Update on the Recommendations on Breast Cancer Screening by the Cancer Expert Working Group on Cancer Prevention and Screening

Cancer Expert Working Group on Cancer Prevention and Screening (August 2018 to July 2021)
Thomas HF Tsang, Ka-hing Wong, Kate Allen, Karen KL Chan, Miranda CM Chan, David VK Chao, Annie NY Cheung, Cecilia YM Fan, Edwin P Hui, Dennis KM Ip, KO Lam, CK Law, WL Law, Herbert HF Loong, Kam-hung Wong, Martin CS Wong, Rebecca MW Yeung, Anthony CH Ying, Rita KW Ho *

ABSTRACT

Breast cancer (BC) is the most common cancer among women in Hong Kong. The Food and Health Bureau commissioned The University of Hong Kong (HKU) to conduct the Hong Kong Breast Cancer Study (HKBCS) with the aim of identifying relevant risk factors for BC in Hong Kong and developing a locally validated BC risk assessment tool for Hong Kong Chinese women. After consideration of the most recent international and local scientific evidence including findings of the HKBCS, the Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) has reviewed and updated its BC screening recommendations. Existing recommendations were preserved for women at high risk and slightly changed for women at moderate risk. The following major updates have been made concerning recommendations for other women in the general population:

- Women aged 44 to 69 with certain combinations of personalised risk factors (including presence of history of BC 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 BC are recommended to consider mammography screening every 2 years. They should discuss with their doctors on the potential benefits and harms before undergoing mammography screening.
- A risk assessment tool for local women (eg, one developed by HKU) is recommended to be used for estimating the risk of developing BC with regard to the personalised risk factors described above.

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[1] **THF Tsang,** MB, BS, FHKAM (Community Medicine)
[2] **KH Wong,** MB, BS, FHKAM (Medicine)
[3] **K Allen,** PhD
[4] **KKL Chan,** MBBChir, FHKAM (Obstetrics and Gynaecology)
[5] **MCM Chan,** MB, BS, FHKAM (Surgery)
[6] **DVK Chao,** FRCGP, FHKAM (Family Medicine)
[7] **AN Cheung,** MD, FHKAM (Pathology)
[8] **CYM Fan,** MB, BS, FHKAM (Family Medicine)
[9] **EP Hui,** MD (CUHK), FHKAM (Medicine)
[10] **DKM Ip,** MD
[11] **KO Lam,** MB, BS, FHKAM (Radiology)
[12] **CK Law,** FHKCR, FHKAM (Radiology)
[13] **WL Law,** MS, FHKAM (Surgery)
[14] **HHF Loong,** MB, BS, FHKAM (Medicine)
[15] **KH Wong,** MB, ChB, FHKAM (Radiology)
[16] **MCS Wong,** MD, FHKAM (Family Medicine)
[17] **RMW Yeung,** FHKAM (Radiology)
[18] **ACH Ying,** MB, BS, FHKAM (Radiology)
[19] **RKW Ho,** MB, BS, FHKAM (Community Medicine)

[1] *Hong Kong College of Community Medicine, Hong Kong*
[2] *Centre for Health Protection, Department of Health, Hong Kong*
[3] *World Cancer Research Fund International, United Kingdom*
[4] *The Hong Kong College of Obstetricians and Gynaecologists, Hong Kong*
[5] *Hospital Authority (Surgery), Hong Kong*
[6] *The Hong Kong College of Family Physicians, Hong Kong*
[7] *The Hong Kong College of Pathologists, Hong Kong*
[8] *Professional Development and Quality Assurance Service, Department of Health, Hong Kong*
[9] *Hong Kong College of Physicians, Hong Kong*
[10] *School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong*
[11] *Department of Clinical Oncology, The University of Hong Kong, Hong Kong*
[12] *Hong Kong College of Radiologists, Hong Kong*
[13] *The College of Surgeons of Hong Kong, Hong Kong*
[14] *Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong*
[15] *Hong Kong Cancer Registry, Hospital Authority, Hong Kong*
[16] *The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong*
[17] *Hospital Authority (Clinical Oncology), Hong Kong*
[18] *The Hong Kong Anti-Cancer Society, Hong Kong*
[19] *Centre for Health Protection, Department of Health, Hong Kong*

