

Screening for Ovarian Cancer

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Abstract

Ovarian cancer is predominantly a disease of postmenopausal women which presents at a late stage and has an overall 5-year survival of less than 30%. If detected at stage I, survival is dramatically increased and this would suggest that screening for ovarian cancer may reduce mortality. However, the inaccessibility of the ovaries and the absence of a confirmed premalignant condition make screening for preclinical disease difficult. Recent advances in tumour marker interpretation and ultrasound technology have now allowed screening for ovarian cancer to become a real possibility. CA 125 is the most widely used tumour marker for ovarian cancer and it has been shown to be elevated several years before clinical presentation. A new approach to the interpretation of sequential CA 125 results, which uses a mathematical algorithm to determine an individual's risk of cancer, has improved the sensitivity of CA 125 in screening asymptomatic postmenopausal women. Screening using transvaginal ultrasound, Doppler and morphological indices gives encouraging results but, used alone, it currently lacks the specificity required of a screening test for the general population. Multimodal screening using tumour markers and ultrasound in combination gives high sensitivity and specificity and is also the most cost-effective potential screening strategy. The sensitivity and specificity of these techniques are sufficient to warrant large-scale clinical trials of ovarian cancer screening. Three such trials are currently underway and, in due course, will establish whether any screening strategy will ultimately reduce mortality from ovarian cancer.

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Introduction

Ovarian cancer is the most common gynaecological malignancy with over 5000 new cases diagnosed every year in the UK and 22 000 in the United States. Four thousand women die each year of ovarian cancer in England and Wales, and 13 000 die in the USA.^{1,2} This poor prognosis has been attributed to the late stage at presentation of most cases which is a result of the insidious onset and non-specific nature of symptoms. If diagnosed at stage I, when the disease is confined to the ovaries, the 5-year survival is over 80%.³ Survival falls dramatically with increasing stage of disease with only 10% 5-year survival for stage IV ovarian cancer.

These data provide a clear rationale for screening for ovarian cancer. However, unlike cervical cancer there is no confirmed premalignant condition which progresses to invasive disease over a defined period of time. Studies to date have produced only tenuous evidence to suggest that inclusion cysts and other benign or borderline ovarian tumours may represent early stages in ovarian carcinogenesis.⁴⁻⁶ Further molecular studies are in progress to try to provide a conclusive answer. The inaccessibility of the ovaries within the peritoneal cavity precludes direct inspection and sampling of ovarian tissue for

screening purposes. Therefore non-invasive methods of detecting early disease, such as ultrasound and tumour markers, are under investigation.

Developments in ultrasound technology as well as more sophisticated techniques for the interpretation of tumour marker levels have lead to improved specificity and sensitivity of potential screening strategies such that they now have a realistic chance of reducing mortality from ovarian cancer. To establish whether this is the case, several large randomised controlled trials of ovarian cancer screening in the general population are currently in progress. As large numbers of participants are required for adequate statistical power, none of these trials is expected to be completed before the year 2004. However, before any screening programme can be introduced on a national scale it should satisfy a series of criteria set out by the World Health Organisation.⁷ This review will base its discussion of ovarian cancer screening on these criteria.

The World Health Organisation Screening Criteria

The Disease

1. The condition sought should be an important health problem—Ovarian cancer is the fourth leading cause

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of cancer-related deaths in women aged 55 to 74 years in the USA. In England and Wales it is the fourth most common cancer in women and is responsible for more deaths than cervical cancer for which screening programmes already exist throughout the developed world. The mortality to incidence ratio for ovarian cancer is 0.72 reflecting the poor prognosis, particularly of late-stage disease.

