



衛生防護中心
Centre for Health Protection

**Cancer Expert Working Group on
Cancer Prevention and Screening**

**Recommendations on Prevention and Screening
for Ovarian Cancer
For Health Professionals**

Local epidemiology

Ovarian cancer is an important public health issue because it has a poor prognosis and higher mortality rate with the overall 5-year survival rate of 44-46%, mainly due to late detection of the disease.^{1,2} Epithelial ovarian cancer is the predominant type of malignant ovarian tumours which accounts for more than 90% of ovarian cancers in the developed countries¹ and around 80% in Hong Kong,³ on which most epidemiologic studies have focused.

2. In 2015, ovarian cancer was the sixth commonest cancer in Hong Kong females. A total of 569 ovarian cancer cases were newly diagnosed, accounting for 3.8% of all female cancer cases. The crude incidence rate and age-standardised incidence rate (ASIR) of ovarian cancer were 14.5 per 100,000 female population and 9.9 per 100,000 standard population, respectively.^{4,5}



3. There were 227 deaths due to ovarian cancer in 2016, ranking it the seventh leading cause and constituting 3.9% of all cancer deaths in females. The crude mortality rate and age-standardised mortality rate (ASMR) of ovarian cancer were 5.7 per 100,000 female population and 3.3 per 100,000 standard population, respectively.⁶ Over the past three decades, the ASIR showed an upward trend whereas the ASMR showed a downward trend. As compared with other developed countries, the ASIR of ovarian cancer in Hong Kong was higher whereas the ASMR was lower in 2012.⁷

Risk factors

4. There are multiple non-modifiable and modifiable factors determining a woman's risk of ovarian cancer, including

(a) Family history

Being one of the most well-proven risk factors, **family history of ovarian cancer** occurs in about 3% of ovarian cancer cases recorded overseas.⁸ A meta-analysis estimated the pooled relative risk of ovarian cancer in women with an affected first-degree relative was 3.1,⁹ and risk may be even higher for those with multiple relatives affected and with early age of onset.¹

(b) Inheritance of deleterious genetic mutations

Overseas data revealed that about 10-15% of ovarian cancer cases occurred in women with *BRCA1/2* gene mutations which also increased the risk of developing breast cancer.¹⁰ A prospective cohort study estimated that the cumulative risk of ovarian cancer was 44% for *BRCA1* carriers and 17% for *BRCA2* carriers respectively by age 80.¹¹ An estimated lifetime ovarian cancer risk of 6-8% was reported in women

with Lynch syndrome.¹²

(c) Use of Hormonal replacement therapy (HRT)

Among current HRT users, the risk of ovarian cancer was significantly increased even with less than 5 years of use (relative risk [RR] 1.43, 95% confidence interval [CI] 1.31-1.56), and the risk declined after discontinuation.¹³

(d) Obesity

Both the World Cancer Research Fund (WCRF)¹⁴ and International Agency for Research on Cancer (IARC)¹⁵ concluded sufficient evidence that higher amount of body fatness is associated with increased ovarian cancer risk; a 6% significant increase per five Body Mass Index (BMI) units was observed in the WCRF report while positive association was identified in IARC review.

(e) Nulliparity

Nulliparity was associated with a 24% increase in ovarian cancer risk compared to women with one child, and each additional birth in parous women reduced the overall ovarian cancer risk by 6%.¹⁶

(f) Asbestos

Asbestos is classified by the IARC as a Group 1 carcinogen for ovarian cancer.¹⁷ Risk of ovarian cancer mortality was 77% higher among women with occupational exposure to asbestos.¹⁸

(g) Tobacco smoking

Studies to date show that risk of a specific histological type, namely mucinous ovarian cancer, was higher in current smokers compared with never smokers (RR 1.79, 95% CI 1.60-2.00).¹⁹

Primary prevention

5. Women may be able to lower their risk of ovarian cancer by

avoiding certain risk factors, such as maintaining a healthy body weight by having regular physical activities and balanced diet, avoiding or quitting smoking, following occupational safety and health rules (e.g. proper use of personal protective equipment) to reduce exposure to asbestos in the workplace. A meta-analysis showed that breastfeeding was associated with lower risk of epithelial ovarian cancer, and the risk decreased by 8% for every 5-month increase in breastfeeding duration.²⁰ Hence, women are recommended to breastfeed each child and for a longer duration.

