Testing for ovarian cancer in asymptomatic women

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Please note that this information was updated in August 2021 with the final results of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).

Purpose

Cancer Australia Position Statements address significant clinical issues, emerging issues in cancer control and issues of ongoing interest, using the best available evidence.

The purpose of this Position Statement is to provide information and guidance in relation to routine screening of women who are at population risk of ovarian cancer, and surveillance of women who are at high or potentially high risk of developing ovarian cancer. The scope encompasses unimodal and multimodal strategies for early detection of ovarian cancer in asymptomatic women. The scope does not include diagnostic testing for assessment of individual women presenting with symptoms.

The term ovarian cancer is used in this Position Statement to include ovarian, fallopian tube and primary peritoneal cancer.

The intended audiences for this Position Statement are health professionals, medical colleges, consumers, media and policy makers.

This Position Statement has been endorsed by the Australian College of Rural and Remote Medicine, the Australian Society of Gynaecologic Oncologists, Australian Health Ministers' Advisory Council's Standing Committee on Screening, Cancer Council Australia, Ovarian Cancer Australia, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, the Royal Australian and New Zealand College of Radiologists and the Royal College of Pathologists of Australasia.

Cancer Australia has also developed a consumer Frequently Asked Questions (FAQs) resource to assist with promoting and understanding the key messages of the Position Statement.

Guidance

Population screening and early detection of ovarian cancer in asymptomatic women

1. For asymptomatic women at population risk of ovarian cancer, 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. For routine population-based screening for ovarian cancer, 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.

3. Conclusive evidence from large randomised controlled trials is required before current or new tests can be recommended for routine use in a population screening setting.

Surveillance of asymptomatic women at high or potentially high risk of ovarian cancer

1. For asymptomatic women at high or potentially high risk of ovarian cancer, 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. For asymptomatic women at high or potentially high risk of ovarian cancer, 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 surveillance for ovarian cancer.

Practice points

1. Referral for genetic assessment should be discussed with women who are at potentially high risk of ovarian cancer.

2. Bilateral salpingo-oophorectomy is the most effective risk-reducing strategy for ovarian cancer in high-risk women.[1,2]

Background

Incidence and survival

In 2019, it is estimated that 1,510 new cases of ovarian cancer will be diagnosed in Australia and there will be 1,046 deaths from ovarian cancer.[3] The age-standardised incidence rate is estimated to be 9.8 cases per 100,000 females in 2019.[3] In Australia, ovarian cancer is the tenth most common cancer in women and the sixth most common cause of death from cancer in women.

In 2011-2015 Australian women with ovarian cancer had a 45.7% chance of surviving for 5 years compared to their counterparts in the general Australian population.[3] Ovarian cancer is often diagnosed at an advanced stage when survival outcomes are poor. For women diagnosed with advanced disease (Stage III and Stage IV), 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 around 90%.[4] 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 Organization.[5] Based on these principles, the Australian Department of Health has developed an Australian Population Based Screening Framework,[6] which highlights the need for a strong evidence base in making the decision to introduce a screening program, and 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).

Ovarian cancer satisfies some of the criteria for screening, but some criteria represent a significant challenge (see http://www.health.gov.au/internet/screening/publishing.nsf/Content/population-based-screening-framework for further information on population based screening framework). Although an opportunity exists to alter the natural history of ovarian cancer if it can be detected earlier, our understanding of early disease progression from latent to declared disease is incomplete and continuing to develop. Recent evidence suggests that many ovarian cancers originally thought to have arisen in the ovary may have had precursor lesions in the fallopian tubes.[7]

Although various subtypes of ovarian cancer are recognised on the basis of histologic morphology, a new classification scheme now divides ovarian cancers into two broad types based on tumour characteristics.[8] Type I are low-grade, relatively non-aggressive carcinomas, often arising from recognisable precursor lesions (e.g. borderline ovarian tumours). Type I tumours include low-grade serous, mucinous, endometrioid, clear cell, and transitional cell carcinomas. While clear cell carcinomas are categorised as a type I tumour, they may actually belong to an intermediary category due to their mutations and behaviour. Type II tumours are high-grade, genetically unstable, aggressive carcinomas, which have a tendency to metastasise from small, or even microscopic, primary lesions. Precursor lesions for type II tumours have not been described clearly and tumours may develop de novo from the epithelium of the fallopian tube and/or the ovarian surface epithelium.[8] Type II tumours include high-grade serous carcinomas, undifferentiated carcinomas, and carcinosarcomas. Type II tumours constitute the majority of ovarian cancers and, due to their rapid progress from microscopic to widespread disease, are more difficult to detect at earlier stages and have the poorest prognosis. It is now apparent that in addition to identifying Type I tumours, a successful screening test would need to identify Type II tumours in what appears to be a brief window of opportunity prior to their early dissemination. These insights were not

available at the inception of the recent large population screening trials for ovarian cancer.

