Clinical Expert Series

Ovarian Cancer Prevention and Screening

Usha Menon MD, FRCOG

Chloe Karpinskyj, BSc

Aleksandra Gentry-Maharaj, PhD

Affiliation:

Gynaecological Cancer Research Centre

Department of Women's Cancer

Institute for Women's Health

University College London

Maple House 1st Floor

149 Tottenham Court Road

London W1T 7DN

United Kingdom

Corresponding author:

Prof Usha Menon

Tel: ++44 20 3447 2108, Email: u.menon@ucl.ac.uk

Co-authors

Dr Aleksandra Gentry-Maharaj

Tel: ++44 20 3447 2118, Email: a.gentry-maharaj@ucl.ac.uk

Ms Chloe Karpinskyj

Tel: ++44 20 3447 2117, Email: c.karpinskyj@ucl.ac.uk

Fax (for all authors): ++44 20 3447 2129

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Précis

Advances in ovarian cancer prevention and screening include improved risk-prediction models, mounting use of bilateral salpingectomy, proven stage shift with multimodal screening, superior performance of longitudinal biomarker algorithms compared to cut-offs and an increasing focus on tumour DNA both in blood and novel specimens, such as cervical cytology samples.

Abstract (word count: 308)

There has been much progress in ovarian cancer screening and prevention in recent years. Improved tools that combine genetic and epidemiological factors to predict an individual's ovarian cancer risk are set to become available for tailoring preventative and screening approaches.

The increasing evidence on tubal origins of a proportion of ovarian cancer has paved the way to use of opportunistic bilateral salpingectomy at tubal ligation and hysterectomy in the general population. Clinical trials are in progress to estimate the long-term effects on endocrine function. In women at high risk, risk reducing salpingo-oophorectomy remains the standard of care with the current focus on management of resulting non-cancer outcomes, especially sexual dysfunction in younger women. This has led to evaluation of early bilateral salpingectomy and delayed oophorectomy in this population. Meanwhile, modelling suggests that *BRCA* mutation carriers should consider using the oral contraceptive pill for chemoprevention. In the general population, the largest ovarian cancer screening trial to date, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), reported a stage shift with annual multimodal screening using the longitudinal CA125 Risk of Ovarian Cancer Algorithm (ROCA) but not with annual transvaginal ultrasound screening. There was no definitive mortality reduction with either screening strategy compared with no screening. Further follow-up till December 2018 in now underway. Stage shift and higher rates of optimal cytoreduction were also reported during 3-4 monthly multimodal screening in the United Kingdom and U.S. high-risk screening trials. While all agree that there is not yet evidence to support general population screening, recommendations for high-risk screening vary between countries. A key finding from the screening trials has been the better performance of longitudinal algorithms compared to a single cut-off for CA125. A major focus of ovarian cancer biomarker discovery work has been tumour DNA markers both in plasma and novel specimens, such as cervical cytology samples.

Introduction

Ovarian cancer has the highest mortality of all gynecologic malignancies. Worldwide there are 239,000 new cases and 152,000 deaths from ovarian cancer each year.[1] Despite improvements in survival rates over the last 40 years, two thirds of women still die within 10 years of diagnosis.[2] Five-year survival is less than 20% in women diagnosed with advanced stage (stage III or IV) invasive epithelial ovarian cancer but exceeds 90% in those detected at stage I.[3] Efforts have therefore focused on diagnosing early-stage or low-volume disease through risk prediction, prevention, and screening.

Over the past decade a dualistic pathway of epithelial ovarian carcinogenesis has emerged. Type I invasive epithelial ovarian cancers are genetically stable, indolent, and include low-grade serous, endometrioid, clear cell and mucinous subtypes. Type II, mainly high-grade serous cancers, are aggressive genetically unstable tumours usually harbouring *p53* mutations. The subtypes differ in epidemiology, etiology, and treatment, making invasive epithelial ovarian cancer a heterogenous disease where one strategy may not be equally effective for all. As high-grade serous cancers account for 75% of ovarian cancers and majority of the mortality, the most urgent need is for novel preventative and screening strategies targeting this subtype. Risk stratification is key to implementation of all such approaches.

A literature review on ovarian cancer risk factors, prevention, and screening was undertaken for the period 2010-2017. The evidence summarized below is based where possible on systematic reviews of risk factors and randomized controlled trials (RCTs) and prospective cohort studies on screening.

Risk Factors

Lifetime risk of ovarian cancer varies from 1.3% (1 in 71)[4] to 1.9% (1 in 52)[5] in the general population, to 45% in women with mutations in the *BRCA1* gene.[6] In keeping with the goals of precision medicine,

the growing evidence base on epidemiological and genetic risk factors allows risk to be further

personalized and to better inform design of screening and preventative approaches.

Genetic Predisposition

Inherited conditions account for 5-15% of ovarian cancer cases. Despite the growing list of ovarian

cancer predisposing genes, approximately 60% of excess familial risk remains unexplained.[7]

Mutations in high penetrance genes: BRCA1/2 mutations are most common, conferring a lifetime

(cumulative) risk of invasive epithelial ovarian cancer by age 80 of 44% (*BRCA1*) and 17% (*BRCA2*).[8]

In most populations, incidence of *BRCA* mutations is between 1 in 300 and 1 in 500. In certain

communities such as the Ashkenazi-Jewish, incidence is much higher (1 in 40). So far, identification of

mutation carriers has been based on family history which has poor sensitivity. Even in the Ashkenazi-

Jewish population, 56% of *BRCA* carriers are without family history.[9-11] Among the several approaches

explored to address this, one that has gained wide acceptance is mainstreaming genetic testing, ie,

integrating testing into the cancer patient pathway. For ovarian cancer, it involves offering testing to

all women with nonmucinous invasive epithelial ovarian cancer at the point of diagnosis. This is based

on estimated prevalence of *BRCA* germline mutations of 14% in women with invasive nonmucinous

epithelial ovarian cancer and 22% in those with high-grade serous cancers.[12] As yet, there are no

published studies on cost-effectiveness of such a strategy.[13] A second approach is systematic testing

of populations with a high prevalence of mutation carriers. Systematic testing in the Ashkenazi-Jewish

population has been found to be acceptable, cost-effective,[14] and estimated to prevent 3.6% of

ovarian cancers. Finally, Mary-Claire King (who first identified the link between *BRCA1* mutations and

breast and ovarian cancers) has suggested offering universal *BRCA* mutation screening to all young

women, regardless of family history.[15] As cost-effectiveness is highly sensitive to the cost of genetic

testing,[16] both Next Generation Sequencing and bundling *BRCA* testing with other cancer-associated

genes could improve estimates. In women with Lynch syndrome, lifetime-risk of ovarian cancer is

lower (~2-15%) and varies according to the gene harbouring the mutation,[17] the highest risk being in

MLH1 and MSH2 carriers.

