Gynaecological surveillance in high risk women

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Abstract

In high-risk women, risk reducing surgery remains the cornerstone of prevention. However, the resulting premature menopause has led to continued efforts to develop effective screening strategies for those who wish to delay or avoid surgery. This review describes how the screening of women at risk of ovarian and endometrial cancer has evolved to its current state. Serial monitoring of CA125 is core to ovarian cancer screening and most recent studies have used the Risk of Ovarian Cancer Algorithm (ROCA) to interpret CA125 profile. The additional use of a second tumour marker, HE4, is reviewed. The results to date of key ovarian cancer screening studies in high-risk women are summarised ahead of their concluding findings due later in 2016. The role of both ultrasound and endometrial sampling in the management of women at increased risk of endometrial cancer is outlined. Exciting new methodology, which could help shape the future of screening is investigated. The article summarises the current recommendations and guidelines from recognised international bodies to aid the clinician with management of these women.

Key words

Screening, BRCA, Ovarian, Endometrial, CA125, Transvaginal, ultrasound, Lynch,

Increasing availability of genetic testing and falling costs of the tests suggests that growing numbers of unaffected women will be identified worldwide who are at increased risk of gynaecological malignancies. The challenge in those identified is to prevent and detect the disease early without causing significant harm. Currently surgery remains the cornerstone of management. Most women undergoing surgery do not report a significant deterioration of their physical and mental health-related quality of life (1). However the resulting premature menopause is associated with decrease in sexual functioning and vasomotor symptoms even in women on hormone replacement therapy (HRT)(2)(3). As a result there is a continued effort to develop effective screening strategies for high risk women.

Ovarian cancer screening

Women at high risk of ovarian cancer are in the main BRCA mutation carriers with a 11- 68 % lifetime risk of ovarian/tubal cancer (4)(5). Women with Lynch Syndrome can have a risk of ovarian cancer of up to 24%. (6). Testing is also increasingly be available for moderate penetrance mutations in genes such as RAD51C, RAD51D, BRIP1 where lifetime risks of ovarian cancer are in the range of 5-15%.(7)(8) Finally, the multiple common low-penetrance susceptibility alleles which individually confer relative risks of less than 1.5-fold (7) in combination with lifestyle and reproductive factors are likely to identify additional women with an increased lifetime ovarian cancer. (9)(10). Significant efforts are underway to incorporate recently identified moderate and low risk

loci as well as lifestyle and reproductive factors to models such as the BOADICEA in order to personalise risk prediction(11).(12).

Risk reducing salpingo-oophrectomy (RRSO) after the age of 35 and completion of the family is the primary recommendation in BRCA1/2 carriers and has been proven to substantially reduce the risk of developing ovarian/tubal cancer (13) (14). In those unwilling to explore surgery, screening is an option. The currently available strategies are based on blood tests for tumour markers and adnexal imaging, in particular using transvaginal ultrasound (TVS).

Bimanual pelvic examination, although widely used in clinical practice, lacks sensitivity and specificity for both the detection of ovarian cancer and the ability to distinguish benign from malignant lesions. A systematic review of screening populations that were both asymptomatic and symptomatic and included high risk women found the positive predictive value of an abnormal pelvic examination is only 1% (95% CI=0.67%, 3.0%). (15) (16). Despite this, in a recent survey of US obstetricians and gynaecologists, 47% stated that they performed pelvic examinations for early detection of ovarian cancer (17).

The potential role of ultrasound in ovarian cancer screening was initially explored alongside CA125 in the 1980s (18)(19). Since then, there have been key improvements aimed at increasing the sensitivity as well specificity and positive predictive value of ultrasound screening which include transvaginal rather than transabdominal ultrasound, the introduction of colour Doppler to monitor neovascularisation (20) and use of morphological index (MI) based upon

ultrasound features of the lesion (21) and finally change in serial MI scores as the mean MI for malignant ovarian tumors increases over time, while that of non-malignant tumors decrease or remain stable (22) As ultrasound revealed the natural behavior of cysts and the high incidence of spontaneous regression of benign / functional cysts (23) repeat scanning to confirm persisitence in 4-6 weeks became the norm in ultrasound scanning.

