

Cancer Expert Working Group on Cancer Prevention and Screening

Recommendations on Prevention and Screening for Breast Cancer For Health Professionals

Local epidemiology of female breast cancer

1. Breast cancer has become the most common cancer among women in Hong Kong since the early 1990's. According to the Hong Kong Cancer Registry,¹ there were 3,868 newly registered female breast cancer cases in 2014, accounting for 26.6% of all new cancer cases among women. The median age at diagnosis was 55 years. The age-standardised incidence rate (ASIR) of female breast cancer was 64.6 per 100,000 standard population. In addition, 530 new cases of carcinoma in-situ of breast cancer (also known as ductal carcinoma in situ (DCIS)) were reported in 2014, with the highest ASIR at age 45-49. More than half (58%) of DCIS were diagnosed in females aged 50 and over.

2. In 2015, being the third leading cause of cancer deaths among women, breast cancer caused 637 deaths, representing 10.7% of all female cancer deaths. The age-standardised mortality rate (ASMR) of female breast cancer was 9.7 per 100,000 standard population.² Over the past three decades, female breast cancer new cases and deaths were on a rising trend. After adjusting for population ageing, the ASIR maintained an increasing trend while the ASMR remained relatively stable. More information on breast cancer statistics can be found at the Centre for Health Protection (CHP) website: www.chp.gov.hk/en/content/9/25/53.html.

3. Although the ASIR of female breast cancer has been increasing in Hong Kong, it remained low when compared with rates reported in the west (e.g. United Kingdom (UK) or Australia) and in some Asian countries (e.g. Singapore) in 2012.³

Risk factors of female breast cancer

4. There are a range of factors affecting a woman's risk of developing breast cancer. **Positive family history** has been identified as a strong known risk factor in this regard.

Risk increases with degree of relatedness with affected relatives, number of affected relatives and their age at diagnosis.⁴⁻⁷ Having one first-degree relative with breast cancer would double a woman's risk while having an affected second-degree relative would increase her risk by 50%.⁴ The risk increases especially when the relative has been diagnosed before age of 50.⁶

5. Women with certain **deleterious gene mutations** are associated with higher risk for breast cancer. Germline mutations in *BRCA1/2* genes are associated with an approximately 40% to 85% lifetime risk of breast cancer and is the most common cause of hereditary breast cancer.⁸⁻¹¹ It has been estimated that *BRCA1/2* mutations contribute to about 5-10% of overall breast cancer cases in western countries.^{11, 12} Yet, the prevalence of *BRCA* mutation in the general population of Hong Kong remains unknown. According to the findings from Hong Kong Hereditary Breast Cancer Family Registry on 2,117 clinically high-risk breast or ovarian cancer patients, *BRCA* mutation was found in 9.3% of patients, among whom 41.6% were *BRCA1* and 58.4% were *BRCA2*. This is noticeably different from patients in the western countries where majority of mutations are *BRCA1* mutations.¹³ Other less common gene mutations (e.g. *TP53*, *PTEN*) are also associated with an increased risk of developing breast cancer.⁹⁻¹¹

6. Additional established risk factors for female breast cancer include:^{4, 5, 9, 14-17}
- (a) History of receiving radiation therapy at young age
 - (b) History of breast cancer, ovarian cancer or endometrial cancer
 - (c) History of benign breast diseases (e.g. atypical hyperplasia)
 - (d) Exposure to exogenous hormones (e.g. combined oral contraceptives or hormone replacement therapy)
 - (e) Reproductive factors (e.g. early menarche or late menopause, nulliparity, late first live birth)
 - (f) Alcohol consumption.
 - (g) Obesity after menopause
 - (h) Physical inactivity
 - (i) Increasing age

Primary prevention

7. Certain breast cancer risk factors are related to personal lifestyle and behaviour. Women can lower the risk of getting breast cancer by adopting the following primary preventive measures:^{14, 15, 18, 19}

- **Be physically active.** Women should do at least 150 minutes of moderate-intensity or equivalent aerobic physical activities per week e.g. climbing stairs or brisk walking etc.
- **Do not drink alcohol.** Alcohol is a Group I carcinogen as classified by International Agency for Research on Cancer (IARC), World Health Organization. Sufficient evidence exists to show that alcohol can cause, *inter alia*, female breast cancer. With respect to cancer risk, there is no safe level for drinking alcohol. For women, drinking 10 grams of alcohol per day (e.g. 250 ml of canned beer with 5% alcohol content, a small glass (~100 ml) of red or white wine with 12 % alcohol content) increases the risk of premenopausal breast cancer by 5% and postmenopausal breast cancer by 9%.¹⁹ The more one drinks, the higher the risk not only of breast cancer but at least six or seven other cancers.¹⁴
- **Maintain a healthy body weight and waist circumference.** Asian women should aim for a body mass index (BMI) between 18.5 and 22.9, and a waist circumference of less than 80 cm (~32 inch).
- **Have childbirth at an earlier age and breastfeed each child for a longer duration.**