Moderate penetrance genes: Newer genetic testing panels include recently described moderate

penetrance genes (Table 1). These mutations are rare (<1% general population) and explain around

20% of the excess familial risk.[7] While estimates of lifetime risk by age 70 are available for *RAD51C*

(5.2%, 95%CI 1.1%-22%),[18, 19] *RAD51D* (12%, 95%CI 1.5%-60%)[18, 20] and *BRIP1* (5.8%, 95%CI 3.6%-

9.1%),[21] the long-term risk of cancer associated with mutations in *FANCM*,[22] *BARD1*, and *NBN*[21] are

still uncertain. Most recent studies report no association between *PALB2* and increased ovarian cancer

risk.[21, 23]

Low risk loci: Variants that are common (1 in 100 individuals) in the population, probably account for

most of the unexplained inherited component of risk. So far, 37 low-penetrance inherited genetic

variants[7] have been identified through the Ovarian Cancer Association Consortium[24-29] and wider

collaborative efforts.[27, 30] These single nucleotide polymorphisms (SNPs) individually confer a 1.2 to

1.4-fold increase in epithelial ovarian cancer risk with a few conferring a relative risk reduction (up to

0.8).[27] Twenty seven of these explain approximately 6.4% of the polygenic risk in the general

population.[7] More recently, subtype-specific risk has been described.[27, 31, 32] There are likely to be

many more genetic variants, each with an extremely small effect. As most of these are common, some

women will carry multiple risk variants. However, even in combination these variants will not confer

a large increase in risk. Women carrying the greatest number of variants are estimated to only have

an absolute lifetime risk of ovarian cancer of around 2.8%.[33]

Hormonal, Reproductive, and Lifestyle Factors

Twenty-one percent of epithelial ovarian cancers are linked to major lifestyle and other risk factors.[34,

35] There is a large volume of literature on these risk factors (Table 1). Many such as oral contraceptive

pill use, pregnancy, breastfeeding, and tubal ligation are well-established protective factors.

Conversely, nulliparity and infertility are associated with increased risk. This effect is thought to be

due to the reduction in the number of ovulatory cycles (incessant ovulation hypothesis).

Oral contraceptive pill (OCP) use has a protective effect proportional to duration of use, with 10 years

of use providing a 50% risk-reduction in both the general population[36] and women with *BRCA1/2*

mutations.[37,38] The reduction persists following cessation of use[36] and applies to all subtypes.[32]

Conversely, hormone therapy (HT, both estrogen only and estrogen–progesterone), especially if taken

for more than 5 years is associated with increased risk.[39]

It has long been established that parity decreases risk with women with one, two, three, or more

pregnancies having a reduced risk of 28%, 43%, and 54% compared with nulliparous women.[40] A

duration-dependent trend was also confirmed with breastfeeding conferring risk reduction of 21%,

28%, and 33%, respectively, for <6 months, 6-12 months, and >13 months compared with no

breastfeeding. As these events are inexorably linked, it is important to consider the effect of both

combined.[40] Women who have two livebirths and who have breastfed in total for <6 months have a

50% reduction in ovarian cancer risk compared to nulliparous women who have not breastfed.[40] The

rise in ovarian cancer incidence observed in Southern and Eastern Europe is thought to have been

affected by a shift in reproductive choices with women having fewer children and reducing

breastfeeding.[41] A reduction in risk ranging from 13% to 34% in invasive epithelial ovarian cancer risk

has been reported with tubal ligation (sterilization),[32, 42-44] with the magnitude varying by subtype.

There is some emerging evidence that Type I cancers are more hormonally driven compared to Type

II. The protection that parity confers is much lower in Type II cancers; 0.81 (95% CI 0.72-0.92) for high-

grade serous cancers; 0.35 (95%CI 0.27-0.47) for clear-cell cancers.[32] These subtype differences are of

relevance in risk prediction models especially if they are to be used to aid different type-specific early

detection strategies.

There is conflicting evidence on the effects of hysterectomy on ovarian cancer risk. While older studies showed a protective effect,[45] no association (OR 0.97, 95%CI 0.81-1.14) has been reported more recently.[46] There seems to be a temporal shift with a protective effect in those diagnosed with epithelial ovarian cancer prior to 2000 (RR 0.70, 95%CI 0.65-0.76) but increased risk (RR 1.18, 95%CI 1.06-1.31) in women diagnosed post-2000.[45] However, data on the shift in risk from protective to harmful is limited and the temporal change is probably multifactorial: overall decrease in hysterectomy rates, use of vaginal rather than abdominal approach, fall in salpingo-oophorectomy performed at the same time, poor data-capture on ovarian removal at hysterectomy in older studies and increase in the age of those undergoing the procedure.

Endometriosis increases risk of invasive epithelial ovarian cancer, with risk associated with clear cell, low-grade serous, and endometrioid but not with high grade serous cancers, mucinous or borderline ovarian tumors.[47] The null-effect on Type II cancers makes this factor less important when trying to estimate an individual's risk of developing these aggressive cancers.[32] Timely treatment of endometriosis could reduce ovarian cancer risk.

A recent meta-analysis suggests modest risk reduction in ovarian cancer in the general population with aspirin use (RR 0.89, 95%CI 0.83–0.96),[48] with equivocal results for non-aspirin non-steroidal anti-inflammatory drugs.[49] Strongest inverse associations have been reported with long-term, regular, low-dose aspirin use.[48] A non-significant risk reduction of ovarian cancer was seen with aspirin use in Lynch Syndrome women in the CaPP2 (Cancer Prevention Project) trial.[50] Preliminary data suggesting decreased risk with statins was not confirmed in a large Danish nationwide study which found a neutral association (OR 0.98, 95% CI 0.87-1.10).[51]

There is extensive literature on risk-reduction associated with various other lifestyle factors (such as alcohol,[52] obesity,[53, 54] cigarette smoking,[55] talc use,[56] diet, and physical activity), which has been

summarized in Table 1. While some have a global effect on ovarian cancer risk, others such as cigarette smoking and obesity are subtype-specific.

