Chapter 10

Screening for Ovarian Cancer

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Additional information is available at the end of the chapter

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Abstract

Ovarian cancer is often diagnosed at an advanced stage and is associated with poor survival. Screening aims at detection of early stage disease with a view of improving overall survival. Incidence of ovarian cancer is about 1–2% in the low-risk and 10–40% in the high-risk population. Transvaginal ultrasound (TVS) and serum CA125 levels have been used for early detection. Annual screening with TVS and serum CA125 levels (using a cut-off value) has not demonstrated detection of ovarian cancer at an early stage. Multimodal screening (MMS) using sequential CA125 levels (with interpretation of risk using Risk of Ovarian Cancer Algorithm—ROCA) and ultrasound as the second-line test have been shown to have improved sensitivity when compared to annual ultrasound in the detection of ovarian cancer. However, no impact on survival has been demonstrated, and therefore, screening cannot be recommended in the general or high-risk population. There is evidence now to suggest that high-grade serous cancers originate from the fallopian tube where precursor lesions have been identified. Newer screening strategies are likely to shift the focus to detecting these precursor lesions with novel techniques such as exfoliative cytology, circulating tumour DNA and use of microbubbles in ultrasound imaging.

Keywords: screening, transvaginal ultrasound, CA125, ovarian cancer, multimodal screening

1. Introduction

Ovarian cancer is the seventh most common cancer in women worldwide, accounting for 4% of cancers in women. Incidence of ovarian cancer is increasing, especially in Europe and Northern America, being the fifth most common cancer in European women [1]. Even though the life time risk of developing ovarian cancer is 1–2% in the general population, since it is often diagnosed at a later stage, ovarian cancer has the highest mortality rate associated with gynaecological cancers in the developed world [2]. Therefore, there is a need to introduce a screening programme for early detection of this disease.

Screening for any disease is aimed at detection of premalignant conditions or early stage disease. Cervical cancer screening is a successful programme as the progression from premalignant to malignant disease is well understood. However, until recently, precursor lesions were not recognised for ovarian cancer. Now, there is evidence to suggest that some of the high-grade serous cancers start as premalignant lesions in the fimbrial end of the fallopian tube as serous tubal intraepithelial carcinoma (STIC) [3]. Strategies to detect these premalignant lesions are likely to change the approach to ovarian cancer screening.

2. Role of pelvic ultrasound in ovarian cancer screening

Ultrasound has been used as a screening tool to detect early malignant lesions in the ovary and fallopian tube. Features such as presence of septa, papillary projections and solid areas are used to distinguish possible malignant lesions from benign ones. The use of colour flow Doppler to detect altered blood flow as a result of neo-vascularisation has also been explored in diagnosing ovarian neoplasms.

Transvaginal ultrasonography (TVS) has long been considered a useful modality for estimating morphological factors of carcinogenesis. Non-invasiveness and ease of implementation are amongst its benefits for screening, and women generally find TVS an acceptable modality for detection [4]. Factors often used for the assessment of ovarian masses include morphology and volume analysis, but more advanced methods such as Doppler and neuronal network analyses are being investigated for their efficacy.

There are many challenges to overcome in the utilisation of TVS as a screening modality. Variation in operator competence is one such challenge. The United Kingdom Collaborative Trial for Ovarian Cancer Screening (UKCTOCS) trial overcame this challenge by providing standardised training regimes to all sonographers. Although this could be a viable solution, there will always be variation in competence based on operator experience. For example, more experienced sonographers may be better at detecting borderline cysts than less experienced sonographers. The lack of standardised terms to describe ovarian sonographic features is another issue. The International Ovarian Tumour Analysis (IOTA) Group have created a set of recommendations to address this by setting definitions for morphological features such as ‘septum, solid, smooth, irregular’, and so on. [5].

Patient acceptability of screening modality is also an essential factor to consider. In a recent study, 72.7% of women (n = 651) reported no discomfort during TVS, 23.3% of women reported some pain or discomfort and 3.5% documented moderate to severe pain during the TVS procedure. Increasing pain was attributed to history of hysterectomy and a prolonged scanning time. Interestingly, those who experienced pain were noted less likely to return for a subsequent scan 1 year later [4].

