 units above the lower cut-off points. CRP was elevated in 67% of the cases. At the end of treatment 9% of cases had low prealbumin, 25% had low albumin and 24% had elevated CRP. Prealbumin is the preferred nutritional status assessment method for this study. Like albumin, it is a negative acute-phase protein, which can be affected by inflammation. However its half-life of 2–3 days allows it to be used as a more reliable indicator of acute changes in a patient's nutritional status (375). It correlated well with other outcomes in our study including change in diet (shown in appendix 6), change in weight and overall health status/quality of life shown in Table 35. Others have also suggested that prealbumin is the preferred marker for malnutrition because it correlates with patient outcomes in a wide variety of clinical conditions (376). Moreover, for cases, it significantly increased ($p < .01$) between baseline and the end of treatment despite the fact that some women had residual disease. Cases had significantly lower prealbumin than controls at baseline ($p < .01$) but not at

the end of treatment. Long term protein depletion and inflammation were confirmed by low albumin at baseline in 19% of cases with another 14% with albumin just 1-3 units above the cut-off level. Albumin has been found to be low in women diagnosed with ovarian cancer in other studies (208, 212). Low albumin in our study included some women with stable weight and those who gained weight, confirming on-going inflammatory processes. That more than 50% of the albumin pool is located in the extravascular compartment and only about 5% is produced by the liver daily, means that a patient's day protein consumption has little effect on their albumin level (377). That, and its long half-life of up to 20 days and potential to be affected by a number of inflammatory conditions, renders it an unreliable marker of nutritional status (378). Albumin correlated well with quality of life and was associated with the presence of ascites and late stage disease These all confirmed that it is a marker of wellness.

Epidemiologic studies suggest that in patients with several types of solid cancers, elevated circulating levels of CRP are associated with poor prognosis, whereas in apparently healthy individuals from the general population, elevated levels of CRP are associated with increased future risk of cancer of any type, lung cancer, and possibly colorectal cancer, but not breast or prostate cancer. The association between CRP and cancer risk is not well understood but may be due to; 1) causality: elevated CRP levels cause cancer; 2) reverse causality: occult cancer increases CRP levels; 3) or confounding: where a third factor such as inflammation, increases both CRP levels and the risk of cancer. Our findings highlight the need for nutritional intervention from early on. We revealed that some women lose weight, lean mass, in the case of older women and also have depleted serum proteins and inflammation (elevated CRP) at baseline, all pointing to ongoing cachectic processes. The presence of residual disease in some women, and the high recurrence rate (up to 50% within 18 months of diagnosis), indicate an imminent need for second line of treatment at a time when the women's bodies will be weaker to deal with it. For these reasons targeting interventions at the earliest point when a confirmed diagnosis of late stage ovarian cancer is made, would be the ideal.

9.2 Dietary intake

Sixty-four percent of cases reported making dietary changes in the 3-month phase leading to treatment. Dietary changes were associated with advanced disease (stage III and IV) ($p < .05$). Women who reported dietary changes were overall less well with low a prealbumin ($p < .01$) and albumin ($p < .05$) (Table 29) and were more likely to be treated with neo-adjuvant chemotherapy treatment ($p < .05$). Women with early stage disease made fewer changes. There is a school of thought that women with early stage disease have biologically less aggressive tumours than women with late stages (379, 380). This is supported by the evidence that few serous ovarian cancers present at stage I, most present at stage III or IV. Changes to diet were largely reactional and/or sometimes involuntary in response to symptoms such as loss of appetite, feeling full too quickly, fluid in the abdomen and anxiety about cancer or fear of the consequences of consuming an unhealthy diet while faced with a diagnosis of cancer. The effect of "eating healthy" could not be estimated in this study due to the small sample size. Besides, 'healthy eating' is a subjective term, it is debatable if its adoption when women are facing major surgery and chemotherapy treatment can be considered as 'positive'. Moreover problems with digestion, loss of appetite, nausea and vomiting in some patients, makes maintaining the necessary caloric intake difficult (359). The symptoms force patients to spontaneously reduce their calorie intake. However healthy eating, i.e. eating foods that one believes will maintain or improve their health status was an important concept, as was revealed in the focus group discussions.

We did not observe any specific dietary patterns or preferences during the treatment phase, despite more than half of the women stating that they made dietary changes. The single most common reason for changing diet in this phase was change in taste. Cravings, increased appetite, and wanting to "eat healthy" were also mentioned. Gruenigen et al in 2006 also found that women with ovarian cancer did not exhibit large fluctuations in intake of fruit/vegetables and fat following surgery and during chemotherapy (381). This affirms that the changes we observed prior to treatment were related to signs and symptoms, anxiety or

possible 'intention to please' or to be seen to eat healthy. Change in diet during treatment was associated with weight loss ($p < .01$) and a decrease in dry lean mass ($p < .05$). Since there is no evidence that residual disease had an impact on weight loss during treatment, it seems that how a woman responds physically and emotionally to her treatment plays a more significant role in her diet choices.

9.3   Quality of life

Our analysis of individual EQ-5D dimensions for cases and controls (Figure 27 and Figure 28) revealed that the prevalence of pain/discomfort and anxiety/depression was higher in premenopausal cases than their menopausal counterparts across all time points. These findings are consistent with a recent literature review by Astrup at al., (2016) (382) showing that among oncology patients, younger patients significantly reported more symptoms that older patients. Their review found no evidence that this was due to younger patients receiving more aggressive treatments. In this study, it was expected that controls would report similar levels of problems to cases at baseline because pelvic pain has been found to be the reason women present to general gynaecological departments for investigations (94% of the time) (383). However the relatively high symptom burden at the end of treatment in controls is baffling. It is possible that controls had chronic problems or had not fully recovered from surgery. We found the frequency of anxiety and depression in our study to be higher than previously reported for ovarian cancer patients. In a meta-analysis by Watts et al., (2015) (384), depression was found to be highest prior to treatment (25.3%), decreasing to (23%) during treatment with a further decrease at the end of treatment (12.7%). They reported anxiety separately. It was lowest prior to treatment (19.1%) then rising and plateauing 'during' and at the end of treatment (26.2% and 27.1%, respectively). The differences between these results and our own may be partly explained by the differences in the instruments used to collect data. The Euroqol EQ-5D records 'some problem', which women might complete as 'no problem' if they were asked a 'yes' or 'no' question as was the case with the study specific questionnaire. It is also possible that the NHS Trust where recruitment took place saw more complex cases that would have been the case

prior to the setup of referral centres. Watts et al., also suggest that the onset and progression of psychological distress in patients with cancer is likely to be chronic, with peaks and troughs of severity that occur during key stages of the cancer journey. In the general population, depression disproportionately affects women, with a lifetime prevalence of 21% (385).

We found no association between all nutritional status outcomes (weight, BMI, body fat, dry lean mass and lean mass) and problems with all 5 dimensions at baseline, during treatment and at the end of treatment for cases and for controls. There was significant association found using the Kruskal Wallis test between pain/discomfort and extracellular water, $p < .05$ and a borderline association $(p = .06)$ between pain/discomfort and total body water at baseline. These associations were found when using pain data from Euroqol EQ-5D and not medical records or the study specific questionnaire (affirming the issue of different data sources sometimes yielding different results). Since BIA analysis is meant to account for fluid changes, we expected to find some association between ascites and extracellular water. These associations provide a possible link between ascites and total and extracellular water in that ascites causes distension which in turn is associated with pain/discomfort. Prealbumin was the only outcome to be significantly associated with difficulties with usual activity, $p < .05$ at baseline for cases. This suggests a link between nutritional status and women's abilities to carry out their daily activities. While Devlin et al., (2017) (386) analysed the contribution of each dimension of the EQ-5D to quality of life in prostate cancer patients, we found no evidence of such analysis in the nutritional status of ovarian cancer or gynaecological patients.

On the VAS scale where 0 was the 'worst' health and 100 the 'best' health, cases were shown to have lowest scores at baseline 50 (range: 10-100), 57 (range: 0-100) during treatment and 70 (range: 20-100) at the end of treatment. The related sample Wilcoxon signed rank test showed that the difference between 'during treatment' and end of treatment was, $(p < .05)$. The Kruskal Wallis showed a significant association between health status and the presence of ascites at

baseline, *p* < .05 and between health status and type of first treatment, *p* < .01. We know that women who are treated with chemotherapy first have more advanced disease and or comorbidities. It is therefore logical that this would be reflected in their perception of their overall health. We only observed significant differences by the age of menopause, during treatment where younger women had higher health status scores. This could be explained by the fact that younger women tend to have early stage disease and therefore are likely to have successful surgery. Alternatively, in other mainly older women it may have been too early in the treatment process for the benefits of chemotherapy to be felt. Controls had lower overall health status throughout. Median scores increased from 45 (range: 3-95) at baseline to 66 (range 8-93) at the end of treatment. Our findings contradict others who have found cancer patients to have lower quality of life than other groups (384). Personal experience of the researcher with women newly diagnosed with ovarian cancer revealed a sense of determination by women to 'beat' the cancer. Perhaps there was a conscience effort to be 'positive' about treatment and the future which may have translated into higher health scores.

Spearman's correlation, (Table 26), showed that out of all nutritional, body composition and biochemical markers, prealbumin, (r = .478, *p* < .01) and albumin (r = .42, *p* < .05) were the only ones to positively and significantly correlate with quality of life at baseline. These findings confirm albumin as a marker of well-being. Significantly, they also show a strong relationship between nutritional status nutritional status (assessed by prealbumin) and quality of life. In their meta-analysis Lis et al., (387) found that studies that looked at nutrition and quality of life focused on weight and BMI. We have not found evidence of studies that used prealbumin in gynaecological patients. However, similar findings to ours were observed by Rambod et al., (2017) (388) in haemodialysis patients. They found that prealbumin correlated with both markers of nutritional status and inflammation without any statically significant interaction between dietary protein intake and inflammatory cytokine. Our study showed in Table 29 that low prealbumin was associated with changes to diet at baseline. Rambod et al., concluded that the clinical associations of prealbumin with quality of life and

survival (which they found) indicates that it is a useful marker to stratify risk even when patients have normal albumin. Prealbumin had a borderline significant correlation with quality of life in controls, (r = .494, *p* = .07) at baseline. Albumin was not assessed in these patients. Better nutritional status was found to be positively associated with better QoL in gynaecological patients (389).

Our study has shown that prior to treatment for ovarian cancer or benign conditions, women report problems with most dimensions of quality of life assessed using the Euroqol EQ-5D. Most of the problems persist particularly in younger controls. We also showed that quality of life is worst among controls, which was unexpected. Importantly we have shown a link between quality of life and prealbumin for cases and controls at baseline. Quality of life assessment could therefore be useful in identifying vulnerable patients such as younger women or those whose find it difficult to carry out their usual activities. Appropriate symptom management strategies would then be employed.

9.4 Women's perceptions of current nutritional support

Women in both our studies did not perceive that they are provided adequate nutritional support. Other researchers also confirm that patients and family caregivers express a lack of acknowledgement from healthcare professionals regarding cancer cachexia (390) and that they perceive physicians to focus on disease and treatment outcomes and not patient's individual experiences (391, 392). Nutritional intervention was associated with increased albumin (*p* < .05) in our observational study. This increase is likely due to helpful nutritional support/advice that improved patients eating habits and therefore wellbeing. The advice may also have helped women to eat well and continue with treatment, which improved their underlying health status. Nutritional intake (protein consumption in particular) and illness are the two most influential factors regulating hepatic albumin synthesis (393). It could also have been coincidental since albumin detects underlying illness (394), women with low albumin could

have been less well and therefore more likely to request help or be identified as needing help/support even though we found no evidence that low albumin was a selection criteria for intervention.

The intervention in our study was based on current practice and was ad hoc at best. We could not establish referral criteria (that is, on what basis women received intervention). The intervention itself ranged from patients being handed a Macmillan nutrition and cancer leaflet to counselling and prescription of nutritional supplements. Different members of the clinical team including a nurse, clinical nurse specialist, pharmacist, doctor or dietician delivered it. The goals for the intervention given were not always clear. They could have been to maintain food intake, counter certain symptoms such as pain, nausea etc., to increase nutrient intake to counter weight loss, or any combination of these. For these reasons, we cannot firmly conclude that the non-effect on other markers of nutritional status was due to the ineffectiveness of intervention. Halfdanarson et al., (244) in their systematic review and meta-analysis of the effect of diet counselling on quality of life in cancer patients found a borderline statistically significant effect ($p < .05$) suggesting that dietary counselling may provide positive impact on QoL. More evidence is required and another promising randomised controlled trial, Eating as Treatment (EAT) a health behaviour change intervention provided by dieticians to improve nutrition in patients with head and neck cancer undergoing radiotherapy has recently started recruiting in Australia (395). The results are awaited with much anticipation as their findings may be relevant to or need to be replicated/adapted in other cancers.

Although the role of diet and specific dietary constituents in survival from ovarian cancer is not clearly understood, women identified it as an important aspect of their recovery from disease and for their new life, living with a cancer diagnosis. Women changed their diet as early as 3 or more months prior to a confirmed diagnosis. The relationship between symptoms, advanced disease and change in diet is substantiated by the consistency of our findings with those of Goff et al (396) who showed that women experienced symptoms for a median of 2–3

months before consulting a health care provider and that women with advanced stage disease were significantly more likely to have symptoms than women with early stage disease. Unfortunately, lack of consensus among health care providers (159) on how to manage diet following a diagnosis of ovarian cancer means that women are inadequately supported. This lack of clarity permeates down to other mediums of communication and instruction such as books, the Internet and leaflets etc.). As a result women reported women are frustrated and feel alone in their quest for constructive information. Their diet management efforts often hampered by the difficulty in sustaining motivation, the negative side effects of chemotherapy and the need to satisfy cravings and increased appetite due to steroids and chemotherapy. Women made changes sometimes based on unfounded self-determined or Internet researched ideologies or myths such as consuming only organic foods, or the theory that "sugar feeds cancer". There is no evidence that high sugar intake increases the risk or progression of cancer, however, sweets and beverages are rich in calories and thus can promote weight gain, which may be undesirable. In addition most foods that are high in added sugar contribute little other nutrients to the diet and often substitute more nutritious food choices (157). There is no evidence either that organically grown vegetables and fruits are have more potential cancer-preventive constituents (157), although respondent six's perspective that chemicals used in production and preservation of non-organic food are her main concern cannot be dismissed without evidence. Recently diagnosed women talked more about immediate concerns relating to symptoms and surgery complications while women who had been living with cancer longer talked more about a healthy lifestyle. Diet and nutritional needs are therefore constantly changing and women have to adapt at each stage of their journey.

