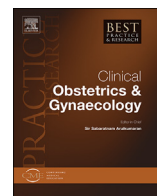




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Ovarian cancer screening: Current status and future directions



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A B S T R A C T

Ovarian cancer is the third most common gynaecological malignancy and the most lethal worldwide. Most patients are diagnosed with advanced disease which carries significant mortality. Improvements in treatment have only resulted in modest increases in survival. This has driven efforts to reduce mortality through screening. Multimodal ovarian cancer screening using a longitudinal CA125 algorithm has resulted in diagnosis at an earlier stage, both in average and high risk women in two large UK trials. However, no randomised controlled trial has demonstrated a definitive mortality benefit. Extended follow up is underway in the largest trial to date, UKCTOCS, to explore the delayed reduction in mortality that was noted. Meanwhile, screening is not currently recommended in the general population. Some countries offer surveillance of high risk women. Novel screening modalities and longitudinal biomarker algorithms offer potential improvements to future screening strategies as does the development of better risk stratification tools.

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Introduction

Screening is looking for early signs of a particular disease in apparently 'healthy' people who do not have 'any symptoms'. There are an increasing number of cancer screening programmes [1] with the aim to decrease mortality through detection of latent pre-cancerous and/or early stage invasive disease. The most successful and widely implemented of these is cervical cancer screening which has managed to decrease both disease incidence and mortality. A cancer for which there have been ongoing efforts to explore screening is ovarian cancer (OC).

Principles of screening

While the central idea is essentially simple, 'decreasing mortality by finding and treating those with previously undetected disease while avoiding harm to those who do not have the disease', the reality is far from straight forward. To address this, Wilson and Jungner published their classic screening criteria in 1968. Although modified with time, these principles continue to underpin any successful screening programme [1,2]. This review critically examines screening for ovarian cancer through the prism of these principles of screening. In addition, it describes the new risk stratification tools that would allow better identification of the target population and a literature update (Jan 2010 to September 2019) on novel and emerging biomarkers, imaging techniques, and longitudinal algorithms.

The condition should be an important health problem

OC is the third most common gynaecological malignancy worldwide and carries the highest mortality. OC has an incidence of 11.7–12.1 per 100,000 in the USA and Europe, with slightly lower rates of disease in Asia and the Middle East [3].

Most patients (60%) are diagnosed with advanced disease [3] which is associated with significant mortality. 5-year survival rates for FIGO stage I disease is 90%, stage II 65%, stage III 34%, and stage IV 15% [3]. As a result, the case fatality ratio is thrice that of breast cancer with approximately 240,000 new cases and 140,200 deaths worldwide in 2016 [4,5]. Improvements in treatment have only resulted in modest increases in survival and in most developed countries, 10-year survival is around 35% [6].

There should be an accepted treatment for patients with recognised disease

Treatment varies by stage of disease and both national and international guidelines are available. The cornerstone is a combination of maximal surgical cytoreduction and platinum and taxane based chemotherapy. Primary surgery is followed by adjuvant chemotherapy if it is anticipated that all visible disease can be removed. However, in advanced disease, if the surgical team feel the latter is not achievable, neo-adjuvant chemotherapy is undertaken followed by interval debulking. There is increasing use of anti-angiogenic therapies, polyADP-ribose polymerase (PARP) inhibitors, inhibitors of growth factor signalling, or folate receptor inhibitors, as well as several immunotherapeutic approaches as adjuncts to conventional chemotherapy in advanced disease [7].

The natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a recognisable latent or early symptomatic stage

There have been significant advances in this area with both the primary site assignment (WHO 2014) and staging (FIGO 2014) classifications recently revised. The primary anatomy of the disease referred to as 'ovarian cancer' has now been formally documented to include epithelial cancers of the ovary, fallopian tubes, peritoneum and pelvic cancer where site cannot be assigned specifically to one of the latter [8]. The revisions codify what has been in clinical use for the last decade or so and incorporates many major scientific advances in our understanding of precursor events, lineages, and molecular characteristics.