The main blood tumour marker is serum CA125, which was first described by Bast in 1981. It is a 200kd glycoprotein recognised by the OC125 murine monoclonal antibody (24). There are a number of CA125 assays available, most of which correlate well with each other and are clinically reliable. The results are often interpreted using a cut-off value based upon the 99% centile of normal distribution which in pre menopausal women is 35 U/mL. (25). However CA125 values can show wide variation, being influenced by race, age, menstrual cycle, pregnancy, a range of benign gynaecological conditions and inflammatory conditions such as pancreatitis and pleuritis. Elevated levels are found in approximately 85% of women with epithelial cancer (26)(27), with raised levels in the preclinical asymptomatic phase being described as early as 1988. (26).

It has become increasingly clear that in ovarian cancer screening, a key issue is how tumour marker levels are interpreted. When interpreting CA125, which is not cancer specific, a single threshold rule is not effective. In screening trials in high risk women, CA125 interpreted using a cut-off has been used in a number of older studies. Between 1993 and 2005, 888 women with a BRCA 1/2 mutation underwent annual screening with transvaginal ultrasound (TVS) and serum

CA125 interpreted using a cutoff. There were 10 incident cancer of which five were interval cancers which were diagnosed in women with a normal CA125 screening result 3-10 months before diagnosis. Eight of the ten were stage III/IV (28). The strategy of annual TVS and serum CA125 with a cut-off lacked adequate sensitivity at 42%. In a cohort study of 1,100 women who were moderate-risk (4% to 10% lifetime risk) and high-risk (>10% lifetime risk) by Sterling (29) using a similar strategy of annual TVS and CA125 with a cut off, lead to the screen detection of ten of the 13 cancers, but majority were not detected at an early stage. In phase I of the UK Familial Ovarian Cancer Screening Study (UKFOCSS), between 2002 and 2008 3,563 women underwent annual screening with serum CA125 and TVS. CA125 cutoffs were 35U/mL for premenopausal and 30U/mL for postmenopausal women. Whilst the study showed encouraging sensitivity for the detection of OC/FT cancer within a year of the last annual screen, only 30.8% of the cancers detected by screening were Stage I/II. Advanced stage disease (>IIIC) was more likely in those that did not adhere to annual screening compared to those that did (85.7% versus 26.1%; p=0.009) (30).

Serial monitoring is an essential part of screening.(31) Consequently efforts have been made to develop a more sophisticated approach to replace using absolute cut off levels for interpretation of CA125 levels. Analysis of data the pilot trial of ovarian cancer screening (32) of 22,000 volunteers who were followed up for a median of 8.6 years and included more than 50,000 serum CA125 measurements revealed that elevated CA125 levels in women without ovarian cancer were static or decreased with time, whereas levels associated with malignancy tended

to rise (33). These results were used to develop the Risk of Ovarian Cancer Algorithm. (ROCA), that uses age-specific incidence of ovarian cancer and comares the CA125 profile of the individual with known cases and controls (34) The risk increases the more the CA125 profile follows that of known ovarian cancer cases. Input of a woman's age and dates and results of her serum CA125 levels results in an estimated risk of the women having ovarian cancer, for example a ROC of 2% would indicate a risk of 1 in 50.

Most high risk women wishing to access screening are pre- menopausal and interpretation of screening results is complicated by the presence of benign conditions (ovarian cysts, endometriosis) and changes in physiology (menstrual cycle) which both elevate CA125 levels and result in abnormalities on TVS and therefore a higher false positive rate. In a study by Sterling (29) of high risk women, annual screening with TVS and CA125 cutoff had a high false positive rate leading to unnecessary surgical intervention. Interpretation of CA125 using ROCA has been shown to improve specificity as women with static but elevated levels are being classified as low risk. The use of ROCA resulted in high specificity and positive predictive value in low risk population screening.(35)

