Screening for ovarian cancer: progress and challenges

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Introduction

Ovarian cancer is one of the most aggressive gynaecological malignancies, the high mortality being a direct result of the advanced stage of the disease at the time of diagnosis. However, survival rates of greater than 90% have been reported with Stage I disease. Consequently there is considerable interest in the development of screening methods for the early detection of ovarian cancer. In the second of two reviews I discuss the challenges of screening for ovarian cancer, the screening tests that are available, the target populations and the screening trials currently in progress.

Rationale for ovarian cancer screening

Primary carcinoma of the ovary is the leading cause of death from gynaecological malignancy in the Western world. In the UK, it is the fourth most common cause of cancer death among women: there were almost 7000 new cases reported in 2002 (which equates to a lifetime risk of 1 in 48) and there were 4600 deaths from the disease in 2003.[1]

Despite recent advances in surgical techniques and novel chemotherapeutic agents, mortality from ovarian cancer has changed little in the last decade. It is thought that the advanced stage at presentation is primarily responsible for the poor prognosis associated with ovarian cancer. Because it is associated with vague and non-specific symptoms, about 75% of women with ovarian cancer will have advanced stage disease (Stage III or IV) at the time of diagnosis.[2] Despite aggressive treatment, the 5-year survival for advanced stage disease is only 30% compared to survival rates of 60–90% for early disease (Stage I or II), depending on the degree of tumour differentiation (Figure 1).[2] Thus there is considerable interest in developing screening methods that detect ovarian cancer at an earlier stage when treatment is more effective and mortality may be reduced.

Challenges of ovarian cancer screening

Screening for ovarian cancer, however, presents a number of challenges: little is known of the natural history of the disease, a premalignant precursor lesion has yet to be identified, and diagnosis requires surgery in the form of a laparotomy or a laparoscopy. In addition, the incidence of the disease is low, with a lifetime risk estimated to be 1.8%. Thus there is a considerable risk that the morbidity associated with surgery for a false-positive screen will outweigh the potential benefits of screening. It widely accepted that in order to be acceptable a screening test for ovarian cancer must achieve a positive predictive value of at least 10% (i.e. a maximum of 10 surgical procedures for every cancer identified). In order to achieve this target the test must have a minimum specificity of 99.6%.[3] Thus appropriate screening tests must be selected on appropriate target populations to balance the benefits and costs of screening.

Target population

There are two main target populations that are at risk of ovarian cancer: women in the general population and women at high risk of ovarian cancer by virtue of their family history of the disease.

Ovarian cancer incidence increases with age: over 70% of cases occur after the age of 50 years, with a maximum incidence of 60.5 per 100 000 in the 75–79 years age group.[4] Some 90% of women with the disease will have no family history of it.[5] Thus screening programmes directed at all postmenopausal women are most likely to have the biggest impact on mortality.

Approximately 10% of ovarian carcinomas have a hereditary basis, the majority caused by a mutation in one of the cancer predisposing genes, BRCA1 and BRCA2. The average cumulative risks by the age of 70 years for ovarian cancer are 39% (18–54%) in BRCA1 mutation carriers and 11% (2.4–19%) in BRCA2 carriers.[6] Compared to sporadic disease, familial ovarian cancer is often diagnosed in younger women at a later, less curable stage of disease. Thus devising early detection strategies is particularly important in this group of women. However, screening of high-risk women is associated with two problems: high false-negative and false-positive rates.[7] As many of the women in this group are premenopausal, a higher screen false-positive rate is associated with physiological conditions such as ovulation and common benign conditions. The higher screen false-negative rate is due to the inability to detect multifocal peritoneal disease, which may be associated with familial ovarian cancer.

Screening tests

A number of screening tests have been or are currently being evaluated, including pelvic examination, ultrasound examination and the measurement of various circulating proteins.