Risk Stratification

The potential of risk stratification is to triage women so that those at highest risk of ovarian cancer can be offered preventative surgical strategies, those at moderate risk screening and chemoprevention, and those at lowest risk, symptom awareness. Target populations for population cancer screening programs have, to date, used age and gender. In ovarian cancer, these are usually women at low (1-2%) or moderate risk (3-10%) who have no family history of ovarian cancer, a single first-degree relative with ovarian cancer, or a more significant history but no mutations in *BRCA* genes. Performance could be improved by targeting those most at risk and therefore most likely to benefit. Introduction of risk-stratified cancer screening in the next 5 years[57] is in fact one of the priorities of the UK Cancer Strategy.[58] Risk stratification using genetic and non-genetic factors is currently being evaluated in breast cancer screening trials.[59] [57] In breast screening, modelling suggests that risk-based screening (if set at a 10-year risk of 2.5%) could result in 31% fewer women being screened and only 2% fewer cases detected.[57] This could have a major effect on reduction in health care costs.

Eligibility for high-risk (often defined as lifetime risk >10%) programs include family history and cancer-predisposing gene mutations. Most current predictive models (eg, BRCAPRO, BODICEA, Myriad II) of similar discriminatory ability[60] use family history to estimate mutation risk in *BRCA* genes and lifetime risk of ovarian cancer. The ovarian cancer risk estimates in *BRCA* mutation carriers vary according to family history, suggesting that other genetic factors modify cancer risk in this population.[8] A subset of common SNPs which influence ovarian cancer risk in the general population have been shown to also modify risk in *BRCA* mutation carriers.[61] Efforts are now underway to refine individual ovarian cancer risk prediction in these women at high risk by incorporating these and other risk factors.

In the low-risk (general) population, work has focused on building models using genetic and epidemiological (lifestyle and reproductive) risk factors. Decision aids to communicate such risk[60, 62] have been developed and incorporated into applications for smart phones and tablets, eg, QCancer.[63] A model combining OCP use, parity, tubal ligation, endometriosis, first-degree family history of ovarian cancer, and 13 low-risk SNPs suggests risk could vary from very low risk of about 0.35% to as high as 8.78%, with the majority of those in the highest quartile of risk not having any family history.[64] Nearly all women with an estimated 4-9% lifetime risk had not used OCP or undergone tubal ligation.

Validation of the general population ovarian cancer risk models are urgently needed before they can be widely used clinically. Effectiveness, cost-effectiveness, acceptability, accessibility, anxiety, and feasibility of such approaches needs to be considered. Implementation challenges will need to be addressed in parallel to training of health care professionals to deliver such risk information.

Risk Reduction Strategies

As with all interventions, these strategies are associated with harms which need to be balanced against an individual's ovarian cancer risk. Surgery is offered to those at highest risk. This has traditionally been set at 10% lifetime risk with many limiting offer of surgery to mutation carriers only. This threshold is now being debated. Modelling suggests that risk-reducing surgery could be cost-effective at lower thresholds: a lifetime risk of >4% in premenopausal women on the condition that they take HT till age 50 and ≥5% in postmenopausal women aged over 50.[65]

Risk-Reducing Surgery

Based on the growing evidence of tubal origins of epithelial ovarian cancer, this has broadened to include salpingectomy alone in addition to bilateral salpingo-oophorectomy.

Risk-Reducing Bilateral Salpingo-oophorectomy

Recent reviews and meta-analyses of published risk-reducing bilateral salpingo-oophorectomy (often

referred to as "RRSO") studies have shown a significant ovarian cancer risk-reduction of approximately

80% and an all-cause mortality reduction of 70% in *BRCA* mutation carriers.[66, 67] This was based on

relatively short (4-year) follow-up.[66]

A breast cancer risk reduction of 50% was considered an added benefit of oophorectomy in *BRCA*

mutation carriers.[67, 68] However, recent data suggests that there might be little or no effect on breast

cancer risk (HR 1.09, 95%CI 0.67-1.77).[69, 70] It needs to be noted that a trend to risk reduction was

noted for breast cancer diagnosed before the age of 50 in *BRCA2* mutation carriers (age-adjusted HR

0.18, 95%CI 0.05 to 0.63, p=0.07).[70] *BRCA1* mutation carriers and older *BRCA2* patients should be

counselled that the impact of oophorectomy on breast cancer risk reduction is uncertain.

Risk-reducing bilateral salpingo-oophorectomy is routinely recommended to women at high risk

following completion of their family. In *BRCA1* mutation carriers this is usually from the age of 35 and

definitely by 40, as below the age of 40 the risk of ovarian cancer is only 2%.[71] In those with *BRCA2*

gene mutations, there is growing acceptance that women have until the age of 45 to undergo surgery

since their cumulative risk of ovarian cancer by age 50 is only 0-1%.[8, 66] The preferred route for risk-

reducing bilateral salpingo-oophorectomy is laparoscopic and inspection of the abdomen and pelvis is

mandatory. It is associated with an overall complication rate of about 3-4% (including minor

complications such as wound infection).[72] It is essential that the specimens are subjected to detailed

sectioning according to the SEE-FIM (Sectioning and Extensively Examining of the Fimbriated end)

protocol[73] to ensure occult cancer or serous tubal intraepithelial carcinoma lesions in the tube are not

missed. In an analysis of >3,000 *BRCA* mutation carriers who underwent risk-reducing bilateral

salpingo-oophorectomy, the incidence of occult cancers was 5.7% (3% serous tubal intraepithelial

carcinoma, 2.7% invasive epithelial ovarian cancer).[74] This is similar to findings in more recent case

series.[72, 75] Peritoneal washings for cytology[76] contribute to accurate staging of occult cancers. It has

been reported that 4.5-6% of serous tubal intraepithelial carcinoma recur 43 months after risk-reducing surgery.[77] There is controversy about the need for adjuvant therapy in women with serous tubal intraepithelial carcinoma lesions especially those with positive peritoneal washings.[78] The majority view is that routine surveillance with tumor markers and imaging is not warranted.