2. There should be a recognisable latent or early symptomatic stage—At present there is no conclusive evidence to support a premalignant ovarian lesion and symptomatology is unreliable for detecting early disease. However, clinically detected stage I disease has a very good prognosis, and until such time as a precursor lesion is identified, stage I disease may be considered to fulfil this WHO criterion. Screening for a premalignant lesion would obviously have a greater impact on mortality and this may become possible in due course.
3. The natural history of the condition, including development from latent to declared disease, should be adequately understood—Considering stage I disease to be an “early latent phase” of ovarian cancer is potentially problematic. Firstly, stage I tumours may be a separate disease entity and behave very differently from more advanced-stage tumours. It is possible that they would seldom progress further even if they were not identified and treated. Although unlikely, it is difficult to completely refute this argument based on our current knowledge. Secondly, the time course of progression from early to late stage disease is largely unknown. If transition occurred very rapidly, then screening intervals would need to be short in order to detect early-stage disease and reduce mortality. This would be impractical in terms of cost and compliance. However, research described in this article suggests that annual screening using serum markers and ultrasound will be sufficient to have a significant impact on mortality.⁸

The lack of knowledge of a precursor lesion which progresses to invasive ovarian cancer over a defined period of time should not delay randomised trials using stage I disease as the “early latent phase”. These trials will take several years to complete, and in a disease where there has been little change in survival over the past 30 years, any reduction in mortality gained through screening on this basis would be a great step forward.

The Treatment

1. There should be accepted treatment for patients with recognised disease—The surgical management of women with an ovarian malignancy is well established and chemotherapeutic agents are used as adjuvant treatment if extra-ovarian spread is identified.⁹ The vast majority of patients with stage Ia or Ib

ovarian cancer have an extremely good prognosis following surgery alone.

2. Facilities for diagnosis and treatment should be available—The two most extensively investigated diagnostic methods used for ovarian cancer screening, the tumour marker CA 125 and real-time ultrasonography, are now routinely available to most practitioners throughout the developed world. Transvaginal probes can be added to standard equipment used for other purposes. Surgical and chemotherapeutic facilities for treatment of ovarian cancer are widely available whether in specialist centres or general hospitals.

The Screening Test

1. There should be a suitable test or examination—Both high sensitivity (the probability of the test being positive in individuals with the disease) and high specificity (the probability of the test being negative in individuals without the disease) are important requirements for a screening test. Unfortunately, an increase in the sensitivity of a test often results in a reduction in specificity and vice versa. In ovarian cancer screening the outcome of a positive test will be a diagnostic surgical procedure and neither patients nor clinicians will accept large numbers of operations for each case of cancer detected. Therefore, specificity is a major consideration when deciding on which test to use for screening.

A variety of modalities have been used to detect ovarian cancer in asymptomatic women:

i) Vaginal examination

Several studies have investigated the use of vaginal examination in ovarian cancer screening and all of them have shown that the specificity of this method is insufficient for use as a first-line screening tool in asymptomatic women.¹⁰⁻¹²

ii) Tumour markers

Non-invasive tests are the most likely to be acceptable to individuals participating in a screening programme and therefore many tumour markers for ovarian cancer have been investigated. Serum levels of oncofetal proteins such as carcinoembryonic antigen (CEA) and alpha-fetoprotein, as well as antigens defined by monoclonal and polyclonal antisera have been assessed as markers for epithelial ovarian cancer. Enzymes, hormones and metabolic products have also been studied. However, the only tumour marker to have been studied prospectively is CA 125 and the results of retrospective analyses of other markers cannot be extrapolated to screening asymptomatic women with any confidence.

CA 125, an antigenic determinant on a high molecular weight glycoprotein recognised by a mouse monoclonal antibody (OC 125) developed using an ovarian cancer

cell line as an immunogen, is the most widely studied tumour marker for monitoring clinically diagnosed ovarian cancer.¹³ Serum levels of CA 125 have been found to be elevated in 50% of patients with stage I and 90% of those with stage II epithelial ovarian cancer and levels correlate well with the stage of disease.⁸ However, CA 125 is not specific to ovarian cancer and can be elevated in benign and physiological conditions as well as in other malignancies (Table I). Despite this, CA 125 is potentially valuable for ovarian cancer screening as the majority of these conditions are either clinically detectable or occur infrequently in postmenopausal women, who would form the target population for an ovarian cancer screening programme.