Breast awareness and early diagnosis

8. Symptoms of early breast cancer may not be easily noticed. Therefore, all women are advised to be breast aware. That is, being familiar with the normal look, feel and cyclical changes of the breasts so that unusual features can be noticed early, such as

- breast lump
- change in the size or shape of the breast
- change in skin texture of the breast or nipple (e.g. red, scaly, thickened or “orange-skin” appearance)
- rash around the nipple
- retracted nipple
- discharge from one or both nipples
- new and persistent discomfort or pain in the breast or axilla
- new lump or thickening in the axilla

9. Women should visit the doctor promptly if suspicious symptoms appear because delay in seeking medical attention may lead to more advanced stage at presentation and poorer survival.²⁰

Screening for general female population at average risk

10. Breast self-examination, clinical breast examination and mammography are widely used breast cancer screening modalities.

(i) Breast self-examination (BSE)

11. Breast self-examination has low sensitivity (17%-26%) in detecting breast cancer. Two large population-based trials in Shanghai and Russia did not find any beneficial effect of teaching screening by BSE in terms of reduction in breast cancer mortality, but noted greater harm due to increased numbers of benign lesions and biopsies performed.²¹ Hence, there is insufficient evidence to recommend regular BSE (i.e. a regular, formally taught and ritual examination of woman's breasts by oneself at a monthly interval) as a screening tool. Women are advised to be breast aware and report breast changes to the doctors as soon as they are detected.

(ii) Clinical breast examination (CBE)

12. There are three randomised controlled trials (RCTs), one conducted in the Philippines²² and two in India,^{23, 24} compared the efficacy of CBE alone versus no screening. All three trials reported that annual CBE has a moderate sensitivity (52%-57%) and high specificity (92%-100%) and can detect smaller and earlier stage of tumours or cancers. As the Filipino study was discontinued due to poor compliance and other two Indian studies are currently underway, no conclusion on the effectiveness of CBE on reduction in breast cancer mortality can be drawn yet.

(iii) Mammography

13. Evidence from some western countries suggests that organised breast screening programmes by mammography are effective in detection of tumours at an earlier stage and reduction in breast cancer mortality in their populations. Nevertheless, harms such as false-positives, false-negatives, overdiagnosis (the diagnosis of breast cancer, in particular to DCIS, as a result of screening that would not have been diagnosed or never have caused harm in a patient's lifetime if screening had not taken place), overtreatment and potential complications arising from subsequent invasive investigations or treatment may outweigh benefits.²⁵⁻³²

14. A Cochrane review in 2011 and 2013 estimated that mammography screening resulted in a 15% reduction in breast cancer mortality, but led to 30% increase in overdiagnosis and

overtreatment. For every 2,000 women invited for mammography screening throughout 10 years, one would avoid dying of breast cancer; 10 healthy women would be treated unnecessarily; and at the same time more than 200 women would be falsely alarmed and experience significant psychological distress because of false-positive findings.^{33, 34}

15. In UK, the Independent Breast Review in 2013 showed that mammography screening led to a relative risk reduction of 20% in breast cancer mortality and an estimated 11% overdiagnosis rate.³⁵

16. The Swiss Medical Board reported in 2013 that for every 1,000 women with regular mammography screening, one to two women's lives could be saved, but around 100 women would also undergo unnecessary investigations and treatment. The cost-effectiveness ratio was found to be very unfavourable. The Board concluded that introduction of mammography screening programme was not recommended and a time limit should be set on existing programmes. The Board further recommended thorough medical assessment and comprehensive information about the benefits and harms should be provided to women considering mammography screening.^{36, 37}

17. The 25 year follow-up of the Canadian National Breast Screening Study in 2014 revealed that women aged 40-59 who underwent annual mammography screening received no benefit on breast cancer mortality but resulted in 22% over-diagnosis, prompting the need of policy makers to reassess the rationale of screening.²⁵

18. In 2015, the IARC evaluated the cancer-preventive and adverse effects of different breast cancer screening methods. It was estimated that women aged 50-69 years invited to mammography screening have a 24% reduced risk of mortality from breast cancer. Notwithstanding this, there was also sufficient evidence that mammography screening led to overdiagnosis at an average rate of 6.5% (ranged from 1% to 10%). The estimated cumulative risk of false-positive results was about 20% for a woman who had 10 screens from age 50 to 70, leading to short-term negative psychological consequences.^{9, 38}

19. Moreover, in some regions of Asia where organised mammography screening programmes (e.g. Singapore, Korea, Taiwan) are implemented, there was a lack of published peer-reviewed articles in the public domain documenting systematic programme evaluation or modelling studies that estimate or report on the extent of overdiagnosis and the number of lives saved at the time of review by CEWG.