* Corresponding author: head_ncdb@dh.gov.hk

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癌症預防及普查專家工作小組對乳癌預防及篩查的最新建議

癌症預防及普查專家工作小組（2018年8月-2021年7月）
曾浩輝、黃加慶、Kate Allen、陳嘉倫、陳志梅、周偉強、張雅賢、范婉雯、許斌、葉啟明、林嘉安、羅振基、羅偉倫、龍浩鋒、黃錦洪、黃至生、楊美雲、應志浩、何家慧

乳癌是香港女性最常見的癌症。食物及衞生局委託香港大學進行香港乳癌研究以找出本港女性患乳癌的相關風險因素，並研發了一套獲確認適用於香港華裔女性的乳癌風險評估工具。經審視最新的海外及本地科學證據和香港乳癌研究的結果後，癌症預防及普查專家工作小組（下稱「專家工作小組」）修訂了乳癌篩查的建議。就高風險和中等風險的婦女的乳癌篩查建議，專家工作小組分別維持現狀和作出微調，而對其他一般婦女的建議有主要修訂如下：

- 44至69歲的婦女如有某些組合的個人化乳癌風險因素（包括有直系親屬曾患乳癌、曾診斷患有良性乳腺疾病、從未生育或第一次生產年齡晚、初經年齡早、體重指數偏高和缺乏體能活動）令她們罹患乳癌的風險增加，建議她們考慮每兩年接受一次乳房X光造影篩查。在接受乳房X光造影篩查前，應諮詢醫生以了解篩查的潛在好處和風險。
- 建議採用為本港婦女而設的風險評估工具（例如由香港大學所開發的工具），按照上述個人化乳癌風險因素評估她們罹患乳癌的風險。

Introduction

In Hong Kong, the Cancer Coordinating Committee, chaired by the Secretary for Food and Health, was established in 2001 to formulate strategies regarding cancer prevention and control. The Cancer Expert Working Group on Cancer Prevention and Screening (CEWG), under the Cancer Coordinating Committee, was formed in 2002 to regularly review international and local evidence, then make local recommendations on cancer prevention and screening.

Breast cancer (BC) is the most common cancer among women in Hong Kong. Although evidence from other countries suggests that organised mammography screening is effective for detecting BC at an earlier stage and reducing mortality among affected patients, there is a lack of information concerning its usefulness and cost-effectiveness in Hong Kong. While BC risk prediction models such as the Gail model were developed in other areas for estimation of an individual's risk of BC, such models have not been validated in Hong Kong.

To address the aforementioned evidence gaps, the Hong Kong SAR Government previously commissioned The University of Hong Kong to conduct the Hong Kong Breast Cancer Study (HKBCS) for the quantification of relevant BC risk factors and development of a model for BC risk stratification among women in Hong Kong. Based on the findings of the HKBCS and other relevant studies, as well as epidemiological findings in Hong Kong and other countries, the CEWG updated its recommendations on BC screening; these updated recommendations were endorsed by the Cancer Coordinating Committee in June 2020. This article focuses primarily on the revised CEWG screening recommendations for women at average risk of BC in the general population; it also discusses the rationale for such recommendations.

Local epidemiology

In Hong Kong, 4761 invasive BC cases in women were recorded in 2019; this constituted 27.4% of all new cancer cases in women.[1] The median age at diagnosis was 58 years; 72% of patients had stage I or II BC.[1] In 2020, BC was the third leading cause of cancer death in women (751 deaths).[2] The age-standardised incidence rate in 2019 and age-standardised mortality rate in 2020 were 70.9 and 9.7 per 100 000 world standard population, respectively.[2] Over the past three decades, the age-standardised incidence rate has demonstrated an upward trend while the age-standardised mortality rate did not significantly change.[2]