TABLE I: EXAMPLES OF CONDITIONS ASSOCIATED WITH AN ELEVATION IN SERUM CA125 LEVELS

Gynaecological	Miscellaneous
Endometriosis	Pericarditis
Fibroids	Polyarteritis nodosa
Haemorrhagic ovarian cysts	Renal disease (serum creatinine >2.0)
Menstruation	Sjögren's syndrome
PID (acute)	Systemic lupus erythematosus
Pregnancy (first trimester)	
Gastro-intestinal / Hepatic	Malignancy
Acute pancreatitis	Ovary
Colitis	Breast
Chronic active hepatitis	Endometrium
Cirrhosis	Lung
Diverticulitis	Liver
	Pancreas
	Bladder
	Non-Hodgkin's lymphoma

PID: pelvic inflammatory disease

Several large studies provide encouraging evidence that CA 125 can be used to screen asymptomatic women for ovarian cancer. In the JANUS study,⁸ retrospective analysis of stored serum showed that CA 125 levels were higher in 105 women who later developed ovarian cancer than in matched controls. The results indicated that at least a proportion of women who develop ovarian cancer have elevated levels of CA 125 several years prior to clinical presentation. In a study of 5500 healthy volunteers in Stockholm, where pelvic examination, serial CA 125 measurements and transabdominal ultrasonography were performed, all six cases of ovarian cancer which occurred in postmenopausal women were associated with elevated levels of CA 125.¹⁴ Five of the six cases had a doubling of CA 125 over the course of one year or a level >95U/ml. CA 125 was used as a first-line test, with ultrasound as a second-line test if the CA 125 was abnormal, in a study of 22 000 postmenopausal women in the UK. This multimodal strategy achieved a specificity

of 99.9%, a sensitivity of 78.6% and a positive predictive value (PPV) of 26.8% at one-year follow-up.¹⁵ It is clear that a multimodal approach using sequential CA 125 measurements and ultrasound can achieve high specificity and encouraging sensitivity in screening for ovarian cancer.

A novel approach to improving sensitivity has been the development of a mathematical algorithm for interpretation of the pattern of change in CA 125 over time. Both the Stockholm and London studies revealed that the levels of CA 125 in women with ovarian cancer increase with time, whereas women with false positive elevations of CA 125 have stable or decreasing levels. Skates *et al*¹⁶ described this observation in a Risk of Cancer (ROC) algorithm which achieved high sensitivity and specificity when retrospectively applied to the Stockholm study data. Use of the algorithm in the interpretation of CA 125 results from the 22 000 women in the London study has confirmed the improvement in performance over interpretation of absolute levels alone (Personal communication—Skates *et al*).

The use of a combination of tumour markers to increase sensitivity and specificity has been widely investigated and the marker which appears to exhibit the most complementarity to CA 125 is OVX 1. This is a mouse monoclonal antibody developed using sequential immunisation with three different ovarian cancer cell lines.¹⁷ However, recent preliminary data suggests that OVX 1 may be unstable unless serum is separated rapidly. This complicates the use of OVX 1 in population screening if samples are to be taken and sent by mail to a central laboratory for analysis.

iii) Ultrasound

Ultrasonographic assessment of the ovaries has been extensively investigated. Transabdominal ultrasound examination, when evaluated prospectively in 5540 women had a high false positive rate (5.4%).¹⁸ Many of the false positive cases had benign or functional ovarian cysts, but 25.7% of the false positives had no ovarian pathology at diagnostic operation. It is difficult to distinguish between benign or functional ovarian masses and malignant tumours using transabdominal ultrasound, but transvaginal scanning offers greater resolution and has improved the quality of ovarian morphological assessment.

Attempts have been made to quantify the information obtained through ovarian ultrasound scanning in the form of a morphological index which scores the findings giving a risk of malignancy estimation. Using this strategy in a prospective study of 8500 women at the University of Kentucky, 8 ovarian malignancies were identified in 121 patients undergoing surgery giving a positive predictive value close to the level required for a screening programme.¹⁹

Colour Flow Doppler imaging has been used to improve specificity in the assessment of ovarian masses. The neovascularity which arises in malignancies contains less smooth muscle than benign masses and therefore offers less resistance to blood flow. This can be measured as the pulsatility index of the vessel. A scoring system based not only on the pulsatility index of the vessels but also on the vessel pattern has been used in a study of 1000 women.²⁰ In this study an abnormal transvaginal scan resulted in a Doppler assessment which lead to the diagnosis of 27/29 malignancies. Doppler alone had a specificity of 95% and a sensitivity of 96% while the scoring system increased specificity to 98% with a reduction in sensitivity to 90%. However, in this study 257/1000 women screened were symptomatic and all but four of the malignancies occurred in this group. These results should therefore be interpreted cautiously since the majority of malignancies occurred in a group of individuals with a clinical presentation.

