Screening for gynaecological conditions

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Abstract

Well-organised cervical screening programmes have reduced the mortality from cervical cancer by up to 50% in the developed world. Despite the successful development of human papilloma virus vaccines there is likely to remain a need for cervical screening for the foreseeable future. In contrast, the value of mass screening for ovarian cancer remains unproven, although current screening methods can detect early stage disease in asymptomatic individuals. Breast screening does appear to be associated with a reduction in mortality in women aged 50–69 years but disagreement remains about its value in younger and older women. Testing for sexually transmitted infections is effective in reducing morbidity but tends to be selective at present because of concerns over the cost and psychosocial implications of general population screening.

Keywords breast, endometrial and ovarian cancer; cervical screening; Chlamydia; HPV; mass screening

Introduction

Screening is defined as a procedure to help identify, in an organised way, a specified disease or condition among asymptomatic individuals. Screening programmes may be applied to a general population or targeted at specific groups that are considered to be at particular risk. The aim is to detect disease early in order to facilitate effective treatment. Effective screening offers improved prognoses for some cases, less radical treatment for others and potential resource savings for society. However, screening also has its limitations. It is important that people have realistic expectations of what a screening programme can deliver. Screening can reduce the risk of developing a condition or a condition's complications but it cannot offer a guarantee of protection. In any screening programme there are an irreducible minimum of false-positive results (when patients are wrongly reported as having the condition) and false-negative results (when patients are wrongly reported as not having the condition). Screening may lead to longer morbidity for cases in which the prognosis is unaltered or over treatment of questionable abnormalities. Low technology tests have low specificity, burdening already hard-pressed secondary care facilities with patients who have non-life-threatening conditions.

Table 1 lists some of the criteria desirable for an effective screening programme. Ideally there should also be evidence from a good quality randomised controlled trial, analysed on an intention-to-treat basis, that the proposed screening programme is effective in reducing mortality or morbidity before it is introduced. To assess whether a screening test is reliable and valid, independent standards of reference are measured. Sensitivity is defined as the proportion of individuals with the target condition who screened positive. High sensitivity implies that a large proportion of individuals with the target condition have a positive result on the screening test. Specificity is defined as the proportion of individuals without the disease who have a negative result on the screening test. High specificity reflects a low proportion of people falsely labelled as having the disease when they are in fact disease free. Predictive values are important in clinical practice since they are the probabilities that someone testing positive really has the condition and someone testing negative does not. Positive predictive value is the proportion of people with a positive test who have the target disorder; negative predictive value is the proportion of people with a negative test who do not have the target disorder.

Criteria for the desirable characteristics of a successful screening programme

1. The condition being screened for should represent a significant cause of mortality and have a significant prevalence in the population
2. An accepted treatment must be available for the latent or early phase of the condition that improves outcomes
3. The facilities for diagnosis and treatment must be available
4. A latent or early symptomatic stage must exist
5. A sensitive and specific screening test must be available
6. The test must be acceptable to the population
7. The natural history of the condition should be well characterised
8. An agreed treatment policy must exist
9. Screening should be cost-effective
10. Case finding must be a continuous process

Table 1

Gynaecological cancers

Gynaecological cancers account for one-sixth of female cancers with an estimated 942,000 new cases worldwide per year or 18.6% of all incident cancers and 15.3% of cancer deaths in women. With increased life expectancy, early diagnosis and prevention of cancer is an increasingly important issue. Important aspects of screening, including psychological impact, cost-benefit and uptake are receiving better attention. Genetic testing is now in place in clinical gynaecology to identify women at an increased risk of gynaecological cancer.

Ovarian cancer

More than 6000 new cases of ovarian cancer are diagnosed each year in the UK, making it the fourth most common cause of female cancer and accounting for 4.7% of all cancers. The annual incidence of ovarian cancer in the general population increases with age to 40 per 100,000 in women aged over 45 years. Although the lifetime risk of developing the disease has increased from one in 70 to one in 55 over the past 30 years there was an 8% fall in the number of new cases between 1995 and 2004. The

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5-year survival for patients diagnosed with stage I disease is more than 80% but this falls to 22% and 14% for stages III and IV, respectively. Despite the good prognosis for early stage disease the overall 5-year survival rate is less than 45%, largely because most patients have disease that has spread outside the ovary by the time of clinical presentation. The aim of screening is the detection of asymptomatic early stage disease. Unlike cervical cancer, no precursor lesion has been identified and direct inspection of the ovaries is not possible without surgical intervention. Furthermore, the natural history of the condition is not well characterised. The relatively low prevalence of the disease means that any screening test must have high specificity to avoid unnecessary surgical interventions. For example, in order to have a positive predictive value of 10% or better for the general population over 50 years, a screening test for ovarian cancer would need to have specificity of at least 99.6%. Screening based on reported symptoms was shown to detect about two-thirds of women subsequently diagnosed with ovarian cancer but was less sensitive than CA 125 measurement and 12% of healthy controls reported similar symptoms. Bimanual palpation is not recommended because of its low sensitivity for early stage disease and the relatively high incidence of benign adnexal disease (1.5%). Cervical cytology may reveal malignant cells but the sensitivity for the detection of ovarian cancer is only 10–30%. Current screening strategies are based on serum tumour markers or ultrasound imaging of the ovaries.