A variety of tumours, such as epithelial (EOC), germ cell, and specialized stromal cell tumours, are included under ovarian cancer. The vast majority of OCs are epithelial and consist of five major types –

high grade serous (HGSC), low grade serous (LGSC), endometrioid, and clear cell and mucinous carcinomas. Alternatively, EOC can be subdivided based on these histological subtypes into two main groups: Type I and Type II tumours [9].

Type I (low grade serous, endometrioid, clear cell carcinomas, and mucinous carcinomas) are less common and represent 30% of all tumours. Precursor lesions include borderline serous tumours (LGSOC) and endometriosis (endometrioid, clear cell) [10]. These tumours may have a relatively indolent course [9].

The most common type of EOC are Type II lesions, which are aggressive HGSCs that carry significant mortality. These cancers are the main target and markers that are able to distinguish them from more indolent cancers are key to a successful screening strategy. They exhibit a complex genomic terrain, marked by copy number alterations and the almost universal presence of TP53 tumour suppressor gene mutations [11]. Whilst previously thought to arise from the ovarian surface epithelium, the origin of the majority of HGSOC is now understood to be the fallopian tube, specifically the secretory cell of the fimbrial epithelium [12]. Serous tubal intraepithelial carcinoma (STIC) lesions have been identified as a premalignant lesion of epithelial OC and have been found histologically in the fallopian tube of up to 60% of sporadic serous OC cases [12]. In addition, a nonproliferative 'p53 signature' in the secretory cells of the adjoining tubal epithelium, harbouring the same TP53 mutation as the STIC lesion and HGSOC have been described. To date, STIC lesions are diagnosed during risk reducing salpingo-oophorectomy (RRSO) in high risk women, alongside HGSOC, and as incidental findings when tubes are removed during surgery for benign conditions. There are a number of efforts underway to develop possible screening tests to detect the lesion: direct visualisation using microlaparoscopy to achieve an optical biopsy [13], the accuracy of which may be improved with the addition of autofluorescence imaging [14]; brush cytology of the fallopian tubes [15]; and lavage cytology of the uterine cavity and proximal fallopian tubes [16].

The focus of ovarian cancer screening trials has therefore been, by necessity, the detection of early stage invasive disease. Modelling suggests that HGSC grow over four years and may exist as clinically undetected Stage III cancers for up to a year prior to diagnosis. They have a median diameter of ~3 cms when they metastasise into stage III or IV. To have a 50% sensitivity for Stage I/II, an annual screen would need to detect these adnexal tumours when they are ~1.3 cm in diameter [17]. No current strategies are able to consistently detect cancers this small.

There should be an agreed policy on whom to screen

There is agreement that there are two target populations for screening. The general population where an average individual's lifetime risk of OC is 1.3–2% [18] and the high-risk population, currently identified on the basis of family history and limited genetic testing, with a lifetime OC risk of 10% or more. However, there is wide variation in an individual's OC risk due to lifestyle, reproductive, and genetic factors.

As many as 21% of epithelial ovarian cancers are linked to lifestyle and reproductive risk factors, although the impact of each factor is relatively modest [19]. Obesity, as measured by BMI, is associated with increased risk in a dose dependant fashion. In women with BMI >22, HR of 1.07 (95% CI 1.02–1.12) per 5 kg/m² have been reported [20], and in those with BMI >40, there is a 22% increase in risk (OR 1.22 95% CI 1.05–1.41) [21]. Talc use and black tea consumption have also been associated with increased risk with OR 1.31 (95% CI 1.24–1.39) [22] and OR 1.56 (95% CI 1.07–2.28) [23], respectively.

Conversely, low dose, continuous, long term, aspirin use has been reported as a protective factor and is associated with OR 0.56 (95% CI 0.32–0.97) [24]. Alcohol consumption, statin use, and physical activity have all shown a non-significant trend towards reduced risk [24–26], whilst cigarette use shows conflicting results, with no association [27] or increase risk of mucinous OC only (OR 1.31 95% CI 1.03–1.65) [28].

