衞生防護中心
Centre for Health Protection

Cancer Expert Working Group on Cancer Prevention and Screening (CEWG)

Recommendations on Prevention and Screening for Breast Cancer For Health Professionals

Local epidemiology

Breast cancer (BC) has been the most common cancer among women in Hong Kong since the early 1990's. In 2018, there were 4,618 newly registered female BC cases, accounting for 27.2% of all new cancer cases in females.[1] The median age at diagnosis was 57 years and the lifetime risk before age 75 was 1 in 14.[1] The age-standardised incidence rate (ASIR) of female BC was 65.5 per 100,000 female population.[1] Being the third leading cause of cancer deaths among women in 2019, BC caused 852 deaths, representing 13.7% of all female cancer deaths.[2] The age-standardised mortality rate (ASMR) of female BC was 10.2 per 100,000 female population.[2]

2. After adjusting for population ageing, the ASIR of female BC had an upward trend for the period between 1991 and 2018 while the ASMR between 1991 and 2019 did not change significantly. The ASIR and ASMR of female BC in Hong Kong remained low when compared with the rates reported by a number of developed economies in the West (e.g.

Australia, United Kingdom [UK]) and the neighbouring Singapore.[3]

Risk factors for female breast cancer

3. A range of factors accounts for women's risk of BC, among which family history being a strong known one.[4,5,6,7,8,9] Generally, for women with a family history of BC, the risk of developing BC increases with increasing degree of relatedness to the affected relatives; increasing number of affected relatives; and decreasing age at which affected relatives diagnosed with BC. Having one first-degree relative with BC doubles a woman's risk while having an affected second-degree relative increases risk by 50%.[4,8]

4. Women with certain deleterious gene mutations are at high risk of BC. Germline mutations in *BRCA1/2* genes are associated with 40% to 90% lifetime risk of BC and are the most common cause of hereditary breast cancer.[7,8,10,11,12] It has been estimated that *BRCA1/2* mutations contribute to 5% to 10% of breast cancer cases in Western countries.[7,8] Local data on the prevalence of *BRCA* mutations in the general population are limited, but information from the Hong Kong Hereditary Breast Cancer Family Registry suggested that *BRCA* mutation could be found in 9.6% of subjects out of 2,549 clinically high-risk* breast or ovarian cancer patients.[13]

5. Other established risk factors include increasing age, history of receiving radiation therapy at young age, history of BC or ovarian cancer, history of benign breast diseases, exposure to exogenous hormones, reproductive factors (e.g. early menarche or late menopause, nulliparity, late first live birth), obesity after menopause, alcohol consumption and physical inactivity.[4,7,8,9,14,15,16,17,18,19,20,21,22,23,24,25,26,27]

* based on young age at diagnosis, multiple members with breast/ovarian/prostate and BRCA-related cancers in the family

Primary prevention

6. Certain BC risk factors are modifiable and related to personal lifestyle and behaviour. Women can lower their risk of getting BC by pursuing primary preventive measures below:[7,25,26,27]

- *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) of the World Health Organization (WHO). There is strong evidence that alcohol can cause, inter alia, female BC. 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 beer with 5% alcohol content, a small glass (~100 ml) of red or white wine with 12% alcohol content) increases the risk of premenopausal BC by 5% and postmenopausal BC by 9%.[27]

- *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

7. Symptoms of early-stage BC may not be easily noticed. Therefore, all women are advised to be breast aware (i.e. being familiar with the normal look and feel of the breasts) and should visit doctors promptly if suspicious symptoms develop, examples of which included the presence of breast or axillary lump, change in the size or shape of the breasts, change in skin texture of the breasts or nipple, nipple rash, discharge or retraction, new and persistent discomfort or pain in the breast or axilla, etc. Delay in seeking medical attention may lead to more advanced stage at presentation and poorer survival.[7,28]

Screening for general female population

8. Breast cancer screening aims to detect BC in asymptomatic population before symptoms develop so as to achieve better treatment outcome and improve survival. Subject to nature and performance, screening tests have both benefits (e.g. improvement in the detection of early-stage cancer when it is still treatable, reduction in BC mortality) and harms (e.g. psychological distress due to false-positives, over-diagnosis and over-treatment) to screened populations. Over the years, breast self-examination (BSE), clinical breast examination (CBE) and mammography (MMG), alone or in combination, are most widely studied screening modalities for BC screening.