6. Women who have used oral contraceptives (OC) have a 30-40% lower risk of ovarian cancer,¹ and the longer duration of OC use, the greater the reduction of the risk and this protection lasted at least 30 years after cessation.²¹ Notwithstanding this, OC pills do have some side effects and risks, such as increase in risk of breast cancer or venous thromboembolism.²¹⁻²⁴ Women considering taking OC for ovarian cancer prevention should discuss the potential risks and benefits with their doctor.

Early detection

7. Symptoms associated with ovarian cancer (like pelvic or abdominal pain, urinary urgency or frequency, increased abdominal size or bloating, difficulty eating or feeling full) are often non-specific. Women and healthcare professionals should be vigilant of suspicious signs and symptoms of ovarian cancer. Women should seek medical attention when these symptoms become more frequent or persistent.

Screening in women at average risk

8. Common methods used to screen for ovarian cancer include pelvic examination, transvaginal ultrasonography (TVUS), and serum tumour

markers such as cancer antigen 125 (CA125).

I. Effectiveness

9. Two large-scale and good-quality randomised controlled trials (RCTs) were conducted to evaluate the effectiveness of ovarian cancer screening. In the United States, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial were randomly assigned 78,216 healthy average-risk women aged 55 to 74 years to receive either annual screening (i.e. CA125 for 6 years and transvaginal ultrasound (TVUS) for 4 years) or usual care (i.e. no screening).²⁵ The largest and more recent one is the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) which randomised 202,638 postmenopausal women aged 50 to 74 years using different screening protocols: (i) multimodal strategy (i.e. CA125 testing using the risk of ovarian cancer algorithm (ROCA) as a triage and TVUS as a second-line test); or (ii) TVUS only; or (iii) usual care.²⁶ Data and figures quoted below are extracted from these two studies unless specified otherwise.

A. Pelvic examination

10. The sensitivity, specificity and positive predictive value (PPV) of pelvic examination for detecting ovarian cancer were 5.1%, 99.0% and 0.4%, respectively.²⁷ Pelvic examination is not recommended as screening method in asymptomatic women due to its poor sensitivity.^{2, 28}

B. Transvaginal ultrasonography (TVUS)

11. The majority of adnexal masses detected by TVUS is found to be benign.² The UKCTOCS trial demonstrated that although TVUS alone was

quite sensitive (84.9%) and of good specificity (98.2%) for screening for all primary ovarian and tubal cancers, the PPV was only 5.3% in the study cohort.²⁹

C. CA125 screening

12. Elevated CA125 levels can be caused by other diseases (e.g. inflammation of the peritoneum, benign cysts), inferring that using this marker alone is associated with a significant risk of false-positive screening results.^{30, 31} Notwithstanding this, when coupled with TVUS, the sensitivity, specificity and PPV of CA125 test for the detection of all primary ovarian and tubal cancers were improved to 89.4%, 99.8% and 43.3%, respectively, leading to fewer repeat tests and surgeries in the study population.²⁹

13. Nonetheless, the UKCTOCS trial found no significant difference among ovarian cancer mortality reduction in multimodal screening strategy (i.e. annual CA125 screening and TVUS as a second-line test compared with no screening).²⁶ The PLCO trial also concluded that screening with CA125 and TVUS did not reduce ovarian cancer mortality,²⁵ and this result is reaffirmed in its updated analysis after follow-up of 15 years.³²

II. Cost-effectiveness

14. Data on the cost-effectiveness of ovarian cancer screening are limited. One modelling study using UKCTOCS data estimated the incremental cost-effectiveness ratio (ICER) comparing multimodal screening strategy with no screening was £8,864 per QALY, but the long-term effectiveness of strategy in reducing ovarian cancer mortality remains uncertain.³³ It is estimated that a national ovarian cancer screening based on

multimodal screening strategy could potentially be cost-effective if a definitive mortality benefit of 20% is confirmed at the end of ongoing follow-up of the UKCTOCS.³⁴