Multiple reproductive factors have been shown to be protective, including ever use (Odds ratio OR 0.73 95% CI 0.66–0.81) and greater than 10 years use (OR 0.43 95% CI 0.37–0.51) of the combined hormonal contraceptive (CHC) [29]. Similarly, increasing parity is associated with reduced risk: Para 1: RR 0.72 (95% CI 0.65–0.79). Para 2: RR 0.57 (95% CI 0.41–0.52) Para 3 or above: RR 0.46 (95% CI 0.41–0.52) [30]. Breast feeding also decreases risk: less than 6 months (RR 0.79 95% CI

0.72–0.87), six to twelve months RR (0.72 95% CI 0.64–0.81), greater than 13 months (RR 0.67 95% CI 0.56–0.79) [31].

Gynaecological risk factors include endometriosis (OR 1.46 95% CI 1.31–1.63) [31] and current-or-recent hormone replacement therapy (HRT) use (RR 1.37 95% CI 1.29–1.46) with this risk persisting 10 years after stopping long-duration HRT (RR 1.25 95% CI 1.07–1.46) [32]. The data on OC risk in women who have undergone hysterectomy are conflicting, varying from neutral [33,34] to decreased [35] and to modestly increased [35]. The most recent, a population based health record linkage study of 837,942 Australian women has found no evidence of an association [36]. This is likely because the tubes are often left behind when the ovaries are conserved during benign hysterectomy. Hysterectomy with unilateral salpingo-oophorectomy appears protective (OR 0.65 95% CI 0.45–0.94) [33] with similar effect estimates as seen in women who have undergone unilateral salpingectomy (OR 0.71 95% CI 0.56–0.91) or bilateral salpingectomy (OR 0.35 95% CI 0.17–0.73). Similarly, tubal ligation appears to be protective (OR 0.87 95% CI 0.78–0.98) [37]. These findings are in keeping with the tubal origins of OC.

Moderate to high penetrance genes account for 5–15% of OCs. Mutations in high penetrance genes confer substantially increased risk by 80 years of age (44% BRCA1 and 17% BRCA 2 carriers [38]) with lower risk in MLH1 and MSH2 (Lynch syndrome) of 10–15% [39]. RAD51C and RAD51D have a risk of 11–12%, BRIP1 is 5.8%, and PALB2 is 5% [40–42]. Low-penetrance inherited genetic variants (single nucleotide polymorphisms, 'SNPs'), of which 37 have been identified thus far, individually confer a 1.2–1.4 fold increase in epithelial OC risk with a few conferring a relative risk reduction (up to 0.8). It is likely that a large number of as yet unidentified low risk loci, each with a small effect size, make up the majority of the remaining 60% of unaccounted inherited risk and cumulatively contribute to the polygenic risk to OC [43].

There are significant efforts underway to combine these genetic, reproductive, and lifestyle factors to better understand an individual's risk. This would help better stratify the population such that those at highest risk of OC can be offered preventative surgery with screening targeted at high risk women who refuse or wish to delay risk reducing surgery and as well as those at moderate risk. This would improve performance characteristics of screening and make it more cost effective. Risk-stratification using genetic and non-genetic factors is currently being evaluated in breast cancer screening trials.

Existing OC screening trials (Table 1) have used age and family history of ovarian cancer to identify target populations for screening. In addition, high risk trials have also used mutation status. A recent model combining reproductive factors (CHC use, parity, tubal ligation, and endometriosis), family history of OC in first-degree relatives, and 13 low-risk SNPs suggests that it would be possible to risk stratify women from the general population from 0.35% lifetime risk (very low risk) to up to 8.8% lifetime risk (moderate risk levels) of OC, with the majority of those in the highest risk quartile having no family history [44]. There are a number of models of similar discriminatory ability that mainly predict BRCA carrier status (e.g. BRCAPro, BODICEA, Myriad II), but also in some instances risk of ovarian cancer (e.g. BODICEA). The current focus is to incorporate additional SNPs, epidemiological, lifestyle, and reproductive factors to individualise OC risk prediction [45]. CanRisk (BODICEA V) is one such recently released ovarian and breast cancer risk assessment tool that can assist clinicians during a consultation [46]. Alongside this, there are studies such as 'FORECEE' exploring molecular markers and methylation profiles in cervical cytology cells for risk prediction of ovarian and other (breast, cervical, and endometrial) women's cancers [47].

