The value of ovarian cancer screening

Ovarian cancer is the commonest cause of death from a gynaecological malignancy. Diagnosis of the disease at an early stage is associated with significantly improved survival rate. This suggests that screening may impact on disease mortality. This review addresses the current methods of screening, the ongoing trials and future of screening for ovarian cancer.

Ovarian cancer is the fourth commonest cause of cancer deaths in women. Despite advances in management, the incidence in the UK is unchanged with approximately 6900 cases detected and 4600 deaths annually (Cancer Research UK, 2005). The worldwide incidence of ovarian cancer as per the GLOBOCAN database (http://www-dep.iarc.fr/) was 204499 cases in 2002. The overall 5-year survival rate is about 30% in advanced disease. Diagnosis at an early stage increases survival to over 90%, demonstrating the need for early detection methods.

As no premalignant lesion has been identified so far, the main focus of screening is on detecting the disease early. Screening has been shown to result in a survival benefit in a randomized screening trial in the general population (Jacobs et al, 1999), but it is still not known if it will impact on disease mortality. There are two ongoing ovarian cancer screening trials in the general population and two trials in the high-risk population in the USA and UK. Screening strategies based on serum CA125 testing and ultrasound scanning are being evaluated. The finding that protein patterns may be able to discriminate normal women from ovarian cancer patients by analyses of the serum proteomic may lead to novel biomarkers and further refinements of the screening strategies.

Precursor lesions in ovarian cancer

It is not known which lesions will develop into ovarian cancer. A small number of cancers arise from the benign cysts or endometriotic tissue (Scully, 1995). However, a study of 5479 asymptomatic self-referred women concluded that removal of benign ovarian cysts was associated with no significant decrease in the number of ovarian cancer deaths (Crayford et al, 2000). In the ongoing prostate, lung, colon and ovarian (PLCO) cancer screening trial, an analysis of women with complex ovarian cysts revealed that they did not share the same risk factor profile as ovarian cancer patients, suggesting that majority of the complex cysts and other clinically suspicious abnormalities detected on ultrasonography were not immediate precursors of ovarian cancer (Hartge et al, 2000). There is some evidence that certain borderline tumours can progress to invasive cancers but the evolution and frequency of this occurrence is unclear (Scully, 2000). Most cancers seem to arise de novo from the surface epithelium or inclusion cysts of the peripheral cortex of the ovary. This limits the goal of screening to detection of asymptomatic, preclinical low-volume disease.

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Target populations

Two separate populations are at increased risk for ovarian cancer. The majority of ovarian cancers are sporadic and occur in the general population. Over 90% of sporadic cancers occur in women aged over 50 years. Screening studies in the general population usually target this group. Around 5–10% of ovarian cancers are familial (hereditary syndromes include ovarian cancer alone, breast and ovarian cancer or hereditary non-polyposis colorectal (HNPCC) and ovarian cancer). The high-risk population comprises women who are first-degree female relatives of affected persons in such families. Their lifetime risk of developing ovarian cancer is >10%. Germline mutations in the genes, BRCA1 and BRCA2, account for a proportion of this risk.

Screening strategies

Multimodal strategy based on serum CA125

The multimodal strategy uses CA125 as the first-line test and pelvic ultrasound as the second-line test in women with abnormal CA125 levels.

CA125 is the most widely assessed tumour marker for ovarian cancer. This antigen is expressed by coelomic epithelium and amnion during fetal development. In adults, it is expressed in tissue of coelomic and mullerian epithelial origin. It is not found in fetal or adult normal ovarian epithelium. CA125 is detected using a murine monoclonal antibody OC125 raised in response to antigenic determinants from an ovarian cancer cell line (Bast et al, 1981). CA125 can also be raised in conditions other than epithelial ovarian cancer. These include pancreatic cancers and cancers of the breast and lung and also benign conditions such as endometriosis, ectopic pregnancies, fibroids, arthritis and renal disease (Meden and Fattahi-Meibodi, 1998; Sjovall et al, 2002). Fifty per cent of patients with stage 1 disease and over 90% of women with more advanced stages are found to have elevated levels of CA125 (Fritsche and Bast, 1998). The commonly used cut-off for serum CA125 in clinical practice is 35 U/ml. Lower cut-offs of 25 U/ml or less may be more appropriate in postmenopausal women and those who have had a hysterectomy in the past (Alagoz et al, 1994; Bon et al, 1996).

Initially in this strategy, a fixed cut off was used to interpret CA125 levels. When levels were elevated and ultrasound scanning was performed as a second-line test, a sensitivity of 76%, specificity of 99.9% and positive predictive value (PPV) of 26.8%, resulting in four operations performed for each ovarian cancer detected (Jacobs et al, 1993, 1996). To increase sensitivity, the multimodal screening strategy has been refined using a statistical algorithm to interpret CA125 levels (Skates et al, 2003). The algorithm integrates age, age specific incidence of ovarian cancer, rate of change and absolute levels of CA125 to calculate individual risk of ovarian cancer (ROC) and is based on the finding that CA125 levels in women without ovarian cancer remain static or decrease with time while levels associated with malignancy tend to rise (Skates et al, 2003).