There are negative aspects related to premature menopause that could contribute to increase in morbidity and mortality. It is therefore important to follow the guidelines for women undergoing premature menopause[79] and advise use of HT until age of natural menopause (median 51 years), unless there are contraindications such as hormone receptor-positive breast cancer.[80] Unlike in older postmenopausal women,[81] in this younger population HT use has not been shown to increase breast cancer risk. However, it needs to be highlighted that the mean duration of follow-up in published studies involving *BRCA* mutation carriers is currently about 3.6-5.5 years.[82-84] The current focus is on management of noncancer endpoints, including monitoring of bone and cardiovascular health[85] and fine-tuning of HT regimens in women who experience vaginal dryness and sexual discomfort. While HT-users post risk-reducing bilateral salpingo-oophorectomy have significantly fewer endocrine symptoms compared to nonusers, their symptom levels remain well above those of premenopausal women undergoing screening, and sexual discomfort is not alleviated by HT.[86, 87] The latter has been disputed in a more recent prospective study, which found that women using HT following risk-reducing bilateral salpingo-oophorectomy report approximately the same levels of endocrine symptoms and sexual functioning as women in the screening group.[88]

While in women with Lynch syndrome, the risk-reducing surgery includes hysterectomy in view of their endometrial cancer risk, in *BRCA* mutation carriers the current consensus is not to undertake hysterectomy. A multicenter prospective cohort study has shown a small increase in risk of serous or serous-like endometrial carcinoma in *BRCA1* mutation carriers.[89] Hysterectomy can simplify HT for management of premature menopause and may be of relevance to those using tamoxifen for breast

cancer risk reduction as the drug is associated with a small risk of endometrial cancer. Recently

published modelling suggests that the addition of hysterectomy to risk-reducing bilateral salpingo-

oophorectomy in a 40 year old *BRCA1* mutation carrier could result in a mean gain of 4.9 additional

months of life and is cost-effective[90] but some of the assumptions such as the low cost of hysterectomy

in this setting are controversial.

Bilateral Salpingectomy

The wide acceptance that a large proportion of high-grade serous cancers originate in the fallopian

tube and involve the ovary secondarily[91] has led to the exploration of salpingectomy as a means of

reducing risk, while maintaining ovarian function in premenopausal women.

Risk-Reducing Salpingectomy and Delayed Oophorectomy in Women at High Risk

In high-risk premenopausal women the proposed approach is salpingectomy rather than salpingo-

oophorectomy, followed by an oophorectomy closer to or after the menopause.[92, 93] Such efforts may

be cost-effective and acceptable alternatives for women unwilling to undergo risk-reducing bilateral

salpingo-oophorectomy.[92, 94, 95] A recent meta-analysis has indicated that salpingectomy does not

impact ovarian reserve in the short-term,[96] however longer-term effects remain unclear and need to

be assessed. Radical removal of the fimbrial end of the tube as a way to reduce risk in these women

is being trialed in a study in France,[97] while in the United States, a clinical trial of bilateral

salpingectomy with delayed oophorectomy in *BRCA* mutation carriers is currently underway.[93] In the

United Kingdom, a similar trial is to launch soon. There is debate about the timing of oophorectomy,

whether it should be undertaken in the 40s or after the menopausel. In this respect, it is important to

note that there is a small but statistically significant trend of earlier menopause in mutation carriers,

with an average age of 48.8 years in *BRCA1* carriers, 49.2 years for *BRCA2* compared with 50.3 years

for nonmutation carriers.[98]

The effects of this approach on ovarian cancer incidence and mortality is difficult to estimate. In a small histopathological study, remnants of fimbriae were found adherent to the ovary in 15% of risk-reducing bilateral salpingo-oophorectomy specimens.[99] This was confirmed more recently in a study where tubes and ovaries were removed separately during surgery and examined histologically as two separate specimens; residual fimbrial tissue was found on the ovarian surface in 16% of cases.[100] This suggests that salpingectomy may not prevent all cases even when the origins are tubal. It highlights the importance and need for well-designed prospective trials to define more precisely the level of benefit.

Opportunistic Salpingectomy in the General Population

Between 75% and 85% of all ovarian cancers occur in the general (low-risk) population. Opportunistic bilateral salpingo-oophorectomy when women undergo abdominal surgery is an option in this population.[101] Retrospective population-based data on bilateral salpingectomy with ovarian conservation from Sweden and Denmark suggests that it is associated with a 42%[44] and 65%[102] ovarian cancer risk reduction, respectively. Both studies compared salpingectomy with no surgery as opposed to hysterectomy without salpingectomy, and neither was free from bias. Data collection in a retrospective cohort study of hysterectomy compared with hysterectomy with concomitant salpingectomy (retro-HOPPSA; Hysterectomy and OPPortunistic SAlpingectomy) has been completed[103] and its results should help better quantify the risks and benefits of such as approach. Currently there is insufficient evidence to estimate the magnitude of epithelial ovarian cancer risk reduction with opportunistic salpingectomy.

The effect on long-term endocrine function is unknown.[104, 105] Women undergoing hysterectomy have a two-fold increased risk of ovarian failure compared with controls,[106] and the concern is whether salpingectomy would add to this risk. This morbidity resulting from premature menopause is likely to be magnified in younger women undergoing salpingectomy instead of tubal ligation. Other important

issues include the need for surgical precision and a good knowledge of anatomy to ensure complete

removal of the entire fallopian tube including all fimbriae with minimal damage to the ovarian blood

supply. More evidence on procedure-related safety is needed as it is currently only observational and

short-term. Prospective trials (ideally RCTs) to fully understand the risks and benefits of opportunistic

salpingectomy are recommended. One such RCT (HOPPSA)[107] is underway in Sweden. Women aged

20–54 years who are undergoing hysterectomy for a benign indication are randomized to

salpingectomy (intervention) or no salpingectomy (control). The short-term primary outcomes which

will be available in 2021 include surgical complications and menopausal symptom score at one year

follow-up. The long-term primary outcome, epithelial ovarian cancer risk reduction, will only be

available in 2050, 10-30 years after surgery is undertaken.

While many agree that opportunistic bilateral salpingectomy should be offered within a context of a

clinical trial,[105] there is also a strong opinion that it should be immediately rolled out to the

population.[108] National gynecologic oncology societies of the United Kingdom, United States,

Australia, New Zealand, and Germany have issued advice that women undergoing pelvic surgery

should be counselled on the possible benefits of concomitant salpingectomy. Emerging evidence

suggests that distal salpingectomy could also be performed during Caesarian delivery as safely as tubal

ligation and requires minimal additional theater time.[109] A survey of UK gynecologists reported that

most were willing to undertake it at hysterectomy (92%) and tubal ligation (65%).[110] Indeed, this

appears to be the trend globally, with reports of 64% and 70% of surgeons recommending, or

practicing opportunistic bilateral salpingectomy in Japan and Austria, respectively. Opportunistic

salpingectomy has been widely implemented in women undergoing pelvic surgery in Canada.[111] Data

from the United States also shows a significant increase in opportunistic bilateral salpingectomy as a

method for sterilization since 2011.[112] Practice and consensus meetings are likely to spearhead future

adoption of salpingectomy. The caveat is that the impact of adopting this procedure will not be

realised for a long time.

Chemoprevention

Chemoprevention strategies are best targeted at those at moderate-to-high risk, depending on the spectrum of harm.

