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Ovarian cancer screening

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Introduction

Ovarian cancer is the most common gynaecological malignancy in the developed world. It also carries the worst prognosis with an overall 5-year survival of 30%. This is likely to be due to the disease frequently presenting late, the ovary position within the peritoneal cavity resulting in minimal local irritation, or interference with vital structures until ovarian enlargement is considerable, or metastasis occurs. Seventy per cent of women are diagnosed with stage III or IV disease, with 5-year survivals of 15–20% and less than 5%, respectively[1]. Despite an increase in understanding of the molecular events underlying malignancy, and advances in both surgery and chemotherapy, the overall prognosis of ovarian cancer has changed little over the last 30 years. However, women who are diagnosed at an early stage do have a significantly improved prognosis, with survival of above 80% in stage I disease, and above 90% in those diagnosed at stage Ia[2]. The best way of improving outcome may be, therefore, to detect the condition at an early stage, when the prognosis remains relatively good, via a screening programme. This is an exciting prospect and screening trials have shown some encouraging results. However, as yet screening has not been shown conclusively to reduce mortality from ovarian cancer. In addition, our lack of knowledge about disease progression and of primary peritoneal cancer, as well as the possible surgical and psychological morbidity that may result from screening, should be considered. There are also, of course, cost implications.

What to screen for

A screening programme should ideally be based on the detection of a pre-malignant condition in order to lower disease incidence and maximize mortality reduction, as is the case with the cervical screening programme. Although it is suggested that inclusion cysts and benign and borderline ovarian tumours may be pre-malignant, this remains speculative. Crayford *et al*. recently analysed follow-up data from an ovarian cancer screening trial to assess whether removal of persistent ovarian cysts was associated with a reduction in mortality from ovarian cancer[3]. No such reduction was found relative to other cancers, although it is difficult to interpret the findings in the absence of a control group, and incidence may have been a more appropriate end-point than mortality. In the absence of confirmed pre-malignant change, screening for ovarian cancer is directed at present to the detection of pre-clinical disease.

What is required from a screening test

A suitable screening test requires both high sensitivity and specificity. Women who have a positive screen require further investigation, often in the form of exploratory surgery. It is therefore imperative to maximize specificity in order to obtain a high positive predictive value, and decrease the number of false-positive screens. In the general population, a specificity of 99.6% is required to achieve a positive predictive value of 10%[4], i.e. to limit the number of unnecessary surgical

procedures to 10 for each case of cancer detected. A specificity lower than this is likely to be unacceptable in this population, although may be acceptable to those with a strong family history of ovarian cancer.

Screening tests

The ovaries are not easily accessible. Although vaginal examination is important in assessing symptomatic women, it lacks both the sensitivity and specificity required for a first-line screening test in asymptomatic women. In one study only 30% of women with ovarian masses on transvaginal ultrasound had an abnormal pelvic examination[5]. Visualization or direct sampling to detect malignant disease, or perhaps in the future to detect a pre-malignant condition, is being investigated in preliminary studies using office laparoscopy and cytological examination of brush samples from the ovarian surface in screening high-risk populations. The possibility of using optical methods, such as optical spectroscopy is also being investigated. However, the current accepted screening methods are serum tumour markers and ultrasound ± Doppler imaging.

Tumour markers

The most extensively studied tumour marker is the large glycoprotein CA125, first discovered in 1981. It is elevated to above 30 U/ml in over 80% of patients with ovarian cancer. Levels correlate well with the stage of disease and are raised in 50% of stage I, and 90% of stage II ovarian tumours[6]. However, levels may be raised in a variety of other physiological and pathological conditions, which may be gynaecological or non-gynaecological, benign or malignant. An algorithm has been developed in post-menopausal women from the general population that determines the risk of ovarian cancer based on CA125 profile with time[7]. This is based on the observation that women with ovarian cancer tend to have increasing levels of CA125, whereas women without ovarian cancer tend to have static or decreasing levels, even if they remain above a cut off of 30 U/ml. The greater the rate of rise in CA125 levels, the greater the risk of ovarian cancer. Other tumour markers that have been investigated include OVX1 and, more recently plasma lysophosphatidic acid (LPA).

Ultrasound

Ultrasound has been used as a screening test for ovarian cancer for over a decade. Although specificity was poor with transabdominal scanning, it was much improved with the introduction of transvaginal scanning, colour flow Doppler imaging and morphological scoring systems. Malignant masses have increased blood flow in diastole, helping to distinguish them from benign ones. The number of women undergoing surgical investigation for each case of ovarian cancer detected has been reduced from 50[8] to between 10 and 20[9], when using an ultrasound-based screening strategy.