More recently, the same group reported the results of Doppler screening of 5013 asymptomatic women aged 40 years and over.²¹ Thirty-eight women were operated on for suspected ovarian malignancy, of whom 4 had ovarian cancer, giving a positive predictive value of 10.5%. However, no true or false negative rate was reported in this study so it is impossible to comment on sensitivity and specificity.

The available data suggest that, although ultrasonography may play an important role in ovarian cancer screening, it does not currently possess adequate specificity on its own for screening the general population.

iv) Other modalities

Other imaging methods used in the assessment of clinically detected ovarian masses such as computed tomography (CT), magnetic resonance imaging and radioimmunoscinigraphy cannot be advocated for screening purposes due to their cost and availability as well as patient acceptability and, in the case of CT, radiation exposure. However, they may have an important role as tertiary tests.

v) Multimodal screening

The use of multimodal screening to detect early ovarian cancer has three major advantages over strategies relying on only one modality. Firstly, using serum tumour markers as a first-line test reduces the cost of screening. Secondly, reserving ultrasound examination for those women with an abnormal first-line test reduces the number of women requiring this expensive and more uncomfortable examination. Finally, there is now good evidence that combining different modalities can achieve high specificity and sensitivity. The results of the two studies which have utilised a multimodal strategy were encouraging^{14,15} and further improvement may be achieved by the use of the ROC algorithm.

2. There should be an agreed policy on whom to screen—In order to reduce overall mortality from ovarian cancer by screening, the target population must include the majority of women likely to develop the disease. The incidence of epithelial ovarian cancer increases rapidly after the age of 50, with double the rate of cancer in women aged 60 to 64 years compared with women aged 45 to 49 years.²² Incidence rates peak in the 70 to 74 years age group and remain high thereafter. Less than 15% of ovarian cancers occur in women under 50 years of age and many of the malignancies in younger women are non-epithelial and therefore are not amenable to screening using CA 125. By screening postmenopausal women or those over the age of 50, the screened population would include over 80% of ovarian cancer cases whilst requiring screening of less than half of the female population.²³ Ovarian cancer is a relatively uncommon disease even in women over 50 and a test would require 99.6% specificity and at least 80% sensitivity to achieve a positive predictive value (PPV) of 10% in this group of women.²⁴ This level of specificity would limit the number of diagnostic operations for every case of cancer diagnosed to ten.

As the incidence of a disease increases, the specificity required to achieve a given positive predictive value decreases. As illustrated in Figure 1, a test with 90% specificity would yield a PPV of 10% in BRCA 1 mutation carriers, because the incidence of ovarian cancer is extremely high in this population. Thus, a test which lacks the specificity required for screening the general population may be suitable in a high risk population.

There have already been encouraging results from a screening study of both pre- and postmenopausal women

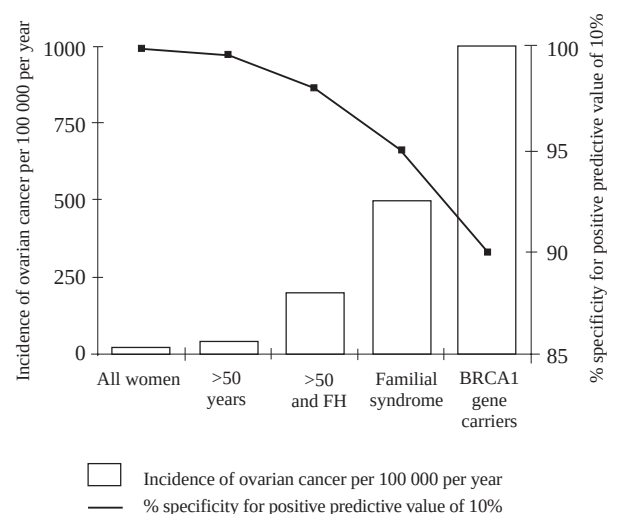


Fig. 1. The level of specificity required for a positive predictive value (PPV) of 10% in populations with a different incidence of ovarian cancer. FH = family history of ovarian cancer (1 first degree relative only). Familial syndrome = 2 or more first degree relatives with ovarian or early onset breast cancer.

with one or more first or second degree relatives with ovarian cancer. Using ultrasound with a morphological index and Doppler to increase specificity, 8 out of 9 ovarian cancers which developed during the study were detected by screening and 6 of these were stage I at diagnosis.^{25,26} The false positive rate was virtually the same in both pre- and postmenopausal women and the results suggest that screening in a high risk population using these methods may be feasible and acceptable.