The ROCA also increases the sensitivity of CA125 compared with a single cut off value. For a target specificity of 98%, the ROC calculation achieved a sensitivity of 86% for preclinical detection of ovarian cancer in the low risk population (36). The use of ROCA for general population screening in UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) doubled the number of screen-detected

invasive epithelial ovarian cancer (iEOC) during incidence screening compared to a fixed cut off. ROCA detected 86% of the women with iEOC diagnosed within one year of screening, whereas using annual serum CA125 fixed cut-offs of >35, > 30, and >22 U/mL would have identified only 41%, 48%, and 66%, respectively. (31) Other serial algorithms incorporating change in an individual's CA125 over time as the cancer evolves has also been shown to have superior sensitivity and specificity in retrospective analysis of data from the US ovarian cancer screening trial. (37) (38).

The ROCA is incorporated into a multimodal screening strategy. Women who undergo annual screening with CA125 that is interpreted using ROCA are subsequently triaged to routine screening if risk is normal, repeat testing with CA125 and /or TVS if risk is intermediate/ elevated and to clinical assessment if risk is severe. In the general/low risk postmenopausal population, UKCTOCS provided the first evidence that such a strategy may reduce deaths from ovarian cancer. (39).

The ROCA was used in UKFOCSS Phase II (2007-2009) with more frequent 4-monthly screening compared to the annual screening used in low-risk populations and previously adopted in high-risk trials . The preliminary results presented at the American Society of Clinical Oncology meeting in 2013 suggest that this strategy had high (67-100%) sensitivity for detection of ovarian and tubal cancers, with no interval cancers reported. However, only 42% of incident screen-detected OC/FT cancers were Stage I/II. This is in keeping with the

modelling studies from Brown & Palmer that suggest that for most of the occult period high grade serous ovarian cancers are less than 1cm in diameter and progress to stage III or IV when they are about 3cms. (40) There is a growing acceptance that while stage is important, tumour volume maybe a better prognostic indicator in invasive epithelial ovarian/tubal cancer. Most encouragingly in UKFOCSS Phase II, 92% of the incident cancers were completely cytoreduced compared to 62% on Phase I (p=0.16), implying detection of lower volume disease. While the results were encouraging, it is important to note that screening at present cannot be considered an effective alternative to risk-reducing surgery(41). However in women who wish to delay or are not prepared to undergo RRSO a strategy of intensive surveillance as in UKFOCSS Phase II together with ongoing discussions about RRSO might be a safer option than symptom awareness alone. The study is expected to report its final results on the performance characteristics of multimodal screening using ROCA in high risk women in 2016.

A similar screening strategy based on 3-monthly serum CA125 levels interpreted using ROCA was also assessed prospectively in the US screening trials in high-risk women undertaken under the auspices of the Cancer Genetics Network (42) and Gynaecology Oncology Group (43). Sub group analysis of women who underwent RRSO at enrolment found significant association with abnormal CA125/TVS and detection of clinically occult neoplasm (44). Screening is complete in all of these trials with results expected later this year, and possible meta-analysis in the future.

HE4 a more recently described tumour marker is elevated in ovarian cancer but less frequently elevated in benign conditions such as endometriosis and studies suggsest it may help improve the performance of the screening strategy. (45). It is commercially available as Risk of Ovarian Malignancy Algorithm, ROMA, a test that combines HE4, CA125 II and menopausal status. Recent systematic review by Ferraro et al looking at the performance of HE4 and CA125 in identification of ovarian cancer in symptomatic women with suspected gynaecological disease concluded that HE4 is superior to CA125 using a cut off (46). More recently, the Copenhagen Index (CPH-I) which combines CA125, HE4 and age has been described and validated as an index that is easier to use as it does not include ultrasound findings and menopausal status(47) . Karlan et al studied the use of CA125 and HE4 in a screening study of women with increased risk of ovarian cancer defined by one of the following criteria 1) BRCA1/2 germline mutation, 2) fulfilling National Comprehensive Cancer Network (NCCN) high risk criteria and HPNCC or TP53 deleterious mutation 3) having 3 of 6 risk factors (<1 year of oral contraceptive use, null parity, no breastfeeding, no tubal ligation, Ashkenazi Jewish, >1 year of menopausal hormone therapy) or CA125, HE4, MMP7, or Mesothelin values exceeding the 95% population threshold. HE4 was either used as a first line test in conjunction with CA125 or as a second line screen after CA125. The results were interpreted using the parametric empirial Bayes (PEB) serial algorithm. The results suggested that in high-risk women HE4 may be useful as a confirmatory test in a multimodal strategy when CA125 alone was used as the primary screen. Additionally women were more likely to agree to a surgical consultation and procedure if recommended when rising CA125 was confirmed by a concurrent rising HE4. (48)