While prescribing OCPs is not recommended for primary ovarian cancer risk reduction, it provides this additional advantage to those using it for contraception or other medical indications. Meta-analysis in both the general population[37] and *BRCA* carriers[113] has shown that ever use of OCP was not associated with a significant increase in breast cancer risk. An increased risk was only associated with older (<1975) OCP formulations and not with more recent preparations. In the general population, simulation modelling of OCP for primary prevention concluded that the decrease in ovarian cancer risk was likely equivalent to combined increase in risk of breast and cervical cancers and vascular events.[114] There was additional protection against endometrial and colorectal cancers and an increase in life expectancy of 1 month. However it was felt that the evidence was insufficient to recommend for or against the use of OCP solely for the primary prevention of ovarian cancer.[114, 115] The exception was *BRCA* mutation carriers who were recommended to consider taking OCP to reduce their ovarian cancer risk by the US Society of Gynecologic Oncology in 2015.

Aspirin as a cancer chemopreventative agent (600 mg per day for at least 2 years) is now being prescribed in women with high-risk Lynch syndrome, based on data from the CaPP2 RCT[50] to reduce risk of colorectal as well as ovarian and endometrial cancer. The lowest dosage that would confer the protection is yet to be established with the latest trial (CaPP3)[116] exploring the risk reduction of 100, 300, and 600 mg per day in these women. The data will be available in 2020. An important consideration is that the protective effect of aspirin on endometrial cancer in women with Lynch syndrome is strongest for women who are obese and may not benefit those who have a healthy

weight.[117] Until this data matures, it is important that the risks, benefits, and current limitations of

available evidence are discussed with patients.

Screening for Ovarian Cancer

Efforts have been underway since the mid-1980s to develop an ovarian cancer screening strategy that

can reduce disease mortality.

General Population

Data from the Barts Pilot trial of the mid-1980s suggested survival advantage in women who

developed ovarian cancer in the group screened using serum CA125 (using a cut-off of ≥35 kU/l) with

ultrasound in those with elevated levels. Since then, four large studies or trials have been set up. The

Kentucky single-centre study[118] of 37,293 women who underwent annual transvaginal ultrasound

screening demonstrated higher 5-year survival rates (p<0.001) in women who developed ovarian

cancer in the screened cohort (74.8% +/- 6.6%) compared with women who were treated for ovarian

cancer in the same institution but were not in the screening study (53.7% +/-2.3%). However as this

was not an RCT, lead time effect of screening and the likelihood of a significant healthy volunteer

effect in participants makes it difficult to interpret the true effects of intervention on disease mortality.

The Japanese Shizuoka Cohort Screening Study, an RCT of 82,487 women of whom 41,688 were

randomized to screening using pelvic ultrasound and serum CA125 using a cut-off (≥35 kU/l) and

gynecologic examination and 40,799 to control (no screening) has not reported on mortality benefit.

In the screen arm (63%), there was a nonsignificant (p=0.23) increase in epithelial ovarian cancer

(borderlines included) diagnosed at early stage (Stage I and II) compared with control (38%).[119] In the

ovarian arm of the multicenter US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening

Trial, an RCT of 78,216 women, 30,630 women underwent annual screening with serum CA125 (≥35

kU/l cut-off) and transvaginal ultrasound for 4 years followed by CA125 alone for a further 2 years. At

a median follow-up of 12.4 years, there was no mortality benefit (mortality rate ratio of 1.18, 95%CI

0.91-1.54) between screen and control arm for invasive epithelial ovarian, tubal, and peritoneal

cancer.[120] In the screen arm, 22.2% of cancers were early stage (Stage I and II) compared with 21.6%

in the control arm. The complication rate in women undergoing false-positive surgery was high (15%).

On median extended follow-up of 14.7 years, the lack of mortality benefit (1.01; 95% CI: 0.97-1.05)

persisted.[121]

The largest trial and most recent RCT to report is the United Kingdom Collaborative Trial of Ovarian

Cancer Screening (UKCTOCS).[122] Between 2001 and 2005, 202,638 women from the general

population were randomized to no intervention (control, n=101,359) or annual screening using either

transvaginal ultrasound alone (n=50,639) or serum CA125 interpreted using the 'Risk of Ovarian

Cancer Algorithm' (ROCA) with transvaginal ultrasound as a second-line test (multimodal screening,

n=50,640). Sensitivity for detection of invasive epithelial ovarian, tubal or peritoneal cancer diagnosed

within a year of screening was 86.2% (95%CI 80.8-90.6) with multimodal and 63.3% (95%CI 55.4-

70.6%) with ultrasound screening. Per 10,000 screens, 14 women underwent unnecessary (false

positives with benign or normal adnexa) surgery in the multimodal and 50 in the ultrasound arm. The

complication rate in the latter women were similar (3.1% multimodal; 3.5% ultrasonography) in both

arms. Screening did not appear to raise anxiety but higher psychological morbidity (worry) and lower

pleasure scores were reported by those who had to undergo Level 2 (transvaginal ultrasound with or

without CA125) screening due to abnormal results on the annual screen.[123-125]

At a median follow-up of 11.1 years, compared to the control arm, the trial demonstrated a significant

(p=0.0001) stage shift in invasive epithelial ovarian, tubal and peritoneal cancers with multimodal

screening (36.1% Stage I or II) compared with control (23.9%) but not with ultrasound screening

(22.4%; p=0.604).[122] There was a trend to reduction in mortality which was not statistically significant

in either screen arm (Figure 1). In keeping with other screening trials, the mortality impact was delayed

with a reduction in mortality for invasive epithelial ovarian, tubal and peritoneal cancers of 4%

(multimodal) and 2% (ultrasound) in years 0-7 from randomisation and 18% (multimodal) and 17%

(ultrasound) in years 7-14. At censorship, ovarian cancer mortality rates seemed to be rising in the

control arm and levelling off in the screen arms, suggesting that the full extent of the mortality benefit

had not been reached. Follow-up has therefore been extended in UKCTOCS until December 2018 with

results of a second mortality analysis expected by the end of 2019. The within-trial economic

evaluation found that MMS was less expensive than USS and economically viable according to NICE

thresholds if a mortality benefit was confirmed in 2019.[126,127]

A key difference between the trials was that CA125 was interpreted in the ovarian arm of PLCO using

a cut-off of 35 kU/l while the longitudinal CA125 'ROCA' algorithm was used in the multimodal arm of

UKCTOCS. The latter resulted in high sensitivity (89.7% prevalence screening, 83.8% incidence

screening) and specificity (99.8% prevalence screening, 99.8% incidence screening) for detection of

invasive epithelial ovarian, tubal and peritoneal cancers diagnosed within one year of screen with 4.4

operations per cancer detected.[128] Similar high specificity and positive predictive value of ROCA was

reported from a prospective single-arm US study of 4,051 low risk postmenopausal women.[129] Most

importantly half of the screen-detected cancers during multimodal screening would have been missed

at the relevant annual screen as the CA125 was <35 kU/l.[128] Use of longitudinal biomarker algorithms

rather than a predefined cut-offs are probably applicable to screening for other cancers.