Visualisation of the ovary is a further quality assurance factor to overcome in ovarian cancer screening. Decreasing follicular activity and ovarian shrinkage in postmenopausal women makes visualisation problematic. In a study involving TVS of 43,867 women (median age 60.6 years), factors affecting visualisation of ovaries in postmenopausal women included

previous hysterectomy, unilateral oophorectomy, tubal ligation, increasing age and obesity. Interestingly, factors that increased visualisation of the ovaries included a history of infertility and increasing age at menopause [6].

One of the biggest challenges in ovarian screening lies in differentiating between benign and malignant macroscopic changes. Ovarian morphology varies greatly from patient to patient, and thus benign lesions can give rise to false positive results, leading to unnecessary interventions. Unilocular cysts and those with simple septations are often benign and self-resolving. Features increasing the risk of malignancy include identification of neo-angiogenesis, multiple loculations, presence of papillary structures and solid foci [7–9]. False positives can be reduced with serial ultrasonography [10] as many ovarian lesions resolve without intervention. Benign lesions such as cysts and non-malignant solid lesions are also prevalent in the older population. In a study involving histological and ultrasound characterisation of ovarian cysts from autopsy material from 52 postmenopausal women who had died from causes other than gynaecological cancers, 56% were found to have histologically benign ovarian masses. This evidence suggests that many women will have benign lesions and so ultrasound testing could potentiate unnecessary over-investigating and surgical interventions [11]. The malignant potential of inclusion cysts are yet to be determined, however, it has been proven that TVS is a valid system for detecting malignancy after initial assessment at 1 year. In a study assessing the malignant potential of inclusion cysts, of the 1234 patients carrying ovarian inclusion cysts and 22,914 patients with normal ovaries, 432 women were diagnosed with ovarian cancer, respectively. Overall, the study showed the wider potential of application of TVS as a screening modality [12].

A well-defined criteria or reliable method of quantification needs to be introduced in order to differentiate between benign and malignant cysts. The University of Kentucky has developed a morphological index (MI) score looking at ovarian volume and macroscopic features. In their study, malignancy correlated to an increase in MI score with serial imaging, whereas benign tumours correlated to a decreased or stable MI score [13]. There is scope, therefore, for more accurate quantification of malignant potential, using risk predictors and TVS-led assessment.

New strategies to aid in accurate detection of malignant tumours include neuronal networks and pattern recognition models [14]. These developments are still in their infancy; however, a multicentre study demonstrated that borderline tumours, struma ovarii, papillary cystadenofibromas and myomas proved most difficult to reliably differentiate using ultrasound even with logistic regression models [15].

Magnetic resonance imaging (MRI) is a further imaging modality to consider for screening, due to its detailed visualisation of the pelvis. As an option for screening, however, implications of cost, duration of test, contra-indications for the wider population including placement of metal work, all pose great hurdles to acceptability.

3. Tumour markers

Tumour markers are substances, mostly proteins produced by the tumour cells, which can be detected in the blood and other bodily secretions of the affected individual. These markers

can be produced by normal tissue as well but their levels are usually significantly elevated during a malignant process. Tumour markers are used for the early detection, to guide management and to assess treatment response in cancer.

CA125 is the most commonly used tumour marker for the detection of ovarian cancer. In 1981, Bast et al. developed OC125, a murine monoclonal antibody, which was found to react with ovarian carcinoma cells [16]. An immunoassay was then developed to detect the antigen CA125 in the serum of patients affected by non-mucinous ovarian cancer. CA125 levels were found to be elevated in 82% of women affected by non-mucinous epithelial ovarian cancer, and it was useful in monitoring the treatment response [17].