Risk factors and primary prevention

Established risk factors for BC include family history of BC, inheritance of certain gene mutations, history of radiation therapy at a young age, personal history of BC or benign breast diseases, hormonal and reproduction factors, alcohol consumption, obesity after menopause, and physical inactivity.[3-17] The relative risks (RRs) associated with established risk factors for BC are summarised in Table 1.[3-15]

Primary preventive measures are important for lowering the risk of BC because some risk factors are modifiable. These preventive measures include regular physical activities, avoidance of alcohol consumption, and the maintenance of a healthy body weight and waist circumference.[15] Moreover, women are recommended to extend breastfeeding and give birth at an earlier age to reduce their BC risk.[12,15]

Breast awareness

Breast awareness refers to a woman's familiarity with the normal look and feel of her breasts, which facilitates prompt reporting of any abnormality to doctors for early diagnosis and treatment. Delayed pursuit of medical attention could lead to worse survival in patients with BC; for example, the 5-year survival rate was 7% higher among BC patients who began treatment <3 months from symptom onset than among patients who began treatment 3 to 6 months from symptom onset.[18]

TABLE 1. Relative risks associated with established risk factors for breast cancer

Risk factors	Magnitude of risk*	Reference with study design
Non-modifiable factors		
Age, y		Anderson et al, 2006 (data from Surveillance Epidemiology, and End Results Program)[3]
<50	1.0 (reference)	
50-59	6.6 (6.5-6.7)	
60-69	9.2 (9.1-9.3)	
70-79	11.1 (10.9-11.2)	
≥80	10.1 (10.0-10.3)	
Family history of breast cancer		Pharoah et al, 1997 (meta-analysis)[4]
First-degree relative	2.1 (2.0-2.2)	
Second-degree relative	1.5 (1.4-1.6)	
Deleterious gene mutations	Cumulative risk to age 80	Risch et al, 2006 (cohort)[5]
BRCA1	90%	
BRCA2	41%	
History of radiation therapy at young age (≤30 y)		Travis et al, 2003 (case-control study)[6]
Dose of ≥4 Gy	3.1 (1.4-8.2)	
Dose of >40 Gy	8.0 (2.6-26.4)	
Personal history of benign breast disease (eg, atypical hyperplasia)	4.24 (3.26-5.41)	Hartmann et al, 2005 (cohort)[7]
Personal history of breast cancer (breast carcinoma in situ)	Standardised incidence ratio 1.96 (1.79-2.14)	Robinson et al, 2008 (retrospective cohort)[8]
Hormonal and reproductive factors		
Exposure to exogenous hormones		
Combined oral contraceptives	Current use: 1.24 (1.15-1.33)	Collaborative Group on Hormonal Factors in Breast Cancer, 1996 (meta-analysis)[9]
Hormonal menopausal therapy	For ≥5 years: 1.35 (1.21-1.49)	Collaborative Group on Hormonal Factors in Breast Cancer, 1997 (meta-analysis)[10]
Young age at menarche	Per 1-year decrease: 1.05 (1.044-1.057)	Collaborative Group on Hormonal Factors in Breast Cancer, 2012 (meta-analysis)[11]
Older age at menopause	Per 1-year increase: 1.03 (1.025-1.032)	Collaborative Group on Hormonal Factors in Breast Cancer, 2012 (meta-analysis)[11]
Older age at first live birth	Per 1-year increase: 0.03 (standard error, 0.003)	Collaborative Group on Hormonal Factors in Breast Cancer, 2002 (meta-analysis)[12]
Nulliparity	2.6 (1.4-4.7)	Singletary, 2003 (review)[13]; Brinton et al, 1983 (case-control)[14]
Modifiable factors		
Alcohol consumption	Per 10 g/day:	WCRF/AICR, 2017 (meta-analysis)[15]
Premenopausal	1.05 (1.02-1.08)	
Postmenopausal	1.09 (1.07-1.12)	
Obesity after menopause	Per 5-kg weight gain: 1.06 (1.05-1.08)	WCRF/AICR, 2017 (meta-analysis)[15]
Vigorous physical activity (high vs low)		WCRF/AICR, 2017 (meta-analysis)[15]
Premenopausal	0.83 (0.73-0.95)	
Postmenopausal	0.90 (0.85-0.95)	

Abbreviations: AICR = American Institute for Cancer Research; WCRF = World Cancer Research Fund

* Data are shown as relative risk (95% confidence interval), unless otherwise specified

Screening for women in the general population

Importantly, BC screening is intended to detect BC in asymptomatic women before symptom onset; this facilitates a better treatment outcome and improves survival. Breast self-examination, clinical breast examination, and mammography are the most widely studied screening modalities for BC.