There should be a suitable test or examination that has a high level of accuracy

A lack of awareness of symptoms of OC is a potential barrier to early presentation [48]. However, there is little evidence that patient education and routine enquiry about OC symptoms (persistent abdominal bloating, abdominal pain, and feeling full quickly) can result in detecting early stage disease [48,49]. Similarly, pelvic examination has been found to have poor sensitivity (5.1%), with no additional OC cases detected by the addition of bimanual examination to screening using CA125 or transvaginal ultrasound alone [50]. The focus of finding an accurate test for pre-clinical detection of OC has therefore been biomarkers (initially in blood and increasingly in other bodily fluids) and imaging techniques.

Table 1

Key interventional trials in Ovarian Cancer Screening.

Trial Name	Trial Design	No. Of participants	Screening Strategy	Key outcomes	Additional Comments
General population Trials					
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) (59,90)	Randomised controlled trial (RCT)	Recruited 78,286 aged 55–74 39,105 screen arm 39,111 No screening (control)	1. Six annual serum CA125 screens (interpreted using a cut-off of >35 units/mL) and transvaginal ultrasound for initial four years	At 15 years of follow-up, compared to control arm, no reduction in mortality (RR 1.06; 95%CI 0.87–1.3)	No difference in OC stage between screen and control arm
UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) (52,61)	RCT	Randomised 202,638, aged 50–74 50,640 multimodal arm 50,639 ultrasound arm 101,359 No screening (control)	1. Eleven (median 8) annual multimodal screens (Longitudinal serum CA125 interpreted using Risk of Ovarian Cancer Algorithm (ROCA) followed by transvaginal ultrasound and repeat CA124 if risk not normal) 2. Eleven (median 8) annual transvaginal ultrasound screens followed by repeat transvaginal ultrasound if ovarian scan not normal	At 11.9 years of follow-up, compared to control arm; 1. Non-significant average mortality reduction of 15% (95% CI –3 to 30; $p = 0.10$) Delayed reduction in mortality 0–7 years 8% (95%CI –20, 31) 7–14 years 23% (95%CI 1, 46) Significant increase in Stage I and II invasive epithelial OC on intention to screen analysis (36.1% vs 23.9%; $p = 0.00013$) 2. Non-significant average mortality reduction of 11% (95% CI –7 to 27; $p = 0.21$) Delayed reduction in mortality 0–7 years 2% (95% CI –27,26); 7–14 years 21% (95% CI –2, 42) No difference in Stage I and II invasive epithelial OC on intention to screen analysis (22.4% vs 23.9%; $p = 0.642$)	Follow-up ongoing as mortality curves were continuing to separate at censorship Compared to national UK willingness to pay thresholds, lifetime cost-effectiveness with MMS is promising (95,96) No long term psychosocial harms (89)
Japanese Shizuka Cohort Screening Study (60)	Multicentre RCT	82,487 Eligible 41,688 Screen arm 40,799 Control arm	Annual combined screens of serum CA125 (interpreted using a cut-off of >35 units/mL) and transvaginal ultrasound	On an intention to screen analysis, compared to control arm of all ovarian cancers, non-significant increase in Stage I disease in screen arm (63% vs 38%; $p = 0.2285$). Compared to a cohort of unscreened women at the same institution, significant increase in 5 year survival (74.8% $\pm$ 6.6% vs 53.7% $\pm$ 2.3%; $P < 0.001$)	Analysis of stage includes borderline epithelial ovarian cancers. No mortality results published
University of Kentucky Study (82,83)	Single centre, single arm prospective interventional trial	25,327 aged 25–92	Annual screen of transvaginal ultrasound followed by repeat ultrasound if ovarian screen not normal		Includes lead time bias
High Risk trials					