(a) Breast self-examination (BSE)

9. Breast self-examination is a regular, formally taught and ritual examination of a woman's breasts by oneself at a monthly interval. Meta-analysis[29] and large-scale randomised controlled trials (RCTs) in Shanghai[30]

and Russia[31] respectively showed no difference on the size or stage of BC and number of BC deaths for women who had been taught to use systematic approach for BSE screening compared with those who had not. Instead, BSE were found to result in greater harm due to increased number of benign lesions and biopsies performed. Due to lack of evidence on the benefits of BSE screening but potential harms associated with false-positives, international guidelines[32,33,34,35] no longer recommend women to perform regular BSE screening, but rather support all women being aware of changes in their breasts and discussing these changes with clinicians.

(b) Clinical breast examination (CBE)

10. Clinical breast examination is physical examination of the breasts and the underarm area by a trained healthcare professional. Three RCTs (one conducted in the Philippines[36] and two in India[37,38]) on the efficacy of CBE screening alone versus no screening showed that screening by CBE could detect smaller and earlier stage of tumours or cancers, but did not report the effects of CBE on BC mortality. Studies from the Cochrane,[29] the American Cancer Society (ACS),[32,39] and the U.S. Preventive Services Task Force (USPSTF)[33,34] found either no or insufficient evidence to assess the association between population-based screening using CBE and BC mortality while the IARC [7,35] concluded inadequate evidence that screening by CBE reduces BC mortality.

(c) Mammography (MMG)

Benefits of mammography screening

11. Currently, standard MMG (i.e. 2-dimensional (2D) MMG) is the most common modality of screening women for BC. Evidence from Western countries suggests that organised MMG screening programmes are effective in

the detection of early-stage tumours and reduction in BC deaths in their female populations, especially among women aged 50-69 years.[7,35,39,40,41,42]

12. The ACS systematic review found that MMG screening was associated with an approximately 20% reduction in BC mortality of average-risk women after 13 years of follow-up.[39] When comparing with women aged <50, screening women aged ≥50 was associated with slightly greater BC mortality reduction, mostly due to greater reduction in women aged 60-69.[39] The USPSTF's review on the effectiveness of BC screening in average-risk women at different age groups showed the reduction in BC mortality for women aged 39-49 (relative risk [RR] 0.92, 95% CI 0.75-1.02), aged 50-59 (RR 0.86, 95% CI 0.68-0.97), aged 60-69 (RR 0.67, 95% CI 0.54-0.83) and aged 70-74 (RR 0.80, 95% CI 0.51-1.28) over 10 years of follow-up.[40] The IARC also found that women aged 50-69 years who attended organised MMG screening had about 40% reduction in the risk of BC mortality.[7,35]

Harms of mammography screening

13. Although evidence supporting the use of MMG as tool for BC screening is not lacking, it is not 100% accurate for cancer detection and may even lead to harms by exposing women to risks, such as false-positives, false-negatives, over-diagnosis (the diagnosis of breast cancer, in particular to ductal carcinoma in situ [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), over-treatment, and complications arising from subsequent invasive investigations or treatment, and psychological distress.[7,35,39,42,43,44,46]

False-positives

14. False-positive screening results lead to recalls for additional imaging and subsequent invasive procedures (biopsy) with benign outcome. It has been reported that the 10-year cumulative false-positive rates and biopsies

were higher with annual screening than biennial screening (61% vs. 42% and 7% vs. 5%, respectively), for women aged 40 to 49 years and those with dense breasts.[34,43] The IARC estimated that the cumulative risk of false-positive recall in organised screening programmes was about 20% for woman who had 10 screens between the ages of 50 and 70 years, where less than 5% of all false-positive screens reported an invasive procedure.[7,35]