Breast self-examination and clinical breast examination

In contrast to breast awareness, breast self-examination refers to the regular and systematic self-examination of a woman's breasts. Meta-analysis and two randomised controlled trials (RCTs) in Shanghai and Russia showed that the use of breast self-examination did not produce significant differences in the size or stage of BC, or in the number of BC deaths; however, it generated false-positive findings, including more benign lesions detected and unnecessary biopsies performed.[19-21] Thus, international health agencies including the International Agency for Research on Cancer (IARC), the American Cancer Society, and the US Preventive Services Task Force (USPSTF) recommend against teaching women breast self-examination as a screening modality for BC[17,22-24]; these agencies encourage women to become more aware of breast changes and promptly seek medical advice regarding changes.[17,24,25] With respect to clinical breast examination, three RCTs showed that this screening modality could detect smaller lesions and earlier stages of BC.[26-28] However, there is inadequate evidence that clinical breast examination screening reduces BC mortality among asymptomatic women.[17,21-24]

Mammography screening

Evidence from other countries suggests that organised mammography screening programmes are effective in detecting tumours at an early stage and reducing BC deaths, with the greatest benefit observed among women aged 50 to 69 years.[17,22-24,29-33]

Mammography screening was associated with an approximately 20% reduction in BC mortality among women of all ages at average risk after 13 years of follow-up, as reported in meta-analyses of RCTs (RR=0.80-0.82), a meta-analysis of cohort studies (RR=0.75), and modelling studies (median RR=0.85).[22,29] When compared with women aged <50 years, mammography screening for women aged ≥50 years was associated with slightly greater BC mortality reduction (14%-23% vs 15%), mostly because of greater mortality reduction among women aged 60 to 69 years (31%-32%).[29]

A systematic review by the USPSTF reported the effects of mammography screening in different age-groups. Fair-quality evidence from a meta-analysis of mammography trials showed that the RRs for BC mortality were 0.92 (95% confidence interval [CI]=0.75-1.02) among women aged 39 to 49 years, 0.86 (95% CI=0.68-0.97) among women aged 50 to 59 years, 0.67 (95% CI=0.54-0.83) among women aged 60 to 69 years, and 0.80 (95% CI=0.51-1.28) among women aged 70 to 74 years; the mortality benefit generally increased with age.[30] Similarly, the Canadian Task Force on Preventive Health Care reviewed the benefit of mammography screening for average-risk women aged 40 to 74 years; screening resulted in a modest reduction in BC mortality, with the lowest absolute benefit among women aged <50 years.[33]

Biennial mammography screening is recommended for some women in some developed countries such as Australia, Canada, the US, and European countries.[24,33,34] The IARC has evaluated the effectiveness of biennial mammography screening in some of these countries; approximately 40% reduction in BC mortality was observed among women aged 50 to 69 years who had undergone screening.[17,23] Additionally, a significant reduction in advanced BC was observed among women aged ≥50 years who underwent screening (RR=0.62, 95% CI=0.46-0.83), but not among women aged 39 to 49 years.[30]