The modelling study (40) of occult serous ovarian cancer detected at RRSO in BRCA1 carriers suggest that to achieve 50% sensitivity in detecting tumours before they advance to stage III, an annual screening test would need to detect tumours that were 1.3cm in diameter at sizes 200 times smaller than those clinically apparent. To achieve 80% sensitivity, the tumours would have to be detected when 0.4cms in diameter. This would require a truly ovarian cancer-specific biomarker and/or alternative novel approaches. Mutations in cancer-related genes *TP53*, *EGFR*, *BRAF*, and *KRAS* are among the most common early molecular genetic events in ovarian cancer. This opens up the possibility of detecting circulating tumour cells or tumour-derived DNA (ctDNA) in the blood (49) (50,51) or other novel samples such as endocervical. It has been shown that small amounts of tumour derived DNA containing these mutant alleles in cell-free body fluids can be quantified with unprecedented sensitivity by new technologies such as BEAMing (52). BEAMing, is a form of massive parallel sequencing that allows the transformation of a population of DNA fragments into a population of beads each of which contains thousands of copies of the identical sequence. By using labels which distinguish beads containing DNA sequences of interest the incidence of these can be quantified. In high grade serous carcinoma, where TP53 mutations are ubiquitous, (53) Forshew et al reported detecting high levels of ctDNA using tagged-amplicon deep sequencing (TAm-Seq) for TP53 mutations in over 50% of patients with advanced high grade serous ovarian cancer. (54). Tam-Seq will however need to achieve a more sensitive detection limit (<2% allele frequency) for identification of mutations in patients with early stage cancer. Further optimisations will hopefully allow high

throughput, low cost 'liquid biopsy' to allow detection of small tumours. Using liquid cytology cervical samples from 14 women with OC who had mutations, Kinde et al using massive parallel sequencing were were able to identify the expected tumour specific mutations using a panel of 12 genes. (55). Further encouraging results from a pilot study illustrates the feasibility of uterine cavity lavage to detect shed cancer cells and its ability to provide sufficient amounts of DNA in all patients. Using massive parallel sequencing and singleplex analysis mutations were identified in 80% (24/30) of women with ovarian cancer. (56)

A separate but allied strategy explores use of autoantibodies (AAb) to tumor-derived proteins. A study by Anderson et al. using sera of women diagnosed with ovarian cancer has identified autoantibodies to p53, PTPRA, and PTGFR as potential biomarkers for early detection of ovarian cancer.(57). Yang has reported detecting TP53 AAb more commonly in speciemens from women with ovarian cancer than control groups. Additionally TP53 was found to be postivie prior to a rise in CA125 and also in women where the CA125 levels did not rise at all.(58) Another potentially minimally invasive approach is using saliva. Salivary transcriptomes have also been evaluated as possible OC markers. In a small study, Lee et al. showed that combination of five biomarkers (AGPAT1, B2M, BASP2, IER3 and ILI1) had a high sensitivity (85.7%) and specificity (91.4%) (59). Further evaluation is required but the technique illustrates another potential minimally invasive future screening technique.