Women told of diet being one of the few areas they felt they had control over. This is common in cancer patients (397, 398). Focusing on the subjective experience of individuals through qualitative research provides insight into an additional layer of the complexity of this syndrome and the potential opportunity to incorporate psychosocial support for improving its management (399). Thus, understanding dietary change in the context of a behaviour change model may

help to develop effective ways to influence and positively alter behaviour. Diet and eating habits are a complex behavioural phenomenon that results from an interaction of many social, economic, religious, gender, health and practical factors (110). A sustainable change in eating habits therefore entails behaviour modification which is often difficult to achieve as it encompasses social, emotional and cognitive factors (275). Whether by design, because of symptoms or due to perceived lack of support by clinicians, women demonstrated varying degrees of self-efficacy in how they managed their dietary needs. Self-efficacy is the individual's belief in his or her capacity to execute behaviours necessary to produce specific performance attainments and reflects confidence in the ability to exert control over one's own motivation, behaviour, and social environment (281). The behaviours that were discussed closely related to some health behavioural change models in particular the 'Health Action Process Approach' (HAPA) (275). This is an open framework of various motivational and volitional constructs that are assumed to explain and predict individual changes in health behaviours. We observed the 2 implicit phases of the model; the intention to act (women stating that they were eating more fruit and vegetables or wanting to be healthy) and the post intentional volition or actual behaviour (mixed behaviours due to choice, side effects of treatment or stage of survival-relaxing rules when in remission). The model acknowledges that intention (to consume a healthy diet) is not a proxy for action (intake) (321). The verbalised concepts of a 'new life', 'helping one's body to cope better', anxiety from consuming unhealthy food and not wanting to die are in line with risk perceptions and outcome expectancies of this model. Moreover the emphasis on self-efficacy at each action, coping and maintenance strategy were well exhibited or desired by women. Support and provision of accurate information by health care providers would empower women to deal more effectively with barriers that arise in their journeys. This model explains how women responded to the intrinsic and extrinsic factors that determine their reaction to a diagnosis of ovarian cancer with regards to their dietary habits. Some immediately wanting to use their diet to promote healing, others wanting to change their diet but being restricted by health limitations etc. This understanding can assist future interventions/practice by incorporating techniques which promote healthy eating self-efficacy by using behavioural education such as confidence building, shaping positive attitudes towards health behaviours,

overcoming automatic negative thoughts (275) as part of the intervention. Some women stated that they wanted reassurance that they were eating appropriately while some admitted that they wanted support to make the right choices. These women could potentially benefit from interventions that also include confidence building and shaping positive attitudes. Our research confirmed that nutrition and diet are important for women and they expect clinicians to engage with this aspect of their care. Furthermore evidence suggests that interaction with health care professionals is more efficient in helping to modify behaviour (400) than information or awareness alone. It is important that clinicians are empowered through evidence to effectively carry out their role.

9.5   Women's needs and how they could be better met

Women conveyed that a one to one consultation with a designated member of the clinical team reinforced by a well-constructed leaflet for further reference would be an ideal form of intervention. Designing a diet-based intervention was not an aim of this research, however this information provides understanding of what might be an effective intervention approach in future studies. Emphasis is on a diet based intervention. The British Dietetic Association recommends that intake via ordinary foods and beverages is the first step in the process of providing nutritional support and that nutritional supplements are a second step which may be used for some people (401). Some authors have demonstrated the impact of contact with clinicians in affecting health behaviours and improving some nutritional outcomes. Bourdel-Marchasson et al (402) found that individual dietary counselling in older patients at risk for malnutrition during their chemotherapy treatment for cancer was associated with an increase in dietary intake although not with change in weight or decrease in mortality. Similarly Baldwin et al (403) found that dietary advice with or without oral nutritional supplements may improve weight, body composition and grip strength, sadly they found no evidence of benefit on survival. A large randomised control trial looking at the effect of individualized nutritional counselling on muscle mass and treatment outcome in patients with metastatic colorectal cancer undergoing chemotherapy is yet to report (404). The Enhanced Recovery After Surgery

(ERAS) (238), a perioperative treatment protocol introduced just over a decade ago which included early introduction of oral diet and fluids after surgery showed improved individual recovery that resulted in patients leaving the hospital earlier (405). It must be noted that early introduction of diet is only one component of this program whose underlying goals are to decrease variability in practice, reduce morbidity, enhance rate of recovery, and shorten postoperative length of stay (406). Other regular diet based forms of intervention have been through telephone interviews. Telephone interviews have been shown to successfully improve dietary intake (407) in a healthy population. None of the trials so far have been specific to ovarian cancer patients or have demonstrated improvement in survival in cancer patients. The impetus is to now evaluate the association between post diagnosis diet and ovarian cancer survival.

Preferred timing of the intervention was controversial; women who preferred it to commence as soon as possible around the time of surgery were likely to view nutrition as potentially therapeutic. They were prone to follow strict protocols of chosen diets such as consuming fruit and vegetables only, follow the Budwig protocol or consume only organic foods. The ideal time for the majority of women was suggested to be around the start of chemotherapy. This time seems more suitable for intervention for the following reasons; 1) a number of women are diagnosed and staged during surgery, 2) women who undergo neoadjuvant chemotherapy treatment undergo rigorous clinical work-up procedures to confirm diagnosis, and extent of the spread 3) ascites is likely to be well documented or drained at this stage and 4) nutritional issues arising from surgery can be addressed while also focussing on possible side effects from chemotherapy.

Malnutrition can negatively affect the clinical decision to resect tumour, which is the main and potentially curative step in the management of cancer or it can also necessitate a reduction in the dose of cytotoxic agents and/or modify the radiation timing between temporary or definite cessation of treatment (408). Stopping or delaying treatment can reduce time of remission and overall survival (409). Yet there are no internationally accepted protocols for nutritional intervention in the

management of disease related malnutrition (214). Furthermore cancer survivors receive inconsistent and non-evidence based advice from many sources about foods they should eat or avoid (157) which can be confusing. Our mixed method, multiple assessment technique research prospectively investigated changes in the markers of nutritional status in women undergoing first line treatment for ovarian cancer. We also solicited women's views on the importance of nutrition and dietary intake. This places our study in a unique position to confirm that current practice could be improved. Patient involvement and perspectives on what would constitute a suitable nutritional intervention should be considered.

We demonstrated that weight loss may not be the 'cardinal diagnostic criterion' (410) of cachexia in this particular population. In fact an additional category of 'weight gain' is necessary for ovarian cancer patients where ascites is prevalent particularly prior to treatment. Baracos et al., (2011) also showed that 61% of male and 31% of the female patients with non-small-cell lung cancer (NSCLC) were sarcopenic despite the fact that 50% of all the patients were overweight or obese. This confirms that malnutrition and or cachexia are not just in the severely underweight patient (411). The high prevalence of obesity in the general population means that patients may have normal weight even if they have lost significant muscle (412). In addition the concept of paradoxical weight gain due to ascites and oedema in some cancer patients is acknowledged in research (88), yet there is no evidence of translation of this knowledge into clinical practice when assessing patient nutritional status. These can mask true nutritional deterioration as well as be signs that the patient is progressing towards refractory cachexia (88). The opportunity for intervention could therefore be missed or be identified late in the disease trajectory, when patients are in the refractory stage of cachexia with little opportunity to reverse their malnutrition. Emphasis on cachexia being characterised by severe weight contributes to the notion that nothing can be done, when in fact earlier intervention can potentially make a difference.

Women demonstrated concerted efforts in seeking nutritional information on their own or with the help of family in keeping with evidence that cancer survivors seek

information about food choices, physical activity, and dietary supplements to improve their treatment outcomes, quality of life, and overall survival (157). Women with ovarian cancer in particular have been shown to express a stronger need for information and participate in their health care than patients with either breast cancer or prostate cancer (352) which has been ascribed to demonstrate a need to control and cope with a diagnosis of a disease with very poor prognosis (352). Seeking information is empowering and helps women to make informed lifestyle choices (157). This understanding presents an opportunity to capitalise on the possible 'teachable moment' (159) to provide nutritional support to meet short and long term needs. Since a cancer diagnosis is an event or opportunity when individuals might be more motivated to make changes that may reduce their health risks (413-415), intervention opportunities including modifying health behaviours must be maximised on.

The phases of cancer survivorship are marked 1) active treatment and recovery; 2) living after recovery, including survivors who are disease free or who have stable disease; and 3) advanced cancer and end of life (157). Our research focused on identifying and understanding nutritional challenges in first phase, our suggested "ideal teachable moment". The hope is that latter phases can be positively impacted by intervention that starts in this phase. Ovarian cancer survivors live with a disease that has a 20% and 6% 5 year survival if diagnosed with stage 3 and 4 respectively (290); a 40-50% rate of recurrence of cancer within 3 years in women who achieve a remission after first-line chemotherapy, and an average duration of survival of 12 to 18 months after recurrence (289). This means that the patient-clinician contact is likely to be more frequent than in other chronic diseases. Therefore a model of care that involves both clinicians and patients taking control of meeting or supporting the meeting of nutritional needs is urgently required.

People who are identified as malnourished in hospital and in the community may be considered for referral to a dietician. In routine clinical practice the poor nutritional status of many patients is not recognised and many do not receive any

advice (416, 417). Evidence from our study supports this. Women are generally investigated for ovarian cancer as outpatients. The Clinical Nurse Specialists (CNSs) or other clinicians use their judgement as to who receives support (source: CNS). The emphasis on From Home To Operation (FHTO) (418) versus conventional admission the day before surgery protocols now apply to most women undergoing surgery. This scenario limits opportunities for nutritional screening and/or assessment to be carried out prior to surgery. European, American, and Australian guidelines on the nutritional management of malnourished patients with cancer emphasis that it should be a priority. These guidelines recommend that nutrition receives prompt attention and interventions are commenced in malnourished patients or those in whom difficulties with eating are anticipated (246, 419, 420). The NHS guidance on 'Holistic assessment of the supportive and palliative care needs of people with cancer', published in 2007 (421) states that 'holistic needs assessment' should be part of every cancer patient's care. It further says that this assessment can make a huge difference to a patient's overall experience and has the potential to improve outcomes by identifying and resolving issues quickly and can enable patients to more fully engage in their care and facilitates choice. NICE guidelines state that all hospital inpatients should be nutritionally screened on admission and all outpatients at their first clinic appointment and that screening should be repeated weekly for inpatients and for outpatients if there is clinical concern (422). Furthermore the 'Malnutrition Universal Screening Tool' (MUST) (423) designed to help identify adults who are at risk of malnutrition including cancer patients is the tool of choice in many NHS Trusts. Despite this, malnutrition/cachexia remains rarely identified or managed. Most nutritional activities are conducted on an opportunistic basis in the hospital (424). There are issues of time constraints, lack of training and resources, but there is also evidence to suggest that lack of knowledge about clinical nutrition in the oncology field and a lack of an adequate evidence base for therapy are largely responsible (425). Coa et al., (159) showed that health care providers prioritised the strength of evidence and were less likely to discuss diet with their patients if they perceived the evidence base as weak.

9.6 Recommendations for the future

9.6.1 Randomised Control Trial (RCT)

Our primary recommendation is the implementation of a well-designed prospective, multicentre, randomised control trial assessing the effectiveness of individual dietary counselling (aiming to optimise energy and protein intake) versus regular diet. Our earlier work found no evidence of such a trial in patients diagnosed with ovarian cancer (5). More recent reviews have concluded the same, Billson et al. (2013) (237) and Obermair et al., (2017) (426). We feel that there is a sufficient theoretical basis for conducting such a trial. None has been done in this patient group, others have found such intervention to help maintain weight in other cancer sites (427) and there is evidence from this thesis that women are open to it. We have identified our study population as women newly diagnosed with ovarian, fallopian tube cancer or primary peritoneal cancer because they have the same treatment pathway. Some of the outcomes over and above targeted standard nutrition markers could be endpoints that are key for other disciplines and specialties such as toxicity, frailty and quality of life.

The Medical Research Council, MRC (318) published guidelines on developing and evaluating complex interventions. We would be guided by them and frame our trial along the four main principles of feasibility, development, implementation and evaluation. In the feasibility stage we would aim to 'define our intervention'. We suggest counselling based on a regular diet because it is cost effective can work in everyday practice. Others have combined counselling with leaflets and/or nutritional supplements. A practical and sustainable intervention would be preferred. We also suggest that a health behaviour model in particular the HAPA model be used to improve compliancy and self-efficacy. The next stage would be to 'pilot the study. This is a key step do determine feasibility. At this point we would want to evaluate what is possible to do, in terms of the amount of time patients are willing/or forced by poor health to commit to the study. We would also be interested to identify the best tools of assessment. Recruitment rates will be established in order to estimate the duration of the main trial. Data collected at this stage will help to determine the minimum number of patients to be enrolled

in order to achieve the required statistical power and effect size (the point at which the differences in outcomes between the two groups become apparent). The pilot study will also help to determine the amount of resources required (Cost) i.e. human resources (clinicians, nurses, dietician etc.), materials, laboratory facilities, travel costs etc., and supplements if required. Findings from the pilot study will be used to develop an appropriate study protocol and documents as well as to seek funding. They will also help to guide the type of trial required. Ethical considerations about providing intervention to only the treatment arm will be made. Timing of the intervention will be established. We showed in our study that some women would prefer intervention from the onset, while others preferred the period following surgery but before chemotherapy. Implementation of the larger trial will follow, due analysis and evaluation of the pilot study.

9.6.2 Other recommendations

We recommend that a more objective method of nutritional status/body composition assessment such as CT scans and BIA be adopted for regular use in clinical practice. It could be used alongside the standard body weight which we have been demonstrated to not be able to characterise weight change where ascites is present. CT scans could also be creatively used to accurately assess body composition and its changes over time since virtually all women diagnosed with cancer will be imaged prior to treatment as well as for their follow-up. There would be initial cost in training personnel and acquiring required software, but method would be cost effective long term. BIA is relatively cheap, easy to use, non-invasive and validated for use in cancer patients and can be used where more frequent assessments are required than can be done by CT scanning. These methods could be used with or independently of weight and BMI and would be helpful in clarifying the source of change in body composition or function at little additional cost.

We also recommend that clinicians consider that cancer cachexia is not always indicated by severe weight loss and a low BMI. Ascites and oedema can lead to paradoxical weight gain (88), ascites is common occurring in up to 77% prior to

treatment and 31% in women with relapse (190). Moreover it has been demonstrated that even though some patients may regain weight this weight is from an increase in adipose tissue and not muscle mass which impacts most upon morbidity and mortality (22, 94). It is therefore important that patients' nutritional status is objectively assessed for dose calculation as well as meeting nutritional needs.

9.7 The limitations and strengths of the study

9.7.1 Limitations

The limitations of our observational study include that the study population is generally very ill. The high symptom burden and treatment effects affected the number of patients that were willing to participant, be subsequently followed up and return questionnaires. Our sample size was relatively small, as such our subgroup analysis where used needs to be interpreted with caution. Firm conclusions on some of our findings cannot be inferred. We have assumed that changes had a negative impact on food intake. Furthermore our end of treatment time point ranged from 3-6 months from the completion of chemotherapy, depending on the logistics of identifying and assessing patients when they returned for follow-up. This could have had consequences on body composition. We hope that any effect of this is lessened by that there was no systematic bias to who was assessed at three or six months. The limitations also include that our control group was not matched for age, race or menopausal status. This could have had an impact on age affected nutritional status markers such as dry lean mass and body fat. The controls sample size is so small that subgroup analysis was not always possible. Although all identified potential participants were approached for the observational study, selection bias was possible in our focus group discussions since less ill patients and more nutritionally aware women may have volunteered to participate. Not all collected data has been included in the analysis. Our EORTC quality of life data remains largely unused partly because this instrument is not validated for our non-cancer control group. These data will be analysed and published in peer review journals beyond this thesis. Nonetheless we feel that the weaknesses in our work highlight the need for

further research as highlighted in our recommendations for future work. There were strengths to the study too as highlighted in the next session.