Despite recent encouraging data on sensitivity, stage shift and cost-effectiveness of multimodal

screening,[122, 126, 127] screening for ovarian cancer in the general population is not recommended due to

the lack of a definitive mortality benefit. This has been reinforced in the latest recommendation from

the US Preventative Task Force (USPSTF) [130] and the UK National Screening Committee (UK NSC).[131]

High-Risk Population

In women at high risk, annual screening is not recommended as it is not effective in detecting early stage disease.[132] Trials investigating shorter screening intervals have recently reported. Between 2007 and 2012, in the UK Familial Ovarian Cancer Screening Study (UKFOCSS) Phase II, 4,348 women at high risk underwent 4-monthly multimodal screening with CA125 interpreted using ROCA and annual transvaginal ultrasound. During a median of follow up of 4.8 years, 3.7% (162/4,348) underwent screen-positive trial surgery and 12.3% (534/4,348) risk-reducing bilateral salpingo-oophorectomy. The key findings were that multimodal screening resulted in a significant stage shift (Stage I-IIIA 63% versus 6%; p=0.0004), higher rates of zero residual disease after debulking (95% versus 72%; p=0.09) and lower rates of neoadjuvant chemotherapy (5% versus 44%; p=0.008) in women diagnosed with invasive epithelial ovarian, tubal and peritoneal cancers within 1 year of last screen compared with those diagnosed >1 year after screening ended.[133] Further, while women with an abnormal result experienced a significant transient increase in cancer-specific distress, there was no significant effect on general anxiety or depression.[134]

Concurrently a similar strategy using 3-monthly ROCA screening was evaluated in women at high risk in the US (Cancer Genetics Network, CGN, and Gynaecology Oncology Group, GOG). In 3,692 women (13,080 woman-screening years), 19 (4 screen detected at prevalence and 6 at incidence screen, 9 occult at risk-reducing bilateral salpingo-oophorectomy and one screen negative) cancers were diagnosed during screening.[135] Of the incident cancers, half were detected at early-stage (I or II) and 50% were detected by ROCA before CA125 exceeded 35 kU/l.

There are national differences in the recommendation of screening in women at high risk who opt not to undergo surgery. While screening is not available in the UK on the National Health Service, the US National Comprehensive Cancer Network[136] state that serum CA125 and transvaginal ultrasound, although of uncertain benefit, may be considered at the clinician's discretion starting at age 30-25 and 6–monthly screening is recommended by the US Preventative Task Force.[130] Specialist one-stop

multidisciplinary clinics that deliver tailored risk management (surgery, screening and recruitment into

new trials) for these high-risk populations are the optimum way forward.[137-139]

Future Screening Strategies

Modeling suggests that high-grade serous cancers are at a median diameter of approximately 3cm

when they are at stage III or IV.[140] It estimates that for 50% sensitivity for Stage I or II cancers, an

annual screen would need to detect adnexal tumours when they are approximately 1.3cm in

diameter.[140] In addition, markers would need to distinguish aggressive from more indolent cancers.

Despite decades of international efforts, no marker superior to CA125 has been identified. The most

encouraging data pertains to Human Epididymis (HE4), which is still second best to CA125.[141] In the

last 5 years, efforts have focused on improving the performance of CA125 by addition of new markers

such as HE4,[141] TP53,[142] Protein Z,[143] glycodelin, MMP7, CYFRA21-1,[144] CA72-4, CA15-3 and VTCN1

(Table 2). In parallel are efforts to improve biomarker interpretation using longitudinal algorithms to

interpret CA125 such as the Parametric Empirical Bayes (PEB)[145] and Methods of Mean Trends

(MMT).[146] The emerging evidence that TP53 mutations can be detected in blood[147] opens the

possibilities that circulating - tumor DNA could serve as such a more specific screening test for high-

grade serous cancers. CancerSEEK, a multianalyte test combining TP53 mutations and a panel of eight

biomarkers including CA125 was recently described to have high specificity and a sensitivity of

detecting ovarian cancer of 98%.[148] Several studies are also exploring tumor DNA detection in liquid

cytology samples from the vagina[149] and endocervix, including routinely collected cervical screening

specimens, vaginal self-swab and tampons[147, 150] and uterine lavage samples.[151, 152] In a small sample

of patients with advanced high-grade serous cancers who had a tampon inserted prior to surgery and

removed in operating theatre,[147] TP53 mutations were identified in three of five with intact fallopian

tubes but in none of three who had tubal ligation. There are also studies exploring DNA detection

using methylation profile.[153]

Improvements in imaging include efforts to refine transvaginal ultrasound through ongoing quality

assurance, Doppler flow, microbubble contrast-enhanced transvaginal ultrasound and photoacoustic

imaging, all of which allow high-resolution detection of angiogenesis, with the potential to detect

neovascularisation in early cancers.[154]

Newer screening strategies are being prospectively assessed in screening trials in both the low and

high-risk populations.[155] In the United States, a randomized trial of 6-monthly screening in women at

high risk and annual screening in intermediate risk women is underway using a longitudinal algorithm-

Parametric Empirical Bayes–based approach to interpret the biomarkers. Women are randomized to

(1) CA125 and HE4 as first-line, imaging as second line or (2) CA125 as a first-line screen, imaging and

HE4 as second-line.

Discussion

The insights gained into ovarian cancer biology over the last decade are set to translate into real

improvements in prevention and screening. There is a growing acceptance of the limitations of family

history resulting in efforts to identify those with mutations in high (*BRCA*, *mismatch repair genes*) and

moderate (such as *RAD51C*, *RAD51D* and *BRIP1*) risk genes through extending genetic testing to all

ovarian cancer patients (mainstreaming) and offering systematic testing to high prevalence (e.g.