Over-diagnosis and over-treatment

15. Over-diagnosis occurs when MMG detects DCIS, the majority of which would not progress to invasive cancer if left untreated. As the natural course of DCIS remains uncertain, the condition may be treated radically as invasive disease (e.g. with lumpectomy and radiation therapy) upon diagnosis because of uncertain outcome. That says, these women will be treated unnecessarily, or in other term "over-treatment". Estimation on over-diagnosis varied widely with different study designs. Generally, observational studies estimated higher over-diagnosis rates with a range of 0% to 54% while RCTs suggested it be between 11% and 22%.[34,43,46] Systematic reviews, such as the Cochrane review,[44] reported MMG screening led to 30% over-diagnosis and over-treatment whereas the UK Independent Breast Review[42] estimated 11% over-diagnosis rate.

Psychological distress

16. Women may experience anxiety while waiting for results of MMG screening or further investigations. Studies on psychological impact of false-positives showed varied results. The USPSTF systematic review indicated that women who received clear communication of their negative MMG results had minimal anxiety, whereas those recalled for further testing had more anxiety, breast cancer-specific worry and distress.[34,43] There were also studies showing women having false-positive MMG results generally have short-term negative psychological consequences.[7,35]

Pain and discomfort

17. Although many women reported pain during MMG (ranging from 1% to 77%), those experiencing pain declined future screening varied from 11% to 46%.[43]

Risk of radiation exposure

18. Radiation-induced BC is also a concern for women who are subjected to MMG screening. The IARC reported that the estimated cumulative risk of BC death due to radiation from MMG screening is 1 to 10 per 100,000 women, depending on age and the frequency and duration of screening, and these estimates are smaller than the estimates of BC deaths prevented by MMG screening by a factor of at least 100.[7,35]

Screening interval of mammography screening

19. There has not been any RCTs identified directly comparing annual to biennial MMG screening in women of any age.[32,34] One United States (US) modelling study estimated that biennial screening from age 50 to 74 years avoided a median of 7 BC deaths versus no screening; while annual screening from age 40 to 74 years avoided an additional 3 deaths, but yielded 1,988 more false-positive results and 11 more over-diagnoses per 1,000 women screened. Annual screening from age 50 to 74 years was inefficient as there were similar benefits, but more harms than other strategies.[45] This study concluded that biennial screening is consistently the most efficient strategy for average-risk populations, and decisions about starting ages and intervals will depend on population characteristics and the decision makers' weight given to the harms and benefits of screening.[45] For overseas guidelines, the USPSTF[34] recommends biennial MMG screening for women aged 50-74 years while WHO recommends in well-resourced settings women aged 50-69 years should undergo organised, population-based MMG screening every two years.[46]

(d) Digital breast tomosynthesis (DBT)

20. Digital breast tomosynthesis (also known as 3D MMG) is a technique that produces quasi three-dimensional images of X-ray acquired over a limited range of angles around the breast. Preliminary evidence suggests that although DBT seems to lower recall rates for false-positive results and detect more cancers (both invasive BC and DCIS) as compared with conventional 2D MMG, DBT increases breast biopsy rates, and exposes women to more radiation.[7,34,35,47,48] Yet, current data is uncertain whether all of the extra BC cases detected by DBT actually represent a benefit (that is, cancer that is clinically significant rather than over-diagnosis). More importantly, no studies examined the effect of DBT on important health outcomes for women, such as reduction in morbidity or mortality of BC and quality of life. Currently, overseas professional organisations, such as the USPSTF,[34] Canadian Task Force on Preventive Health Care[41] and IARC[7,35] opined that there is insufficient evidence to support using DBT as a screening tool to reduce BC mortality or achieve lower rate of interval cancers. Future research should be warranted.

(e) Ultrasonography

21. Ultrasonography, used as an adjunct to MMG in women with radiologically dense breasts, has the potential of depicting small breast cancers not visible on MMG.[49,50] However, studies consistently showed that adjunct ultrasonography increased false-positive recall or testing.[7,34,35,49,51] Systematic reviews conducted by the Cochrane,[51] IARC[7,35] and USPSTF[34] concluded that there is insufficient evidence that ultrasonography as an adjunct to MMG screening can decrease BC mortality while the Canadian Task Force on Preventive Health Care[41] recommends not using ultrasonography to screen for BC in women at average risk.