Tumour markers

Serum CA 125 remains the most used tumour marker in ovarian cancer screening. CA 125 is a large glycoprotein of unknown function that is expressed during normal foetal development and by more than 80% of epithelial ovarian cancers. Serum levels are not affected by abdominal or pelvic examination but are elevated in approximately 1% of healthy women and in a number of benign conditions, such as endometriosis, uterine leiomyoma and pelvic inflammatory disease, as well as malignancies of the breast, liver, lung and pancreas. In asymptomatic women, the sensitivity for preclinical lesions ranges from 70–80%, with specificity in postmenopausal women of 98.6–99.4%. The low positive predictive value (3%) makes CA 125 measurement unsuitable as a single screening test for ovarian cancer. In the postmenopausal age group, although approximately two out of three cases of ovarian carcinoma could be detected by annual serum CA 125 measurement, only one-third would be detected in the early stage. About 80% of the pelvic masses will be classified correctly if a cut-off of 65 U/ml and 35 U/ml are used in premenopausal and postmenopausal women with a pelvic mass, respectively. The risk of developing ovarian cancer within the next 5 years in a postmenopausal woman with an elevated serum CA 125 is increased 14-fold. Improvements in sensitivity have been made using algorithms incorporating age, rate of change and absolute levels. These can be used to calculate a risk of ovarian cancer with a sensitivity of 86% and specificity of 98%. Although no other single tumour marker or analyte has been show to have a better predictive value for ovarian cancer than CA 125, a number of combination assays have shown higher rates of sensitivity for the detection of disease. Of these, the most effective to date appears to be an assay using a combination of serum proteins (leptin, prolactin, osteopontin and insulin like growth factor) with CA 125 and macrophage inhibitory factor. Initial studies on women with newly diagnosed disease had positive and negative predictive values of 99.3% and 99.2%, respectively, but data from larger longitudinal studies are not yet available. Micro-array technology and proteomics hold considerable promise in developing new serum markers but have yet to be validated in large population-based studies.

Ultrasound

Transvaginal ultrasound can be used as the sole screening method or as a secondary test after primary screening with serum CA 125. An ovarian volume over 20 cm^3 in premenopausal women and 10 cm^3 in postmenopausal women is considered to be abnormal. Unilocular cysts of less than 5 cm in diameter are found in 3.3% of postmenopausal women but are associated with minimal risk of malignancy, whereas complex cysts are associated with significant risk. Features suspicious of malignancy include solid areas and multiple septations. In most screening programmes, women with an abnormal scan will have a repeat scan 4–6 weeks later. If the abnormality persists, the patient will undergo morphologic indexing of the tumour and may require adjuvant tests like CA 125. The use of colour Doppler assessment of tumour blood flow has not been shown to provide additional information. Depending on these results, the patient may undergo operative removal of the persisting ovarian tumour by laparoscopy or laparotomy. Early studies on women over 40 years of age using ultrasound screening resulted in an unacceptable number of laparotomies for each case of ovarian cancer detected. Subsequent studies concentrated on postmenopausal women over the age of 50 years. The largest of these, in the USA, detected 44 ovarian cancers in 25,327 women screened with a sensitivity of 81% and a positive predictive value of 9.4%. The proportion of stage I cancers detected was greater than expected in an unscreened population (28 out of 44).

Multimodal screening

In essence, this is a screening strategy using CA 125 as the primary screen followed by ultrasound, in those cases where this is either above a particular cut-off or the calculated risk of ovarian cancer is above a certain threshold (see above). A study from Stockholm in 1993 detected six cases of ovarian cancer in 5500 women screened. A total of 175 women had elevated CA 125 levels and 16 women underwent laparotomy. In the UK, a study of 22,000 postmenopausal women found 11 cases of cancer after 41 laparotomies. Eight women with negative screens also developed ovarian cancer (sensitivity 78.6%). In both studies, the positive predictive value was more than 25%, an acceptable level for a screening programme. The results of the first randomised controlled study of general population screening were published in 1999. A total of 11,000 women aged over 45 years underwent annual, multimodal screening for 3 years and the outcomes were compared with a similar size control group who were not screened. Six cases of ovarian cancer were diagnosed in the screened group with a further 10 developing during the period of follow-up, compared with 20 in the non-screened group. The predictive value of a positive screening result was 21%. Although there was no difference in mortality from ovarian cancer in the two groups, the median survival (as measured from entry to the study, not diagnosis) of those women