Elevated CA125 levels are seen in 50% of stage I and >90% of stage II–IV serous ovarian cancers [18]. However, the levels are usually not elevated with mucinous and borderline ovarian tumours. CA125 is also not very specific to ovarian cancer as the levels are increased in other malignancies such that of the gastrointestinal tract, breast and lung; and in benign gynaecological (e.g. endometriosis, fibroids, adenomyosis, benign masses and pregnancy) [18] and non-gynaecological conditions (e.g. heart failure, pancreatitis, hepatitis) [19].

A cut-off value of 35 U/ml is accepted as the upper limit of normal [17]. This cut-off value is acceptable in postmenopausal women, whereas, in premenopausal women, the cut-off value tends to be significantly higher at 50 U/ml [20]. Other factors have also been found to affect the CA125 level. A study on CA125 levels in healthy postmenopausal women observed varying levels with race (highest in Caucasian and lowest in African women), lower levels with previous hysterectomy, regular smoking and caffeine intake, and, higher levels with a previous (non-ovarian) cancer diagnosis. Age of the individual, age at menarche and menopause and previous ovarian cysts were also predictive of baseline levels in postmenopausal women [21].

The CA125 level can be elevated for up to 5 years prior to the diagnosis of ovarian cancer. This finding has been crucial for its application in screening asymptomatic women [22]. Given its low sensitivity and specificity, interpretation of CA125 level using a cut-off value has not been very useful in screening. However, sequential measurements of CA125 as a first-line test and transvaginal ultrasound as a second-line test in multimodal screening have been found to significantly improve its sensitivity and specificity [23].

Human epididymis protein 4 or HE4 is another tumour marker which is elevated in ovarian cancer but not with benign ovarian masses. It can therefore be used to distinguish between the two [24]. In a study using an algorithm combining both HE4 and CA125, 93.8% of epithelial ovarian cancers were accurately classified as high risk [25]. Other markers that have been tested include prolactin, transthyretin, CA72-4 and CA15-3. Combining these markers with CA125 has not shown to improve its efficacy in screening for ovarian cancer [26].

4. Screening population

There are two populations of women who are at risk of developing ovarian cancer—the general population whose life time risk is around 1–2% and the high-risk population (strong family history/gene mutations) whose risk can range from 10 to 46%. Most of the ovarian cancers are

sporadic of which 90% occur in postmenopausal women, and for this reason, screening trials in the general population have been aimed at this cohort. In the high-risk population, however, even premenopausal women are at increased risk and are therefore included in screening studies.

5. Genetic predisposition to ovarian cancer

Approximately, 5–10% of ovarian cancers are attributed to genetic mutations. Mutations in the BRCA1 and BRCA 2 genes increase the risk of developing both breast and ovarian cancer. The life time risk of developing ovarian cancer (up to the age of 70 years) is 40% (95% CI, 35–46%) for carriers of BRCA1 mutation and 18% (95% CI, 13–23%) for BRCA2 mutation carriers [27]. A strong family history of breast and ovarian cancers could be an indicator of the presence of mutations in BRCA genes given their high penetrance [28]. The age of onset of ovarian cancer tends to be younger in BRCA carriers when compared to the general population. Median age at diagnosis is 63 years in the general population [29], 51.2 years for BRCA 1 and 57.5 years for BRCA2 mutation carriers [30].

Lynch syndrome or hereditary nonpolyposis colorectal cancer (HNPCC) is a syndrome secondary to mutations in the mismatch repair genes (MMR)—MLH1, MSH2, MSH6 and PMS2, which not only increases the risk of developing colorectal cancer but also ovarian and endometrial cancer in female carriers. The estimated cumulative risks of ovarian cancer by age 70 years for women with Lynch Syndrome is around 10% (range 6–14%) [31].

Traditionally, testing for gene mutations has been undertaken in individuals with a strong family history of ovarian cancer. Earlier studies looking at family history alone have shown that women with a first degree relative with ovarian cancer have a 4–5% life time risk of developing ovarian cancer. With two affected close relatives, the risk increases to around 10% and can become higher with even more relatives affected by ovarian cancer [32].