UK Familial Ovarian Cancer Screening study UK FOCSS Phase 1 (84)	Single arm prospective trial	3563	Annual combined screen of transvaginal Ultrasound and CA125	Women not screened in the year before diagnosis with greater than stage IIIc disease (85.7% v 26.1%; $P = 0.009$)	Centrally managed
UK Familial Ovarian Cancer Screening study UK FOCSS Phase 2 (85)	Single arm prospective interventional trial	4348	4 monthly serum CA125 interpreted with ROCA and annual transvaginal ultrasound	Comparison - women with invasive epithelial ovarian cancers ($n = 18$) diagnosed greater than one year from last screen in the same cohort In women ($n = 19$) during and within one year of last screen on study, 1. Significant increase in low volume disease (Stage I-IIIa Vs IV) (63% vs 6% $P = 0.0004$) 2. Non-significant zero residual disease after debulking (95% vs 72% $p0.09$) 3. Significant decrease in use of neo-adjuvant chemotherapy (5% vs 44%; $p0.008$)	
US Cancer Genetics Network and Gynaecologic Oncology Group trials (86)	Single arm prospective interventional trial	3692	3 monthly multi-modality screening (CA125 interpreted using ROCA)	Compared to historical BRCA1 controls, in women with invasive epithelial ovarian cancer cases diagnosed with incidence screening Significant increase in Stage I/II (50% vs. 10% $P = 0.016$)	Number of incident cancers were only six

Transvaginal ultrasound (TVS)

TVS permits direct visualisation of the adnexa and detection of disease directly through morphological changes or through characteristics associated with increased OC risk such as increasing ovarian volume [51]. However, many aggressive ovarian cancers metastasise before tumours reach a sonographically-detectable size, with multiple cases documented in the multimodal arm of UKTOCS, wherein serum CA125 levels were rising but ultrasound scans by experienced gynaecological Level II ultrasonographers were normal [52]. In addition, the subjective nature of the assessment is a key limitation, especially in the context of a first line test for general population screening which requires involvement of large numbers of sonographers. In UKTOCS, despite a training and accreditation programme for sonographers and implementation of quality assurance interventions that improved ovarian visualisation rates [53], high levels of inter-observer variation in identification of 'normal postmenopausal ovaries' were reported on an audit of static TVS images between both sonographers and experts and between different experts [54]. In addition to decrease in size of ovaries in older postmenopausal women, ovarian visualisation is technically challenging in women with raised BMI or those who have undergone hysterectomy, tubal ligation, or unilateral oophorectomy [55].

Poor visualisation of the fallopian tube and of tumours below 1 cm in diameter are further limitations. Techniques aimed at improving image resolution such as Doppler flow, microbubble contrast enhanced ultrasonography, and photo-acoustic imaging may allow detection of smaller, earlier cancers in the future [56]. Advanced imaging techniques being investigated in mouse models include the use of immunological biomarkers such as modified macrophages targeting cancer cells [57] and nano-probes [58].

Biomarkers and longitudinal algorithms

CA125 remains the most effective biomarker of high grade serous OC. The application of CA125 in screening has evolved from use of cut-offs, such as $>35\text{IU}$ [59,60] to change over time using longitudinal algorithms, such as the risk of ovarian cancer algorithm (ROCA) [61]. CA125 change as measured by the ROCA has been shown to detect a greater proportion of cancers. Half of the invasive epithelial ovarian cancers detected in trials using the ROCA in high risk [62] and low risk [52] women were detected when CA 125 was $<35\text{IU/L}$ and would have been missed if a single cut-off threshold was used. More recently, retrospective analysis of data from UKTOCS suggests that other longitudinal algorithms to interpret CA125 such as the Parametric Empirical Bayes (PEB) [63] and Methods of Mean Trends (MMT) [64] may have similar performance characteristics for first line screening.

Additional combinations of biomarkers have been suggested to improve sensitivity. Of these, HE4 (Human Epididymis 4) has been the most promising, although its performance, when used alone, is inferior to CA125 [65]. Potential strategies of combining a wide range of blood biomarkers have therefore been considered, using CA125 in addition to HE4, transthyretin, CA15-3, CA72.4 [63], TP53 [66], glycodelin, mesothelin, MMP7 [67], CYFRA 21-1, VTCN1 [63], Protein Z, Fibronectin, and C-reactive protein [68].