The need to detect small serous ovarian cancers has shifted the focus of detection using transvaginal ultrasound from tumour blood flow using colour

Doppler on a macrovascular level to neovascularisation on a microvascular level, using contrast enhanced transvaginal ultrasound with microbubbles that are small enough to pass through capillaries the kinetics of blood flow. Initial reports have indicated significant difference in enhancement patterns between benign and malignant ovarian tumours (60). Another novel way that small tumours and STIC lesions could be visualised is utilising autofluorescence patterns seen in tumours. Ex vivo data suggests that this is feasible and reproducible and is able to detect serous cancers with a high sensitivity (87.5 %) and specificity (92%) (61).

Recommendations regarding OC screening in high risk women

Currently screening of high-risk women is not recommended in the UK in the National Institute for Health and Care Excellence (NICE) guidelines.(62) and is therefore not available on the National Health Service (NHS). NICE does emphasise the importance of discussing the positive effects of reducing the risk of breast and ovarian cancer risk and the negative impact of surgically induced menopause. The NCCN primary recommendation for USA is for RRSO in women with BRCA1, BRCA2 and Lynch syndrome, with insufficient evidence for intervention in those with BARD1, BRIP1, PALB2, RAD51C and RAD51D mutations. In women who have not undergone RRSO, TVS starting age 30-35 and serum CA125 levels may also be considered at the clinician's discretion. NCCN guidelines clearly state that these screening procedures have not been shown to have sufficient specificity or sensitivity and current research does not provide evidence that they are a reasonable alternative to RRSO. It is worth noting that

these guidelines may be revised in due course to incoporate the results of multimodal screening in UKFOCSS Phase II and UKCTOCS (39).

Ocassionally CA125 is used for surveillance of BRCA women post RRSO due to the ssmall residual risk of primary peritoneal cancer. There is little evidence to support this. A recent study found that there was no significant difference in preoperative CA125 levels between BRCA1, BRCA 2 and non carriers. Post RRSO there was a significant reduction in CA125 levels in 48 BRCA1 women ($p=0.04$) but no significant different in 40 BRCA2 women ($p=0.5$). Based on the finding of only one case of post-operative peritoneal cancer in 220 carriers undergoing RRSO,, detected in an asymptomatic women with a raised annual CA125, the authors suggest that serum CA125 monitoring should be discontinued following RRSO. (63)

Symptoms awareness

Studies have shown that 95% of women with ovarian cancer report symptoms prior to diagnosis (64). Development of a symptom index that includes frequency and severity was reported to perform similarly to CA125 to detecting any stage of disease in a case control study that incorporated women from an ovarian cancer early detection study (65). This has led organisations such as the NICE to issue recommendations that further investigations should be initiated if a woman has persistent abdominal distension/bloating, early satiety, loss of appetite, pelvic/abdominal pain and increased urinary urgency/frequency. (66).

Unfortunately symptoms associated with ovarian cancer can be non specific and are commonly found in women who do not have ovarian cancer (67).

The DOvE pilot study found that assessment of symptomatic women via a fast track symptom clinic led to a lower tumour burden compared to those diagnosed via the standard referral route to the gynaecological oncological clinic in same hospital. However this was not asscoaited with an increase in early stage diagnosis. (68). Although the study design has been questioned (69) these findings emphasise the importance of assessing women as soon as symptoms occur. Thus it is important that women at high risk of ovarian cancer are educated about symptom awareness and pathways are set up for rapid referral if key symptoms develop. Given the international variation in the perceived barriers to presenting with symptoms, (70) it is important to pre-empt and tackle any concerns women may have.

Endometrial Cancer screening

Lynch syndrome (previously referred to as hereditary nonpolyposis colorectal cancer /HNPCC) is an autosomal dominant disorder that is characterized by predisposition to early onset colorectal cancer and cancers of the endometrium, small intestine, ovary, hepatobiliary system, kidney, and ureter (71). It is caused by an inherited mutation in one of the following mismatch repair (MMR) genes: MSH2, MLH1, PMS1, PMS2, and MSH6.(72) Individuals are diagnosed according to the Amsterdam II or the Bethesda criteria(72)(73). Endometrial cancer is the most frequent extra colonic cancer in these women and risk estimates may

