Ovarian cancer screening

Dr Stuart Salfinger, Gynaecologic Oncologist,
St John of God Subiaco. Tel 9388 3495

Ovarian cancer is the leading fatal gynaecologic malignancy in Australia, with a lifetime probability of 1.5-2.0% and incidence increase with age. Amongst the 1300 or so Australian women diagnosed with ovarian cancer each year, over 70% are diagnosed when the disease is advanced and difficult to treat successfully, which means that only four out of ten women survive five years beyond their diagnosis. In this setting, what is the value of screening for ovarian cancer?

Interest in early detection to reduce mortality has grown with the use of ovarian tumor markers, particularly CA125, and with the improved diagnostic accuracy of pelvic ultrasonography. However testing for ovarian cancer in asymptomatic women can lead not only to false reassurance for women (false negatives) but it can also result in unnecessary highly invasive procedures (false positives). The anxiety generated by the false positive tests is also significant.

Screening trials

Larger trials have shown that at least 10 laparotomies would be performed on normal patients for every cancer case identified. In some studies this is as high as 18-20. As well, UK costing puts screening at 150,000 pounds per life year saved, which is beyond what is generally accepted in screening progams.

The majority of data so far has suggested that while a small increase in the number of cases detected may result from screening, there has been no impact on outcomes or survival as a result. The problem lies not only with the tests available but also with the nature of the disease.

WHO criteria for disease screening perfectly suit breast or cervical cancers, however ovarian carcinoma does not have a pre-invasive disease stage or latent period. While patients with early stage disease undoubtedly perform better these are exactly the cases that are difficult to identify with any screening test. The poor sensitivity and specificity of the tests is also a problem.

Large scale prospective clinical screening trials are in progress to determine whether either approach reduces mortality from ovarian cancer. Until final results are in, there is a consensus that women at average risk for ovarian cancer should not undergo screening with either method, outside these clinical trials. Intensive research is in progress to identify additional markers and a cost-effective screening strategy for women at average risk.

Available tests explained

CA125. This marker is neither sensitive nor specific for early stage disease. It can be normal in 50% of women with early stage ovarian carcinoma. It can also be elevated by numerous benign conditions including benign cysts, endometriosis, fibroids, PID and even normal menses.

Combined CA125 and transvaginal ultrasound (TVUS) tests. The sensitivity and specificity of the combined test has been enhanced further by using repeat CA125 measurements over time. A Risk of Ovarian Cancer (ROC) algorithm that incorporates serial measurements of CA125 is being further evaluated as part of the UK Collaborative Trial of Ovarian Cancer Screening.

Other biomarkers are being developed with improved specificity and sensitivity to detect ovarian cancer. These include gene microarray profiling proteomic technology either as a single marker, or in a panel of biomarkers, and often in combination with CA125. To date, however, no results are available on the use of these new biomarkers from prospective randomised trials in a healthy, asymptomatic population and there is no evidence for survival advantage using these markers in the screening context.

OvPlex™ is a commercial blood test developed by HealthLinx Limited (Australia) and marketed for the early detection of ovarian cancer. It measures CA125 and four additional protein biomarkers. Unpublished data from the company has reported sensitivity of 94.1% and specificity of 91.3% across all ovarian cancer disease stages, in a Phase II study of 150 ovarian cancer and 212 control samples. No data have been reported from prospective controlled clinical trials.

High risk women

Women with a family history or genetic mutation predisposing them to ovarian carcinoma (BRCA 1&2 and HNPCC) present an interesting challenge. There is no current data that shows screening is effective in this population either, so it is difficult to know what to offer these patients. Many doctors will screen with the proviso that screening has many pitfalls based on false positive or false negative tests and even in this group, most women who develop cancers do so during screening intervals.

The only proven preventive strategy for women with a genetic predisposition is risk reduction bilateral salpingo-oophorectomy (+/- hysterectomy), which removes 99% of the risk of ovarian carcinoma and also halves the risk of breast cancer in BRCA mutation carriers. The other strategy often employed is to use the oral contraceptive pill, which halves the risk of ovarian carcinoma across all women taking it (but is yet to be proven in mutation carriers).

Recommendations, in a nutshell

Recently, the National Breast and Ovarian Cancer Centre (NBOCC) released national guidelines stating that screening is not indicated for asymptomatic women (see Figure 1). The role of screening in high risk populations is a controversial area and definitive consensus is yet to be achieved despite a lack of definitive benefit.

While national guidelines can help in explaining to patients the lack of evidence for screening, unfortunately some still seek testing and the discussion of the pros and cons can take a lot more time than simply handing them a form for a CA125 test. The significant downside and risks of screening in asymptomatic women should be remembered. High risk women should be referred to appropriate genetics counselling and gynaecologic oncology services. ■

Fig 1 NBOCC: Screening and early detection in asymptomatic women

1.	There is currently no evidence that any test, including pelvic examination, CA125 or other biomarkers, ultrasound (including transvaginal ultrasound), or combination of tests, results in reduced mortality from ovarian cancer.
2.	There is no evidence to support the use of any test or combination of tests for routine screening for ovarian cancer.
3.	Further validation in large clinical trials is required before current or new biomarkers could be recommended for routine use in population screening.