More recently there has been a different approach to screening for gene mutations. A randomised controlled trial looking at testing of the population regardless of family history in the Ashkenazi Jewish population reported a slightly higher incidence of BRCA mutations in the population screening group when compared with the family history group [33]. Such studies suggest that unselected testing of the population identifies 50% more carriers of genetic mutations than the traditional approach to screening based on family history alone.

Other than genetic factors, risk of ovarian cancer has also been found to increase with nulliparity, early menarche and late menopause, hormone replacement therapy and endometriosis. Factors suppressing ovulation such as use of the oral contraceptive pill, multiparity, longer periods of lactation have been associated with a decreased risk [34].

6. Symptom-based screening

Symptoms of ovarian cancer occur insidiously, with many patients presenting with non-gynaecological symptoms such as indigestion, abdominal bloating and early satiety,

leading to a cascade of trial therapies and investigations until a diagnosis is reached. Hence, there may be a time lapse from initial presentation to actual diagnosis of ovarian cancer. The National Institute for Health and Care Excellence (NICE) in the UK advises primary care physicians to conduct preliminary testing if a woman reports persistent or frequent symptoms of abdominal distension, early satiety and/or appetite loss, pelvic/abdominal pain or increased urinary urgency and/or frequency [35]. This has been followed-up by a nationwide campaign, encouraging patients to present if any of the aforementioned symptoms occur.

In an effort to trigger early detection in patients presenting non-specifically, Goff et al. developed a symptom index (SI) [36]. The presence of any one of six symptoms was considered a positive result, including bloating, increased abdominal size, pelvic or abdominal pain, difficulty eating and/or early satiety. In the detection of ovarian cancer, the specificity of the SI was higher in women over 50 (90%) when compared to women under 50 (86.7%) years of age [37]. The SI also had a better sensitivity for advanced stage disease (79.5%) when compared to early stage disease (56.7%). Similar data was noted in a further study, when considering the SI as an isolated screening tool [38]. Acceptability of symptom-based screening was assessed in a subsequent prospective study. Encouragingly, of the 1261 women involved, symptom-based screening yielded a mean acceptability score of 4.8/5 and 4.7/5 for TVS and CA125 utilisation, respectively [36]. A multivariate approach involving SI, CA125 and HE4 biomarkers has also been studied for suitability [38]. Use of all three variates combined yielded an overall sensitivity of 83.8% and specificity of 98.5%. The authors concluded that these combined tests could be beneficial as first-line screening tool to aid selection for second-line imaging.

Despite these results, the question still remains as to whether detection using a symptom-based approach increases survival rates. Overall, there has been conflicting data regarding the correlation between symptom onset, referral and diagnostic delays, stage at presentation and overall survival rates in ovarian cancer patients. Several studies have demonstrated no such association [39]. Moreover, a recent Australian study discovered no correlation between time of symptom onset and FIGO stage III and IV disease, and concluded that longer time to diagnosis does not affect survival in women, even with advanced stage ovarian cancer [40]. A large qualitative study noted no difference between duration of symptom onset or time to diagnosis amongst patients with early to more advanced disease. Interestingly, women with advanced disease were more likely to report disregarding their symptoms [41]. Overall, current evidence suggests that the most successful direction of symptom-based detection of ovarian cancer is with a multivariate approach, but further research is required to ascertain its applicability.

7. Trials in ovarian cancer screening

Ultrasound and serum CA125 testing are two main modalities that have been used in ovarian cancer screening. Ultrasound alone has been used in some of the studies. In some other studies, multimodal screening with a combination of serum CA125 and ultrasound have been used. Following are some of the larger trials in the general population.

7.1. The University of Kentucky Ovarian Cancer Screening (UKOCS) trial

This trial was set up in 1987 to assess the efficacy of annual transvaginal ultrasonography (TVS) to detect ovarian cancer in asymptomatic women. All asymptomatic women: (1) 50 years or older and (2) 25 years or older with a family history of ovarian cancer in a first- or second-degree relative were eligible to participate in the trial. The control group for this study consisted of those women diagnosed with epithelial ovarian cancer entered in the University of Kentucky Tumor registry or statewide Kentucky Cancer registry between 1995 and 2001, who had not participated in screening [42].