The ROC calculation on modelling achieves a sensitivity of 86% for preclinical detection of ovarian cancer (Skates et al, 2003). Prospective use in a pilot trial resulted in a specificity of 99.8% and a PPV of 19%. Of the 6532 women who underwent prevalence screening, 16 women underwent surgery and three primary invasive epithelial ovarian cancers were detected (Menon et al, 2005). The ROC algorithm is now being evaluated in the multimodal arm of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial and in the high-risk trials.

Ultrasound-based strategies

The ultrasound strategy uses transvaginal ultrasound as the first-line test. The scan is repeated in 6–8 weeks in women detected to have abnormalities

Transvaginal ultrasonography is the method of choice to view the pelvis as it gives detailed images of pelvic structures. Many morphological features such as cyst volume, regularity of cyst wall, presence of loculations, papillations, septae and solid areas in the cyst are assessed to reduce the number of false positives. Papillations are considered to have the highest, and septations and simple cysts the lowest correlation with ovarian malignancy. There is, however, a need for standard definitions and classification in general gynaecological ultrasonography.

The International Ovarian Tumor Analysis group have attempted to provide standardized terms and procedures to describe anatomical features by B mode imaging and vascular features by colour flow Doppler imaging. All lesions have been divided qualitatively into a total of six categories that include unilocular, unilocular-solid, multilocular, multilocular-solid, solid and non-classifiable tumours (Timmerman et al, 2000). The vascular features are assessed by examination of the entire tumour by colour flow Doppler imaging. Scores of 1–4 are given dependent on the degree of blood flow visualized (Timmerman et al, 2000).

Another issue with ultrasound is that there is significant interobserver variability. In a study by Timmerman et al (1999), recorded images from 300 patients were independently reviewed by five ultrasonographers with different qualifications and degree of experience. Experienced ultrasonographers using some clinical information and their subjective assessment of ultrasonographic images were able to differentiate malignant from benign masses in most cases (accuracy of up to 92%). The accuracy and the level of interobserver agreement both correlated with the degree of experience (Timmerman et al, 1999).

The confidence with which an accurate diagnosis is made may be increased by adding Dopplers to the subjective evaluation of the gray-scale imaging (Valentin, 1999). Colour flow Dopplers may increase sensitivity and specificity to the range of 85–90% and over 90%, respectively (Daskalakis et al, 2004; Szpurek et al, 2004; Guerriero et al, 2005). However, there is significant interobserver variability. Use of three-dimensional (3D) Dopplers in conjunction with 3D ultrasonography may further increase sensitivity and specificity (Kurjak et al, 2000).

Screening based on ultrasound has low specificity. In one of the largest trials based on annual ultrasound scans alone, from the University of Kentucky Ovarian Cancer Screening Program, 11 primary epithelial ovarian cancers were detected in 180 women who underwent surgery for persisting transvaginal sonographic abnormalities (van Nagell et al, 2000). The sensitivity was 81%, specificity 98.9%, and PPV of 9.4%. Ten operations were done for each case of ovarian cancer detected (van Nagell et al, 2000). This screening did not appear to be effective in detecting ovarian cancer when the ovarian volume was normal. In the prevalence screen of the PLCO trial, for every one invasive cancer identified on the ultrasound arm, 41.2 operations were performed (Buys et al, 2005).

Although second-line investigations such as 3D ultrasonography and power Dopplers, computed tomography and magnetic resonance imaging have been used to reduce the number of surgeries for false positives by improving discrimination between benign and malignant lesions, they need further evaluation before incorporation into clinical practice.

Combined strategies

This approach combines the use of both CA125 and ultrasound scan as primary tests with both tests repeated if either is abnormal.

Screening trials in the general population

Currently, there are two ongoing randomized controlled trials in the general population to assess the impact of screening on ovarian cancer mortality. The UKCTOCS is

a randomized control trial with postmenopausal women aged 50–74 years, randomized to either a control group (100 000); multimodal screening using CA125 with transvaginal ultrasound as the second-line test (50 000) or ultrasound screening (50 000). Annual screening is for 6 years. The main outcome of the study is death from ovarian cancer. Cost effectiveness, physical and psychological morbidity, compliance and acceptability of screening are also being evaluated. The trial has now completed recruitment of 202 000 postmenopausal women from 13 centres in the UK. All participants will be followed up via the Office of National Statistics and postal questionnaire (www.ukctocs.org.uk) (Markman et al, 2004).

In the USA, the PLCO Cancer Screening Trial has recruited 78 237 women (28 816 women on the screening arm received at least one test) and will compare a control group with a screened group undergoing primary screening with both CA125 testing and transvaginal ultrasonography for 3 years followed by CA125 testing alone for a further 2 years (Prorok et al, 2000). These women are being followed up annually for 13 years following randomization to assess their health and cause of death (Andriole et al, 2004). Results of these trials will be available in the year 2013 and should inform practice on whether mass screening for ovarian cancer should be implemented.

Screening trials in the high risk population

Prophylactic bilateral salpingo-oopherectomy is the only strategy with proven effectiveness to prevent ovarian cancer. High-risk women should be adequately counselled about the uncertainties of screening and are ideally screened in the context of research trials.

