Ovarian cancer screening

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BACKGROUND
Current tests used in the diagnosis of ovarian cancer are the CA-125 blood test and transvaginal ultrasound.

OBJECTIVE
This article discusses the available evidence and recommendations for ovarian cancer screening in both the general population, and in at risk women.

DISCUSSION
General population screening is not recommended, however there is a large, randomised controlled trial currently underway investigating this. There is no data to support the effectiveness of screening in high risk women (carriers of BRCA1 or BRCA2 mutations, or carriers of mismatch repair gene mutations in the hereditary nonpolyposis colorectal cancer group) as most tumours detected by screening are at an advanced stage at diagnosis. Prophylactic surgery to remove the fallopian tubes and ovaries is recommended after the completion of childbearing to prevent 90% of ovarian cancers in these women. The remaining 10% of these tumours arise in the peritoneal cavity as primary peritoneal cancers and behave in a similar way to ovarian cancers, and, by definition, are advanced at diagnosis. The future holds hope of new screening tests becoming available.

Ovarian cancer is the commonest gynaecological malignancy in women in Australia. The overall lifetime risk is 1.4% with a mean age at diagnosis of 63 years.[1] It is the fifth most common cause of cancer death in women, behind breast, colon, lung and pancreatic cancer. It has an overall 5 year survival of 42%, due to most cases being diagnosed at an advanced stage of disease.[1] Screening requires the availability of a test that is acceptable, easy to perform, sensitive and specific. There should also be a precancerous phase or time at which an early diagnosis can be made. In ovarian cancer there is no known precancerous phase, however stage 1 tumours generally have an excellent prognosis with 92% 5 year survival.[1] Current tests used in the diagnosis of ovarian cancer are the CA-125 blood test and transvaginal ultrasound, which have been found to detect ovarian cancer in the preclinical phase in a substantial proportion of cases.

Natural history of ovarian cancers

There are four main pathologies of epithelial ovarian cancer, each with distinctive behaviours:

- serous (70%) – commonly bilateral and usually stage 3–4 at diagnosis; CA-125 is usually markedly elevated. Serous tumours can be divided into two subgroups: low grade, which may be screen detectable; and high grade, which form the majority of these tumours and which spread early
- mucinous (5–10%) – commonly unilateral, large, low grade; often stage 1 with probable benign to borderline to malignant progression. Carcinoembryonic antigen (CEA), CA-19.9, inhibin often elevated
- endometrioid (20%) – associated with endometriosis, commonly confined to the ovary; 15–20% have an associated endometrial cancer
- clear cell (5–10%) – associated with endometriosis, usually confined to the ovary at diagnosis; CA-125 often normal.

Therefore screening is more likely to detect the latter three types than the serous papillary tumours, which are the most common, have no precursor lesion, and appear to be rapidly progressive with very early spread a common feature.

Screening tools

Ultrasound

Ultrasound is a very useful tool for assessing ovaries, particularly postmenopause. Ideally an ultrasound should be performed by a specialist gynaecological ultrasonologist in a tertiary setting. Multiple cyst formation, bilaterality, septum formation with increased vascularity, papillary projections, and free fluid (ascites) are all manifestations of neoplasia. Unfortunately premenopause ovaries are very active and many of these features are seen in functional cysts, which can be up to 6–7 cm in size, making ultrasound difficult to rely on in younger women. There is also difficulty differentiating endometriosis and cancer on traditional ultrasound and CA-125 testing.

Tumour markers

The CA-125 blood test is a measure of an epithelial antigen protein expressed on the coelomic epithelium, which includes the ovarian surface. Over 90% of advanced ovarian cancers will have an elevated CA-125, but it should be noted that 50% of stage 1 ovarian cancers will have a normal CA-125.[2] Ninety percent of primary ovarian malignancies arise from the ovarian epithelium, the remainder arise from the germ cells and produce tumour markers such as beta human chorionic gonadotrophin (HCG), alpha-fetoprotein (AFP), and/or lactate dehydrogenase (LDH), or stromal (hormone producing) cells which are associated with elevated oestrogen, testosterone and/or inhibin. As germ cell tumours and stromal tumours are rare, and germ cell tumours only occur in younger women (age less than 35 years), screening with tumour markers is not appropriate.