A total of 37,293 women were screened over a period of 24 years between 1987 and 2011 with TVS. Women with an abnormal ultrasound at screening underwent repeat ultrasound in 4–6 weeks. If this scan was also abnormal, then further characterisation of the ovarian mass was performed with tumour indexing, colour Doppler and serum CA125 levels. Women underwent surgery if the second screen was also abnormal. However, if this screen was normal, then the scan was repeated in 6 months. As a result of screening, 47 invasive epithelial ovarian cancers and 15 epithelial ovarian tumours of low malignant potential were detected. An improved survival rate was noted in the screened group when compared to controls. The 5-year survival rate for all women with invasive epithelial ovarian cancer detected by screening as well as interval cancers was 74.8 ± 6.6% compared with 53.7 ± 2.3% for unscreened women with ovarian cancer from the same institution who had undergone treatment using the same protocol ($p < 0.001$) [43].

7.2. The Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS) trial

A total of 82,487 asymptomatic postmenopausal women were enrolled into this study between 1985 and 1999 across 212 hospitals in Shizouka, Japan. They were randomised into an intervention group (n = 41,688) or a control group (n = 40,799) and were followed up for a mean period of 9.2 years. The women in the intervention group were screened with a pelvic ultrasound scan (USS) and a serum CA 125 test. If the USS was normal and if the CA125 was <35 U/ml, then they returned to yearly follow-up. If the scan suggested malignant disease and/or if the CA 125 was elevated, then the women were referred for surgery. However, if the scan was abnormal but suggestive of benign disease, it was repeated every 3–6 months. Also, if the CA125 was above a certain threshold with a normal scan, the women had a repeat scan in 6 months. There was no statistical difference between the number of ovarian cancers detected in the screening arm when compared to the control arm (27 vs. 32). However, there were a higher proportion of stage 1 ovarian cancers in the screened group when compared to the control group (63% vs. 38%) [44].

7.3. The Prostate Lung Colorectal and Ovarian (PLCO) Cancer Screening Randomised Controlled Trial

A total of 78,216 postmenopausal women aged 55–74 years were enrolled into this trial across 10 centres in the US. They were randomised to either annual screening (n = 39,105) or usual medical care (n = 39,111). Main outcome measure was mortality from ovarian/tubal/primary

peritoneal cancers. The women in the screening arm had annual transvaginal ultrasound scan and CA125 (using a 35 kU/L cut-off) for 3 years and CA125 alone for a further 2 years. Women with an abnormal screening result were managed by their physicians. The follow-up period was 13 years in total. A total of 212 women were diagnosed with ovarian cancer in the screening arm when compared to 176 in the no screening (usual care) arm. In the screening arm, there were 118 deaths when compared to 100 deaths in the usual care arm as a result of ovarian cancer (mortality RR, 1.18; 95% CI, 0.82–1.71). This trial concluded that screening with CA125 and transvaginal ultrasound did not reduce mortality from ovarian cancer [45].

7.4. Ovarian Cancer Screening Trials in the UK

In 1993, Jacobs et al. screened 22,000 asymptomatic postmenopausal women with serum CA125 using a cut-off value of 30 kU/L. A transvaginal ultrasound was performed if the CA125 level was ≥30 kU/L. Women were referred for a gynaecological opinion if the ovarian volume was ≥ 8.8 ml. Out of the 41 women who had a positive screening result, 11 had ovarian cancer. Of the 21,959 women with a negative screening result, eight subsequently developed ovarian cancer. This protocol achieved a specificity of 99.9% and a positive predictive value of 26.8% and an apparent sensitivity of 78.6% and 57.9% at the first year and second year of follow-up, respectively [23].