In terms of designing screening trials, the relatively low incidence of ovarian cancer presents a significant challenge; particularly large clinical trials are needed to detect a sufficient number of cases for meaningful analysis of the screening test. Also, the need for surgical removal of ovaries to make a final diagnosis places a stringent requirement on the positive predictive value of any screening test for ovarian cancer, as the consequences of a false positive test result are serious.

Current tests

To be suitable for screening or surveillance, any test for ovarian cancer should be highly sensitive (i.e. most women with ovarian cancer are identified by the test) and have a high positive predictive value (i.e. most test-positive women have ovarian cancer). The latter is critical where diagnosis is associated with surgical removal of ovaries. Additional criteria are a low false negative rate (i.e. not many women with ovarian cancer are missed by the test) and the ability to detect cancers at an earlier stage to allow earlier treatment. Currently, there are several tests available that have been studied alone and in combination for use in screening and/or surveillance:

- **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 50-60% of women with Stage I disease, whereas levels are elevated in 75-90% of women with advanced disease.[9] 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,[9,10] which reduces the positive predictive value of the test.

- **Transvaginal ultrasound (TVUS)** utilises morphology and ovarian volume to detect changes that may signify developing malignancy. Although highly sensitive, TVUS has limitations in distinguishing between benign and malignant masses due to the complexity of ovarian morphology, which can result in unnecessary surgery (low positive predictive value).[7,11]

- **Combining CA125 and TVUS tests** can increase the sensitivity and positive predictive value of screening or surveillance compared to either test alone. Testing can be done in sequence, by limiting a second-line test (e.g. TVUS) to women with abnormal results in the first-line test (e.g. CA125). For example, the Risk of Ovarian Cancer Algorithm (ROCA) is a proprietary test that incorporates changes in CA125 over time, among other factors, to inform secondary testing intervals and triage to other tests such as TVUS. This approach has been used in large screening and surveillance trials in the UK, the USA and Australia, as described below.

Population screening and early detection of ovarian cancer in asymptomatic women

Clinical trials of population screening

Two large, well-conducted randomised controlled trials (RCTs) of population screening for ovarian cancer reported no statistically significant mortality benefit at approximately 11-12 years follow-up using a priori analyses.

From 1993 to 2001, the **Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)** enrolled over 70,000 women in the United States aged 55 to 74 years, who were randomised 1:1 to either a no-screening control group or to screening. The screening tests were CA125 (single threshold) plus TVUS annually for 4 years, followed by annual CA125 (single threshold) only for up to a further 2 years. No statistically significant mortality benefit or stage shift was associated with screening after a median of 12.4 years follow up,[12] but 14.8 false positive surgeries were conducted per screen-detected cancer. Extended follow-up to a median of 14.7 years also found no mortality benefit.[13] Post hoc analysis found no mortality or stage shift benefits with screening for the more aggressive Type II cancers.[14]

From 2001-2005, the **UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)** enrolled over 200,000 post-menopausal women aged 50-74 years, who were randomised 2:1:1 to no screening or to one of two annual screening strategies: TVUS alone or ROCA triage. The latter involved CA125 evaluation using the Risk of Ovarian Cancer Algorithm (ROCA), with the results determining whether or not women received additional testing, which could be either repeat CA125 (Level I) or CA125 and TVUS (Level II).

After a median follow up of 11.1 years, a stage shift was observed in the ROCA triage screening group, with significantly more diagnoses made at Stages I and II compared with the control group.[15] No mortality benefit, however, was associated with screening when analysed using the pre-specified Cox proportional hazard model using data up to 2014.

When analysed post hoc with the weighted log-rank test used in the PLCO trial, which accounts for the expected delay in mortality outcomes, a significant mortality benefit was noted for both screening groups compared with the no-screening group. However, the validity of the post hoc analyses of UKCTOCS has been challenged.[16-19] The lead investigator of this trial has commented that 'for the time being, in the absence of unequivocal evidence of a mortality benefit, large-scale population-based ovarian cancer screening programmes are not justified'.[20]

When classifying borderline tumours as false positives, the rate of false-positive surgeries per screen-detected cancer was 14.8 for TVUS (which is higher than the generally accepted rate of 9 per screen-detected ovarian cancer) and 2.9 for ROCA triage.[15] ROCA triage was also more sensitive than TVUS but, at 74- 84%, remained below what might be acceptable for a screening test.[15] No analyses by tumour type have yet been reported for this trial. Longer term follow-up of UKCTOCS is expected after further censorship in 2018 and 2024, with reporting in 2020.