Ashkenazi Jewish) populations. Risk prediction tools that incorporate genetic and epidemiological risk

factors should soon be available that dramatically improve estimation of an individual's risk, making

possible personalized ovarian cancer preventative and screening approaches. These include

opportunistic bilateral salpingectomy (already adopted by most professional organisations) for low

risk women undergoing hysterectomy or as an alternative to tubal ligation, chemoprevention using low-dose aspirin in women with Lynch syndrome and OCP in *BRCA* mutation carriers and trials of salpingectomy and delayed oophorectomy as an alternative to risk-reducing bilateral salpingo-oophorectomy (current standard) in high risk women. Though multimodal screening using a longitudinal CA125 algorithm resulted in a stage shift, both in the low-risk RCT (UKCTOCS) and high-risk screening studies, the lack of a definitive mortality benefit in UKCTOCS has led to reaffirmation that general population screening should not be undertaken. Extended follow-up is now underway in UKCTOCS to assess longer term impact. Meanwhile recommendations for screening women at high risk differ between countries from no screening to twice a year screening using CA125 and transvaginal ultrasound. Ongoing biomarker research is focused on further assessment of longitudinal biomarker screening algorithms, imaging to better detect neovascularization, circulating tumour DNA and testing of novel specimens such as cervical cytology samples.

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Figure 1: Summary of UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) mortality analysis results comparing multimodal versus control (**A**) and ultrasound versus control group (**B**) for primary (ovarian, fallopian tube, or undesignated cancer) and secondary (which also includes primary peritoneal cancer) outcomes. The primary mortality analysis was done using Cox proportional hazards and Royston Parmar (RP) proportional hazards with a posthoc weighted log rank analysis (as done in the Prostate, Lung, Colorectal and Ovarian [PLCO trial]). *Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet 2016;387:945–956. †Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA 2011;305:2295–303. ‡Proportional hazards. §Hazard ratio weighted by pooled cumulative ovarian cancer mortality.

Table 1: Reproductive, lifestyle and genetic risk factors for ovarian cancer

Reproductive and lifestyle risk factors	Effect on Ovarian Cancer risk	Study design	OR/RR	95%CI	Author, year
Reproductive factors					
Oral contraceptive pill (OCP)	Use decreases risk	Systematic review - 55 studies included	0.73 (ever use)	0.66-0.81	Havrilesky et al, 2013[114]
			0.43 (>10 years use)	0.37-0.51	
Parity	Risk decreases with each pregnancy	Systematic review and meta-analysis	0.72 (para 1)	0.65-0.79	Sung et al, 2016[40]
			0.57 (para 2)	0.41-0.52	
			0.46 (para $\geq$3)	0.41-0.52	
		Cohort study (1245 cases)	0.68	0.57-0.80	Fortner et al, 2015[156]
		Cohort study (623 cases)	0.79	0.63-0.98	Bodelon et al, 2013[157]
		Pooled analysis of 21 studies (5584 cases)	0.69	0.64-0.74	Wentzensen et al, 2016[32]
Breastfeeding			0.79 (<6 months)	0.72-0.87	Sung et al, 2016[40]

	Risk decreases with duration	Systematic review and meta-analysis	0.72 (6-12 months)	0.64-0.81	
			0.67 (>13 months)	0.56-0.79	
Hormone therapy use - combined	Use increases risk	Meta-analysis, 52 studies (2208 cases)	1.55	1.38-1.74	Collaborative Group On Epidemiological Studies of Ovarian Cancer (Beral *et al*), 2015[39]
		Case-control (602 cases)	1.10	1.01-1.18	Koskela-Niska *et al*, 2015[158]
HRT use - oestrogen only		Meta-analysis, 52 studies (2208 cases)	1.58	1.39-1.80	Collaborative Group On Epidemiological Studies of Ovarian Cancer (Beral *et al*), 2015[39]
HRT use - any		Pooled analysis of 21 studies (5584 cases)	1.36	1.28-1.46	Wentzensen *et al*, 2016[32]
Gynecologic procedures					

Tubal ligation	Decreases risk	Pooled analysis of 13 case-control studies	0.81	0.74-0.89	Sieh et al, 2013[159]
		Meta-analysis, 13 studies	0.66	0.60-0.73	Cibula et al, 2011[42]
	Decreases risk	Pooled analysis of 21 studies (5584 cases)	0.85	0.73-0.93	Wentzensen et al, 2016[32]
	Neutral (high-grade serous cancers only)		0.92	0.76-1.11	
	Decreases risk (clear cell only)		0.35	0.18-0.69	
	Decreases risk (endometrioid only)		0.6	0.41-0.88	
	Decreases risk	Case-control study (1684 cases)	0.87	0.78-0.98	Madsen et al, 2014[44]
Hysterectomy only	Neutral	Case-control study (2265 cases, 2333 controls)	1.09	0.83-1.42	Rice et al, 2013[43]
	Decreases risk	Systematic review and meta-analysis	0.70 (prior to 2000)	0.65-0.76	Jordan et al, 2013[45]

	Increases risk		1.18 (after to 2000)	1.06-1.31	
	Increases risk	Cohort study of 66,802 women (403 cases)	1.36	1.03-1.78	Gaudet et al, 2014[160]
	Neutral	Meta-analysis of 38 studies	0.97	0.81-1.14	Wang et al, 2016[46]
Hysterectomy + unilateral salpingo-oophorectomy	Decreases risk	Case-control study (2265 cases, 2333 controls)	0.65	0.45-0.94	Rice et al, 2013[43]
Salpingectomy	Decreases risk	Systematic review	0.58	0.36-0.95	Darelius et al, 2017[104]
	Decreases risk	Cohort study of 5.4 million women (34433 with salpingectomy)	0.35 (bilateral)	0.17-0.73	Falconer et al, 2015[102]
			0.71 (unilateral)	0.56-0.91	Falconer et al, 2015[102]
	Decreases risk	Case-control (16846 cases)	0.58	0.36-0.95	Madsen et al, 2014[44]
Medicines or lifestyle modifications					
Aspirin use	Use decreases risk (continuous long-term low-dose)	Case-control study (4103 cases, 58706 controls)	0.56	0.32-0.97	Baandrup et al, 2014[161]

	Use decreases risk	Pooled case-control, 12 studies (OCAC)	0.91	0.84-0.99	Trabert et al, 2014[162]
		Meta-analysis, 22 studies	0.89	0.83-0.96	Zhang et al, 2016[48]
		Systematic review and meta-analysis	0.85	0.83-0.96	Burn et al, 2016[50]
Obesity	Higher BMI increases risk	Cohort study of 5.24 million women (4733 ovarian cancers)	1.07 (per 5 kg/m2 over 22)	1.02-1.12	leugkaran et al, 2014[163]
		Case-control, 11 studies (13548 cases, 17913 controls) (OCAC)	1.22 (≥40kg/m2)	1.05-1.41	Olsen et al, 2013[54]
Endometriosis	Increases risk	13 case control studies, 7911 cases	1.46	1.31-1.63	Pearce et al, 2012[47]
Cigarette smoking	Neutral	Pooled analysis of 21 studies, 5584 cases	0.99	0.94-1.05	Wentzensen et al, 2016[32]
	Neutral		0.89	0.76-1.05	Faber et al, 2013[55]