3. The test should be acceptable to the population—Both the cervical and breast screening programmes have demonstrated that large numbers of women are willing to undergo uncomfortable, intimate examinations regularly in order to reduce their risk of dying of cancer. The uptake of screening for both of these diseases has been shown to be better in higher socio-economic groups and these are often the groups at lowest risk of developing the disease. However, ovarian cancer is more prevalent in higher socio-economic classes in England and Wales,²⁷ so this type of differential uptake should not have the detrimental effect on case detection seen in other screening programmes. Studies of uptake of both CA 125 and ultrasound in women with a family history of cancer suggest that women's fear of cancer exceeds their fear of screening and that screening may be more acceptable in a high-risk population. Transvaginal ultrasound examination was less acceptable to an older group of women than to younger women in a study carried out in an inner-city population in England.²⁸ Educational attainment did not increase uptake in this study and Caucasians were less likely to be screened than other racial groups. A further study of 80 women showed that transvaginal ultrasonography was preferred to transabdominal scanning by 56% of the women, probably because it obviated the need for a full bladder during the examination.²⁹

In an English familial ovarian cancer screening programme, subjective anxiety levels increased in women with a positive scan result and in those referred for surgery.^{25,30} However, all women in this study had benign conditions at operation and their anxiety levels returned to baseline after surgery. This information suggests that there are no long-term psychological sequelae in women with a false positive screen result. This was, however, not an ongoing program and only involved a one-off test. The results may not hold for a long-term programme or for true positive cases.

No studies to date have assessed the acceptability of a multimodal screening strategy, but 98.7% of women participating in the London study of 22 000 women complied with follow-up at one-year¹⁵ and this would appear to confirm that the screening strategy was acceptable to the vast majority of participants.

The Screening Programme

1. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole—Urban et al³¹ used sophisticated computer modelling techniques to assess the likely cost per year of life saved of various different screening strategies. Whilst there are limitations to using such techniques, it was concluded that a multimodal approach was the most cost-effective method of mass screening. Annual CA 125 screening followed by transvaginal ultrasound if the CA 125 value doubled or was >35U/ml was estimated to cost \$50 000 per year of life saved. A meta-analysis of studies using CA 125 and ultrasound concurrently, rather than sequentially, suggested a cost of \$445 177 per case of stage I ovarian cancer detected.³² This would translate to a total cost of \$14 billion to screen all women >45 years of age. It is therefore unlikely that a screening strategy using ultrasound in all women will be adopted purely on the basis of cost.
2. Case-finding should be a continuing process and not a "once and for all" project—Very little effect on mortality can hope to be achieved by performing a single screen if a disease process evolves over time. However, since the natural history of ovarian cancer is not known, the optimal screening interval remains to be determined. Even if these screening intervals were known, the actual frequency of screening is often influenced by the cost and acceptability of the test. The current randomised trials will provide valuable information about the optimal screening interval for any ovarian cancer screening programme which may be introduced.

Current Trials of Ovarian Cancer Screening

Studies of the General Population

i) The NIHP LCO Study—This study aims to randomise 74 000 women aged over 60 to either a control group or a screened group who will undergo pelvic examination, ultrasound scanning and CA 125 measurement. Women with abnormal results will be referred to a gynaecological oncologist for further management. The study will have 80% power to detect a 30% reduction in mortality over a study period of 16 years.³³

ii) The St. Bartholomew's Hospital Study—This randomised controlled trial will recruit 120 000 healthy, postmenopausal women over 50 years of age from throughout the UK. Women randomised to screening will undergo annual CA 125 measurements and the results will be interpreted using the ROC algorithm described by Skates et al. Women with an elevated risk of ovarian cancer will be recalled for a transvaginal ultrasound scan and will be referred for surgery if the

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