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2021 evidence update: Long-term follow-up of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)

The median follow-up was 16.3 years. Within the ROCA triage screening group there was a 47.2% increase in stage I and 24.5% decre
stage IV ovarian cancers detected compared to no screening. There was no evidence of a change in stage distribution in the TVUS gr
compared with the no screening group. No significant reduction in mortality was observed in either the ROCA triage or TVUS groups

with no screening. The authors concluded that given screening did not significantly reduce ovarian cancer deaths, general populatio screening could not be recommended. The importance of having disease-specific mortality as the primary outcome in ovarian cance trials was emphasised.

Reference: Menon U, Gentry-Maharaj A, Burnell M, Singh N, Ryan A, Karpinskyj C, et al. Ovarian cancer population screening and mo long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. The Lancet. 387(10290): 2182-2193.

Surveillance of women at high or potentially high risk of ovarian cancer

A family history of breast and ovarian cancer is the most significant risk factor for ovarian cancer but does not necessarily imply an inherited genetic cause. Of women in Australia with non-mucinous invasive epithelial ovarian cancer, 14% were found to have a heritable (germ-line) mutation in the BRCA1 or BRCA2 genes.[21] However, over one-third of women in Australia with invasive epithelial ovarian cancer in whom a heritable BRCA1/2 mutation is identified have no known family history of breast or ovarian cancer.[21-23] For women with a BRCA1 mutation, the risk of developing ovarian cancer by the age of 80 is 44%, and for women with a BRCA2 mutation the corresponding risk by age 80 is 17%.[24]

In some ethnic populations such as the Ashkenazi Jewish population, prevalence of heritable BRCA1/2 mutations in women with ovarian cancer is high due to common founder mutations. The frequency of BRCA1/2 mutations for the Ashkenazi Jewish population has been estimated at approximately 2.5% in Australia compared to less than 1% in the general population.[25,26] Heritable BRCA1/2 mutations are found in approximately 30% of Ashkenazi Jewish women with ovarian cancer.[26,27]

A small proportion of hereditary ovarian cancers are due to mutations in a number of DNA mismatch repair genes associated with Lynch syndrome (e.g. MLH1, MSH2, MSH6).[28] Heritable mutations in other genes are also associated with ovarian cancer, though the ovarian cancer risk is uncertain.

Definition of high or potentially high risk

The category of high or potentially high risk of ovarian cancer covers less than 1% of the female population. Lifetime risk of ovarian cancer varies but may be up to 50%.[24] Individual risk may be higher or lower if genetic test results are known.

Women are at high risk of ovarian cancer if they:

- have had genetic testing and been found to have a high-risk ovarian cancer-related gene mutation (e.g. in BRCA1/2, or one of the Lynch syndrome-associated genes such as MLH1, MSH2, MSH6).

Women are at potentially high risk if they:

In a family that has had genetic testing

- are an untested member of a family in which the presence of a high-risk ovarian cancer gene mutation has been established.

In a family where no genetic testing has been done

- have one first-degree relative diagnosed with invasive epithelial ovarian cancer aged less than 60 years;
- have more than one first-degree or second-degree relative with invasive epithelial ovarian cancer diagnosed at any age (on the same side of the family);
- have a strong family history of both breast and epithelial ovarian cancer; or

- have a family history of breast and/or epithelial ovarian cancer with Ashkenazi Jewish heritage.

For women at potentially high risk who have not undergone genetic testing, consider referral to a family cancer clinic.

Clinical trials of surveillance in women at high risk or potentially high risk

Two large cohort studies assessed surveillance of women at high or potentially high risk of ovarian cancer using a ROCA triage strategy, and one cohort study used threshold testing of CA125 for surveillance.

Studies to date have been focused on sensitivity, specificity and stage shift. No randomised controlled trials of surveillance among high-risk or potentially high-risk women have been conducted. Due to ethical and practical limitations in randomising this population group between surveillance and control groups, it is unlikely that a randomised controlled trial will be conducted in the future.

The **Cancer Genetics Network and Gynecologic Oncology Group (CGN/GOG)** study combined the results from two screening trials that used the same ROCA triage testing strategy; CGN (United States; 2001-2011) and GOG-0199 (United States and Australia; 2003-2006). Women over 30 years of age were eligible if: (1) they or a first or second degree relative had a BRCA1/2 mutation, or (2) they or a first or second degree relative had been diagnosed with ovarian and/or breast cancers (at least two cancer diagnoses). A total of 3,818 women were recruited for ROCA evaluation of CA125 every 3 months (with triage to additional CA125 and/or TVUS where indicated) plus annual TVUS.[29] Nine ovarian cancers were screen-detected but the rate of false-positive surgeries was high, occurring at a rate of 20.7 per screen-detected cancer.