	Increases risk (mucinous only)	Pooled analysis of 21 case control studies, 11972 invasive epithelial ovarian cancer cases	1.31	1.03-1.65	
	Decreases risk (clear cell only)		0.96	0.92-0.99	
Tea, coffee, caffeine	Black tea increases risk	Case-control (524 cases, 1587 controls)	1.56	1.07-2.28	Leung *et al*, 2016[164]
Alcohol consumption	Neutral	Pooled analysis of 12 case-control studies, 5,342 cases, 10,358 controls	0.94 (1 drink), 0.92 (>3 drinks)	0.83-1.02; 0.76-1.01	Kelemen *et al*, 2013[52]
Statin use	Neutral	Case-control (4103 cases, 58706 controls)	0.98	0.87-1.10	Baandrup *et al*, 2015[51]
Physical activity	Trend towards decreasing risk	Case-control (638 cases, 683 controls)	0.69	0.47-1.00	Moorman *et al*, 2011[165]
Talc use	Increases risk (all subtypes)	Systematic review and meta-analysis	1.31	1.24-1.39	Penninkilampi R and Eslick GD, 2017[56]
	Increases risk (serous)		1.32	1.22-1.43	

	Increases risk (endometrioid)		1.35	1.14-1.60	
		Meta-analysis	1.22	1.13-1.30	Berge et al, 2017[166]
Genetic risk factors					
High penetrance					
BRCA1 **mutation**	Increases risk	Norquist 2016, 1345 and 570 cases	29.0	22.7-37.1	Norquist et al, 2016[167]
			48.9	24.0-100.0	
BRCA2 **mutation**			12.7	9.7-16.4	
			14.0	8.2-23.8	
HNPCC syndrome- *MLH1* **mutation**		248 with mutation	cumulative risk of 20% by age 70	1-65	Bonadona et al, 2011[17]
HNPCC syndrome- *MSH2* **mutation**		256 with mutation	cumulative risk of 24% by age 70	**3-52**	
Moderate penetrance					
RAD51C **mutation**	Increases risk		3.4-15.8		Loveday et al, 2012[19]

		Norquist 2016, 1345 and 570 cases; Song 2015 3429 cases, 2772 controls; Loveday 2012, 480 cases, 2912 controls			Norquist et al, 2016[167]
					Song et al, 2015[18]
RAD51D mutation		Norquist 2016, 1345 and 570 cases; Song 2015 3429 cases, 2772 controls; Loveday 2011, 911 cases, 1060 controls	6.3-12.0		Norquist et al, 2016[167]
					Song et al, 2015[18]
					Loveday et al, 2011[20]
BRIP1 mutation		Norquist 2016, 1345 and 570 cases; Ramus 2015 3374 cases, 3487 controls; Rafnar 2011, 601 cases and 43455	6.4-12.0		Norquist et al, 2016[167]
					Ramus et al, 2015[21]
					Rafnar et al, 2011[168]

Table 2: Summary of biomarkers explored in a screening context (all nested case-control studies)

Biomarker	Study	No. of women and samples included per study	Sensitivity and /orlead time	Author, year
CA125, HE4, transthyretin, CA15.3 and CA72.4	EDRN, SPORE, PLCO	118 women with invasive epithelial ovarian cancer/FT/PPC; 474 matched controls	In PLCO samples predating diagnosis by 6 months, the sensitivity for detection of ovarian cancer was 86% for CA125 and 73% for HE4.	Cramer *et al*, 2011[141]
CA125 and TP53	AOCS, MD Anderson, UKCTOCS	378 cases of invasive epithelial ovarian cancer; 944 age-matched healthy controls (50 cases - MD Anderson, 108 cases - AOCS, 220 cases - UKCTOCS)	Using a cut-off of 78U/mL and specificity of 97.4%, TP53 autoantibodies were elevated in 30% OCs from MD Anderson, 21.3% AOCS and 21% UKCTOCS. In the UKCTOCS screen-detected cancers, TP53 autoantiobodies were elevated 11 months prior to CA125. 16% of cases missed by ROCA in UKCTOCS had elevated TP53 autoantibodies, 22.9 months prior to diagnosis.	Yang *et al*, 2017[142]

CA125 and Protein Z	UKCTOCS	482 serial serum samples from 49 women with primary ovarian cancer (30 Type II, 19 Type I - 9 invasive ovarian cancer and 10 borderline) and 31 controls, spanning up to 7 years prior to diagnosis	CA125 combined with Protein Z had a significantly higher AUC compared to that of CA125 alone for both Type I (0.82 vs 0.77, p = 0.00033) and Type II (0.82 vs 0.76, p= 0.00003) OCs. Protein Z was down-regulated up to 2 years pre-diagnosis (p = 0.000000411) in 8 of 19 Type I OCs; up-regulated up to 4 years before diagnosis in Type II OCs (p = 0.01).	Russell et al, 2016[143]
CA125, HE4, glycodelin, mesothelin, MMP7 and CYFRA 21-1	UKCTOCS	47 women who went on to develop primary invasive epithelial ovarian cancer/FT/PPC (170 samples); 179 matched controls (893 samples)	A model combining CA125, HE4, and glycodelin had slighlty higher AUC (0.967) compared to that of CA125 alone (0.957), which decreased in samples >6 months from diagnosis (0.789). HE4 was the only marker significantly elevated in the screen negative OCs.	Blyuss et al, 2015[144]

| CA125, HE4, CA72-4, CA15-3 and VTCN1 (Cramer 5-marker panel for ovarian cancer) | EDRN | Cases with samples closest to diagnosis (average 9 months); 951 controls (475 general population, 238 with false positive CA125, and 238 with family history of breast or ovarian cancer; 90 quality controls) | Data being generated to allow algorithm development. | https://edrn.nci.nih.gov/biomarkers/cramer-5-marker-panel-for-ovarian-cancer |

Footnote: EDRN - Early Detection Research Network; SPORE - Ovarian Cancer Specialized Program of Research Excellence; PLCO - Prostate Lung Colorectal and Ovarian Cancer Screening trial, AOCS - Australian Ovarian Cancer Study; UKCTOCS - United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)