exceed those of colorectal cancer (74)(75). The exact lifetime risk varies with the gene mutation. Mutations in MLH1, MSH2, MHS6 and PMS2 confer a risk ranging from 15-54% compared to a general population risk of <2% (6)(76) Endometrial cancers in Lynch syndrome differ from sporadic endometrial carcinomas. They are more likely to be poorly differentiated, have lymphatic/vascular invasion and be diagnosed at an advanced stage (77). Cowden syndrome is an autosomal dominant syndrome that is characterised by hamartomatous tumors in multiple organ systems and it too is associated with an increased risk of endometrial cancer (78). Lifetime risk of developing endometrial cancer range between 10-28% (79). However, as the prevalence of Cowden's syndrome is only 1 in 200,000, there are no uniform recommendations for risk management of endometrial cancer (79).

Surveillance for women at risk of endometrial cancer is aimed at detection of atypical endometrial hyperplasia (AEH) or endometrial cancer at an early stage. It is based on detecting increased endometrial thickness (ET) on transvaginal ultrasound. While ET cut-offs have be defined in postmenopausal women, in premenopausal women ET can be difficult to interpret as it varies through the menstrual cycle. Hence in LS annual or biennial pelvic ultrasound is not a very effective method to detect early endometrial carcinoma. In 269 Lynch Syndrome women during 825.7 women years of screening using transvaginal ultrasound, two cases of endometrial carcinoma were reported but both were not detected by screening. (80). Another study using annual TVS, reported on 41 women totalling 197 women years of screening. While three cases of AEH were detected,

one woman presented with an interval endometrial cancer detected as a result of clinical symptoms.(81).

This has led to the use of endometrial sampling in addition to TVS in LS. In a Finnish study of 175 women (759 screen years) who underwent screening using TVS and intrauterine biopsy, endometrial cancer occurred in 14 women, 11 of whom were diagnosed by surveliance (8 by uterine biopsy, 4 by TVS . Intrauterine biopsy detected 14 additional women with premalignant hyperplasia. The authors concluded that surveillance with biopsy was more effective. (82). Gerritzen et al also found significantly more AEH and endometrial cancers in women using microcurretage or hysteroscopy and curettage combined with annual TVS compared to screening using by TVS alone (83). However, this was not confirmed in a separate study by Helder-Woolderink et al, who found that the addition of endometrial sampling using Pipelle to annual TVS had no additional value in detection of endometrial lesions (84). However, the accuracy of endometrial sampling depends on the method used. Pipelle sampling can have an inadequate tissue yield and failure rate of approximately 10% (85). In contrast to endometrial biopsy, hysteroscopy has a high sentivity for the detection of hyperplasia or cancer with some studies reporting this to be 100%.(86) A systematic review undertaken in 2011 concluded that detection of endometrial cancer or hyperplasia in asymptomatic women belonging to LS families is improved by adding routine endometrial sampling along with transvaginal ultrasound for surveillance visits.(87). More recently out- patient hysteroscopy and endometrial sampling (OHES) was compared to TVS alone in

41 LS women who had both annually. OHES had similar specificity of 89.8 % (CI 79.2, 96.2 %) as TVS, but higher positive likelihood ratio 9.8 (CI 4.6, 21) and lower negative likelhood ratio (zero) compared to. These results suggest that OHES is an acceptable screening method with a high diagnostic accuracy for endometrial cancer and atypical endometrial hyperplasia (88).

A survey of women who underwent screening with regards to pain or discomfort associated with the procedures revealed that TVS was associated with less discomfort than hysteroscopy or Pipelle biopsy and that the majority of women would choose TVS if only a single test was required. The survey also found that there was no significant difference between the pain scores for hysteroscopy and Pipelle biopsy (89). A more recent prospective study of women undergoing combined colon and endometrial screening under conscious sedation reported high levels of satisfaction and more convenience in the combined procedure. In this patient-centred approach women reported significantly lower levels of pain compared with an office based procedure, even when accounting for parity (90).