Jacobs et al. then conducted a randomised controlled trial to assess the feasibility of a multimodal approach using serum CA125 level and transvaginal ultrasound to screen for ovarian cancer [46]. A total of 21,935 postmenopausal women aged ≥45 years were randomised to either a screening group (n = 10,958) or a control group (n = 10,977). In the screening group, women were offered three annual screens using serum CA125 level as the first screening test. If the CA125 level was ≥30 kU/L, a transvaginal ultrasound scan was performed as a second test. If the ovarian volume was ≥8.8 ml on ultrasound, the women were referred for a gynaecological opinion. Twenty-nine women with a positive screening test had surgical intervention out of which six were found to have ovarian cancer and the remaining 23 had a false positive result. Therefore, the positive predictive value of screening was 20.7%. During the 8 year follow-up period, 10 more women in the screening group developed ovarian cancer bringing the total to 16 in the screened group. In the control group, 20 women were diagnosed with ovarian cancer. The median survival was better in the screening group when compared to the control group—72.9 months versus 41.8 months (p = 0.0112). There were nine deaths from ovarian cancer in the screened group when compared to 18 in the control group, which was not statistically significant (relative risk 2.0, 95% CI, 0.78–5.13; p = 0.083).

7.4.1. Risk of Ovarian Cancer Algorithm (ROCA)

The two UK studies discussed earlier used a cut-off value of CA125 of 30 kU/L for screening. Analysis of the serial serum CA125 data in women who subsequently developed ovarian cancer revealed a significant rise in the CA125 level after a 'change point'. In the unaffected women, however, the CA125 maintained a flat profile, fluctuating around the individual's baseline levels. The ROCA takes into account an individual woman's age, serial CA125 profile and estimates her risk of developing ovarian cancer based on known cases of ovarian cancer

compared with the flat-profile model of known controls [47]. The ROCA calculates and updates the risk based on the most recent CA125 level. The risk is categorised as elevated, intermediate and normal. Women with an elevated risk are referred for an ultrasound, intermediate risk for repeat CA125 within a few months and normal risk for an annual CA125 test [48]. The ROCA has been used in subsequent screening trials.

7.4.2. The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)

Between 2001 and 2005, 202,638 women were randomly assigned to a control arm (n = 101,359) and an intervention arm (n = 101,279). The intervention arm was further subdivided into a multimodal screening (MMS) arm with annual CA125 screening (interpreted using the ROC algorithm) followed by ultrasound as a second-line test (n = 50,640) or annual screening with ultrasound (USS) alone (n = 50,639). Randomisation into the control arm and the two-intervention arm was carried out in a 2:1:1 ratio. The main aim of the trial was to determine the impact of screening on mortality from ovarian cancer [49].

Women in the MMS arm had their serum CA125 tested at recruitment and their risk was interpreted using the ROC algorithm. They went on to have (1) ultrasound scan if their risk was elevated or (2) repeat CA125 in 12 weeks if their risk was intermediate and (3) annual CA125 screening if the risk was low.

Women in the USS arm had transvaginal ultrasound at recruitment. They had repeat scans if the initial scan was abnormal. Women with persistent abnormalities were referred for clinical evaluation and had surgery if indicated. This trial was conducted across 13 centres in the UK.

Analysis of the prevalence screen results revealed that the MMS strategy was superior to ultrasound alone for detection of ovarian cancer (sensitivity of 89.4% and specificity of 99.8% for multimodal screening group compared to sensitivity of 84.9% and specificity of 98.2% for ultrasound only group) [50].

During the follow-up period, a total of 1282 women were diagnosed with ovarian cancer (median follow-up—11.1 years). A total of 652 women in the screening arm were diagnosed with ovarian cancer, which included 338 women in the MMS group and 314 women in the USS group when compared to 630 in the no screening group. A total of 148 women in the MMS group, 154 women in the USS group (n = 302) and 347 women in the no screening died from ovarian cancer. There was no significant reduction in mortality from ovarian cancer demonstrated in the primary analysis. However, after exclusion of the prevalent cases, further analysis of the mortality data revealed a significant reduction in mortality in the MMS group when compared to the no screening group. An overall average reduction in mortality of 20% was observed in the MMS group, with a reduction of 8% in years 0–7 and 28% in years 7–14. However, the authors concluded that further follow-up was required to ascertain the benefits of screening [51].

