



Cancer and the Ovaries

Understanding ovarian cancer
and screening methods

by Dr Anthony Siow

Ovarian cancer is a leading cause of death in many countries. In Singapore, it is the fifth most common cancer. The lifetime risk of a woman developing ovarian cancer is about 2%. This risk can be higher, to as high as 10%, if the woman has a strong family history of cancer (see box).

When ovarian cancer is diagnosed early and confined to the ovary (Stage 1), the five-year survival rate can be as high as 90%. Unfortunately, ovarian cancer is usually diagnosed late and the overall five-year survival rate can be lower than 35%.

The recognition that early detection of ovarian cancer may have the potential to improve prognosis prompted the development of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO Trial).

PLCO Cancer Screening Randomised Controlled Trial

This large randomised trial which looked at the effect of screening for ovarian cancer in women with average risk of ovarian cancer, concluded that screening did not reduce the ovarian cancer mortality rates.

In this study, 78,216 women aged 55 to 74 years were randomly assigned to annual CA-125 and transvaginal ultrasound or usual medical

care. Two hundred twelve women (5.7 per 10,000 person years) in the screening group and 176 women (4.7 per 10,000 person years) in the usual care group were found to have ovarian cancers. The mortality from ovarian cancer was 3.1 vs 2.6 per 10,000 person years in the screening group and usual care group, respectively, a result that was not statistically different.

One would assume that with screening, the cases of ovarian cancers detected would be in the early stages, resulting in an observation called stage shift. However, the study failed to show a stage shift with annual CA-125 screening and transvaginal ultrasound. In the screening group, 69% of ovarian cancers diagnosed were in the late stages as compared to 78% in the usual care group, a difference that was not statistically significant. A possible explanation for this could be that when the ovarian cancer was in an early stage, it was still too small to be detected by transvaginal ultrasound or too indolent to cause a rise in CA-125. Another possible explanation could be that ovarian cancers progress rapidly through the early stage, limiting the ability for annual screening tests to detect them.

The screening for ovarian cancer led to a false positive result of about 5% at each round. In this trial, a total of 3,285 women had false positive results with 1,080 of them undergoing surgery. As a result of surgery, 163 (15%) women experienced at least one serious complication. This underlies the fact that screening for ovarian cancer is not without risks.

The investigators concluded that annual screening for ovarian cancer with simultaneous CA-125 and transvaginal ultrasound does not reduce the mortality in women at average risk for ovarian cancer, but does increase surgical procedures and associated harms.

Symptoms of Ovarian Cancer

It was historically thought that ovarian cancer is a 'silent killer' with the woman being asymptomatic until the cancer is advanced. Recently, this concept has been challenged as more studies have come to reveal that women are commonly symptomatic for months, before investigations are even done to screen for ovarian cancer.

It might well be that the best way to detect early ovarian cancer is a high index of suspicion, when an elderly woman presents with some symptoms suggestive of ovarian cancer. A systematic review by Bankhead et al shows that abdominal or gastrointestinal symptoms (like pain, distension, bloating) are the most common complains occurring between 60% to 80% of the time. Interestingly, abdominal swelling, abnormal vaginal bleeding, urinary symptoms and loss of appetite were only present in around 30% of the time.

Hence, patient and physician education to improve symptom awareness may result in detecting ovarian cancer at an earlier stage. Although there are currently ongoing research to validate this concept, the National Institute for Health and Clinical Excellence (NICE) guidelines on detecting ovarian cancer in the primary care setting, reiterates the need to be vigilant for the symptoms and signs of ovarian cancer.

NICE Guidelines on Recognition of Ovarian Cancer in Primary Care

The guideline recommendations are:

- Refer the woman urgently if physical examination identifies ascites and/or a pelvic or abdominal mass (which is not obviously uterine fibroids).
- Carry out tests if a woman (especially over 50 years old) reports having any of the following symptoms on a persistent or frequent basis –

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particularly more than 12 times per month:

- persistent abdominal distension (women often refer to this as 'bloating')
 - feeling full (early satiety) and/or loss of appetite
 - pelvic or abdominal pain
 - increased urinary urgency and/or frequency.
- Consider carrying out tests if a woman reports unexplained weight loss, fatigue or changes in bowel habit.
 - Carry out appropriate tests for ovarian cancer in any woman above 50 years old experiencing symptoms of irritable bowel syndrome (IBS) within the last 12

months, because IBS rarely presents for the first time in women of this age.

- Advise any woman who is not suspected of having ovarian cancer to return to her GP if her symptoms become more frequent and/or persistent.