Screening is usually offered from the age of 35 years. As many of the high-risk women are premenopausal, there may be significantly higher numbers of false-positive results on both ultrasound and CA125 testing as a result of physiological and benign conditions. There are two ongoing multicentred, prospective, non-randomized ovarian cancer screening studies in the high-risk population.

The United Kingdom Familial Cancer Screening Study aims to recruit 3000 high-risk women by the end of 2006. Currently over 2200 participants are being screened annually with CA125 and ultrasound. The women have been donating serum samples every 4 months to the serum bank. From the year 2006, these samples will be assayed prospectively for CA125 and results interpreted using the ROC algorithm. Women with elevated ROC values will have a transvaginal scan (Markman et al, 2004). The Cancer Genetics Network study in the USA has about the same number of participants and the screening strategy involves assessment of CA125 levels every 3 months using the ROC algorithm with second-line transvaginal ultrasound of women with elevated ROC values (Markman, 2004). Results of both these trials are expected in the year 2012 and will shed light on this very controversial subject.

Proteomics

New tests for early detection of ovarian cancer involving profiling of serum proteins using time of flight mass spectrometry followed by analysis with a combination of bioinformatics tools and algorithms to detect protein patterns associated with malignancy are being explored (Markman, 2004). Although the studies are in their infancy, the implication of proteomic spectrum analysis for the identification of novel tumour markers is huge. It is likely that in the future, the early detection of ovarian (and other) cancer may involve high throughput proteomic profiling either alone or in combination with markers already in use today.

Conclusions

No definite precursor lesions have been described for ovarian cancer and it is presumed that most arise de novo from the surface epithelium or inclusion cysts of the peripheral cortex of the ovary. This limits the goal of screening at present to detecting asymptomatic, preclinical low-volume disease and much is dependent of how long it takes cancer to progress from early to advanced disease. Screening has been shown to result in a survival benefit in a randomized screening trial in the general population but it is still not known if it will impact on disease mortality. The current screening strategies are based on CA125 and ultrasonography. The role of colour flow Doppler imaging needs further evaluation. Overall the data from the large prospective screening studies in the general population suggests that the multimodal strategy has superior specificity and PPV with similar sensitivity as ultrasound.

The two large prospective ovarian cancer screening trials (PLCO in the USA and UKTOCS in the UK) should provide definitive answers whether screening can impact on ovarian cancer mortality in the general population. They will also provide evidence of the benefits and harms of ovarian cancer screening. These trials will report in the year 2013. In addition, screening within the context of research trials is available for premenopausal women at risk of familial cancer. However, these women should be counselled adequately about the uncertainties of this approach so that they can make an informed choice between screening and prophylactic removal of the ovaries and fallopian tubes. If the trials show benefit factors such as the infrastructure, workforce planning, quality assurance of the screening tests and logistics of referral, investigations and treatment need to be addressed before implementation.

In all the current trials, large serum banks are being built up. Given the advances in human proteomics and genomics, it is most likely that in the next decade novel serum markers will be discovered. The banks will allow validation of these markers without the need to conduct further large prospective studies.

At present, in the absence of evidence of efficacy of ovarian cancer screening and significant potential for harm from needless surgery and anxiety, screening should not be carried outside the context of clinical trials. Presently, routine screening for ovarian cancer is not recommended by any medical organization (American College of Obstetricians and Gynaecologists, 2000). Instead, the American College of Obstetricians and Gynaecologists suggests that generalist obstetrician-gynecologists should remain vigilant for the early signs and symptoms of ovarian cancer, such as abdominal or pelvic pain and unexplained weight loss, and that these symptoms be evaluated by pelvic examination, CA125 or ultrasound (American College of Obstetricians and Gynaecologists, 2000). These recommendations will need to be revised once the results of the ongoing trials are available. BJHM

Conflict of interest: none.

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KEY POINTS

- Ovarian cancer is the commonest cause of deaths from gynaecological cancers and the fourth commonest cause of cancer deaths in women.
- Screening has been shown to result in a survival benefit in a randomized screening trial in the general population but it is still not known if it will impact on disease mortality.
- No definite precursor lesions have been described in ovarian cancer
- The main screening strategies are serum CA125 followed by transvaginal ultrasound if levels are abnormal (multimodal screening) or transvaginal ultrasound alone.
- The main refinement of the multimodal screening strategy is the introduction of a novel algorithm called risk of ovarian cancer to interpret CA125 results.
- The main issue with an ultrasound only strategy is the lower specificity, which leads to an increased number of unnecessary investigations and surgery.
- Recruitment into the large multicentre screening trials in the general population (United Kingdom Collaborative Trial of Ovarian Cancer Screening, and prostate, lung, colon and ovarian cancer screening trial) is complete and results will be available by the year 2013.
- Currently in the high-risk population prophylactic bilateral salpingo-oopherectomy is the only strategy with proven effectiveness to prevent ovarian cancer. High-risk women should be adequately counselled about the uncertainties of screening before recruitment into the ongoing screening trials.