III. Potential harms

15. Reported false-positive rates of CA125 testing and TVUS screening were nearly 9.7% across all screening rounds in the PLCO trial, of whom nearly one-third of false-positive cases received diagnostic surgery and major complications occurred in 15% of these surgeries.²⁵ In the first screening round of the UKCTOCS, reported false-positive rates of multimodal screening were 9.0% (1% of them underwent diagnostic surgery and 3.1% complications recorded) while 11.9% for TVUS screening (3.2% of them underwent diagnostic surgery and 3.5% complications recorded).^{2,26,29}

16. In the analysis of women with recall screening in the UKCTOCS trial, there was a significant increased risk of psychological morbidity among women requiring higher level repeat screening (OR 1.28, 95% CI 1.18-1.39). Screening did not appear to raise anxiety, but psychological morbidity was elevated by more intense repeat testing following abnormal annual screening.³⁵

Screening in women at increased risk

17. For women at increased risk for ovarian cancer, data regarding screening and risk reduction are limited. Although phase I of the United Kingdom Familial Ovarian Cancer Screening Study (UKFOCSS) reported that annual screening with CA125 and TVUS did not lead to an appreciable shift in stage diagnosis,³⁶ the phase II of UKFOCSS showed that CA125 screening incorporated with ROCA every four months and TVUS (at an interval determined by the ROCA) achieved significant stage shift. Hence,

ROCA-based screening may be an option for high-risk in UK setting though survival improvement remains unknown.³⁷

International recommendations on ovarian cancer screening

18. Given that there is currently no screening test proven to be effective in reducing ovarian cancer mortality, a number of major international medical and public health organisations, including USPSTF,^{2, 38} American Cancer Society,³⁹ Canadian Task force on Preventive Health Care,⁴⁰ UK National Screening Committee,⁴¹ Cancer Council Australia⁴², does not recommend ovarian cancer screening in asymptomatic women at average risk. Currently, a few overseas organisations (e.g. American College of Obstetricians and Gynecologists,⁴³ National Comprehensive Cancer Network⁴⁴) recommends women at high risk (e.g. with deleterious mutations in *BRCA1/2* or Lynch syndrome) may consider screening for ovarian cancer after assessment by physicians.

Conclusion

19. To date, no scientific evidence has proven that screening with TVUS and tumour markers (in particular CA125), alone or in combination, for the early detection of ovarian cancer among average-risk women can reduce mortality. Additionally, the ability of currently available screening tests to detect ovarian cancer at a stage early enough to ensure that treatment can reduce mortality remains questionable. On the other hand, there is sufficient evidence that screening for ovarian cancer can lead to harms, such as surgical complications due to diagnostic surgery for false-positive results. Hence, awareness of symptoms and signs, timely investigations and referral in primary care setting play a key role in early detection of ovarian cancers to improve the prognosis. There is also no local study on the effectiveness of ovarian cancer

screening for women at average or increased risk. Additional research is needed to better understand the risk factors or causes of ovarian cancer in local Chinese women.

20. Balancing benefits and harms, there is insufficient evidence to recommend screening for ovarian cancer among average risk populations. The CEWG will keep in view the latest development and emerging evidence on this issue, especially findings from the ongoing UKCTOCS trial. For women at increased risk (e.g. with strong family history of ovarian or breast cancer, carriers of *BRCA1/2* deleterious gene mutations or Lynch syndrome), there is limited evidence to support regular ovarian cancer screening. As such, they are recommended to seek advice from doctors for assessment of their ovarian cancer risk and the need for and approach of screening if necessary.

Recommendation

21. Taking into consideration local epidemiology, emerging scientific evidence, local and overseas screening practices, the Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) formulated the recommendations on ovarian cancer screening in November 2017 as follows:

For women at average risk	
1.	Screening for ovarian cancer is not recommended in asymptomatic women at average risk.
For women at increased risk	
2.	Women at increased risk, such as with strong family history of ovarian/breast cancer or inherited deleterious gene mutations (e.g. <i>BRCA1/2</i> , Lynch syndrome), should consider seeking advice from doctors for assessment of their ovarian cancer risk and the need for and approach of screening.

July 2018

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