Screening strategies

There are three main strategies. An ultrasound approach based on primary screening with transvaginal ultrasound, with repeat testing after a fixed time interval if an abnormality is detected. Multimodal screening which incorporates primary screening using a tumour marker, usually CA125, with repeat assessment of the marker and transvaginal ultrasound as a second-line test. CA125 results are interpreted using the Risk of Cancer algorithm previously alluded to. The third, combined, approach uses both serum CA125 and transvaginal ultrasound as first-line tests to maximize the detection rate and its use is limited to screening the high-risk population. The optimal screening strategy is yet to be established.

Target populations

The bulk of ovarian cancers occur in the general population, and age greater than 50 years and post-menopausal status have been used to define those eligible for screening. One study looked at national statistics to determine the number of years of life lost through deaths from a particular cancer at each age[10]. It concluded that screening would be most effective, i.e. save the most number of lives per person screened, if done 5 years before loss of life peaked. The peak occurred in ovarian cancer during the age range 55–59 years, and the authors' argument provides further justification for using 50 years as the cut-off to commence population screening. Approximately 5–10% of ovarian cancers are inherited, and the optimal strategy for screening the population at risk of familial ovarian cancer needs to be developed. Risk may be assessed on the basis of family history, genetic predisposition, or both. Mutations in BRCA1 and BRCA2 genes account for about 75% of families with a highly penetrant dominantly inherited breast or ovarian cancer family history. Mutation analysis therefore has an important role in the management of high-risk populations.

Screening trials

Although over 25 prospective screening studies for ovarian cancer have been published, none have been able to demonstrate conclusively a reduction in mortality from ovarian cancer in the screened group, for either the general or the high-risk population. Jacobs *et al.* recently reported the findings of the first randomized controlled trial of ovarian cancer screening[11]. Post-menopausal women aged 45 years or older were randomized to a control group ($n=10\,977$) or to a screened

group ($n=10\,958$). The screened group underwent annual multimodal screening for 3 years. All women were followed up to see whether they developed invasive epithelial ovarian cancer. Compliance was excellent and the positive predictive value of a positive screen was high at 21%. Although the study was too small to assess impact on mortality, median survival (72.9 months) was significantly higher in women with ovarian cancer in the screened group than in those in the control group (41.8 months). Other recently reported transvaginal ultrasound trials from Kentucky[9] and from Japan[12] have also recently reported encouraging results. The Kentucky trial showed a 5-year survival of $83.6 \pm 10.8\%$ in the screened group, and the Japanese trial found there was an increase in the percentage of stage I tumours diagnosed and treated in the department from 29.7% to 58.8% after the trial was initiated. These results need to be interpreted with caution due to the lack of control groups, but all emphasize the need for a randomized control trial. This needs to, in addition to establishing the impact of screening on ovarian cancer mortality, comprehensively tackle the issues of target population, compliance, health economics and physical and psychological morbidity of screening. Such a trial has now been initiated, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), funded by the Medical Research Council, the Cancer Research Campaign, the Imperial Cancer Research Fund and NHS Research and Development and co-ordinated by the Gynaecology Cancer Research Unit at St Bartholomew's Hospital, London. The three-armed randomized control trial aims to recruit 200 000 post-menopausal women, aged 50–74 years, randomized in a 1:1:2 ratio to ultrasound screening, multimodal screening using the Risk of Ovarian Cancer algorithm and a control group who will not be screened. Participants will be invited from regional age/sex registers, overcoming the inherent flaws of self-referral. Screening will occur in 12 collaborating gynaecological oncology centres in the UK and participants randomized to screening will undergo six screens at annual intervals. All participants will be followed up by postal questionnaire and via the cancer registry. The primary end-point of the study is ovarian cancer mortality 7 years after randomization. Additional end-points include quality of life, health economics, morbidity and compliance with screening. The performance of the two screening strategies will also be compared. The results of this trial will form the basis for making an informed decision about the implementation of general population screening for ovarian cancer. The adoption of annual screening as standard practice in the high-risk population makes it impossible to institute a randomized control trial with a control group who are not screened in this group. However, in order to develop an optimal screening strategy in the high-risk population, a multicentre National Familial Ovarian Cancer Screening Study (UK-FOCSS) involving 5000 women is being set up in the UK. A similar trial is underway in the USA.

Conclusion

Ovarian cancer most commonly presents as advanced stage disease with a poor prognosis. In the absence of a known pre-malignant condition, the ability to detect early-stage disease is clearly desirable. However, despite numerous screening studies, some showing some very encouraging results, there is not yet any conclusive evidence that screening reduces ovarian cancer mortality. Although there is insufficient evidence to implement general population screening for ovarian cancer at present, this evidence will, we hope, be available in the future as results from large trials such as UKCTOCS become available.

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