20. Furthermore, some international and local evidence suggests a reduction in breast cancer mortality could be attributable to improved survival due to treatment advancement and improved health service delivery rather than screening *per se*.^{30, 32, 39, 40}

21. In Hong Kong, the ASIR of breast cancer is relatively low when compared with that in western countries. Hence, it is reasonably expected that the positive predictive value of mammography will be even lower, generating more false-positive results and the ensuing unnecessary follow-up investigations may cause complications and psychological distress.^{41, 42} Bear in mind there were also local modelling studies showing that population-based mammography screening is not a cost-effective public health intervention in Hong Kong as compared with other strategies in the prevention and control of breast cancer.^{43, 44}

(iv) Ultrasonography

22. Ultrasonography, used as an adjunct to mammography in women with radiologically dense breasts, has the potential of depicting small breast cancers not visible on mammography.^{45, 46} However, both the Cochrane review in 2013⁴⁷ and IARC review in 2015^{9, 38} concluded that there is insufficient evidence that ultrasonography as an adjunct to mammography screening can decrease breast cancer mortality.

Screening for women at increased risk

23. Locally, there is lack of consensus on how to identify women at increased risk of breast cancer. The Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) has based its conclusions on international studies and overseas practices to derive a local definition of increased risk by adopting a set of qualitative risk stratification criteria, which include *BRCA1/2* deleterious mutation carrier status, characteristics of family history and personal risk factors (refer to paragraphs 4-6). Women at increased risk are categorised as being at ‘high risk’ or ‘moderate risk’ as shown in Table 1.⁴⁸

(i) Mammography

24. Enhanced surveillance for early detection of breast cancer has been suggested as secondary preventive measures for women at increased risk. Although there has been no RCT of mammography screening specifically in women at increased risk, previous observational studies concluded that mammography screening in high risk population could be effective, despite differences in study populations, criteria for risk stratification, screening

protocols and measures of effectiveness.⁴⁹⁻⁵⁵ Having said that, mammography generally has lower sensitivity in younger women and those with genetic predisposition to breast cancer due to increased mammographic density obscuring the radiological features of early breast cancer in premenopausal women, and a higher likelihood of benign mammographic images for *BRCA*-related breast cancer.⁵⁶

(ii) *Magnetic resonance imaging (MRI)*

25. Magnetic resonance imaging has been recommended as an adjunct to routine mammography for the surveillance of women at high risk in some countries (e.g. US⁵⁷, UK⁵⁸). MRI is more sensitive than mammography for the detection of breast cancer among *BRCA1/2* mutation carriers.^{59, 60} The IARC review found improved sensitivity (95% vs 40%) but lower specificity (80% vs 95%) of MRI plus mammography compared with mammography alone.⁹

26. In this regard, several studies have reported that breast cancer screening with MRI in women at increased risk has significantly shifted the stage at diagnosis from advanced stage to earlier and pre-invasive stage, when compared with other common screening modalities, such as clinical breast examination, mammography and ultrasonography.⁶¹⁻⁶³

27. A modelling study of three large *BRCA1/2* screening projects in UK,⁶⁴ Canada⁶⁵ and the Netherlands^{66, 67} demonstrated that screening with mammography and MRI (combined screening) detected relatively more DCIS and smaller invasive cancers in *BRCA2* mutation carriers than *BRCA1* mutation carriers, resulting in larger reductions in breast cancer mortality that ranged from 41.9% (for mammography alone) to 50.1% (combined screening) for *BRCA1* and from 46.8% (for mammography alone) to 61.6% (combined screening) for *BRCA2*.⁶⁸

28. One survival analysis among 959 UK women with high-risk genetic mutations reported that 10-year survival was significantly higher in the MRI-screened carriers of *BRCA1/2* mutations (95.3%) compared with unscreened mutation carriers (73.7%). However, the analysis did not show any significant difference in 10-year survival between the combined mammography plus MRI and mammography-only groups.⁶⁹ The IARC review also found variable all-cause survival results among the reviewed cohort studies in women with *BRCA1/2* mutation.⁹

29. Notwithstanding the above, studies showed that MRI was superior to mammography

in detecting hereditary breast cancer. The radiation risk and the false-positive rate of different screening strategies should be considered when making individual screening decisions.⁷⁰ Regarding the effectiveness of screening Chinese women at higher breast cancer risk, there is currently a lack of local studies on the role and effectiveness of MRI and/or mammography.