Of particular interest is the analysis of free tumour DNA. The recently described 'CancerSEEK' panel combined mutations (including TP53) in circulating free DNA with 8 circulating protein biomarkers, including CA125. This initial case control study recruited clinically diagnosed patients and 812 controls from an asymptomatic population. Sensitivity was 98% with 79% specificity for invasive epithelial ovarian cancer. Further validation is however required with independent sample sets and in the context of screening (samples preceding diagnosis) [69]. More recently, fragmentation patterns of cell free DNA in plasma have demonstrated high specificity and acceptable sensitivity in the detection of a range of malignancies, including ovarian cancer [70]. Similar approaches to detect tumour DNA using mutation profiling have been reported in novel lower genital tract specimens such as vaginal and endocervical liquid cytology samples [71], tampons [72,73], and uterine lavage [16,74].

Aberrant O-glycosylation, which is an inherent and specific property of cancer cells, has been studied to potentially aid in differentiating cancer from these benign conditions, thereby improving specificity of the assay. Microarray glycoprofiling of CA125 [75] as well as glycopeptide spectra analysis of serum [76] have been explored to differentiate between early stage clear cell carcinoma and benign pathology, especially endometriomas.

Screening strategies

Tests are usually used in combination (first line or sequentially) in screening to increase accuracy. In ovarian cancer screening, this a first line combined strategy of serum CA125 (interpreted using a cut-off of >35 units/mL) and TVS was used in the ovarian arm of the U.S. Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) [61] and Japanese Shizuoka Cohort Screening Study [62]. Sequential use has utilised two strategies. One involving CA125 followed by repeat CA125, (interpreted initially using a cut-off [77] and, more recently, a longitudinal risk algorithm in the multimodal arm of UKCTOCS [61], the pilot RCT that preceded it [78] and the pilot US general population trial [79]); and TVS. The other involving TVS as a first line test, followed by repeat ultrasound (University of Kentucky Study [80,81] and ultrasound arm of UKCTOCS [61]).

Studies in high-risk populations (UK Familial Ovarian Cancer Screening study UK FOCSS Phase 2 [82,83] and the US Cancer Genetics Network and Gynaecologic Oncology Group trials) have adopted a multimodal strategy utilising ROCA, similar to that used in the general population trials [59].

Screening is usually performed annually in general population settings and more frequently in high-risk populations (4-monthly in UKFOCSS Phase II [83] and 3-monthly in Cancer Genetics Network [62] and Gynaecologic Oncology Group [84] Studies).

There should be evidence from randomised controlled trials of a mortality benefit

Only two RCTs have reported the impact of screening on disease specific mortality. In the U.S. Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) of 78,286 women at a median of 14.7 years, there was no difference in deaths due to OC between the screen and no screen arms (RR 1.06; 95%CI 0.87–1.3) [59].

In the UKCTOCS, between 2001–5, a total of 202,638 postmenopausal women, at average population risk of OC and aged 50–74, were randomised (2:1:1) to no screening, longitudinal CA125 based multimodal screening (MMS), or annual TVS (USS). Screening (involving 673,765 annual ultrasound and CA125 screens) continued until the end of 2011 with women receiving a median of 9 and a maximum of 11 annual screens. Follow-up included electronic health records linkage to cancer and death registry and postal questionnaires. At a median follow-up of 11.1 years (IQR 10.0–12.0), there was a higher proportion of women diagnosed with low-volume invasive epithelial ovarian and peritoneal cancer (stage I, II, and IIIa) in the MMS (40%; $p < 0.0001$) but not in the USS group (24%; $p = 0.57$) compared to the 'no screening' group (26%). In both groups, there was a non-significant trend towards an average reduced OC mortality of 11% (95% CI –7 to 27; $p = 0.21$) in USS and 15% (95% CI –3 to 30; $p = 0.10$) in the MMS group using the Cox proportional hazards model. When prevalent cases were excluded in the MMS arm, a significant decrease in mortality from OC was observed ($p = 0.021$) [61]. Mortality reduction was greater in years 7–14 than years 0–7 from randomisation. As the mortality rates were still rising in the 'no screening' arm at censorship, extended follow-up is underway to assess the long term effect of screening on mortality [85].