The first test that the woman should have, in the above scenarios, is a CA-125. If the result is 35 IU/mL or greater, then an ultrasound of the abdomen and pelvis should be arranged. If the ultrasound suggests ovarian cancer, the woman should be referred urgently to see a specialist gynaecologist. If the woman has a normal CA-125, or an elevated CA-125 but a normal ultrasound, she should be carefully assessed for other causes of her symptoms. If there are no other clinic causes to explain her symptoms, she should be advised to return for a reassessment if her symptoms worsen or become more frequent.

Despite enormous effort, minimal progress has been made to reliably detect ovarian cancer at an early stage. To date, routine screening for ovarian cancer in the general population of women without an increased risk of ovarian cancer has not been entirely successful in terms of mortality reduction. However, for women with an increased risk of cancer,

there may be a role for ovarian cancer screening as evidence in the latest UK Familial Ovarian Cancer Screening Study.

Family history can be used to define women at increased risk of ovarian cancer.

- **Two or more individuals with ovarian cancer, who are first degree relatives of each other**
- **One individual with ovarian cancer at any age, and one with breast cancer diagnosed under age 50 years, who are first degree relatives of each other***
- **One relative with ovarian cancer at any age, and two with breast cancer diagnosed under 60 years, who are connected by first degree relationships***
- **Known carrier of relevant cancer gene mutations (e.g. BRCA-1 or BRCA-2)**
- **Untested first degree relative of a predisposing gene carrier**
- **Three or more family members with colon cancer, or two with colon cancer and one with stomach, ovarian, endometrial, urinary tract or small bowel cancer in two generations. One of these cancers must be diagnosed under age 50 years**
- **An individual with both breast and ovarian cancer**

In these categories, a second degree relative may be counted if the transmission is via the paternal line (e.g. a sister and a paternal aunt or a sister and two paternal aunts).

UK Familial Ovarian Cancer Screening Study (UKFOCSS)

This study aimed to see how good a yearly screening programme with CA-125 and ultrasound would be at picking up ovarian cancers in women thought to be at high risk of the disease. The result shows that annual ovarian cancer screening in this group of women did pick up the majority (81%) of ovarian cancers.

This study followed up 3,563 women aged above 35 years old from 2002 to 2008. All the women were felt to have an increased lifetime risk (10%) for ovarian cancer. They included women with strong family history of cancer or are themselves carrier of the BRCA or Lynch mutation cancer gene.

This initial result suggests that ovarian cancer screening in this group of women can lead to an earlier diagnosis. Women who had been screened within the previous year were less likely to be diagnosed with advanced ovarian cancer, as compared

to women who had not been screened for over a year. Thirteen women in the group that had been screened within the previous year were found to have ovarian cancer, of which four were early stage. Among women who had not been screened for over a year, seven out of eight women had cancers detected in the later stages of III and IV.

The investigators suggest that screening high-risk women more frequently, coupled with swift surgical treatment where necessary, might improve the chances of finding more ovarian cancers at an earlier stage. Hence in the second phase of the trial, they have reduced the screening interval from 12 months to four months and will present the findings in the near future.

Conclusion

Ovarian cancer is a highly lethal disease of low prevalence. Routine ovarian cancer screening with CA-125 and transvaginal ultrasound has not been shown to reduce disease specific mortality. Educating women about the early symptoms of the disease and getting doctors to carry out timely diagnostic tests may help in early detection. Identifying women with increased risk of ovarian cancer for more frequent screening may also help detect a significant percentage of ovarian cancers in the early stage. **IMG**



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Dr Siow graduated with a degree in Medicine and Surgery from the National University of Singapore, obtained his Masters Degree in 2000 and became a Member of the Royal College of Obstetricians and Gynaecologist in the United Kingdom as well as the Royal Australia & New Zealand College of Obstetricians and Gynaecologists.

He has a special interest in laparoscopic surgery and was awarded a MOH scholarship in Advanced Laparoscopic Surgery in Sydney, Australia. He is the first Gynaecological Surgeon in Singapore trained in Laparoscopic Pelvic Floor Repair and also the first in Singapore to perform Single Incision Total Laparoscopic Hysterectomy and Myomectomy. He is one of the few gynaecologists in the region to have done more than 100 cases of Single Incision Laparoscopic procedures. Dr Siow travels regionally to lecture on gynaecological issues, as well as perform live surgery to teach laparoscopic procedures. He has published extensively in leading international medical journals on work on laparoscopic management of ectopic pregnancy.

Apart from laparoscopy, Dr Siow constantly keeps himself abreast of the best evidence-based management for general conditions like bothersome vaginal discharges, menstruation irregularities, infertility and menopausal adjustments. He still enjoys guiding his patients through their pregnancy and finds the birth of their newborn the ultimate joy one can experience together with the patients.

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