7.5. Screening in the high-risk population

Screening studies in the high-risk population also adopted the following two strategies: (1) annual screening with transvaginal ultrasound and CA125 and (2) multimodal screening with 3–4

monthly measurement of serum CA125 as the first and transvaginal ultrasound as the second-line test based on the CA125 levels.

In a Dutch multicentre observational study, 880 BRCA1 or BRCA2 carriers who had annual screening with CA125 and transvaginal scan were followed-up between 1993 and 2005. There were 10 incident cancers diagnosed. Five out of these ten cancers were in women who had previously had a normal screening within the last 3–10 months preceding the diagnosis. Eight out of the ten incident cancers were stage III–IV. In this study, despite annual screening, a large majority of the cancers were interval cancers that were diagnosed at an advanced stage. This study concluded that annual screening with TVS and CA125 neither helped in early diagnosis nor reduced mortality in high-risk women from ovarian cancer [52].

In the UK, Stirling et al. conducted a study involving 1110 high-risk women who were screened in three cancer genetic centres with annual CA125 and transvaginal ultrasound, between 1991 and 2004 [53]. Thirteen ovarian cancers were detected (including one borderline tumour). Three of these were detected during the first screen and seven during annual follow-up. The remaining three were interval cancers out of which one was an incidental finding following prophylactic surgery 2 months after a normal screen and the remaining two presented with symptoms, 4 and 12 months after a normal screening, respectively. This study also concluded that annual screening with CA125 and TVS was not effective in early diagnosis of ovarian cancer to have an impact on prognosis. In addition, the false positive rate was high in pre-menopausal women leading to unnecessary surgical intervention.

7.5.1. United Kingdom Familial Ovarian Cancer Screening Study (UK FOCSS)

Between 2002 and 2008, 3563 high-risk women (≥10% estimated lifetime risk) aged 35 years or above were recruited into this multicentred study across 37 centres in the UK. The trial had two phases—1 and 2.

In Phase 1, women underwent screening with annual transvaginal ultrasound scan and serum CA125 measurement. For CA125, a cut-off of 35 IU/ml for premenopausal women and 30 IU/ml for postmenopausal women was used.

A total of 27 primary ovarian/fallopian tube/peritoneal cancers were diagnosed during the course of screening and a further 10 cancers developed after 365 days following the last screen (median 539 days, range, 382–1369) in Phase 1 of the study. Nine of the primary ovarian/fallopian tube cancers were diagnosed during the prevalent screen and 13 were incident, screen-detected cancers. The positive predictive value was 25.5% (95% CI, 14.3–40.0) and negative predictive value was 99.9% (95% CI, 99.8–100) for the incident screen. Of the 13 incident cancers, only four were stage I or II. There was a delay in surgical intervention in the prevalent and screen-detected cancers (median—79 days). This study concluded that annual screening was not adequate in high-risk women for early detection of ovarian/fallopian tube cancer.

Following from the results of Phase I, women underwent more frequent screening with CA125 testing in Phase 2 (2007–2012) of the study. Serum CA125 levels were measured every 4 months, and the risk of developing ovarian cancer was estimated using the Risk of Ovarian Cancer algorithm (ROCA). Ultrasound was used as a second-line screen depending on the

ROCA estimated risk [54]. If the risk was normal, TVS was performed annually and if it was abnormal, then TVS was performed within 2 months.

There were 13 screen-detected and 6 occult (diagnosed following risk reducing salpingo-oophorectomy) primary ovarian/fallopian tube cancers in women who had been screened in the preceding year. Five out of the 13 screen-detected cancers and five out of the six occult cancers were stage I–II. Of these 19 women, 18 underwent optimal cyto-reductive surgery, with zero residual disease. This protocol had a high sensitivity of 94.7%, high negative predictive value of 100% and a positive predictive value of 10.8% for the detection of ovarian/fallopian tube cancers within 1 year of screening. The conclusion from Phase II was that ROCA-based screening could be an option for high-risk women who declined risk-reducing surgery. However, there was no conclusive evidence to suggest an impact on survival.