9.7.2 Strengths

This is the first study to use a mixed method approach including a health behaviour perspective to objectively identify the problem of malnutrition and also to gain insight of the problem and possible intervention from patients' perspectives. Assessing nutritional status at multiple time points enabled us to show changes over time. A future intervention incorporating patients' suggestions is likely to be more acceptable to them and may yield more informative results. Use of multiple methods for the assessment of nutritional status allowed for identification of those markers that are more effective in capturing malnutrition in a population where weight and BMI are not very informative at individual level. Our study collected pre-diagnosis diet and weight change data which confirmed that nutritional and diet changes are already occurring in this time, information that may be lost if history was not included. In addition the study of controls in our observational study enabled us to identify that dry lean mass, which had been previously reported as unchanged in other studies, had in fact already changed at baseline assessment. We used all our observational study data in the analysis because there was no systematic bias to who or when women were assessed. The group discussions involved women at different stages of survival, from recently diagnosed to 10 year survivors. This allowed for different perspectives that are related to the cancer trajectory to be captured. The insight gained warrants an intervention that incorporates some of women's views and suggestions. Our quality of life findings showed that nearly all dimensions/domains are affected in cases and controls and that younger women report more problems.

9.8 Conclusion

Conclusive evidence is essential for raising attention to clinical problems, associated with malnutrition/cachexia. Well-designed, targeted, randomised controlled trials with specific interventions incorporating health behaviour approaches aimed at preventing rather than treating nutritional complications, may improve both nutritional status outcomes such as lean body mass and oncology outcomes such as longer disease free intervals and improved survival. The potential for benefit of interventions remains at the early stage rather than later when the patient has become likely refractory to anti cachexia treatment. Ovarian cancer is aggressive and highly lethal which warrants nutritional interventions that target a woman's entire life. Such interventions will require a partnership between clinicians and patients, since most of oncologic care occurs in outpatient settings.

10   References

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11 Appendices

Appendix 1: Non-invasive nutritional intervention in gynaecological malignancy

Author	Type of study	Type of patients	No of patients	Objective	Relevant findings	Conclusions
Pearl et al., 1998 (428)	A randomized controlled trial	All gynaecological oncology patients	200	To evaluate the safety and efficacy of early oral feeding after intra-abdominal surgery in gynecologic oncology patients.	Time to development of bowel sounds, time to initiation of clear liquid and regular diets, and hospital stay significantly longer in the traditional group	Early postoperative feeding in gynecologic oncology patients undergoing intra-abdominal surgery is safe and well tolerated.
Steed et al., 2002 (429)	A randomized controlled trial	Gynaecological oncology/	107	To compare early oral intake and the traditional timing of feeding after major gynecologic surgery and the effects on the length of hospital stay.	Significant reduction in the LOS* for those patients on the early feeding regimen. Median length of stay for was 4.0 days (P =0.001) compared to 6.0 days for traditional group. There was no difference in the incidence of emesis	Early postoperative dietary advancement resulted in a decreased LOS* and appears to be safe, with no increased adverse effects
Schilder et., al., 1997 (258)	A prospective controlled trial	Mixed Gynecology	96	To determine whether, when compared with traditional dietary advancement, early oral intake following major gynecologic surgery leads to a reduction in the length of hospitalization	No statistical difference in the number of subjects who required postoperative antiemetics or biscodyl suppository. Statistically significant reduction in the LOS* for those patients on the early feeding regimen, (4.02 days +/- 0.30 versus 3.12 days +/- 0.16 (P = 0.008))	Early postoperative oral intake results in a decreased LOS* and is well tolerated when compared with traditional dietary management
Cutillo et al., 1999 (430)	A randomised controlled study	Gynaecological oncology	61	To evaluate the feasibility, safety, and tolerance of early feeding in patients undergoing surgery for gynecologic malignancies	Early oral feeding was associated with a significantly faster resolution of postoperative ileus (P < .01), with a more rapid return to a regular diet (P < .01), with an earlier first passage of stool (P < .01), and with a shorter postoperative stay (P < .05) than patients in arm B	Early feeding is feasible and well tolerated and is associated with reduced postoperative discomfort and a more rapid recovery

Author	Type of study	Type of patients	No of patients	Objective	Relevant findings	Conclusions
Pearl et al., 2002 (431)	A randomized controlled trial	Gynaecological Oncology	254	To prospectively evaluate the safety and efficacy of a regular diet as the first meal after intra-abdominal surgery in gynecologic oncology patients	The time to development of bowel sounds, passage of flatus, and hospital stay were comparable for both groups. Febrile morbidity, pneumonia, wound complications, and atelectasis occurred equally in both groups	A regular diet as the first meal after intra-abdominal surgery in gynecologic oncology patients is safe and efficacious
Minig el al., 2009 (432)	A randomized controlled trial	Gynaecological oncology	51	To assess the outcome of early oral postoperative feeding (263) compared with traditional oral feeding (309) in gynecologic oncology patients undergoing laparotomy with associated intestinal resection.	Hospital stay in patients who received EOF was 6.9 days versus 9.1 days in the TOF group (P = 0.022). Use of analgesic and antiemetic drugs, intensity of pain, intestinal function recovery, mean levels of postoperative satisfaction, postoperative complications, and quality-of-life scores did not differ	Early resumption of oral intake is feasible and safe and significant reduction in LOS* was demonstrated.
Gerardi et al., 2008 (257)	A Clinical Pathway	Ovarian and primary peritoneal	64	To evaluate the safety, feasibility, and economic impact of a clinical pathway, including rapid diet advancement, for patients undergoing recto sigmoid colectomy as part of cytoreductive surgery for advanced ovarian and primary peritoneal cancers.	Patients who had rapid diet advancement had a significantly shorter median LOS* (7 days vs. 10 days, p=0.014) and lower median 30-day post-operative hospital cost ($19,700 vs. $25,110, p=0.028)	A critical pathway incorporating rapid diet advancement is feasible, safe, and associated with a significant reduction in LOS* and hospital-related costs

Author	Type of study	Type of patients	No of patients	Objective	Relevant findings	Conclusions
Gupta et al., (256)	Retrospective chart review	Ovarian Cancer	98	The impact of improvement in nutritional status on ovarian cancer survival	Patients with an improved nutritional status at three months had significantly better survival than those with deteriorated nutritional status independent of age, stage at diagnosis, prior treatment history, and tumour response.	Improvement in nutritional status is associated with better survival. **Note:** Study treats patients who had and had not received treatment at baseline similarly. Also some patients received parenteral nutritional support.

*LOS Length of hospital stay/hospitalization

Appendix 2: Bio electrical impedance analysis output data


```
                Bodystat®

Time              14:42:50
Date              22/11/11
Test Number          142
Gender            Female
Age                 57 Yrs
Height             163 cm
Weight            71.6 kg
Activity      Low/Medium
Waist               99 cm
Hip                103 cm

Fat               40.1 %
Normal          22 - 30 %
Fat               28.7 kg
Normal          13 - 17 kg
Lean              42.9 kg
Normal          41 - 45 kg

Total Wt          71.6 kg
Normal          55 - 61 kg

Dry Lean          10.2 kg

TBW               45.7 %
Normal          50 - 60 %
TBW               32.7 lt
Normal          36 - 43 lt
ECW               21.7 %
Normal              20 %
ECW               15.5 lt
ICW               25.2 %
Normal              30 %
ICW               18.1 lt
Body Cell Mass    25.8 kg
3rd Space Water   -0.8 lt
Nutrition         0.46
Normal            0.40

Illness Marker    0.799

BMR              1376 kcal
BMR/Weight       19.2 kcal/kg
EAR              2064 kcal
BMI               26.9
Normal          20 - 25
BFMI              10.8
Normal           5 - 6
FFMI              16.1
Normal          15 - 17

Waist/Hip         0.96
High Risk         0.80 >
Impedance 5 kHz    685 Ω
Impedance 50 kHz   601 Ω
Impedance 100kHz   569 Ω
Impedance 200kHz   547 Ω
Resistance 50kHz   598 Ω
Reactance 50 kHz  60.5 Ω
Phase Angle 50 k   5.8 °
```

Appendix 3: Questionnaires

Appendix 3.1 Baseline questionnaire including quality of life questionnaires

Nutritional Status of Women Referred to a Gynaecological Oncology Centre for Treatment of a Pelvic Mass

Patient questionnaire I

We are interested in collecting some information about you, your health and your nutrition. Please answer all the following questions, even if you are not sure about exact details/dates. If you wish, you can give additional information on the sheet provided at the end of the questionnaire. We understand that some questions may appear to be negative, please be assured that we do not want to upset you, and we make no prior assumptions about your experiences. We would like you to answer the questions as honestly as you can as this will help us understand your current situation before we can make any suggestions for the future interventions. We appreciate your help and support with this study.

Section 1: PERSONAL INFORMATION

1.1	Today's Date	☐☐ / ☐☐ / ☐☐☐☐
1.2	Study Ref.	☐☐☐☐☐
1.3	Surname	☐
1.4	Name	☐
1.5	Date of Birth	☐☐ / ☐☐ / ☐☐☐☐
1.8	Contact Tel	☐☐☐☐☐☐☐☐☐☐☐

1.9 ETHNIC GROUP
What is your ethnic group? Choose one section from A to E, then select the appropriate option to indicate your ethnic group
A. White
1. British
2. Irish
3. Any Other White background, please write in _____

B. Mixed
4. White and Black Caribbean
5. White and Black African
6. White and Asian
7. Any Other Mixed background, please write in _____

C. Asian or Asian British
8. Indian
9. Pakistani
10. Bangladeshi
11. Any Other Asian background, please write in _____

D. Black or British Black
12. Caribbean
13. African
14. Any Other African background, please write in _____

E. Chinese or other ethnic group
15. Chinese
16. Any Other, please write in _____

1.10   What is your marital status? (please tick)

☐ Single   never married   ☐ Cohabiting/Married   ☐ Widowed   ☐ Separated/divorced

☐ Other (please specify)

1.11   What qualification do you have from school, college or the equivalent? (please tick)

☐ "O" level or equivalent

☐ "A" level or equivalent

☐ Clerical or commercial qualification (e.g. secretarial)

☐ Nursing or teaching   ☐

☐ College/University degree

☐ None of the above

Section 2: HEALTH and LIFESTYLE INFORMATION

This section focuses on your health, diet and eating habits. It is to help gather information that we currently do not know about in women referred with a pelvic mass. There are no right or wrong answers. Please complete all the questions. If you wish to include extra relevant information, please use the additional sheet provided at the end of the questionnaire.

2.1   Has your weight changed in the last 3 months?

☐ Yes   ☐ No   ☐ I don't know

If you have gained or lost weight please indicate which and by how much

☐ Gained weight   ☐ Lost weight   (please tick)

☐☐ . ☐ kg   or   ☐☐ st   ☐☐ lbs

2.2   **Have your eating habits changed in the last 3 months? Please tick**

☐ Yes   ☐ No (if no go to 2.6)

2.3   **If yes please tell us what brought about this change**

2.4   **What are you eating now that you were not eating more than 3 months ago (list).**

2.5   **What are you avoiding now, that you were eating more than 3 months ago? (list)**

2.6   **Have you noticed any change in the smell of certain foods in the last 3 months?**

☐ Yes   ☐ No (if no go to 2.8)

2.7   **If yes, please tell us how this change affects what you eat**

2.8   **Have you noticed any change in taste in some foods in the last 3 months?**

☐ Yes   ☐ No (if no go to 2.10)

2.9   **If yes please tell us how this change in taste affects what you eat.**

2.10   **Have you ever been a regular smoker?** ☐ **Yes**   ☐ **No (If no go to 2.15)**

2.11   **If yes, how many cigarettes per day do you currently smoke?**

2.12   **How many cigarettes per day did you smoke 3 months ago?**

2.13   **If you have given up, when did you give up smoking (month and year)** ☐☐ / ☐☐☐☐

2.14 On average how many cigarettes did you smoke per day before you gave up?

2.15 Do you drink alcohol? ☐ Yes   ☐ No (if no go to Section 3)

2.16 If yes; how many of the following do you drink per week?

Alcohol and amounts	Drinks per week?
Wine (glass)	
Beer, Lager or cider (half pint**)**	
Port, sherry, vermouth, liqueurs (glass)	
Spirits, e.g. brandy, whisky, vodka	

2.17 How much alcohol did you drink 3 months ago?

Alcohol and amounts	Drinks per week 3 months
Wine (glass)	
Beer, Lager or cider (half pint**)**	
Port, sherry, vermouth, liqueurs (glass)	
Spirits, e.g. brandy, whisky, vodka	

Section 3:MENSTRUAL AND MEDICAL HISTORY

In this section we ask about information relating to your menstrual history and any other medical conditions you may have. Please complete all the questions in the following section. Feel free to provide additional information on the extra sheet provided

3.1   **Have your periods stopped completely?** (have you gone at least 6 months without having a period and you are not pregnant or on the contraceptive pill**)**

☐   Yes

☐   No

☐   Don't know as I started to take HRT before my periods had stopped

(If 'no' or 'don't know', go to 3.4)

3.2   **If yes, how old were you when your periods stopped completely? Years** ☐☐

*Nutritional status of women referred to a gynaecological cancer centre: **Q1-Baseline v2 Dec 4/13/2010***

3.3   **What was the reason your periods stopped?**

☐ Natural menopause

☐ Surgery (e.g. hysterectomy/removal of ovaries)

☐ Chemotherapy, radiation or other treatment

☐
Don't know

☐
Other (please specify) [   ]

3.4   **Do you currently have abdominal pain or discomfort**

☐ Yes   ☐ No (if no go to 3.5)

If yes please indicate which

☐ Pain   ☐ Discomfort

Has the pain/discomfort been   **continuous** ☐   or **intermittent**? ☐

Please tell us for how long this has been going on [   ]

3.5   **Have you been diagnosed with any other medical condition in the past?**

☐ **Yes**   ☐ **No (if no go to 3.7)**

3.6   **If yes please list all the conditions and the year of diagnosis**

Medical Condition	Year of diagnosis

*Nutritional status of women referred to a gynaecological cancer centre: **Q1-Baseline v2 Dec 5/13/2010***

3.7 Do you currently take regular (that is every day or almost every day) **medication including hormones e.g. HRT or supplements e.g. vitamin C?**

☐ Yes   ☐ No (if no go to Section 4)

If yes, please give the name of the medication and how long you have been using it.

Name of Medication	No of years/months using			
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

Extra Information

Please feel free to add extra relevant information on this page

<u>Additional Information from Section 1 of Questionnaire</u>

<u>Additional Information from Section 2 of Questionnaire</u>

<u>Additional Information from Section 3 of Questionnaire</u>

Thank you for helping us with our research

Section 4: QUALITY OF LIFE

In this section we ask you to evaluate your diet and general well-being using 3 questionnaires that have been used in other studies in the past and shown to provide useful information. The questions are about how you perceive your health or some aspects of your health to be in the specified time period. The first questionnaire, the functional assessment of anorexia/cachexia therapy asks you about your appetite and food intake while the last two are about your general well being.