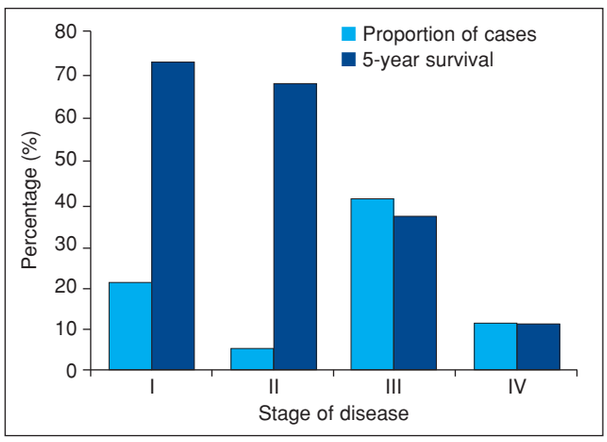

Figure 1 *Ovarian cancer: proportion of patients presenting and 5-year survival by stage of disease (data from the Surveillance Epidemiology and End Results Program of the National Cancer Institute[2])*

J Fam Plann Reprod Health Care 2006; **32**(3): 173–175
(Accepted 6 June 2006)

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Pelvic examination

Bimanual pelvic examination of asymptomatic women has been disappointing in the early detection of ovarian cancer, lacking sufficient sensitivity and specificity. Andolf *et al*. reported that in one patient with ovarian cancer, two with borderline tumours and 18 of 24 patients with benign ovarian cysts, the bimanual examination was said to be normal prior to the pelvic ultrasound scan.[8]

Ultrasonography

Ultrasonographic imaging of the ovaries allows the detection of ovarian enlargement and morphological abnormalities. Initial investigations using the transabdominal approach lacked sufficient specificity due to difficulties in imaging the pelvic organs through the abdominal wall and because of the poor resolution of the older machines used in these initial studies.[9] These problems have been addressed by transvaginal ultrasonography (TVS), which is used with the intention of detecting the earliest morphological changes in the ovary. TVS has demonstrated encouraging sensitivity in the early detection of ovarian cancer but specificity continues to be limited. In a review of results from early studies, Karlan reported sensitivity as high as 100% and specificity of approximately 98%.[10] Improvements in the specificity of TVS can be achieved by the use of a morphology index or through the use of colour Doppler but usually at the cost of some reduction in sensitivity.[11,12]

Tumour markers

CA125, the most widely investigated ovarian tumour marker, is a high molecular weight glycoprotein that is detected in the serum. Using a cut-off threshold level of 30–35 IU/l, approximately 90% of all advanced ovarian cancers and 50% of cases with disease confined to the ovaries will have a level exceeding this threshold.[13] However, specificity is poor as levels can be elevated by a number of other conditions – both benign and malignant – such as pregnancy, endometriosis, fibroids and breast cancer, as well as conditions that promote any type of peritoneal irritation.[14] Using CA125 alone in women aged 50 years or over, a positive predictive value of 4.6% was achieved in a study of 4290 volunteers.[15] However, improvements in the sensitivity and specificity of the test can be made by studying the woman's age-related risk in combination with the rate of rise of CA125 rather than the absolute level. The use of a computerised algorithm 'risk of ovarian cancer' (ROC) based on the Bayes' theorem, which compares each individual's pattern of CA125 to the pattern in controls (where levels are static or fall with time) and the pattern in cancers (where the levels rise), has led to an improved specificity, sensitivity and a positive predictive value for predicting the ROC in the year following the previous screen.[16]

Screening strategies

When used alone, none of the available tests achieves the specificity and sensitivity required. However, superior specificity and positive predictive values have been achieved with sequential, multimodal screening in the general population.

In a recent pilot randomised control trial (RCT) in the UK, 22 000 women aged 45 years or older were randomised to routine pelvic examinations or screening.[17] Screening involved annual CA125 measurements with TVS if the CA125 was ≥30. Although the study did not achieve statistical significance the results were encouraging, with improved survival in women diagnosed with ovarian cancer in the screened group compared to the control group (72.9 vs. 41.8 months, respectively) suggesting that a multimodal approach may be efficacious. In this study, lead time bias was eliminated by measurement of survival from randomisation rather than diagnosis.

In a 10-year ovarian cancer screening trial in Japan, 58.8% of cancers diagnosed after the introduction of ultrasound screening were Stage I compared to 29.7% before.[18]

A possible survival benefit was also observed in another study involving 15 000 women where the 5-year survival of patients with screen-detected ovarian cancer was 83.6 ± 10.8%.[12] However, the lack of a control group in this study raises the possibility of a 'healthy volunteer' bias.

Recently, Olivier *et al*. reported that in a series of 312 high-risk women screened with CA125 and TVS, screening was not effective as the cancers associated with either an abnormal ultrasound scan or a raised CA125 were found in patients with high-stage disease.[19] High specificity, sensitivity and positive predictive values were achieved. However, the study was limited by the small number of ovarian cancer cases.