Overseas' screening practice and recommendations for women at average risk

22. Overall, age-based population screening with MMG is a common practice among developed economies including US, Australia, Canada, UK, Germany, Italy, Norway, Finland, and Singapore. Screening age from 50 to 69 years are more commonly adopted in European countries whereas extension of screening age from 50 to 74 are practised in US, Canada and Australia.[52] Screening for BC every 2 years is recommended in most of the countries (e.g. US, Australia, Germany, Norway, Singapore, etc).[52]

Screening for women at moderate and high risk

(a) Risk assessment and stratification

23. In Western populations, a number of validated risk assessment tools (e.g. Gail model[53]) are available for prediction of individual woman's risk of developing BC in a quantitative manner based on different combination of risk factors. Each risk assessment tool has its own limitations and so far there is insufficient comparative evidence to recommend one tool over another.[54] Different countries adopt different algorithms for assessing risk and also different criteria for stratifying risk.[54,55,56]

24. Due to lack of comprehensive local data to identify women at moderate and high risk of BC, the CEWG based on its review on international studies and overseas practices (e.g. US,[54] UK,[55] Australia[56, 57]), made recommendations and derived local definition of women at moderate risk and high risk in 2010 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. Generally, the criteria promulgated by the

CEWG are in line with that of the aforementioned Western economies.

(b) Mammography for women at high risk

25. Although there has been no RCT on MMG screening specifically in women at high risk, observational studies concluded that MMG screening for high-risk population could be effective despite differences in study populations, criteria for risk stratification, screening protocols, and measures of effectiveness.[58,59,60,61] Having said that, MMG generally has lower sensitivity in younger women and those with a genetic predisposition to BC due to increased mammographic density obscuring the radiological features of early BC in premenopausal women, and a higher likelihood of benign mammographic images for *BRCA*-related breast cancer.[62]

(c) Magnetic resonance imaging (MRI) for women at high risk

26. Magnetic resonance imaging has been recommended as an adjunct to routine MMG for surveillance of women at high risk for its superior sensitivity over MMG alone for the detection of BC among *BRCA1/2* mutation carriers.[63,64] Studies reported that screening with MRI in women at high risk has significantly favourable shifting of cancer stage at diagnosis from advanced to earlier and pre-invasive stage when compared with other screening modalities (such as CBE, MMG, and ultrasonography).[65,66,67] UK survival analysis among women with high-risk genetic mutations reported that 10-year survival was significantly higher in the MRI-screened carriers of *BRCA1/2* mutations compared with unscreened ones, however no significant survival difference was found between the MMG plus MRI and MMG-only groups.[68] The IARC concluded with sufficient evidence that MRI as adjunct to MMG increases the sensitivity and decreases the specificity of screening in women with high familial risk and *BRCA1/2* mutation.[7,35] The radiation risk and false-positive rate of different

screening strategies (such as intensive MMG screening, with a combination of MMG and MRI) should be considered when making individual screening decisions.[69]

27. In addition, the 2019 USPSTF guideline recommended that clinicians should assess high-risk women with an appropriate familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing.[54] There is also adequate evidence that the benefits of risk assessment, genetic counseling, genetic testing, and interventions are moderate for women with high risk whereas the associated harms are small to moderate.[54]

Hong Kong Breast Cancer study (HKBCS)

28. To bridge the knowledge gap for risk prediction of BC in the local female population, the Government commissioned The University of Hong Kong (HKU) to conduct a case-control study in October 2015, funded by the Health and Medical Research Fund administered under the Food and Health Bureau. The study collated and analysed local data (3,501 BC cases and 3,610 controls) with the aim of developing a locally-validated, evidence-driven quantitative risk prediction tool for BC screening of higher risk individuals.[70]

29. HKBCS's risk stratification model estimated that the average lifetime risk of invasive BC among Hong Kong Chinese women was 6.8%, whereas the average lifetime risk of BC mortality was 1.1%. The HKU research team has developed a personalised risk assessment tool to estimate the risk of developing BC in women depending on a list of risk factors including age, presence of family history of BC among first-degree relatives, history of benign breast disease, age at menarche, age at first live birth, BMI and physical activity level.[70]