4.1 The Functional Assessment of Anorexia/Cachexia Therapy (FAACT) (A/CS-12)

4.2 EORTC QLQ-C30 (version 3)

4.3 EuroQol EQ-5D

Nutritional status of women referred to a gynaecological cancer centre: **Q1-Baseline v2 Dec 2010**

The Functional Assessment of Anorexia/Cachexia Therapy (FAACT) (A/CS-12) questionnaire

Please answer all of the questions yourself by circling the number that best applies to you.

During the past 7 days;

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have a good appetite	0	1	2	3	4
The amount I eat is sufficient to meet my needs	0	1	2	3	4
I am worried about my weight	0	1	2	3	4
Most food tastes unpleasant to me	0	1	2	3	4
I am concerned about how thin I look	0	1	2	3	4
My interest in food drops as soon as I try to eat	0	1	2	3	4
I have difficulty eating rich or "heavy" foods	0	1	2	3	4
My family or friends are pressuring me to eat	0	1	2	3	4
I have been vomiting	0	1	2	3	4
When I eat, I seem to get fully quickly	0	1	2	3	4
I have pain in my stomach area	0	1	2	3	4
My general health is improving	0	1	2	3	4

EuroQol EQ-5D Quality of life questionnaire

University College London Hospitals **NHS**

NHS Trust

Nutritional Status of Women Referred to a Gynaecological Cancer Centre for Treatment of a Pelvic Mass

Patient Questionnaire II (During treatment)

We are interested in collecting some information about your health and your nutrition during your treatment so far. Please answer all the following questions, even if you are not sure about exact details/dates. If you wish, you can give additional information on the sheet provided at the end of the questionnaire. We understand that some questions may appear to be negative, please be assured that we do not want to upset you, and we make no prior assumptions about what your experiences are. We would like you to answer the questions as honestly as you can as this will help us understand your current situation before we can make any suggestions for the future interventions. We appreciate your help and support with this study.

<u>Section 1: PERSONAL INFORMATION</u>

1.1   Today's Date /   /

1.2   Study Ref.

1.3   Surname

1.5   Date of Birth

Section 2: HEALTH and LIFESTYLE INFORMATION

This section focuses on your health, diet and eating habits. There are no right or wrong answers. Please complete all the questions. Please complete all the following questions. If you wish to include extra relevant information, please use the additional sheet provided at the end of the questionnaire.

2.0 Do you currently live (please tick all relevant)

Alone ☐   Partner/Spouse ☐   Parents ☐   Relative/s ☐   Child/ren ☐   friend ☐

Other (please specify) [   ]

2.2 Have your eating habits changed since you had surgery or started chemotherapy? Please tick

Yes ☐   No (if no go to 2.6) ☐

2.3 If yes please tell us what brought about this change

[   ]

2.4 What are you eating now that you were not eating at surgery/start of chemotherapy? (please list).

[   ]

2.5 What are you avoiding now, that you were eating at surgery/start of chemotherapy? (please list)

[   ]

2.6 Have you noticed any change in the smell of certain foods since surgery or start of chemotherapy?

☐ Yes   ☐ No (if no go to 2.8)

2.6.1   If yes please describes this change

[   ]

2.7 Please tell us how this change affects what you eat

2.8 Have you noticed any change in how some foods taste since surgery/start of chemotherapy?

☐ Yes   ☐ No (if no go to 2.10)

2.8.1   If yes please describe the change

2.9 Please tell us how this change in taste affects what you eat

2.10 Do you smoke? ☐ Yes   ☐ No (if no go to question 2.15)

2.11 If yes, how many cigarettes per day do you smoke? [   ]

2.15 Do you drink Alcohol? ☐ Yes   ☐ No (if no go to Section 3)

2.16 If yes; how many of the following do you drink per week?

Alcohol and amounts	Drinks per week?
Wine (glass)	
Beer, Lager or cider (half pint**)**	
Port, sherry, vermouth, liqueurs (glass)	
Spirits, e.g. brandy, whisky, vodka (single**)**	

Section 3: MEDICAL HISTORY

In this section we ask about information relating pain and other medical conditions you may have. Please complete all the questions in the following section. Feel free to provide additional information on the extra sheet provided

3.4 Do you currently have abdominal pain or discomfort (please indicate which one)

☐ Yes   ☐ No (if no go to 3.7)

If yes please indicate which   ☐ Pain   ☐ Discomfort

Has the pain/discomfort been?   ☐ Continuous   or ☐ Intermittent

Please tell us for how long this has been going on [   ]

3.7 Do you take regular medication (that is every day or almost every day) including hormones e.g. HRT or supplements such as vitamin C?

☐ Yes   ☐ No (if no go to Section 4)

If yes, please give the name of the medicine and how long you have been using

Name of Medication	No of years/months
	☐☐ ☐☐
	☐☐ ☐☐
	☐☐ ☐☐
	☐☐ ☐☐
	☐☐ ☐☐
	☐☐ ☐☐
	☐☐ ☐☐

Section 4: QUALITY OF LIFE

The quality of life questionnaires were the same as those administered at baseline questionnaire 1

University College London Hospitals **NHS**

NHS Trust

Nutritional Status of Women Referred to a Gynaecological Cancer Centre for Treatment of a Pelvic Mass

Patient Questionnaire III (End of treatment)

We are interested in finding out about your health and nutrition throughout your treatment journey which just ended. Please answer all the following questions, even if you are not sure about exact details/dates. If you wish, you can give additional information on the sheet provided at the end of the questionnaire. We understand that some questions may appear to be negative, please be assured that we do not want to upset you, and we make no prior assumptions about what your experiences are. We would like you to answer the questions as honestly as you can as this will help us understand your current situation before we can make any suggestions for the future interventions. We appreciate your help and support with this study.

Section 1: PERSONAL INFORMATION

1.1   Today's Date /   /

1.4   Study Ref.

1.5   Surname

1.5   Date of Birth

Section 2: HEALTH and LIFESTYLE INFORMATION

This section focuses on your health, diet and eating habits. There are no right or wrong answers. Please complete all the questions. Please complete all the following questions. If you wish to include extra relevant information, please use the additional sheet provided at the end of the questionnaire.

2.0 Do you currently live with (please tick all relevant)

Alone ☐   Partner/Spouse ☐   Parents ☐   Relative/s ☐   Child/ren ☐   friend ☐

Other (please specify) [   ]

2.2 Did your eating habits change during the treatment period? Please tick

☐ Yes   ☐ No (if no go to 2.6)

2.3 If yes please tell us what brought about this change?

[   ]

2.4 Please list all foods that you are eating now, that you did not normally eat before your diagnosis?

[   ]
[   ]

2.12 Please list all foods that you ate before your diagnosis but are now avoiding?

[   ]
[   ]

2.13 Did you notice any change in the smell of certain foods during treatment?

☐ Yes   ☐ No (if no go to question 2.8)

2.13.1   If yes please describe this change

[   ]

2.14 Please tell us how this change affected what you ate during treatment

[   ]

2.15 Did you notice any change in the taste of certain foods during treatment?

☐ Yes   ☐ No (if no go to 2.10)

2.15.1 If yes please describe the change

[ ]

2.16 Please tell us how this change affected what you ate during treatment

[ ]

2.17 Do you smoke? [ ] Yes   [ ] No (if no go to 2.15)

2.18 If yes, how many cigarettes per day do you currently smoke? [ ]

2.15 Do you drink Alcohol? [ ] Yes [ ] No (if no go to 2.17)

2.16 If yes; how many of the following do you drink per week?

Alcohol and amounts	Drinks per week?
Wine (glass)	
Beer, Lager or cider (half pint)	
Port, sherry, vermouth, liqueurs	
Spirits, e.g. brandy, whisky, vodka	

2.17 Did you receive any nutrition information, advice, counselling or support from hospital staff (for example nurses, doctors, dieticians etc.) as part of your care?

[ ] Yes   [ ] Yes but not enough   [ ] No (If no go to 2. 21)

2.18 If yes please tell us from whom you received the information, advice, counselling or support

[ ]

2.19 Was this information helpful to you at the time?

☐ Yes ☐ No

2.20 If yes please tell us how it was helpful

[ ]

2.21 Please tell us what kind of nutrition information, advice, counselling or support you think might have been helpful to you during your treatment?

[ ]

2.22 On your own initiative, since diagnosis, have you sought out information on diet and nutrition from other sources such as the internet, leaflets, friends, GP etc.?

☐ Yes ☐ No (If no go to 2.24)

2.23 If yes can you please tell us where you sought this information

[ ]

2.24 Please tell us why you sought/or did not seek this information

[ ]

2.25 Do you feel that you know enough about what to eat to give your body the best nutritional support for recovery?

☐ Yes ☐ No

2.26 Can you tell us what your health care team could do to support you more with your nutrition and diet?

Section 3:MEDICAL HISTORY

In this section we ask about information relating pain and other medical conditions you may have. Please complete all the questions in the following section. Feel free to provide additional information on the extra sheet provided

3.4 Do you currently have abdominal pain or discomfort (please indicate which one)

☐ Yes ☐ No (if no go to 3.5)

If yes please indicate which

☐ Pain ☐ Discomfort

Has the pain/discomfort been? ☐ Continuous or ☐ Intermittent

Please tell us for how long this has been going on [＿＿＿＿＿]

3.7 Do you take regular medication (that is every day or almost every day) including hormones (e.g. HRT, Thyroxine or supplements such as Vitamin C?

☐ Yes ☐ No (if no go to Section 4)

If yes, please give the name of the product, how long you have been using it and whether you are currently using it.

Name of Medication	No of years/months
	☐☐ ☐☐
	☐☐ ☐☐
	☐☐ ☐☐
	☐☐ ☐☐
	☐☐ ☐☐

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Extra Information

Please feel free to add extra relevant information on this page

Additional Information from Section 1 of Questionnaire

Additional Information from Section 2 of Questionnaire

Section 4: QUALITY OF LIFE

The quality of life questionnaires were the same as those administered at baseline and during treatment in questionnaires I and II.

Nutritional Status of Women Referred to a Gynaecological Cancer Centre for Treatment of a Pelvic Mass

Patient Information leaflet

We invite you to take part in a research study looking at the nutritional status of women who are referred to the centre with a pelvic mass. Please read this leaflet which tells you about the study and what it involves and ask the researcher if there is anything that is not clear. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
The purpose of the study is to gather detailed nutritional information from women diagnosed with either a non-cancerous (benign) or cancerous pelvic mass. We know that nutrition is important for patients who are having surgery and/or other treatments in hospital. Good nutritional status increases patients' ability to undergo treatments, and improves quality of life. What we do not know is whether malnutrition is a problem at the very beginning of the treatment pathway of women referred with a pelvic mass or how it changes over time. We also do not have solid research evidence about when and what to provide as nutritional intervention to improve short and long term patient health outcomes. This study is the first step to investigating this.

In the study we gather information about factors that underlie a person's nutrition and how these may change during investigations and treatment of a pelvic mass. We want to thoroughly investigate these factors in the period before treatment, through surgery and during any additional treatment. Gathering accurate information about how nutritional status may change during this period will help to decide the best timing and future design of tailored nutritional intervention to improve the existing nutrition support in gynaecological oncology treatment here at UCLH and also in other NHS centres.

Why have I been chosen?
You have been invited to take part in the study because you are undergoing investigations and treatment of a pelvic mass at the gynaecological oncology centre. Your doctor will have discussed your diagnosis with you or mentioned that at this time we do not know what your final diagnosis will be. You are eligible to participate whether investigations show you have a non-cancerous (benign) mass or if unfortunately the mass you have is shown to be a cancer. We understand and recognize that this is often a difficult time for women. This study will not interfere with your regular care in any way. You are being asked to take part in the study at this time because it is important to find out in detail the status of your nutrition and how it may change leading up to your surgery or treatment. This information may be important in any future effort to improve women's nutrition to enable them not only to tolerate treatment better, but to also modify their diet and lifestyle for long term benefit. We

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want to gather information that will allow us to make comparisons between women who may have different nutritional needs. These comparisons will be made at the end of the study and will be important in designing future nutrition interventions specific to the needs of each group.

What does the study involve?

The researcher, Nyala Balogun, will explain the study to you, give you a copy of this information sheet and answer any questions you may have. You are free to take the leaflet away to consider whether or not you are willing to take part. If you are willing to take part you will be asked to sign a consent form and will be given a signed copy to keep, and a copy will also be placed in your hospital records. You will still be free to withdraw from the study at any time without giving a reason.

Taking part in this study involves 3 or 4 assessments depending on your diagnosis. Each assessment will last approximately 45 minutes and will include weight, height and measurement of body composition (the proportion of fat and fat-free mass in the body). You will also be required to complete a questionnaire and donate a blood sample. Assessments will be carried out on entry to the study, immediately before surgery, 2-3 weeks after surgery and in the case of further treatment at completion of this.

Measurement of body composition will be done while you are lying down. This test is done using a small portable machine called a Quadscan. Small stickers called electrodes are attached to your wrists and ankles and connected via wires to the Quadscan machine. The machine works by passing a small electrical current through the body. The current passes freely through the fluids contained in muscle tissue, but encounters some resistance when it passes through fat tissue in your body. The resistance of the fat tissue to the electrical current is the 'bioelectrical impedance' measurement. When considered alongside a person's height, gender and weight, the measurements can then calculate figures for body fat, and fat-free (lean) mass. This method of measuring body composition is called Bioelectrical Impedance Analysis (BIA). It is safe and painless and will take no more than 5 minutes. This will be carried out in clinic but where it is more convenient to you the nurse researcher will arrange to visit you at home.

You will also be asked to donate 4 tubes of blood in total (2 for serum and 2 for plasma) throughout the study. Each tube holds about half a tablespoon of blood (10ml). You will be asked to donate two samples at your first or second assessment and 2 more samples at your final assessment. The blood samples will be used for this study to analyse indicators of nutritional status such as serum albumin. Results from the samples taken pre-operatively will be compared with those taken at the end of treatment. We will also compare group results from samples taken from women with benign ovarian tumours to those from women with cancer. Any remaining samples after these analyses will be stored at University College London. Use of these samples in future related studies would need the approval of an independent Ethics Committee.

You will also be asked to complete a questionnaire. The questions ask you about your nutrition and your recent and current health. For example we ask if you have noticed any weight change

in the last 3 months. You can complete the questionnaire at the time of your body composition assessment or you can complete it at a later date and post it back to the research team in a prepaid envelope provided. The questionnaire will take about 20 minutes to complete.

The assessments are designed to coincide with your hospital appointments and treatment where possible. The initial and second assessments are similar for all women who participate, carried out at entry to the study, and immediately before treatment. Afterwards the assessment schedule will depend on your treatment pathway. If you are diagnosed with a benign mass and only require surgery as treatment, your 3rd and final assessment will be conducted when you attend outpatient clinic for your post operation follow-up, usually 2-3 weeks after the surgery. If you have a cancer diagnosis and require further treatment, the 3rd

assessment will be at your post operation follow up clinic (2-3 weeks after surgery). You will also have a 4th and final assessment at the end of your additional treatment which may be 4-5 months after your surgery.