Current screening trials

There are currently two large trials in progress to assess the impact of screening on ovarian cancer in the general population: the Prostate, Lung, Colon and Ovary (PLCO) trial in the USA and the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). In order to assess the impact of screening on ovarian cancer in high-risk women, the UK Familial Ovarian Cancer Screening Study (UKFOCSS) is currently underway.

The PLCO Trial has completed enrolling 74 000 women aged 55–74 years. In this RCT, TVS and CA125 are being used together annually as a first-line screen for 3 years and CA125 alone for a further 2 years.[20] Women are randomised either to the interventional arm with annual screening or to an observational standard care control arm. A positive result in either of the screening tests results in a gynaecological referral. Follow-up is for 13 years from the point of randomisation, with the endpoint of the study being the health status and/or cause of death.

UKCTOCS is an RCT in which 200 000 postmenopausal women are randomised into one of three treatment arms: annual screening with CA125 as the primary test and ultrasound as a secondary test, an ultrasound group and a control group with no screening.[21] All the women will be followed up for 7 years. At the time of writing, patient enrolment and randomisation have been completed and results are expected in 2011. Although the primary endpoint of the study is ovarian cancer mortality,

Table 1 *Criteria for defining high-risk families in the UK Familial Ovarian Cancer Screening Study (UKFOCSS)*[22]

1	Two or more first-degree relatives with ovarian cancer regardless of age.
2	One first-degree relative with ovarian cancer and one first-degree relative with breast cancer below the age of 50 years.
3	One first-degree relative with ovarian cancer and two first-degree relative with breast cancer below the age of 60 years.
4	An individual with one of the ovarian cancer predisposing genes.
5	Three first-degree relatives with colorectal cancer with at least one diagnosed before the age of 50 years and at least one first-degree relative with ovarian cancer.
6	Criteria 1–3 are modified when paternal transmission is occurring. Families where affected relatives are related by second degree through an unaffected intervening male relative who has an affected sister.

Table 2 *Ovarian cancer screening: key points*

- Ovarian cancer is the leading cause of death from gynaecological malignancy in the Western world.
- No precancerous lesions have been identified.
- Bimanual examination is of no value as a screening test.
- Transvaginal screening has a high sensitivity for ovarian cancer; however, the detection of benign lesions may lead to unnecessary operations.
- High CA125 levels may be caused by many benign and physiological conditions. Measuring CA125 is of more benefit when used as part of a multimodal strategy.
- Women in the general population should not be screened unless they are taking part in clinical trials.
- Although there is currently no evidence of any benefit, screening is currently recommended for high-risk women.

other issues such as health economics, patient compliance and psychological and physical mortality associated with screening will also be addressed.

In UKFOCSS, a single-arm prospective study, 5000 high-risk women have an annual TVS scan and CA125.[22] Additional 4-monthly blood samples are analysed retrospectively for CA125 and novel tumour markers with the aim of deriving a familial risk of ovarian cancer (FROC) index similar to the ROC used in the general population. Criteria for defining high-risk families in UKFOCSS are summarised in Table 1.

The results of these trials will not only provide evidence for whether screening provides a survival benefit at an acceptable financial cost, but will also address other issues such as the optimal age for the commencement of screening, optimal screening intervals, physical and psychological morbidity, and acceptability.

Conclusions

Progress into the early detection and treatment of ovarian cancer has been hampered by the lack of precursor lesions and the uncertainty regarding the duration of the preclinical phase of the disease. However, our understanding of ovarian cancer progression and detection will be improved by the large randomised trials that are currently in progress. Until these data become available, women in the general population should not be screened unless they are taking part in clinical trials. For high-risk women, screening is currently recommended as part of ongoing research, but these women need to be counselled that there is, as yet, no evidence of any benefit (Table 2).

Statements on funding and competing interests
Funding. None identified.
Competing interests. None identified.

Acknowledgements
The author wishes to thank Professor Ian Jacobs and Dr Usha Menon for their contribution in the field of ovarian cancer screening and their support.

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ERRATUM

'Economic evaluation. Part 1: Introduction to the concepts of economic evaluation in health care',
Emma McIntosh, Ramon Luengo-Fernandez**,** *J Fam Plann Reprod Health Care* 2006: **32**(2): 107–112

Due to a typesetting error on page 107, the title of Box 1 was incorrect. The correct title is: **Box 1: Glossary of terms**.

The Journal wishes to apologise for this inadvertent error and for any inconvenience caused to readers or to the authors of the article in question.