Evidence from other trials

In the Japanese Shizuoka Cohort Screening Study which randomised 82,487 women, at a mean follow-up of 9.2 years, the proportion of women with stage I OC was higher in the screened group (63%) than in the control group (38%) but did not reach statistical significance ($p = 0.2285$). No mortality results have been published from this trial [60]. The University of Kentucky Study was a single arm prospective study in which 25,327 women underwent TVS screening. Sensitivity for detection of primary OC was 81%. 5-year survival rates were higher in screened women who developed OC compared to unscreened women treated for OC using the same institutional protocols. ($74.8\% \pm 6.6\%$ vs $53.7\% \pm 2.3\%$ $P < 0.001$) [80,81]. Whilst these results are encouraging, it is likely that there is a significant healthy volunteer effect, given the cohort design.

In high-risk women, evidence is limited to cohort studies as it was thought to be unethical to randomise to 'no screening'. Further, in high risk populations, no studies have reported mortality, with all using performance characteristics and stage shift as the primary outcome.

UK FOCSS Phase I demonstrated that annual screening is ineffective in detecting early stage disease [82]. In Phase II, 4-monthly screening, use of the longitudinal ROCA algorithm and central management of results was undertaken. Between 2007 and 2012, 4348 women, who declined standard of care (risk reducing salpingo-oophorectomy, RRSO) underwent 13,728 women-years of screening. They were encouraged to undergo RRSO throughout the study. Median follow up was 4.8 years. In women diagnosed with OC during and within one year of the last screen, there was a significantly higher proportion with low-volume stage I-IIIa disease (63% vs 6% $P = 0.0004$), and less need for neoadjuvant chemotherapy (5% vs 44% $P = 0.008$) compared with women diagnosed with OC > 1 year after the end of screen [83]. In two similar studies conducted in the USA by the Cancer Genetics Network and Gynaecologic Oncology Group, 3692 high-risk women underwent 13,080 woman years of 3-monthly multimodal screening using CA125 interpreted using the ROCA algorithm. Of 15 incident cancers, six were detected through screening (50% stage I/II), nine at RRSO and one woman was missed [62].

There are two ongoing trials in high-risk populations. In the UK, a pilot NHS study, 'Avoiding Late Diagnosis of Ovarian Cancer (ALDO)' is underway in BRCA mutations carriers who decline RRSO. Instigated based on the encouraging data from UKFOCSS Phase II, it uses a multimodal screening strategy with CA125 interpreted using ROCA [86]. In the United States, a randomised trial is underway with high-risk women undergoing 6-monthly screening and intermediate-risk women undergoing annual screening. Women are being randomised to CA 125 and HE4 at every screen or CA 125 as first line test followed by HE4 as second-line test. The longitudinal PEB algorithm is being used to interpret the blood biomarkers with those with high scores undergoing confirmatory biomarker measurements followed by TVS [83].

Morbidity (physical and psychological)

All screening is associated with morbidity due to false positive and false negative results. False positive results lead to 'unnecessary' operations with its attendant risk of complications in women who have no cancer. In UKTOCS, in the MMS group 4.4 and the USS group 11 operations were undertaken per OC detected. 3.5% of women undergoing 'unnecessary' operations, without resultant diagnosis of malignancy, suffered a major surgical complication [61]. In the PLCO, a higher serious complication rate of 15% was reported in women undergoing surgery, with findings of false positive screening result [87]. The other issue is the cancers being missed and the misleading reassurance of false negative results. In UKTOCS, of ovarian, tubal, and primary peritoneal cancers diagnosed within a year of a screening, 16% were missed in the MSS and 29% in the USS group [61].

Screening for disease in the general population did not increase anxiety [88] or result in a reduction in sexual activity or functioning [89]. However, an abnormal screening result and need for second line tests did result in increased psychological morbidity, primarily due to worry [88], as well as decreased sexual pleasure in the short term [89].

In the high risk population, screening for disease was reassuring and acceptable to the majority of women. However, the limitations of screening were not always understood. This resulted in false reassurance and disappointment if screening was ineffective [90].