If there are no further planned hospital visits before treatment commences, the researcher will ask if you are willing to telephone her on the number or for her to telephone you after a minimum of 24 hours to ask if you are willing to participate. In this case you have an option of a visit at home by the researcher, where this is convenient and acceptable to you to take informed consent and perform the assessments. Where no other acceptable options are available, we will take informed consent when you attend for treatment on the ward or outpatients clinic.

The researcher will telephone you following each assessment to reassure you about your participation in the study and to address any concerns that may have arisen following your assessment. Your participation in the study will not jeopardise your care in any way. Your care team will already be monitoring your progress throughout this time, but if we have a concern about any result that we find we will seek your permission to inform your consultant so that you are supported appropriately.

Some information we collect during the study such as the questionnaire quality of life information and Bio electrical impedance information is for the purposes of the research only and will not be analysed until the end of the study. However tests such as your weight which are used in clinical practice can be fed back to you throughout the study.

The researcher will also collect information about your condition and hospital investigations and treatment from your medical records. Only members of the research team involved in the project may look at your hospital notes.

Your nutrition will be monitored by your care team including a dietician as part of your regular care through out this period. At the end of the study we will provide you with your individual full results summary showing your nutrition 'foot print' throughout the study. We will seek

guidance from the dietician and clinical team on how best to provide self-management information and counselling where it is appropriate based on your results.

Do I have to take part?

You do not have to take part. It is entirely up to you to decide whether or not to take part in the study and you can withdraw at any time, without giving a reason. A decision not to take part or a decision to withdraw from the study will not affect the care or treatment you receive in any way.

What tests will be carried out on the samples I give for this study?

Your blood samples will be analysed for markers of nutritional status before treatment and at the end of treatment using known proteins such as serum albumin. Any remaining samples after analysis will be frozen and stored for future studies.

What are the possible disadvantages and risks of taking part?

The assessments and questionnaires involve your time and there is the possibility of local bruising when blood is taken from a vein in your arm. We will try as far as possible to arrange for the blood to be taken

during your other routine tests, to avoid an additional needle stick. Where this is not possible a nurse- researcher trained as a phlebotomist will take the sample.

We understand that facing the possibility of a cancer diagnosis can be a difficult time for some women. We assure you that if there were any issues raised by the study that are upsetting to you or which you feel you need support with, the researcher would ensure your consultant was aware of your concerns so that appropriate care could be arranged.

What are the possible benefits of the study?

You may find participation in the study benefits you personally because you can discuss your dietary and food habits with the researcher. Information obtained will help us design an effective and acceptable nutritional support package for women in the future.

At the end of the study when the results have been analysed we will provide each woman with the results of their nutritional status throughout the time that they were in the study. You may find this information useful to you for making decisions about your diet for the future.

How will the blood samples and questionnaires be used in the future?

If any blood samples remain after the study, they will be coded, frozen and stored for future use. The samples and information collected during the assessment including quality of life questionnaire information will be stored indefinitely at the Women's Cancer Research

Department, under the custodianship of University College London. If in future there are circumstances where further studies are designed for the benefit of women then the researchers will approach the ethical committee for approval to use the samples from this study. All samples and data will be anonymised for storage and will not be traceable back to you.

Will what I contribute to the study be confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. Assessment measures and completion of questionnaires will take place in private, and the information will not contain your name or any personal information, only a study identification number. Questionnaires will be held together with information from your medical records in a lockable draw or password protected computer in the Department of Gynaecological Oncology, at University College, London. Only those members of the research team who are directly involved in analyzing the information will have access to the files on the computer. All the samples you give will be coded and Dr. Anne Lanceley the Chief Investigator for this project has the overall responsibility for confidentiality and data security. Identities of participants will not be revealed in any publication or report relating to this research.

Involvement of your doctor

The health professional in charge of your care here at UCLH and your GP will be informed in writing of your participation in this study. A copy of your signed consent form will be kept in your hospital notes.

What will happen to the results of the research study?

The results of the study will be written up as part of a PhD thesis. We will publish peer reviewed papers & articles for the media which cater to clinical academics & to practitioners and users in health care settings. No personal identifiers will be used in reports and publications. The full results of the study will be available in 2013, two years after the beginning of recruitment when we will send a full summary of the findings to every participant. We will also provide you with your individual full results summary showing your nutrition 'foot print' throughout the study. We will seek guidance from the dietician and clinical team on how best to provide self-management information and counselling where it is appropriate based on the results. You may find this information helpful in the period following your treatment. The results of the study will also be made available to relevant gynaecological charities, including The Eve Appeal and Ovacome. In addition, we will collaborate with the UCLH / UCL Patient and Public Involvement (PPI) in Research Coordinator and with the UCLH/UCL press offices to develop contacts with local and national media and to contribute material for the UCL/UCLH websites (including to the dedicated pages on the Research Patients Support Network and PPI in Research).

Who is organising and funding the research?

Dr. Anne Lanceley is the Chief Investigator and Professors Martin Widschwendter & Alastair Forbes are co-supervisors of the study. The study is run from the Women's Cancer Research Department; Institute for Women's Health, University College London and is funded by the Comprehensive Biomedical Research Centre (CBRC) at University College London Hospital

(UCLH)/University College London (UCL). No payments are made to the researchers conducting this study.

Who has reviewed this study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by North London Research Ethics Committee 3.

What do I do if I wish to make a complaint about the research?

If you wish to complain about any aspect of the research, you should contact the nurse-researcher or the Chief Investigator, Dr. Anne Lanceley on 0207 7679 6807 or by email at (a.lanceley@ucl.ac.uk). If you feel you do not receive a satisfactory response and wish to take the matter further you should contact patient Advice and Liaison Service (PALS), either on line at www.pals.nhs.uk or your local PALS office giving the project title and the Chief Investigator's contact details.

Contact details

If you are interested in participating or you would like to ask questions about any aspect of the study please contact the researcher Nyala Balogun:

By telephone:

By email: Nyaladzi.Balogun@ucl.ac.uk

By post: Women's Cancer Research Department

Institute for Women's Health University College London

1st Floor, Maple House

149 Tottenham Court Road

London, W1T 7DN.

Thank you very much for taking time to read this information about the study.

Appendix 4.2 Controls

Nutritional Status of Women Referred to a Gynaecological Cancer Centre for Treatment of a Pelvic Mass

Patient Information leaflet

We invite you to take part in a research study looking at the nutritional status of women who are referred to UCLH with a pelvic mass or for a gynaecological condition that requires surgery. Please read this leaflet which tells you about the study and what it involves and ask the researcher if there is anything that is not clear. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
The purpose of the study is to gather detailed nutritional information from women diagnosed with a benign (non- cancerous) gynaecological condition that requires surgery to remove the womb and/or ovaries or a cancerous pelvic mass. We know that nutrition is important for patients who are having surgery and/or other treatments in hospital. Good nutritional status increases patients' ability to undergo treatments, and improves quality of life. What we do not know is whether malnutrition is a problem from the very beginning of the treatment pathway for women and how it changes over time. We also do not have solid research evidence about when and what to provide as nutritional intervention to improve short and long term patient health outcomes. This study is the first step to investigating this.

In the study we gather information about factors that underlie a person's nutrition and how these may change during investigations and treatment of a gynaecological condition. We want to thoroughly investigate these factors in the period before treatment, and through surgery. Gathering accurate information about how nutritional status may change during this period will help to decide the best timing and future design of tailored nutritional intervention to improve the existing nutrition support in our gynaecological departments here at UCLH and also in other NHS Trusts.

Why have I been chosen?
You have been invited to take part in the study because you are undergoing investigations and treatment of a gynaecological condition (involves your womb or ovaries and fallopian tubes). Your doctor will have discussed your condition with you and told you that you will have an operation to remove the mass, womb and/or the tubes and ovaries. We understand and recognize that this is often a difficult time for women. This study will not interfere with your regular care in any way. You are being asked to take part in the study at this time because it is important to find out in detail the status of your nutrition and how it may change leading up to your surgery and after. This information may be important in any future effort to improve women's nutrition to enable them not only to tolerate treatment better, but to also modify their diet and lifestyle for long term benefit. We want to gather information that will allow us to make comparisons between women who may have different nutritional needs. These comparisons will be made at the end of the study and will be important in designing future nutrition interventions specific to the needs of each group.
What does the study involve?

The researcher, Nyala Balogun, will explain the study to you, give you a copy of this information sheet and answer any questions you may have. You are free to take the leaflet away to consider whether or not you are willing to take part. If you are willing to take part you will be asked to sign a consent form and will be given a signed copy to keep, and a copy will also be placed in your hospital records. You will still be free to withdraw from the study at any time without giving a reason.

Taking part in this study involves 2 or 3 assessments depending on the length of time from when we first assess you and your treatment. If this period is more than two weeks then we will conduct another assessment before your surgery. Each assessment will last approximately 45 (25min if you chose to take and complete the questionnaire at home) minutes and will include weight, height and measurement of body composition (the proportion of fat and fat-free mass in the body). You will also be required to complete a questionnaire and donate a blood sample. Assessments will be carried out on entry to the study, immediately before surgery, 2-3 weeks after surgery when you attend for your follow-up.

Measurement of body composition will be done while you are lying down. This test is done using a small portable machine called a Quadscan. Small stickers called electrodes are attached to your wrists and ankles and connected via wires to the Quadscan machine. The machine works by passing a small electrical current through the body. The current passes freely through the fluids contained in muscle tissue, but encounters some resistance when it passes through fat tissue in your body. The resistance of the fat tissue to the electrical current is the 'bioelectrical impedance' measurement. When considered alongside a person's height, gender and weight, the measurements can then calculate figures for body fat, and fat-free (lean) mass. This method of measuring body composition is called Bioelectrical Impedance Analysis (BIA). It is safe and painless and will take no more than 5 minutes. This will be carried out in clinic but where it is more convenient to you the nurse researcher will arrange to visit you at home.

You will also be asked to donate 4 tubes of blood in total (2 for serum and 2 for plasma) throughout the study. Each tube holds about half a tablespoon of blood (10ml). You will be asked to donate two samples at your first or second assessment and 2 more samples at your final assessment. The blood samples will be used for this study to analyse indicators of nutritional status such as serum albumin. Results from the samples taken pre-operatively will be compared with those taken at the end of treatment. We will also compare group results to those of samples taken from women who are diagnosed with cancer of the ovary. Any remaining samples after these analyses will be stored at University College London. Use of these samples in future related studies would need the approval of an independent Ethics Committee.

You will also be asked to complete a questionnaire. The questions ask you about your nutrition and your recent and current health. For example we ask if you have noticed any weight change in the last 3 months. You can complete the questionnaire at the time of your body composition assessment or you can complete it at a later date and post it back to the research team in a prepaid envelope provided. The questionnaire will take about 20 minutes to complete. The assessments are designed to coincide with your hospital appointments and treatment where possible. The initial and second assessments are carried out at entry to the study and immediately before surgery and the final assessment at 2-3 weeks after the surgery, when you attend for your follow.

The researcher will telephone you following each assessment to reassure you about your participation in the study and to address any concerns that may have arisen following your assessment. Your participation in the study will not jeopardise your care in any way. Your care team will already be monitoring your progress throughout this time, but if we have a concern about any result that we find we will seek your permission to inform your consultant so that you are supported appropriately.

Some information we collect during the study such as the questionnaire quality of life information and Bio electrical impedance information is for the purposes of the research only and will not be analysed until the end of the study. However tests such as your weight which are used in clinical practice can be fed back to you throughout the study.

The researcher will also collect information about your condition and hospital investigations and treatment from your medical records. Only members of the research team involved in the project may look at your hospital notes.

Your nutrition will be monitored by your care team including a dietician as part of your regular care through out this period. At the end of the study we will provide you with your individual full results summary showing your nutrition 'foot print' throughout the study.

Do I have to take part?

You do not have to take part. It is entirely up to you to decide whether or not to take part in the study and you can withdraw at any time, without giving a reason. A decision not to take part or to withdraw from the study will not affect the care or treatment you receive in any way.

What tests will be carried out on the samples I give for this study?
Your blood samples will be analysed for markers of nutritional status before treatment and at the end of treatment using known proteins such as serum albumin. Any remaining samples after analysis will be frozen and stored for future studies.

What are the possible disadvantages and risks of taking part?

The assessments and questionnaires involve your time and there is the possibility of local bruising when blood is taken from a vein in your arm. We will try as far as possible to arrange for the blood to be taken

during your other routine tests, to avoid an additional needle stick. Where this is not possible a nurse- researcher trained as a phlebotomist will take the sample.

We understand that facing major surgery can be a difficult time for some women. We assure you that if there were any issues raised by the study that are upsetting to you or which you feel you need support with, the researcher would ensure your consultant was aware of your concerns so that appropriate care could be arranged.

What are the possible benefits of the study?

You may find participation in the study benefits you personally because you can discuss your dietary and food habits with the researcher. Information obtained will help us design an effective and acceptable nutritional support package for women in the future. At the end of the study when the results have been analysed we will provide each woman with the results of their nutritional status throughout the time that they were in the study.

How will the blood samples and questionnaires be used in the future?

If any blood samples remain after the study, they will be coded, frozen and stored for future use. The samples and information collected during the assessment including quality of life questionnaire information will be stored indefinitely at the Women's Cancer Research Department, under the custodianship of University College London. If in future there are circumstances where further studies are designed for the benefit of women then the researchers will approach the ethical committee for approval to use the samples from this study. All samples and data will be anonymised for storage and will not be traceable back to you.

Will what I contribute to the study be confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. Assessment measures and completion of questionnaires will take place in private, and the information will not contain your name or any personal information, only a study identification number. Questionnaires will be held together with information from your medical records in a lockable draw or password protected computer in the Department of Gynaecological Oncology, at University College, London. Only those members of the research team who are directly involved in analyzing the information will have access to the files on the computer. All the samples you give will be coded and Dr. Anne Lanceley the Chief Investigator for this project has the overall responsibility for confidentiality and data security. Identities of participants will not be revealed in any publication or report relating to this research.

Involvement of your doctor
The health professional in charge of your care here at UCLH and your GP will be informed in writing of your participation in this study. A copy of your signed consent form will be kept in your hospital notes.

What will happen to the results of the research study?
The results of the study will be written up as part of a PhD thesis. We will publish peer reviewed papers & articles for the media which cater to clinical academics & to practitioners and users in health care settings. No personal identifiers will be used in reports and publications. The full results of the study will be available in 2013, two years after the beginning of recruitment when we will send a full summary of the findings to every participant. We will also provide you with your individual full results summary showing your nutrition 'foot print' when you were in the study. The results of the study will also be made available to relevant gynaecological charities, including The Eve Appeal and Ovacome. In addition, we will collaborate with the UCLH / UCL Patient and Public Involvement (PPI) in Research Coordinator and with the

UCLH/UCL press offices to develop contacts with local and national media and to contribute material for the UCL/UCLH websites (including to the dedicated pages on the Research Patients Support Network and PPI in Research).

Who is organising and funding the research?