7.5.2. Cancer Genetics Network and Gynecologic Oncology Group study

The Cancer Genetics Network (CGN) ROCA study in Australia and the Gynecologic Oncology Group (GOG) study-GOG-0199 in the US used the same protocol to screen women at increased risk of developing ovarian/fallopian tube cancer [55]. All women received an annual transvaginal scan and CA125 testing every 3 months. The ROCA was used to estimate the risk and an interval TVS was performed for an abnormal ROCA result.

A total of 3692 women were screened in the two studies combined. There were four prevalent cancers and six incident cancers detected as a result of screening. Nine additional cancers were detected following risk reducing surgery. Three out of the six incident cases were detected at CA125 levels <35 U/ml using ROCA. The specificity for referral for ultrasound was 92% and the positive predictive value was 4.6%. This study concluded that three monthly CA125 testing with result interpretation using ROCA had a high specificity in the detection of early stage ovarian cancer with half of the incident cancers being diagnosed at CA125 levels <35 U/ml. There was a high rate of complete cytoreduction following surgery for the incident cancers diagnosed during the study period. The authors concluded that this screening regime with three monthly CA125 measurements performed better than 6–12 monthly screening using an absolute CA125 cut-off of 35 U/ml; however, larger studies were required given the small number of incident cases.

Thus, screening studies in high-risk women have demonstrated that annual screening with CA125 using a cut-off value and TVS is likely to miss the cancers that develop during the interval period. More frequent testing with CA125 with result interpretation using the ROCA helps to estimate an individual's risk based on their baseline CA125 level, aiding detection of ovarian cancer at an early stage or advanced cancer with low volume disease that can be optimally cytoreduced surgically. However, there is still paucity of evidence with regards to a mortality benefit from screening. Therefore, screening cannot be recommended as an alternative to risk reducing surgery, which remains the definitive preventative strategy in high-risk women.

7.6. Future of ovarian cancer screening

Ovarian cancer is a heterogeneous group of cancers, which includes both epithelial and non-epithelial neoplasms. Within the epithelial cancers, there are both slow growing Type 1 cancers

that include mucinous, low-grade endometrioid, low-grade serous, clear cell and transitional cell carcinomas; and, the more aggressive, fast multiplying Type 2 cancers, which include high-grade serous carcinomas (HGSC), high-grade endometrioid, undifferentiated and carcinosarcomas [56]. Given their indolent nature, Type 1 tumours tend to be confined to the ovary at diagnosis, are easily detectable on ultrasound at an early stage and carry a better prognosis. Type 2 tumours, however, metastasise early in the natural history of the disease, are diagnosed at a late stage and carry a poor prognosis as a result. Traditional approach to screening using TVS and serum CA125 has not been effective in detecting these Type 2 cancers at an early stage. Detailed pathological examination of the fallopian tube from high-risk women who have undergone prophylactic salpingo-oophorectomy has revealed pre-cancer precursor lesions (serous tubal intraepithelial carcinoma or STIC) thereby, suggesting that a good majority of HGSC originate in the tube rather than in the ovary [3]. Majority of the incidental HGSCs in the low-risk population have also been shown to arise from STICs [57]. STIC lesions exhibit mutation in the TP53 gene which is likely to signal the early stages of carcinogenesis. Exfoliative cytology from the fimbrial end of the tube to detect these precursor lesions [58] and novel assays to detect TP53 mutations in circulating DNA are being explored [59, 60]. Angiogenesis is present early in the development of cancer. The use of microbubbles that are small enough to pass through capillaries is being explored to detect micro-vascularity in ovarian tumours on ultrasound [61].

A better understanding of tumourigenesis is opening up new avenues in ovarian cancer screening. Studies have shown that the target lesion is not always the ovary in 'ovarian cancer' and that STIC is the pre-malignant lesion in a good majority of HGSCs which include primary ovarian/fallopian tube/peritoneal cancers. The focus of future screening strategies will be used to detect low volume early disease either from the primary site of origin using exfoliative cytology or novel imaging modalities, or, in circulation using sensitive assays to detect low levels of tumour DNA and tumour markers.

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