A potential future screening strategy could focus on the detection of micro-satellite instability (MSI), which is found in more than 90% of endometrial cancers developed in Lynch syndrome women. Bats et al report encouraging sensitivity and feasibility of MSI detection in uterine cavity washings in a case series of 10 women with Lynch syndrome undergoing a hysterectomy for benign reasons, risk reduction and treatment of endometrial cancer (91).

A decision analytic model comparing annual screening (ultrasonography, endometrial biopsy, CA 125) and hysterectomy with bilateral salpingo-oophorectomy at age 30 years found that surgery in women with Lynch Syndrome led to the longest life expectancy (92). However, there are costs associated with both screening and preventative surgery. In a hypothetical cohort of women with Lynch syndrome, Kwon et al compared the cost of risk reducing surgery at 30 years, 40 years, annual screening with endometrial biopsy, transvaginal ultrasound, and CA125 from 30 years, annual screening from 30 years until risk reducing surgery at age 40 years (combined strategy) or no prevention. The combined strategy was found to be the most effective gynaecological cancer prevention strategy, but the incremental benefit over prophylactic surgery alone was attained at substantial cost (93). When prophylactic hysterectomy with bilateral salpingo-oophorectomy at age 30 was compared to annual gynaecological screening, risk-reducing surgery carried both the lowest costs and highest QALYs score. However the cost effectiveness of this surgery diminishes with increasing age. (94). A mixed methods study of 24 LS women exploring the impact of surgery suggested that while it does not lead to significant psychological distress, women reported feeling underprepared for menopausal symptoms. (95)

Current guidelines for management of gynaecological cancer risk in LS are a result of consensus, based on the limited reported studies. The Mallorca group which consist of a panel of European experts recommend surveillance of the endometrium by gynaecogical examination, TVS and aspiration biopsy starting

from the age of 35–40 years (96). However they suggest that given the current ack of evidence of benefit, it is best offered within a clinical trial setting. The 2015 American College of Gastroenterology guidelines recommend annual screening using endometrial biopsy and transvaginal ultrasound from 30 to 35 years with surgery offered to LS women who have finished child bearing, optimally at age 40–45 years. (97)The American Society of Clinical Oncology and European Society for Medical Oncology have similar guidelines which include annual screening with TVS and aspiration biopsy with prophylactic gynecological surgery an option from age 35, after childbearing is completed.(98)

Psychological impact of screening

It is essential to recognise the psychological aspect of screening high-risk women. Premenopausal women perceive their ovarian cancer risk to be higher, report greater disease risk-related anxiety, and are more likely to have false-positive screening results than postmenopausal women (99). Brain et al found that women, in UKFOCCS trial, who are recalled for an abnormal result, may experience transient cancer-specific distress, which may prompt reconsideration of risk management options. However frequent 4 monthly ovarian screening in the high risk women did not cause sustained psychological harm or have a significant impact on general anxiety and depression (100). In women who participated in UKFOCSS, experience of previous screening, cancer specific distress and a belief in aging as a cause of OC were significantly associated with withdrawal from screening and opting for surgery (101).

Conclusions

Surgery is recommended as the definitive option to reduce risk in women at high risk of ovarian cancer and to a lesser extent in women at increased risk of endometrial cancer. However, the fear of surgery and the sid effects of premature menopause often result in some women seeking screening in order to either postpone or avoid surgery. However screening in this population of women who are mainly premenopausal has additional challenges when compared to the general postmenopausal population. Annual screening is ineffective and strategies that are being investigated are based on 3-4 monthly screening with serial CA125 levels interpreted using the ROCA together with second line TVS. Detailed results of both the UK and US studies are expected in 2016. With increasing understanding of the natural history, a number of novel ovarian cancer screening strategies are being explored. In Lynch Syndrome women, endometrial cancer screening is offered from 30-35 years and includes annual TVS and endometrial biopsy, with increasing use of outpatient hysteroscopy.

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Declaration of Interest

UM has a financial interest in Abcodia, Ltd., a company formed to develop academic and commercial development of biomarkers for screening and risk prediction. The other authors declare no conflict of interest.