Dr. Anne Lanceley is the Chief Investigator and Professors Martin Widschwendter & Alastair Forbes are co-supervisors of the study. The study is run from the Women's Cancer Research Department; Institute for Women's Health, University College London and is funded by the Comprehensive Biomedical Research Centre (CBRC) at University College London Hospital (UCLH)/University College London (UCL). No payments are made to the researchers conducting this study.

Who has reviewed this study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by North London Research Ethics Committee 3.

What do I do if I wish to make a complaint about the research?
If you wish to complain about any aspect of the research, you should contact the nurse-researcher or the Chief Investigator, Dr. Anne Lanceley on 0207 7679 6807 or by email at (a.lanceley@ucl.ac.uk). If you feel you do not receive a satisfactory response and wish to take the matter further you should contact patient Advice and Liaison Service (PALS), either on line at www.pals.nhs.uk or your local PALS office giving the project title and the Chief Investigator's contact details.

Contact details
If you are interested in participating or you would like to ask questions about any aspect of the study please contact the researcher Nyala Balogun:

By telephone: 020 3447 2119
By email: Nyaladzi.Balogun@ucl.ac.uk
By post: Women's Cancer Department
                Institute for Women's Health University College London
                1st Floor, Maple House
                149 Tottenham Court Road
                London, W1T 7DN.

Thank you very much for taking time to read this information about the study.

Appendix 5: Consent forms

Appendix 5.1 **Consent Form 1: Study A**

Thank you for reading the information about our research project. If you would like to take part, please read and sign this form.

Title of Project: Nutritional Status of Women Referred to a Gynaecological Cancer Centre for Treatment of a Pelvic Mass

Name of local researcher: Ms Nyala Balogun   Initial

I confirm that I have read the attached information sheet dated…………….. (Version ………) for the above study and have been given a copy to keep	
I have been able to ask questions about the study and I understand why the research is being done	
I agree to give samples of blood to be used for this research study and understand that giving a sample for this research is voluntary	
I understand that these tests will be solely for research purposes	
I give permission for the storage of serum and plasma from the blood samples for future research	
I understand that some of the samples may be used for testing for genetic influences on nutritional status in future	
I understand that any future research on my samples will only be carried out with approval from an independent ethics committee and that my confidentiality will be protected at all times	
I agree to complete the questionnaires required for the study	
I give permission to the research team or regulatory authorities to look at my medical notes or pathology slides for research purposes	
I understand that any accessed information will be kept confidential	
I understand that I am free to withdraw my approval for use of the samples at any time, without giving any reason and without my medical care or legal rights being affected	
I agree that the samples I have given and the information gathered can be stored by the custodians, University College London, for use in the current study and for possible use in future studies as described in the information sheet	
I know how to contact the research team if I need to and how to get information about the results of the research	

_____

Name of volunteer Date Signature

_____

Name of person taking consent Date Signature

Study Number:

Appendix 5.2 Consent Form 2: Patient Discussion Group

Thank you for reading the information about our research project. If you would like to take part, please read and sign this form.

Title of Project: Nutritional Status of Women Referred to a Gynaecological Cancer Centre for Treatment of a Pelvic Mass

Name of local researcher: Ms Nyala Balogun

Initial

I confirm that I have read the attached information sheet dated…………………….. (Version …) for the above study and have been given a copy to keep	
I have been able to ask questions about the study and I understand why the research is being done	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected	
I understand that sections of my medical notes may be looked at by responsible individuals from the research team or regulatory authorities where it is relevant. I give permission for these individuals to have access to my records	
I confirm that the interview has been explained to me and I am willing to take part in a tape recorded interview with the researcher for the above study	
I give permission for information from this study to be transcribed, held anonymously in a computer and used for this research	
I give permission for my stored information to be used for future research	
I understand that any future research on my information will only be carried out with approval from an independent ethics committee and that my confidentiality will be protected at all times	
I know how to contact the research team if I need to and how to get information about the results of the research	

_____ _____
Name of volunteer Date Signature

_____ _____
Name of person taking consent Date Signature

Appendix 6: Pearson's Correlations of changes in variables for cases

Variable	Correlation	Pain	Swelling	Ascites	Weight	BMI	%Fat	Dry lean mass	Prealbumin	Albumin	Health state	End of T eating habit	Baseline eating habit1	Prior wt. loss
Pain	Pearson Correlation	1	.025	-.025	.054	.129	-.278	.164	.117	.211	.174	.305	-.142	-.040
	Sig. (2-tailed)		.851	.852	.716	.387	.106	.354	.508	.164	.405	.079	.345	.800
	N	58	58	58	48	47	35	34	34	45	25	34	46	43
Swelling	Pearson Correlation	.025	1	.234	.025	-.011	.216	.105	.342*	.325*	.268	.123	.202	-.244
	Sig. (2-tailed)	.851		.077	.866	.939	.213	.555	.048	.029	.195	.488	.179	.115
	N	58	58	58	48	47	35	34	34	45	25	34	46	43
Ascites	Pearson Correlation	-.025	.234	1	-.256	-.215	-.043	-.251	.497**	.353*	.237	.147	.406**	-.192
	Sig. (2-tailed)	.852	.077		.079	.146	.804	.151	.003	.017	.254	.407	.005	.219
	Pearson Correlation	58	58	58	48	47	35	34	34	45	25	34	46	43
Weight	Pearson Correlation	.054	.025	-.256	1	.829**	.540**	.664**	-.127	.020	.007	-.359*	-.285	.072
	Sig. (2-tailed)	.716	.866	.079		.000	.001	.000	.475	.904	.974	.037	.068	.659
	N	48	48	48	48	47	35	34	34	40	25	34	42	40
BMI	Pearson Correlation	.129	-.011	-.215	.829**	1	.606**	.724**	-.092	-.035	-.093	-.330	-.265	-.231
	Sig. (2-tailed)	.387	.939	.146	.000		.000	.000	.611	.833	.658	.060	.093	.157
	N	47	47	47	47	47	35	34	33	39	25	33	41	39

Variable	Correlation	Pain	Swelling	Ascites	Weight	BMI	%Fat	Dry lean mass	Prealbumin	Albumin	Health state	End of T eating habit	Baseline eating habit1	Prior wt. loss
%Fat	Pearson Correlation	-.278	.216	-.043	540**	.606**	1	.259	-.170	-.062	.215	-.267	.090	-.253
	Sig. (2-tailed)	.106	.213	.804	.001	.000		.139	.426	.750	.391	.197	.631	.186
	N	35	35	35	35	35	35	34	24	29	18	25	31	29
Dry lean	Pearson Correlation	.164	.105	-.251	.664**	.724**	.259	1	.103	.047	-.298	-.345	-.120	-.246
	Sig. (2-tailed)	.354	.555	.151	.000	.000	.139		.630	.809	.230	.091	.528	.207
	N	34	34	34	34	34	34	34	24	29	18	25	30	28
Prealbumin	Pearson Correlation	.117	.342*	.497**	-.127	-.092	-.170	.103	1	.161	.081	.072	.380*	-.340
	Sig. (2-tailed)	.508	.048	.003	.475	.611	.426	.630		.403	.765	.745	.042	.071
	N	34	34	34	34	33	24	24	34	29	16	23	29	29
Albumin	Pearson Correlation	.211	.325*	.353*	.020	-.035	-.062	.047	.161	1	.839**	.236	.319	-.100
	Sig. (2-tailed)	.164	.029	.017	.904	.833	.750	.809	.403		.000	.200	.054	.562
	N	45	45	45	40	39	29	29	29	45	23	31	37	36
Health state	Pearson Correlation	.174	.268	.237	.007	-.093	.215	-.298	.081	.839**	1	.140	.200	.083
	Sig. (2-tailed)	.405	.195	.254	.974	.658	.391	.230	.765	.000		.504	.338	.702
	N	25	25	25	25	25	18	18	16	23	25	25	25	24

Variable	Correlation	Pain	Swelling	Ascites	Weight	BMI	%Fat	Dry lean mass	Prealbumin	Albumin	Health state	End of T eating habit	Baseline eating habit1	Prior wt. loss
During T'tment diet change	Pearson Correlation	.305	.123	.147	-.359*	-.330	-.267	-.345	.072	.236	.140	1	.155	-.316
	Sig. (2-tailed)	.079	.488	.407	.037	.060	.197	.091	.745	.200	.504		.406	.089
	N	34	34	34	34	33	25	25	23	31	25	34	31	30
Baseline diet change	Pearson Correlation	-.142	.202	.406**	-.285	-.265	.090	-.120	.380*	.319	.200	.155	1	-.251
	Sig. (2-tailed)	.345	.179	.005	.068	.093	.631	.528	.042	.054	.338	.406		.104
	N	46	46	46	42	41	31	30	29	37	25	31	46	43
Prior wt. loss	Pearson Correlation	-.040	-.244	-.192	.072	-.231	-.253	-.246	-.340	-.100	.083	-.316	-.251	1
	Sig. (2-tailed)	.800	.115	.219	.659	.157	.186	.207	.071	.562	.702	.089	.104	
	N	43	43	43	40	39	29	28	29	36	24	30	43	43

*. Correlation is significant at the 0.05 level (2-tailed);   **. Correlation is significant at the 0.01 level (2-tailed).

■: Significant;   ■: Close to being significant

Appendix 7: The percentage of women reporting levels 1 to 3 of EQ-3D

Appendix 7.1: Cases reporting levels 1 to 3 by dimension and menopausal status

EQ-5D dimension*		Baseline		During treatment		End of treatment	
		Pre-menopausal	Menopausal	Pre-menopausal	Menopausal	Pre-menopausal	Menopausal
Mobility	Missing	11%	0%	14%	6%	20%	10%
	level 1	45%	53%	43%	37%	60%	53%
	level 2	44%	42%	43%	57%	20%	37%
	level 3	0%	5%	0%	0%	0%	0%
Self-Care	Missing	0%	0%	14%	6%	20%	10%
	level 1	89%	89%	71%	77%	80%	33%
	level 2	11%	11%	14%	17%	0%	10%
	level 3	0%	0%	0%	0%	0%	0%
Usual Activity	Missing	0%	0%	14%	6%	20%	10%
	level 1	89%	42%	29%	14%	60%	43%
	level 2	11%	39%	43%	60%	20%	47%
	level 3	0%	18%	14%	20%	0%	0%
Pain/ Discomfort	Missing	0%	0%	**14%**	6%	**20%**	10%
	level 1	11%	29%	**14%**	6%	**20%**	40%
	level 2	68%	68%	**43%**	66%	**60%**	50%
	level 3	11%	3%	**29%**	3%	**0%**	0%
Anxiety/ Depression	Missing	0%	0%	**14%**	6%	**20%**	10%
	level 1	11%	32%	**29%**	40%	**0%**	60%
	level 2	88%	47%	**43%**	46%	**80%**	27%
	level 3	11%	21%	**14%**	9%	**0%**	3%%
Total (n)		**9**	**38**	**7**	**35**	**5**	**30**

*Level 1 = no problem; level 2 = some/moderate problem; level 3 = extreme problem

Appendix 7.2: Controls reporting levels 1 to 3 by dimension

EQ-5D Dimension		Baseline	End of treatment
Mobility	Missing	0%	10%
	level 1	65%	50%
	level 2	35%	40%
	Level3	0%	0%
Self-Care	Missing	0%	10%
	level 1	100%	80%
	level 2	0%	10%
	level 3	0%	0%
Usual Activity	Missing	0%	0%
	level 1	47%	40%
	level 2	53%	60%
	level 3	0%	0%
Pain/Discomfort	Missing	0%	0%
	level 1	29%	50%
	level 2	65%	40%
	level 3	6%	10%
Anxiety/Depression	Missing	0%	0%
	level 1	29%	50%
	level 2	65%	50%
	level 3	6%	0%
Total (n)		**17**	**10**

Appendix 8: Focus group topic guide

Focus Group Discussion 22/Aug 2012

Introduction

In the last 16 months we have been assessing nutritional status of women referred for investigations and treatment of ovarian masses in two gynaecological cancer centres London. The assessments start from before treatment and we followed women up throughout their treatment surgery/chemotherapy. We looked at weight changes, body composition changes, diet changes and we are analysing blood samples for nutritional protein changes. It is important for us do carry this study out so that we can characterise some of these changes and relate their effects to patient well-being and quality of life. But also help to strategize how and when effective nutrition intervention may be possible. The analysis of some of the results is ongoing, but we do have some preliminary findings, some of which we'd like to explore with you today. But before we do that I would like to open the discussion by asking for your perspectives on

1. **Patient's perspective**
- The issue of nutrition, is it a problem in patients diagnosed with ovarian cancer while they are undergoing investigations and initial treatment of surgery and or chemotherapy?
- If not when is it an issue?
- When do you start to think it is an issue/problem? E.g. weight loss, treatment stoppage, tiredness **etc.**

2. **Self/systematic/clinical management**
- Some of the findings from our study have shown that women loose or indeed gain weight prior to presenting to their GP or A& E for the first time. What were your experiences?
- Did you lose or gain weight at a different time?
- At what point did you think ok, this is a problem; I will have to deal with it? Or this is a big problem my clinicians need to deal with it.

- Were/are you comfortable talking to friends/family/clinician about issues of nutrition.

3. Women told us that they changed their diets somewhere along their journey, avoiding rough food e.g. vegetables, bread, sweets and biscuits, full fat cheeses, alcohol, red meat, acidy food etc.

   They ate soup, green tea, more fruit and veg, raw vegetables, vegan diet, muesli, more omega 3, just greens, more fish etc.,

- I am interested in exploring this further, what are/were your experiences with this.

  What triggers the change? Symptoms, fear, etc.

  Where did you go for the information?

  Who helped you?

  For those out of treatment is this sustainable?

4. The clinical pathway

- Were you satisfied with the nutritional support you received before and during your treatment
- Was it adequate? Did you need help that you feel you did not receive. Could anything have been handled better?
- Did you have easy access to help, a dietician etc.
- What could have been different and of benefit to you?

5. If an additional element of nutrition (assessments/intervention) was added to your care pathway, where would you fit it in and who of the clinical team would you like to deliver this service for you?

Additional if there is time

- How would you describe the impact of your nutrition on your overall health, in view of the disease and treatments?
- If you were in our main group and we have to feedback your nutrition results, how would you have preferred that to be, post, face to face etc.?