The test should be acceptable to the population

The majority of postmenopausal women found TVS acceptable, with only 3.5% reporting moderate or severe pain. However, women reporting pain were more likely to drop out (OR 0.87) compared to those reporting no pain [91]. Pilot studies undertaken in the set-up of UKTOCS have shown that a blood test has high acceptability (personal communication).

It is difficult to assess uptake of OC screening in the context of a national programme. In UKTOCS, of 1,243,282 women invited, acceptance rate varied from 19% to 33% between different parts of the country [92]. Compliance with annual screening in UKTOCS was 78% with USS and 81% with MMS [61]. High risk populations were similarly motivated [78]. This suggests that the screening strategies are likely to be acceptable. However, all such studies are subject to a significant healthy volunteer effect [93] and compliance rates in a screening programme are likely to be lower.

The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced and screening should be a continuing process and not a 'once and for all' project

A number of cost effectiveness analyses using the published UKTOCS data are available. All are based on the assumption of a mortality benefit of multimodal screening being shown in extended follow up of the UKTOCS trial [94]. An analysis of individual trial data by UKTOCS trialists suggested that a national programme of multimodal screening would approach the National Institute for Health and Care Excellence (NICE) cost effectiveness threshold for England [95]. Similarly, a USA model suggested that multimodal screening is potentially cost-effective, however this would only be certain when the size of any mortality benefit is known as well as the cost of the CA125 algorithm [96].

Any implementation of general population screening would require an ongoing multi-year commitment from commissioning bodies if it is to have a long term impact. In the National Health Service in UK, this would be the remit of national screening committee [1] who would make a decision based on assessment of each of the criteria described above. Evaluation of high-risk screening in the UK would fall under the remit of guidelines committees such as NICE. Key issues in addition to cost would be high quality universal coverage and the impact on workforce, particularly of skilled sonographers.

Current guidelines

With no impact on mortality demonstrated in RCTs, population screening of women at average risk is not currently recommended by the UK national screening committee [1] or US National screening committee [97]. Screening for OC in women with a high risk of OC is not routinely offered by the NHS. The U.S. Preventative Task Force, whilst not supporting screening, does give clinicians discretion to allow 6 monthly screening from age 30–35 [98].

Summary

There remains an urgent need for strategies to detect ovarian cancer earlier in order to reduce mortality. Both in the low-risk and in the high-risk population, there is evidence that a multimodal strategy based on longitudinal CA125 profile and second line TVS can lead to earlier diagnosis. However, no screening strategy has been shown to definitively decrease OC mortality. Longer term follow-up is underway in UKTOCS to establish whether the trends in mortality reduction can be confirmed.

A key limitation of current screening strategies is the lack of tests that are able to detect pre malignant and early stage disease. Innovative strategies being investigated include longitudinal biomarker algorithms, detection of tumour DNA in cervical cytology or uterine lavage specimens and blood, and improved targeted imaging of the adnexa.

Increased understanding of the environmental, reproductive, and genetic risk factors for OC is improving risk stratification which is key to defining the target population for screening or primary prevention.

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Declaration of Competing Interest

ZN reports no conflicts of interest. UM has stock ownership awarded by UCL in Abcodia Ltd, which is a UCL spinout company with an interest in biomarkers for early detection of cancer and has the commercial rights to the Risk of Ovarian Cancer Algorithm used in ovarian cancer screening.

Practice points

- Screening for ovarian cancer is not proven to reduce mortality and not recommended in the low risk population.
- Screening for an individual's risk of OC allows intervention with risk reducing strategies in high risk populations.
- A screening strategy using longitudinal CA-125 as first line strategy interpreted with risk of ovarian cancer algorithm and transvaginal combined strategies increases effectiveness of screening.

Research agenda

- Extended follow up in UKCTOCS, the largest RCT to date, to establish if the trend to mortality benefit is confirmed
- Pilot studies of intensive screening alongside risk-reducing surgery in high-risk populations to evaluate impact on detection of early stage disease
- Longitudinal biomarker algorithms, detection of tumour DNA in blood and cervical cytology/uterine lavage specimens and improved targeted imaging of the adnexa to improve sensitivity for detection of early stage and pre-malignant disease
- Refining risk prediction strategies to enable more cost-effective early detection and prevention strategies

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