Local research

30. To bridge the knowledge gap for risk prediction of breast cancer in the local female population, the Food and Health Bureau commissioned the University of Hong Kong in October 2015 to conduct a large scale research study on local assessment of breast cancer risk and the development of a locally-validated, evidence-driven quantitative risk prediction tool for screening. This study is in progress and the findings will facilitate the CEWG to formulate evidence-based recommendations on criteria for breast cancer screening especially for those at higher risk.

31. After considering the local epidemiology, emerging scientific evidence and local and overseas screening practices, the recommendations on breast cancer screening were fine-tuned by the CEWG in June 2016 and reaffirmed in September 2017 as shown in Table 1.

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Table 1: CEWG recommendations on breast cancer screening

For asymptomatic population at average risk	
<p>1. There is insufficient evidence to recommend for or against population-based mammography screening for asymptomatic women at average risk in Hong Kong.</p> <p>2. There is insufficient evidence to recommend regular breast self-examination as a screening tool. Women are advised to be breast aware (be familiar with the normal look and feel of their breasts) and visit doctors promptly if suspicious symptoms appear.</p> <p>3. There is insufficient evidence to recommend clinical breast examination.</p> <p>4. Individuals considering breast cancer screening should be adequately informed by doctors about the benefits and harms.</p>	
For women at moderate risk	
<p>Local definition – with any one of the risk factors:</p> <p>1. Family history of only one first-degree female relative with breast cancer diagnosed at ≤ 50 years of age; <u>or</u></p> <p>2. Two first-degree female relatives diagnosed with breast cancer after the age of 50 years</p>	<p>Recommendation on screening</p> <ul style="list-style-type: none"> • Should discuss with their doctors the pros and cons of breast cancer screening before deciding whether to start screening by mammography every two to three years. • Magnetic resonance imaging (MRI) is not recommended for women at moderate risk.
For women at high risk	
<p>Local definition - with any one of the risk factors:</p> <p>1. Carriers of <i>BRCA1/2</i> deleterious mutations confirmed by genetic testing.</p> <p>2. Family history of breast cancer /ovarian cancer, such as</p> <ul style="list-style-type: none"> • any first-degree female relative is a confirmed carrier of <i>BRCA1/2</i> deleterious mutations; • any first- or second-degree female relative with both breast cancer and ovarian cancer; • any first-degree female relative with bilateral breast cancer; • any male relative with a history of breast cancer; • 2 first-degree female relatives with breast cancer AND one of them being diagnosed at age ≤ 50 years; • ≥ 2 first- or second-degree female relatives with ovarian cancer; • ≥ 3 first- or second-degree female relatives with breast cancer OR a combination of breast cancer and ovarian cancer <p>3. Personal risk factors</p> <ul style="list-style-type: none"> • history of radiation therapy to chest for treatment between age 10 and 30 years, e.g. Hodgkin’s disease • history of breast cancer, including ductal carcinoma in situ (DCIS); lobular carcinoma • history of atypical ductal hyperplasia or atypical lobular hyperplasia 	<p>Recommendation on screening</p> <ul style="list-style-type: none"> • Should seek advice from doctors; and <ul style="list-style-type: none"> – Have mammography screening every year; – Begin screening at age 35 or 10 years prior to the age at diagnosis of the youngest affected relative (for those with family history), whichever is earlier, but not earlier than age 30. – For confirmed carriers of <i>BRCA1/2</i> deleterious mutations or women who had radiation therapy to chest for treatment between age 10 and 30 years (e.g. for Hodgkin’s disease), consider additional annual screening by MRI. <p>Recommendation on genetic testing</p> <ul style="list-style-type: none"> • Women who have any first-degree female relative with confirmed <i>BRCA1/2</i> deleterious mutations should be offered genetic testing to confirm or refute their carrier status. • For women at high risk due to other types of family history who wish to clarify their genetic risk or that of their family, referral to a specialist cancer clinic for advice, counselling and management should be discussed and considered. • Genetic testing should be performed by specialised cancer centres with expertise in genetic counselling, which should be provided before genetic testing. Health care professionals should discuss with their clients in detail about the uncertainties and implications of the test results. Confirmed carriers of <i>BRCA1/2</i> deleterious mutations who wish to consider prophylactic surgery / chemoprevention should also be referred to a specialist cancer clinic for advice and counselling.

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