Appendix 9: Ethics committee favourable opinion letter

North London REC 3
Level 7 Maternity, Room 019
Northwick Park Hospital
Watford Road
Harrow
HA1 3UJ

Telephone: 020 8869 3928
Facsimile: 020 8869 5222

03 March 2011

Dr Anne Lanceley
Senior Lecturer
University College London
1a, 1st Floor Maple House
149 Tottenham Court Road
London
W1T 7NF

Dear Dr Lanceley

Study Title:	**Nutritional Status of Women Referred to a Gynaecological Cancer Centre for Treatment of a Pelvic Mass**
REC reference number:	**11/LO/0001**

Thank you for your letter of 25th February 2011 responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC on 3rd March 2011. A list of the sub-committee members is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Protocol	3, February 2011	
GP/Consultant Information Sheets		
Participant Information Sheet: main study	3, February 2011	
REC application	2	24 February 2011
Questionnaire: Patient Questionnaire 1	2, December 2010	
Questionnaire: Patient Questionnaire 2	2, December 2010	
Questionnaire: Patient Questionnaire 3	2, December 2010	
Patient Questionnaire IV	2, December 2010	
CV M. Widschwendter		
Participant Information Sheet: patient group	2, February 2011	
Evidence of insurance or indemnity		
Investigator CV		
Participant Consent Form: form 1	2, December 2010	
Participant Consent Form: form 2 patient discussion group	2, December 2010	
Covering Letter		25 February 2011
Letter from Sponsor		15 October 2010
Consultant Letter	1, December 2010	
CV N. Balogun (Student)		
CV A. Forbes		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/LO/0001	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Jan Downer
Chair

Email: alison.okane@nwlh.nhs.uk

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
                       "After ethical review – guidance for researchers"

Copy to: *Clara Kalu, UCL/UCLH/RFH Joint Biomedical Research Unit*
                       [R&D office for NHS care organisation at lead site]

North London REC 3

Sub-Committee of the REC in correspondence 3rd March 2011

Dr. J. Downer (Chair)	Consultant Anaesthetist
Mrs. D. West (Vice-Chair)	Lay Member
Ms. F. Nathoo	Lay Member

Appendix 10: Ethics Committee favourable opinion of substantial amendment

NRES Committee London - Harrow

Level 7 Maternity, Room 019
Northwick Park Hospital
Watford Road
Harrow
HA1 3UJ

Tel: 020 8869 3928
Fax: 020 8869 5222

03 November 2011

Dr Anne Lanceley
Senior Lecturer
University College London
1a, 1st Floor Maple House
149 Tottenham Court Road
London
W1T 7NF

Dear Dr Lanceley

Study title:	**Nutritional Status of Women Referred to a Gynaecological Cancer Centre for Treatment of a Pelvic Mass**
REC reference:	**11/LO/0001**
Amendment number:	
Amendment date:	**12 October 2011**

The above amendment was reviewed by the Sub-Committee in correspondence recently.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Information Sheet	1, September 2011	

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/LO/0001:	**Please quote this number on all correspondence**

Yours sincerely

pp **Dr. J. Downer**
Committee Chair

E-mail: alison.okane@nwlh.nhs.uk

Enclosures:	*List of names and professions of members who took part in the review*
Copy to:	*Clara Kalu, UCL/UCLH/RFH Joint Biomedical Research Unit*
	Mr Philip Diamond, University College London Hospitals NHS Foundation Trust

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NRES Committee London - Harrow

Sub-Committee in correspondence November 2011

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Dr. J. Downer (Chair)	Consultant Anaesthetist
Ms. M. Otter	Clinical Pharmacist

Appendix 11: GP letter

GP Name
GP Address

Date

Dear Dr. (GP Name)

Re: Nutritional Status of Women Referred to a Gynaecological Cancer Center for Treatment of a Pelvic Mass

I am writing to let you know that your patient _____ is a participant in the above mentioned study looking at changes in nutritional status in women referred to University College London Hospitals (UCLH) for treatment of a pelvic mass. The study will assess and compare the nutritional status of women with a diagnosis of ovarian cancer with those who are diagnosed with benign ovarian disease from the time of referral and through treatment.

Malnutrition is highly prevalent in this patient population because early diagnosis is not always possible and late diagnosis, when the cancer has spread to the abdomen or further is associated with worsening nutritional and performance outcomes. Furthermore nutrition still lacks consideration as part of the core treatment pathway in gynaecological cancer.

The study uses a Quadscan 4000 (Bioelectrical Impedance) to assess body composition and evaluates it against other parameters such as serum albumin, diet patterns and quality of life scores (EORTC – C30 and EuroQol Group EQ-5D). Patients will be assessed at 3 time points during the course of the study, at baseline (before the start of any treatment), during treatment (after surgery or first cycle of chemotherapy) and at the end of treatment (end of neo/adjuvant chemotherapy). The outcome measures will include the level of nourishment (nutritional status) and quality of life of participants.

The study is in fulfilment of a PhD thesis and we hope to recruit 100 women over a period of 12-15months. If your patient is found to be severely malnourished and requires further primary care support, with her permission, we will inform her dietician and or consultant who may contact you about her follow up.

If you have any questions regarding the study or you require further information, do not hesitate to contact Ms Nyala Balogun at the Gynaecological Cancer Research Centre on 0207 3806919 or via Email: Nyaladzi Balogun@ucl.ac.uk

Yours sincerely,

Dr Anne Lanceley (Senior Lecturer), Lead Investigator
Dept Gynaecological Oncology
Institute for Women's Health
University College London
1st Floor Maple House
149 Tottenham Court Road
London
W1T 7DN

Tel 02076796807

Appendix 12: Ovacome online invitation letter

You are invited to take part in a research study being conducted at University College London (UCL), looking at the nutritional issues faced by women who are diagnosed with ovarian cancer and how they could be supported better. It consists of two stages. The first stage of this study recruited patients receiving care for a pelvic mass at the University College Hospital and assessed how their nutritional status/well-being changed through diagnosis and during the course of their treatment. You are being invited to take part in the second stage of this study where you are asked to be involved in a discussion group that will address issues surrounding nutritional challenges, support and the acceptability of future nutritional interventions packages. The discussion groups will take place on the 22nd of August at 2 PM. You will be compensated for your travel and refreshments will be provided. Please respond directly to the research team on 07933079428/0203 447 2119 or via email Nyaladzi.Balogun@ucl.ac.uk.

Appendix 13: Challenges encountered during treatment

Reason	Challenge
Patient	Patients too unwell to participate
	Patients prioritising care, such as attending for a blood test, ECG or scan
	Family not wanting patients to participate as they perceive them to be too unwell
	Patients not wanting a home visit by researcher
	Patients becoming too unwell for subsequent assessments
	Patients preferring to have treatment first before considering research
Clinician	Gatekeeping (clinician suggesting patients is too unwell or timing is inappropriate)
	Clinicians dismissing patients after consultation (while researcher attends to other patients)
Researcher	Multiple patient appointments
	Other commitments (meetings, conferences etc.)
	Holidays/sickness
Logistical	Appointments or surgery dates being changed
	Patients not having further hospital appointments prior to treatment
	Patients being admitted on the morning of surgery and not willing to consider research at this stage
	Lack of dedicated space for patient assessment
	Patients waiting long to be seen by clinical team and not willing to wait any long for research purposes
Specific to controls	Improved screening algorithms for identifying benign disease and therefore less number of patients being referred to a cancer centre
	Younger population with work commitments and therefore less additional time available for research during clinic visits
	Less clinic visits (opportunity to recruit) prior to surgery
	Clinics randomly spread during the week, coinciding with other researcher commitments
	Frequent changes in clinic appointments
	Patients waiting long hours in preadmission area prior to surgery adding anxiety and change of heart by those who had previously agreed to participate

Appendix 14: Publications

[Balogun N](), [Forbes A](), [Widschwendter M](), [Lanceley A](). **Noninvasive nutritional management of ovarian cancer patients: beyond intestinal obstruction.** Int J Gynecol Cancer. Jul 2012 (25): 1089-95.

Abstract

Objective: Malnutrition, suffered by more than 50% of patients with ovarian cancer during the course of their disease, significantly compromises the effectiveness of treatment, causes distress, and increases morbidity and mortality. This review outlines the nutritional challenges faced by women with ovarian cancer and evaluates the evidence base for current practice and possible opportunities for intervention in clinical settings.

Methods: PubMed and MetaLib databases were searched for literature on nutrition and cancer/ovarian cancer using terms and truncations covering cancer, cachexia, mouse models, malnutrition, and nutrition intervention. MEDLINE and Cochrane databases were separately searched for interventional studies and clinical and randomized controlled trials published in English (UK/United States) that involved oral nutrition and/or supplementation/intervention in ovarian cancer patients.

Results: Malnutrition continues to be a significant challenge in ovarian cancer management despite significant improvement in treatment pathways and understanding of metabolic pathways and the role of inflammation. There is little evidence of studies designed to evaluate the impact of additional oral nutrients in this population. Seven studies found compared "early" versus "traditional" postoperative oral feeding after major gynecological/oncological surgery, and 1 study evaluated the impact of nutritional status on survival. The 7 studies found evidence of safety, tolerability, reduction in length of hospitalization, and rapid recovery after early feeding. There is no evidence of benefit of additional oral nutrients in this population.

Conclusions:
Current guidelines and protocols of nutritional management of ovarian cancer seem to be based on expert opinion. There is need for extensive collaborative evidence for nutritional management decisions made in the treatment of patients. Prospective cohort studies could help evaluate the impact of changes in nutritional status on health/nutritional outcomes, disease recurrence, quality of life, and survival. These would form a basis for well-designed, targeted, randomized controlled trials with specific and controlled nutrients/counseling aimed at preventing rather than treating nutritional complications.

Tumor growth and progression are characterized by specific alterations of energy and nutrient intake and metabolism, which result in the cancer cachexia syndrome.1 This syndrome is complex and is characterized by anorexia, early satiety, severe weight loss, weakness, immunodepression, anemia, edema, and depression.2-4 It can result in death. Tumor growth and the host immune-specific activation are responsible for these processes.5 Chemotherapy treatment often compounds the problem. Current guidelines for protocols of nutritional management of ovarian and other cancer patients are often lacking in evidence and are based on expert opinion.6 Although intestinal obstruction, which affects up to 30% of ovarian cancer patients, is a significant complication, it has been well described elsewhere.7-9 This review focuses on the nutritional challenges faced by patients with ovarian cancer and the limited evidence for noninvasive nutritional intervention. We refer to current practice in the United Kingdom and suggest possible future research in oral nutrition intervention in this patient population.

The Problem of Malnutrition in Ovarian Cancer

The location of the ovarian tumor deep in the abdomen limits the possibility of a precise early diagnosis. Late diagnosis is associated with advanced disease, which in turn is associated with worsening nutritional and performance outcomes. These are caused by (1) reduced ability to eat (feeling too full too quickly, nausea and vomiting), (2) bowel obstruction, and sometimes (3) diarrhea, the consequences of which may cause patients to stop eating. The psychological impact of a disease arising in a reproductive organ consequently reduces appetite and nutritional intake.10 As with other cancers, derived systemic and metabolic disturbances, which lead to specific humoral and inflammatory responses,3 result in detrimental metabolic alterations. In addition, cancer treatments, particularly chemotherapy, often cause complications that compound the nutritional problem. Pathways that result in cancer cachexia are well documented 3 and involve inadequate food intake, metabolic alterations, and specific humoral and inflammatory responses. These pathways and those involving some hormones such as ghrelin, insulin, and leptin; neuropeptides; and neurotransmitters that play a role in the metabolism of nutrients and maintenance of homeostatic functions have since become better understood. Manipulation of these may be significant in the management of cancer malnutrition. The dynamics of individual contributors evolve during the course of the disease, such that malnutrition should be viewed as a continuum that requires regular reassessment.3 Factors that lead to cancer cachexia in ovarian cancer are summarized in Figure 1. Malnutrition compromises both treatment and recovery, resulting in worse overall outcomes and increased resource utilization. One of the challenges so far has been to provide evidence for the place of nutritional care in the treatment pathway. The negligible response of cachexia to available pharmacological and nutritional interventions has led a general view that nothing can be done, and palliation of the worst effects of this complex metabolic picture is all that can be achieved.11 Further challenges have been caused by lack of criterion-standard methods of determining nutritional status, universally accepted clinical definitions of key terms such as

malnutrition and cachexia, and assessment parameters being affected by illness and injury leading to inability to isolate the effect of malnutrition from the influence of disease.12,13. Progress is being made, and international groups are working together to provide universally acceptable and clinically relevant definitions of key terms and consensus statements.11,14 Disease-related malnutrition has recently been defined as the point at which the severity or persistence of inflammation results in a decrease in lean body mass associated with functional impairment and at least partially attributable to a decrease in nutrient intake, but also tightly linked to the effect of the inflammatory state on intermediary metabolism.14 There is emerging evidence indicating that those mechanisms ultimately leading to the severe wasting of cachexia are operating early during the natural history of disease 11 and increased muscle proteolysis suggestive of cachexia being detectable in cancer patients even in the absence of weight loss.15 This and the fact that anorexia is one of the most common symptoms prompting women to see their general practitioner highlight the need for effective early intervention in cancers where malnutrition and cachexia are highly prevalent.

Nutrient Intake/Availability

The detrimental effects of reduced intake due to disease effect or treatment are unquestionable. Currently, there are marked variations in clinical practice.16 Literature and advice on nutritional management of patients undergoing treatment for ovarian cancer are not clear, and recommendations made by advisory bodies in Europe, United States, and Australia for cancer patients lack evidence and are largely based on expert opinion.6 In bowel obstruction, for instance, it has not been clearly identified which patients should be treated aggressively and what mode of therapy should be pursued.7 The lack of clarity is also reflected in often contradictory information given to patients. Patients themselves tend to seek out information and have been shown to reduce consumption of some types of food such as fat, sugar, and red meat and increase consumption of fruit and vegetables with the hope of aiding cure of their disease.17 Patients may see the tumor as a reason to eat "healthy food" and may thus compromise themselves at a time when they need high energy-dense intakes. There is also some evidence that suggests that restricted calorific intake increases longevity in multiple species and slows several age-related biological functions, including decreased immune function and tumorigenesis.18-20 The biological mechanisms of this process are neither clearly understood nor have been demonstrated unequivocally. However, suggesting that deprivation rather than supplementation may be part of the answer to malnutrition and tumor progression seems counterintuitive. There is a need for further research with key carcinogenesis and/or energy balance pathways to provide important understanding of the calorie-cancer relationship.21

Even though nutritional intake has been shown to be substantially reduced in patients with cancer experiencing weight loss,22 it is not always diminished. Once a critical point is reached, the complex interplay between underlying disease, metabolic alterations, and reduced availability of nutrients will eventually and inevitably cause death.11 Adequate intake often fails to reverse the cachectic process where inflammation is present.

Metabolic and Inflammatory Pathways

The metabolic and immune changes in cancer are well documented and are not necessarily cancer-specific. They are thought to be mediated by the pathophysiological process, that is, tumor, or host-derived chemical factors, for example, peptides, neurotransmitters, cytokines, and lipid-mobilizing factors, and are associated with hypertriacylglycerolemia, lipolysis, and acceleration of protein turnover.23 Host and tumor-derived factors seem to interact with intracellular signaling mechanisms to disrupt skeletal muscle protein balance.24 Tumor cells increase nutrient uptake and angiogenesis to support the up-regulation of metabolism necessary for unrestricted growth, and they have a high degree of anaerobic glycolysis and produce large amounts of lactate and a net uptake of amino acids.23 Significant research has been carried out on metabolic pathways and the role of the inflammation on malnutrition and cachexia. These include efforts to understand the role of cytokines as inflammatory mediators that can influence a change in the cognitive and autonomic processing that governs the initiation and cessation of ingestion,25 strategies with molecules able to block cytokine production by either destabilizing their mRNA or inhibiting their synthesis or to interfere with cytokine-receptor interaction,26 and exploration of anticytokine strategies combined with oral supplements and treatments aiming to modulate inflammatory processes associated with cachexia.6 There has also been work on analysis and understanding of DNA sequences, RNA transcripts, and metabolism, which may in the future allow for the identification of specific genotypes and phenotypes that may help with metabolic profiling and lead to individualized dietary therapies,27 although this needs further exploration. In the last decade, there was a surge in interest in hormones that influence metabolic homeostasis including insulin, leptin, and ghrelin and neuropeptides. They are involved in the metabolism of nutrients and maintenance of homeostatic functions.28-36 It is thought that there are relatively normal insulin secretion in cancer and reduced insulin sensitivity (peripheral insulin resistance), resulting in inefficient metabolism and availability of carbohydrates to the body. The other hormones and neuropeptides are implicated in energy control, feeding behavior, and accretion of fat. Understanding their roles presents research opportunities, where manipulating them to stimulate food intake or prevent breakdown of body reserves potentially improving patient outcomes seems a real potential.