30. The HKBCS concluded that while the relative reduction in BC mortality among screenees provided by risk-based and conventional age-based BC screening were similar, the risk-based screening approach would be more cost-effective than the conventional age-based approach with reduction of unnecessary MMG and tissue biopsy due to false-positives among healthy women at low risk.[70] In other words, personalised risk-based biennial MMG screening for BC in women aged 44-69 could be more cost-efficient than universal age-based screening for Chinese women in Hong Kong. Having said that, this conclusion does not apply to the high risk group (e.g. *BRCA1*/2 mutation carriers) and moderate risk group as defined by the CEWG.

Revised recommendations by CEWG

31. After taking into consideration the findings of the HKBCS and available evidence, the CEWG has formulated the revised recommendations on BC screening which were later endorsed by the Cancer Coordinating Committee at its 15th meeting on 19 June 2020. The CEWG's revised BC screening recommendations for local female population include -

(i) **Breast self-examination** is not recommended as a screening tool for breast cancer for asymptomatic women. Women are recommended to be breast aware (be familiar with the normal look and feel of their breasts) and seek medical attention promptly if suspicious symptoms arise.

(ii) There is insufficient evidence to recommend **clinical breast examination** or **ultrasonography** as a screening tool for breast cancer for asymptomatic women.

(iii) It is recommended that risk-based approach should be adopted for breast cancer screening.

(iv) While the BC screening recommendations for (a) **women at high risk** remain *status quo*, those for (b) **women at moderate risk** and (c) other **women at general population** are revised. Details of recommendations for women at different risk profiles are listed as follows:

(a) For women at high risk

CEWG Recommendations on BC screening for high risk:
Local definition - with any one of the risk factors: 1. Carriers of *BRCA1/2* deleterious mutations confirmed by genetic testing. 2. Family history of breast cancer /ovarian cancer, such as - any first-degree female relative is a confirmed carrier of *BRCA1/2* 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 3. Personal risk factors - 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 **Recommendation on screening** 1. Should seek advice from doctors; and - 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),

CEWG Recommendations on BC screening for high risk:
whichever is earlier, but not earlier than age 30. - for confirmed carriers of *BRCA1/2* 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 magnetic resonance imaging (MRI). **Recommendation on genetic testing** 1. Women who have any first-degree female relative with confirmed *BRCA1/2* deleterious mutations should be offered genetic testing to confirm or refute their carrier status. 2. 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. 3. Genetic testing should be performed by specialised cancer centres with expertise in genetic counselling, which should be provided before genetic testing. Healthcare professionals should discuss with their clients in detail about the uncertainties and implications of the test results. Confirmed carriers of *BRCA1/2* deleterious mutations who wish to consider prophylactic surgery / chemoprevention should also be referred to a specialist cancer clinic for advice and counselling.

(b) For women at moderate risk

CEWG Recommendations on BC screening for moderate risk:
1. Women at moderate risk (i.e. family history of only one first-degree female relative with breast cancer diagnosed at ≤50 years of age; or two first-degree female relatives diagnosed with breast cancer after the age of 50 years) are recommended to have mammography every two years and should discuss with their doctors the potential benefits and harms of breast cancer screening before starting screening. 2. MRI is not recommended for breast cancer screening in women at moderate risk.

(c) For other women at general population

CEWG Recommendations on BC screening for average risk:
1. Women aged 44-69 with certain combinations of personalised risk factors (including presence of history of breast cancer among first-degree relative, a prior diagnosis of benign breast disease, nulliparity and late age of first live birth, early age of menarche, high body mass index and physical inactivity) putting them at increased risk of breast cancer are recommended to consider mammography screening every two years. They should discuss with their doctors on the potential benefits and harms before undergoing mammography screening.
2. A risk assessment tool for local women (e.g. one developed by The University of Hong Kong, accessible at www.cancer.gov.hk/bctool) is recommended to be used for estimating the risk of developing breast cancer with regard to the personalised risk factors described above.
3. MRI is not recommended for breast cancer screening in women at general population.

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