CA125 thresholds were used for surveillance in the **United Kingdom Familial Ovarian Cancer Screening Study Phase I (UKFOCSS – Phase I)**, using different thresholds for pre-menopausal and post-menopausal women. From 2002 to 2008, 3,563 women aged at least 35 years and with a lifetime risk of ovarian cancer of 10% or more were recruited for annual testing with both CA125 and TVUS. Nine women were diagnosed with ovarian cancer after a positive test and three women were diagnosed within 12 months of a negative test.[30] There was evidence of a shift to earlier-stage cancers in women diagnosed within a year of screening compared to those diagnosed in the post-screening phase. Although the false-positive surgery rate was within what may be considered acceptable limits, occurring at a rate of 2.4 per screen-detected cancer, sensitivity was poor, which prompted Phase II of the trial, incorporating the ROCA triage test.

From 2007 to 2012, the **UKFOCSS – Phase II** study enrolled 4,531 women aged at least 35 years with a lifetime risk of ovarian cancer of 10% or more. Testing took place using ROCA evaluation of CA125 every 4 months (triaging to additional CA125 and/or TVUS where indicated), plus TVUS every year.[31] Nineteen cancers were diagnosed within 1 year of prior screening; 13 diagnoses were screen-detected and six occult cancers were identified at RRSO. The rate of false-positive surgeries was high at 11.5 per screen-detected cancer (13 cancers and 149 false-positive surgeries).

Phase II of the UKFOCSS study reported a stage shift, finding a significantly higher proportion of low volume disease, defined as stage IIIa or less (corresponding to less macroscopic peritoneal metastasis outside the pelvis) in women diagnosed within one year of screening compared with women diagnosed more than one year after the last screen ($p<0.001$). However, half (6/12) of the low-volume diagnoses made within one year of the last screen were occult cancers discovered during bilateral salpingo-oophorectomy unrelated to screening. The study also reported that the proportion of all cases with zero residual disease after surgery (an important prognostic factor in ovarian cancer) was higher in women diagnosed within one year of screening compared with women from the same cohort in whom cancer was diagnosed more than one year after screening was completed, but this finding was not significant.[31]

Overall, the evaluation of surveillance tests in these uncontrolled trials demonstrates that an acceptable approach to surveillance has not yet been established. The current tests have unacceptably high rates of false positives and/or insufficient sensitivity to detect ovarian cancer.

There is currently insufficient evidence to support ovarian cancer screening and it is not recommended in women at either population or at high or potentially high-risk of ovarian cancer, outside of a clinical trial setting. This recommendation is in line with international guidelines.[32-34]

The utility of ovarian cancer surveillance in high-risk women will be further explored in a clinical trial underway in the UK known as the Avoiding Late Diagnosis in Ovarian Cancer (ALDO) which aims to detect ovarian cancer among asymptomatic women aged 35 years or over with a BRCA1 or BRCA2 mutation, who have chosen to delay risk-reducing surgery to remove their ovaries and fallopian tubes (RRSO).[35]

RCT of population screening re-analysed for women who may have elevated risk

The PLCO population screening RCT was not designed to identify women at high risk of ovarian cancer but, using data that was collected at enrolment, it was possible to identify a subgroup of over 22,000 women who had either a personal history of breast cancer or at least one first degree relative with breast cancer or ovarian cancer.[36] These criteria are less stringent than those defining women at high risk of ovarian cancer and would include some women with no increased risk. When analysed as a group, however, it could be expected that the overall risk is higher than population risk.

Annual screening using CA125 (single threshold) and TVUS was associated with a significant reduction in advanced bulky disease at diagnosis. The clinical significance of this is not clear but, for the important outcome of mortality, no statistically significant benefit was found in this analysis.

Ongoing research

There are no clinical trials of population screening for ovarian cancer in asymptomatic women currently ongoing.

A number of tests for ovarian cancer diagnosis or prognosis are under investigation; however, their potential for application as a screening tool is not yet known. DNA, plasma, serum and tissue samples from the large screening trials are being used to investigate new biomarkers, tests, and prediction models that may improve upon the ROCA algorithm. The use of any new detection tools or strategies would require further validation and testing to assess the potential clinical benefits for ovarian cancer screening or surveillance.

As there are currently no clinical trials of population screening for ovarian cancer in asymptomatic women, no new technologies are likely to be introduced or recommended for screening or surveillance in the short- to medium-term. In light of the emerging understanding of the heterogeneity of ovarian cancers and early disease development, it is highly unlikely that a single biomarker or imaging modality will be sufficient to detect each of the various subtypes at their earliest stages.

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