False positive CA-125 levels are common in a range of situations and are listed in *Table 1.*

Table 1. False positive CA-125 levels

Gynaecological
Endometriosis
Fibroids
Haemorrhagic ovarian cysts
Menstruation
Acute pelvic inflammatory disease
Pregnancy (first trimester)
Cancers other than ovarian
Endometrium
Pancreas
Bladder
Breast
Liver
Lung
Inflammatory conditions
Pericarditis
Systemic lupus erythematosis (SLE)
Sjogren's syndrome
Polyarteritis nodosa
Diverticulitis
Colitis
Acute pancreatitis
Chronic active hepatitis
Other
Renal disease
Cirrhosis

Screening in the general population

The largest randomised screening program into ovarian cancer in the world – the United Kingdom Trial of Ovarian Cancer Screening (UKTOCS) – is currently underway. The trial started as a pilot with 22 000 postmenopausal women. This pilot used initial CA-125 followed by ultrasound for a CA-125 level above 30 in postmenopausal women. Survival for those detected with ovarian cancer during screening was significantly longer (72.9 months) than those not being screened (41.8 months), but this may have been due to preclinical detection rather than a change in the natural history.[3]

The UKTOCS has now randomised 200 000 postmenopausal women to no screening (100 000) or screening with either pelvic ultrasound (50 000) or serial (3 monthly) CA-125 levels (50 000) to calculate a risk of cancer (ROC) algorithm as a first line test. The ROC algorithm was developed by Skates[4] and refers to an increase in CA-125 over time, even if within the normal range. This trial was started in 2001, with the primary endpoint being ovarian cancer mortality, and secondary endpoints being morbidity associated with screening, cost effectiveness, a comparison of the two screening methods, plus the establishment of a serum bank for testing novel tumour markers in the future. This study should give a definitive answer about the role of current tests in general population screening. Preliminary results show a rate of one operation per 500 women screened, with 4.7 operations per cancer detected in the CA-125 followed by ultrasound arm, giving a positive predictive value of 21%, and specificity of 99.9%. In the ultrasound arm there were 30 operations per cancer detected with a positive predictive value of 3.4% and 99.0% specificity. Around 32 cases of ovarian cancer per year were expected and 83 cases were found in the first year of screening,

suggesting a lead time of 2.6 years in terms of earlier diagnosis with screening. The unanswered question to date is whether this will translate to an improvement in mortality from ovarian cancer.

Screening in high risk populations

Only 5–10% of ovarian cancers are thought to be hereditary. Three gene mutations are known to be associated with an increased risk of ovarian cancer, BRCA1, BRCA2 and hereditary nonpolyposis colorectal cancer (HNPCC). Only 0.2% of the population carry a germline mutation in BRCA1 or BRCA2, unless they are of Ashkenazi Jewish descent when the incidence is 2%. If a Jewish woman is diagnosed with ovarian cancer there is a 30–60% risk of a germline mutation.[5] If a woman has a first degree relative with ovarian cancer, that woman has a threefold increased risk of developing ovarian cancer herself, giving her a lifetime risk of 4–5%.

Normal population

Lifetime risk of ovarian cancer: 1.4%
Average age of ovarian cancer diagnosis: 62 years
Histological type: serous papillary 70%, mucinous 10%, endometrioid 5%, clear cell 5%

The current recommendation is 6–12 monthly CA-125 and transvaginal ultrasound, although the optimum screening interval is unknown.

A recent review of ovarian cancer screening for high risk women concluded that screening does not appear to be effective in detecting tumours at an early stage, and risk reducing surgery to remove both the ovaries and fallopian tubes (bilateral salphingo-oophorectomy [BSO]) is the most effective risk reducing strategy at present.[6] It should be noted that in BRCA1 and BRCA2 carriers, a premenopause prophylactic BSO will also reduce the risk of breast cancer by 50%, even if hormone therapy is subsequently used.[7,8] The finding of occult ovarian or fallopian tube tumours at the time of BSO in 4.4% of these women further supports this strategy.

Conclusion

There is no role at the current time for population screening for ovarian cancer. There is an enormous amount of research underway, particularly using new proteomics techniques, trying to find the ideal screening or early detection test for ovarian cancer. Until new tests are fully evaluated we will continue to use the best available – with 6–12 monthly CA-125 in conjunction with ultrasound in high risk populations. Prophylactic BSO remains the best risk reducing strategy once childbearing is complete, particularly given that this reduces the breast cancer risk by 50% in BRCA carriers, and should include the uterus in HNPCC mutation carriers as their lifetime risk of endometrial cancer is 50%.

Conflict of interest: none declared.

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