Importance of Adequate Nourishment in the Face of Disease and Treatment

Up to 40% of all cancer patients die of the effects of malnutrition rather than of the malignancy itself.37 It has been said that the chance of surviving ovarian cancer mainly depends on (1) patient characteristics, (2) tumor biology, and (3) the quality of treatment.38,39 Whereas the first 2 are nonmodifiable, the latter can be. Nutrition is an important aspect of quality of treatment that could potentially impact on patient outcomes38; hence, strategies that support and ensure maintenance of adequate nutrient intake and utilization in the presence of symptoms and through treatment need to be found.

Treatment

Malnutrition alters cellular physiology and organ function, affecting surgical outcome and postoperative morbidity and mortality.40-42 The feasibility of complete cytoreduction is related to tumor volume and location, it is also related to a patient's ability to withstand a long operation (age, performance status, nutritional status).43 Malnourished patients undergoing surgery are more likely to have complications such as increased blood loss, poor wound healing, infections, and admissions to intensive care units,44,45 while those undergoing adjuvant chemotherapy show a decreased response to the treatment, increased risk of chemotherapy-induced toxicity, and increased risk of complications and death during the course of treatment.46 Failure to complete intended chemotherapy regimen is also common. Comorbidities such as chest infections due to decreased immunity and electrolyte imbalance with implications for lung function and cardiac complications are also common.

Quality of Life

A diagnosis of ovarian cancer, pain, anxiety, anger, fear, and difficult treatments affect all aspects of a woman's life including her sexuality,47,48 resulting in reduced quality of life. Low quality of life in turn contributes to psychological distress, which feeds into the vicious cycle of aggravated nutritional intake and weight loss, further plunging quality of life. This cycle is exacerbated by relapse or disease progression, which occurs in the majority of patients within 18 months of diagnosis.

Evidence Base for Current Clinical Practice

We sought to determine what clinical trials or other studies of noninvasive nutrition intervention in ovarian cancer patients had been carried out by searching MEDLINE and the Cochrane databases. The findings were unexpected; no randomized controlled trials were identified that evaluated the impact of additional oral nutrients or other interventions such as diet counseling. Gupta et al39 evaluated the impact of nutrition on survival in a cohort of women diagnosed with ovarian. Interpretation of their results is complicated by the fact that their baseline assessment includes patients who had received treatment and those who had not. The other 7 studies identified (Table 1) evaluated the efficacy and safety of early postoperative feeding compared with delayed feeding. Even so, only 1 study55 focused on only ovarian and peritoneal cancer patients, the rest (6 studies) included all gynecological cancers with one (Schilder et al [1997]51) including noncancer patients.

Health outcomes related to surgical protocols were the primary outcome for all the studies. They showed that the former was safe and well tolerated by patients and also that there was reduction in postoperative complications such as infection and length of stay. This evidence supports the postoperative Enhanced Recovery Programme (oral intake as soon as possible after surgery)56-58 currently practiced in many surgical settings in the UK National Health Service. Gupta et al39 followed up patients in the medium term. Although they found that patients who were well nourished at baseline or whose nutritional status improved at 3 months had significantly better survival than those whose nutritional status deteriorated, the challenge remained in that the baseline was not clearly defined.

The majority of patients treated for ovarian cancer in the United Kingdom do not receive a nutritional management package at the onset. There are exceptions where nutritional problems interfere with planned treatment and patients are referred to a dietitian for intervention. Patients' weight and height are assessed at first contact and before treatment. Comprehensive nutritional screening is often carried out only at the time of admission to a ward. Even so, there are questions of how well applied the assessment outcomes are to daily patient care. Nutritional support tends to be more robust where there are complications or in end stages where enteral and parenteral routes are preferred and usually as part of the palliation. There is no clear evidence of what type of nutrients could be used effectively to slow down or reverse cachexia and what doses and conditions would enable this to happen. Moreover, researchers often focus on very specific and usually short periods (around treatment) for assessment and intervention, whereas we know that the processes that lead to cachexia precede any signs or symptoms.

SUMMARY

It is possible that the limited number and scope of nutrition intervention research highlight the challenges of working with patients diagnosed with this low-incidence but deadly disease. There needs to be clear evidence of the categorical changes in nutritional status of patients in relation to survival or death. The understanding of these changes and how they relate to tumor characteristics (histopathology, stage, grade, etc) and patient characteristics (age, weight, activity level, etc) can move forward attempts to provide targeted and individually tailored nutritional intervention. Prospective cohorts assessing nutritional status over a number of years could be a good starting point. Evidence from such cohorts can be used to design randomized controlled trials to establish whether nutrition intervention at any stage in the disease trajectory will achieve improvement beyond short-term indices such as quality of life, recurrence, prognosis, and survival. So far, only short-term benefits such as length of hospital stay, early return to oral diet, and a reduction in complications and infection rates have been demonstrated. Also, questions need to be answered about which particular nutrients linked to the causation of cachexia can be used effectively to slow down or reverse this condition and what doses and conditions would enable this to happen.

CONCLUSIONS

Guidelines for nutritional management of ovarian cancer patients are largely based on expert opinion. There is a need for a clear, objective, comprehensive, and long-term assessment of nutritional status of patients with ovarian cancer, how this changes at different stages of the cancer trajectory, and how the changes impact health and nutritional outcomes, disease recurrence, quality of life, and survival. This would provide a basis for well-designed randomized controlled trials with specific and controlled nutrients/counseling targeted at identified specific needs

Tables and figures
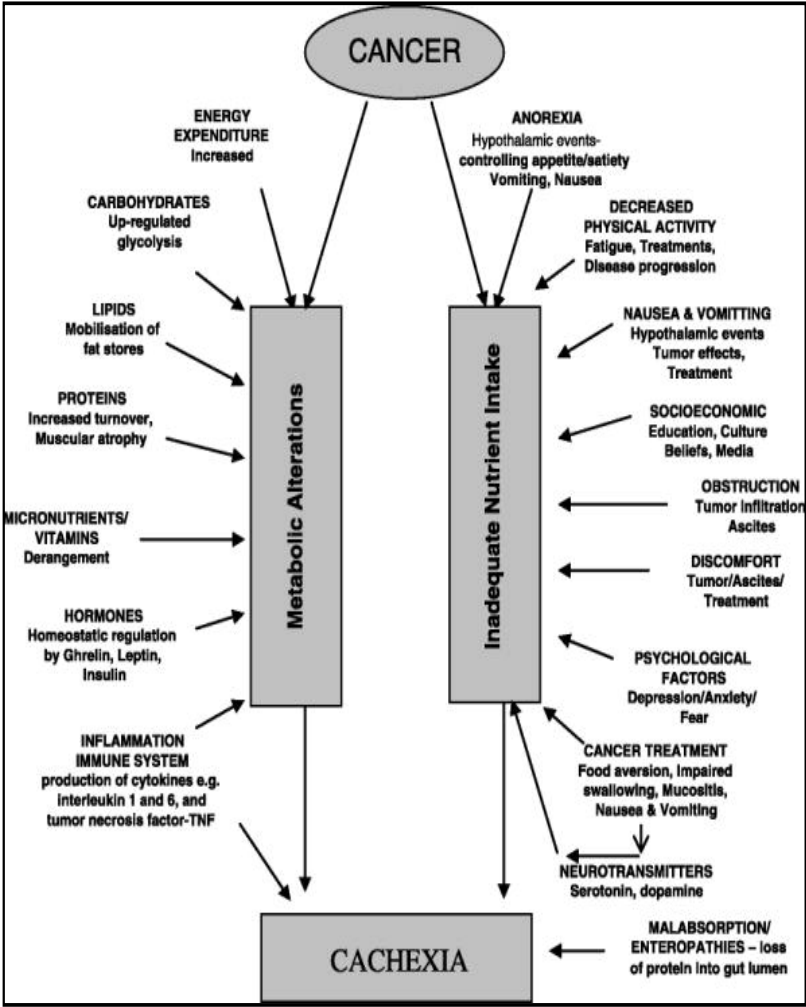
FIGURE 1

FIGURE 1 . Causation of cancer cachexia is multifactorial. Different factors come into effect at various time points along the disease pathway.

Table 1

Author	Type of Study	Type of Patients	No. Patients	Objective	Relevant Findings	Conclusions
Pearl et al, 1998[49]	A randomized controlled trial	All gynecological oncology patients	200	To evaluate the safety and efficacy of early oral feeding after intra-abdominal surgery in gynecologic oncology patients	Time to development of bowel sounds, time to initiation of clear liquid and regular diets, and hospital stay significantly longer in the traditional group	Early postoperative feeding in gynecologic oncology patients undergoing intra-abdominal surgery is safe and well tolerated
Steed et al, 2002[50]	A randomized controlled trial	Gynecological oncology	107	To compare early oral intake and the traditional timing of feeding after major gynecologic surgery and the effects on the length of hospital stay	Significant reduction in the LOS for those patients on the early feeding regimen. Median length of stay for was 4.0 d ($P = 0.0001$) compared with 6.0 d for traditional group. There was no difference in the incidence of emesis	Early postoperative dietary advancement resulted in a decreased LOS and appears to be safe, with no increased adverse effects
Schilder et al, 1997[51]	A prospective controlled trial	Mixed gynecology	96	To determine whether, when compared with traditional dietary advancement, early oral intake following major gynecologic surgery leads to a reduction in the length of hospitalization	No statistical difference in the number of subjects who required postoperative antiemetics or bisacodyl suppository. Statistically significant reduction in the LOS for Those patients on the early feeding regimen (4.02 [SD, 0.30] d vs 3.12 [SD, 0.16] d; $P = 0.008$)	Early postoperative oral intake results in a decreased LOS and is well tolerated when compared with traditional dietary management
Cutillo et al, 1999[52]	A randomized controlled study	Gynecological oncology	61	To evaluate the feasibility, safety, and tolerance of early feeding in patients undergoing surgery for gynecologic malignancies	Early oral feeding was associated with a significantly faster resolution of postoperative ileus ($P < 0.01$), with a more rapid return to a regular diet ($P < 0.01$), with an earlier first passage of stool ($P < 0.01$), and with a shorter postoperative stay ($P < 0.05$) than patients in arm B	Early feeding is feasible and well tolerated and is associated with reduced postoperative discomfort and a more rapid recovery

Table 1 continued

Pearl et al, 2002[53]	A randomized controlled trial	Gynecological oncology	254	To prospectively evaluate the safety and efficacy of a regular diet as the first meal after intra-abdominal surgery in gynecologic oncology patients	The time to development of bowel sounds, passage of flatus, and hospital stay were comparable for both groups. Febrile morbidity, pneumonia, wound complications, and atelectasis occurred equally in both groups	A regular diet as the first meal after intra-abdominal surgery in gynecologic oncology patients is safe and efficacious
Minig et al, 2009[54]	A randomized controlled trial	Gynecological oncology	51	To assess the outcome of early oral postoperative feeding (EOF) compared with traditional oral feeding (TOF) in gynecologic oncology patients undergoing laparotomy with associated intestinal resection.	Hospital stay in patients who received EOF was 6.9 vs 9.1 d in the TOF group ($P = 0.022$). Use of analgesic and antiemetic drugs, intensity of pain, intestinal function recovery, mean levels of postoperative satisfaction, postoperative complications, and quality-of-life scores did not differ between the 2 groups	Early resumption of oral intake is feasible and safe, and significant reduction in LOS was demonstrated.
Gerardi et al, 2008[55]	A clinical pathway	Ovarian and primary peritoneal	64	To evaluate the safety, feasibility, and economic impact of a clinical pathway, including rapid diet advancement, for patients undergoing rectosigmoid colectomy as part of cytoreductive surgery for advanced ovarian and primary peritoneal cancers	Patients who had rapid diet advancement had a significantly shorter median LOS (7 vs 10 d, $P = 0.014$) and lower median 30-d postoperative hospital cost ($19,700 vs $25,110, $P = 0.028$)	A critical pathway incorporating rapid diet advancement is feasible, safe, and associated with a significant reduction in LOS and hospital-related costs
Gupta et al,[39]	Retrospective chart review	Ovarian cancer	98	The impact of improvement in nutritional status on ovarian cancer survival	Patients with an improved nutritional status at 3 mo had significantly better survival than those with deteriorated nutritional status independent of age, stage at diagnosis, prior treatment history, and tumor response	Improvement in nutritional status is associated with better survival
					Note: Baseline assessment not consistent	
					Some patients received parenteral nutrition	

Appendix 15: Copyright authorisations

Appendix 15.1 Evans et al., 2008

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Appendix 15.2 Balogun et al., 2012

Title:	Non-invasive Nutritional Management of Ovarian Cancer Patients: Beyond Intestinal Obstruction.	
Author:	Balogun, Nyaladzi; MSc, BSc; Forbes, Alastair; MD, BSc; FRCP, ILTM; Widschwendter, Martin; MD, MRCOG; Lanceley, Anne	
Publication:	International Journal of Gynaecological Cancer	
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Portion: Figure/table
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Expected completion date: Feb 2018
Expected size (number of pages): 300

Appendix 15.4 Ukleja et al., 2010

Title:	Standards for Nutrition Support	Logged in as:
		Nyaladzi Balogun
		UCL
Author:	Andrew Ukleja, Kevin L. Freeman, Karen Gilbert, et al	
Publication:	Nutrition in Clinical Practice	
Publisher:	SAGE Publications	
Date:	08/01/2010	
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Appendix 15.5 Fearon et al., 2011

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Title of your thesis/dissertation: Nutritional status of women referred to a gynaecological cancer centre for treatment of a pelvic mass
Expected completion date: Feb 2018
Estimated size (number of pages)
300

Appendix 15.6 Bodystat

From: ▬▬▬bodystat.com>
Sent: 12 January 2018 19:47
To: Balogun, Nyala
Subject: Bodystat images

Dear Nyaladzi,

 Thank you for your call to Bodystat yesterday asking permission to use our images.

 We confirm we allow the use of the images from our website for the purpose of your research study using the Quadscan. I have also attached these images should you require a better resolution.

As I mentioned over the phone, please do let us know when your study is published, as we have a huge database of physicians and researchers all over the world who I am sure would be interested to read your published work.

Best of luck with it.

Kind regards,   ▬▬▬

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