

## Population screening and early detection of ovarian cancer in asymptomatic women

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This position statement and supporting background information has been endorsed by the following colleges and agencies: the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, the Royal Australian College of General Practitioners, the Australian Society Gynaecologic Oncologists, Cancer Council Australia, the Screening Subcommittee of the Department of Health and Ageing, and The Royal College of Pathologists of Australasia.

### **Population screening and early detection of ovarian cancer 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, including pelvic examination, CA125, or other biomarkers, ultrasound (including transvaginal ultrasound), or combination of tests, for routine population based 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 a population screening setting.

### **Background**

#### **Incidence and survival**

Although ovarian cancer has a high mortality rate and is the leading cause of death from gynaecological malignancy, it is a relatively uncommon disease with an incidence reported of approximately 10 per 100,000 in Australia.<sup>4</sup> In 2009, approximately 1300 women will be diagnosed and over 800 will die from the disease in Australia.<sup>4</sup> Ovarian cancer is diagnosed at an advanced stage in the majority of patients and for advanced disease the 5-year survival rates are reported to be less than 30%, whereas for patients diagnosed with stage I disease, the 5-year survival is reported to be in excess of 90%.<sup>5</sup> Therefore, in order to improve the mortality rate for ovarian cancer, detection in the early stages of the disease is required.

#### **Screening principles and ovarian cancer**

General principles have been developed as criteria for screening programs by the World Health Organisation<sup>6</sup> and the Australian Population Based Screening Framework has been developed based on these principles.<sup>7</sup> The Framework highlights the need for a strong evidence base in making the decision to introduce a screening program and highlights the requirement that the screening program should offer more benefit than harm to the target population. The Framework also provides criteria for the condition (including that it is an important health problem and that it has a recognisable latent or early symptomatic stage) and criteria for the test (including high sensitivity and specificity, adequate validation, safety, and a relatively high positive and negative predictive value).

The World Health Organisation criteria and related issues for ovarian cancer screening have been identified.<sup>8</sup> Although ovarian cancer satisfies many of the criteria for screening, there are significant limitations. A premalignant precursor lesion for ovarian cancer has not been identified and it is uncertain whether the currently available screening tests can detect ovarian cancer sufficiently early to allow intervention to alter the natural history of the disease.<sup>5</sup>

The low prevalence of ovarian cancer means that even screening tests that have very high sensitivity and specificity have a low positive predictive value for disease detection. Based on a hypothetical situation, for 100,000 screened on a single occasion for ovarian cancer with a disease prevalence 0.05%, assuming sensitivity of 99.99% and specificity of 97.5%, there would be 50 true positives, 2500 false positives, and positive predictive value of only 1.96%. Additionally, due to the high mortality associated with advanced ovarian cancer, there is a strong need for high sensitivity for detection of disease at an early stage before it may cause symptoms. This is difficult to assess using samples from patients with clinically diagnosed disease and prospective randomised controlled trials are required to demonstrate sensitivity in early detection.<sup>5</sup>

## Current Tests

To be suitable for screening, any test must satisfy the criteria of very high specificity and sensitivity, in particular high sensitivity and specificity for detecting ovarian cancer at an early stage, with data required from randomised controlled trials in the healthy population. Currently, there are several tests potentially available for screening, either alone or in combination.

**CA125**, a high molecular weight glycoprotein, is the most thoroughly assessed serum biomarker for ovarian cancer. The utility of CA125 for screening however, is limited by its poor sensitivity in early stage disease, with CA125 levels elevated in only 50% of patients with stage I disease, whereas levels are elevated in over 90% of patients with advanced disease. The specificity of CA125 is also limited, due in part to elevation of the marker in other conditions, including other cancers, benign diseases and physiological conditions.<sup>9</sup>

**Transvaginal ultrasound (TVUS)** utilises morphology and ovarian volume to detect changes that may signify developing malignancy, however it has limitations in distinguishing between masses that are benign or malignant due to the complexity of ovarian morphology. The specificity of the test is low and the high rate of false positives can result in unnecessary surgery. A weighted scoring system or morphological index has been used to decrease false positives, however there is no agreement yet on a standard index.<sup>9</sup>

**Combined CA125 and TVUS tests** have been used to increase the specificity of screening, by reducing false positives. The sensitivity and specificity of the combined test has also been enhanced by using repeat CA125 measurements over time. A Risk of Ovarian Cancer (ROC) algorithm that incorporates serial measurements of CA125 in the individual has been developed and is being further evaluated as part of the UK Collaborative Trial of Ovarian Cancer Screening trial.<sup>5</sup>

**Biomarkers** with improved specificity and sensitivity to detect ovarian cancer in the early stage of the disease have been actively sought. Gene microarray profiling technology has been utilised and proteomic technology, which has been developed extensively in the last decade, has been exploited in this search and holds considerable promise. New protein biomarkers have been identified for detecting ovarian cancer for use as a single marker, or in a panel of biomarkers, and often in combination with CA125. Some examples include lysophosphatidic acids, macrophage colony-stimulating factor, osteopontin and inhibin, and panels of biomarkers reported by groups at Johns Hopkins, Yale and University of California, Los Angeles (UCLA), with reported specificity for early stage ovarian cancer of up to 99% and sensitivity of up to 91%.<sup>9</sup> 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 commercially available blood test developed by HealthLinx Limited (Australia) that is marketed as a test for the early detection of ovarian cancer. The test 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.<sup>10</sup> No data have been reported from prospective controlled clinical trials.

## Ongoing Clinical Trials

Prospective randomised controlled trials in asymptomatic women at population risk are currently underway for CA125 and TVUS.

The **Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)** is a prospective, randomised controlled trial investigating ovarian cancer screening in over 70,000 women aged 55 to 74 years recruited from 1993-2001 in USA. The participants were randomised to control (no screening) or to CA125 and TVUS. The primary endpoint of the study is the effect on ovarian cancer mortality. Preliminary data have been reported<sup>11</sup> based on initial screening results in the group that received screening (n=28,816 women who received at least one test). The positive predictive value for invasive cancer for an abnormal CA125 was 3.7%, for abnormal TVUS was 1%, and if both CA125 and TVUS were abnormal was 23.5%. Results from four rounds of screening have very recently been published<sup>12</sup> and full results from the trial are not expected until after 2010.

The **UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)** is a prospective, randomised controlled trial of over 200,000 postmenopausal women aged 50-74 years recruited from 2001-2005 in the UK. The participants were randomised to control (no screening, n=101,359), annual screening with TVUS (USS; n=50,639) or annual CA125 screening interpreted using a risk of ovarian cancer algorithm with TVUS as a second-line test (multimodal screening [MSS] n=50,640). The primary endpoint of the study is effect on ovarian cancer mortality, with other outcomes being evaluated and a serum bank for future assessment of novel tumour markers being established. Results from the prevalence (initial) screen have recently been published.<sup>3</sup> The sensitivity, specificity and positive-predictive values for all primary ovarian and tubal cancers were 89.4%, 99.8% and 43.3% for MSS, and 84.9%, 98.2% and 5.3% for USS, respectively. The results of ongoing screening are required before the effect of screening on mortality can be determined. Screening of women will continue until 2011 and all women will be followed up until 2014, therefore final results from the trial are not expected until after this time.

## References

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\*\* In February 2008, National Breast Cancer Centre (NBCC), incorporating the Ovarian Cancer Program, changed its name to National Breast and Ovarian Cancer Centre (NBOCC). On 30 June 2011, NBOCC amalgamated with Cancer Australia to form a single national agency, Cancer Australia, to provide leadership in cancer control and improve outcomes for Australians affected by cancer.

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