Although the benefit of using mammography as a tool for BC screening is evident, there are limitations concerning its use as a screening modality.[17,22-24,29-33,35] Possible adverse outcomes related to such use of mammography include overdiagnosis and overtreatment. For example, women with a diagnosis of ductal carcinoma in situ often rapidly undergo radical treatment although they may live with this non-invasive condition in the absence of diagnosis and subsequent treatment. Estimates of the rate of overdiagnosis varied widely, depending on study designs and methodologies. Observational studies generally led to estimated overdiagnosis rates of 0% to 54%, while the rates estimated on the basis of RCT data ranged from 11% to 22%.[32,35,36] A pooled analysis of 13 European studies also reported wide variation, such that crude estimates of overdiagnosis ranged from 0% to 54%; these estimates were reduced to 1% to 10% after adjustment for BC risk and lead-time bias.[17,29]

Mammography screening could also cause false-positive findings which lead to recall for unnecessary, additional imaging and subsequent invasive procedures (mostly biopsies). The USPSTF systematic review of mammography screening revealed that the 10-year cumulative false-positive and biopsy rates were higher for annual screening than for biennial screening (61% vs 42% and 7% vs 5%, respectively); these rates were also higher among

women aged 40 to 49 years and women with dense breasts.[35] The IARC Working Group estimated that the cumulative risk of false-positive recall in organised screening programmes was approximately 20% for women who underwent mammography screening 10 times between the ages of 50 and 70 years, where fewer than 5% of all false-positive mammography screening results led to an invasive procedure.[17,23] Women may experience anxiety while waiting for the results of mammography screening or upon recall for further investigations. Women with false-positive mammography results generally experienced short-term negative psychological consequences, although such effects could be mitigated via clear communication with their physicians.[17,23,35]

Radiation-induced BC is also a concern for women. Systematic reviews estimated that the risk of death from mammography-related radiation-induced BC ranged from 1 to 11 per 100 000 women, depending on age and screening interval; however, such risk is outweighed by the ability of mammography to prevent BC deaths.[17,23,35]

Concerning the frequency of mammography screening, no RCTs have directly compared the benefits of annual to biennial screening in women of any age; however, observational studies found no differences between biennial and annual screening in women aged ≥50 years.[24,29,30] A modelling study from the US estimated that women screened biennially from age 50 to age 74 avoided a median of seven BC deaths versus no screening, whereas women screened annually from age 40 to age 74 avoided additional three deaths; however, annual screening yielded 1988 more false-positives and 11 more overdiagnoses per 1000 women screened, indicating that biennial screening is a more cost-effective strategy for average-risk populations of women.[37] Guidelines from other regions (eg, the World Health Organization, USPSTF, and most developed countries) generally recommend biennial mammography screening for women at average risk of BC.[24,34,38]

Previously, the CEWG considered the available scientific evidence to be insufficient for recommendations regarding population-based mammography screening among women at average risk in Hong Kong. Recently, the University of Hong Kong research team completed a territory-wide case-control study (HKBCS) involving 3501 BC cases and 3610 controls.[39] The study estimated the risk of BC in women based on a list of parameters including age, age at menarche, age at first live birth, family history of BC among first-degree relatives, prior benign breast disease diagnosis, body mass index, and physical activity (Table 2).[39] The RRs of these identifiable risk factors were incorporated to develop a risk prediction model (ie, personalised risk assessment tool) applicable to the Chinese population in Hong Kong, with the aim of guiding mammography screening and improving the cost-effectiveness of mass screening. The HKBCS found that while the relative reduction in BC mortality was similar between risk-based screening and conventional age-based screening, it would be more cost-effective to provide risk-based biennial mammography screening to Hong Kong Chinese women aged 44 to 69 years who had an increased risk of BC according to the newly developed risk assessment tool.[39] Targeted screening in women at increased risk of BC would reduce the potential for harm related to unnecessary biopsy or other invasive tests conducted to confirm false-positive mammography findings; it would also optimise the use of scarce healthcare resources. Women with high risk (eg, *BRCA1/2* mutation carriers) and moderate risk, as defined by the CEWG, should

TABLE 2. Relative hazards in Hong Kong (2016-2019)* [39]

Risk factor	Relative risk/hazard (95% confidence interval)
Age at menarche, y	
≥15	0.66 (0.57-0.75)
12-14	1
≤11	1.19 (1.11-1.30)
Age at first live birth, y	
<25	1
25-29	1.00 (0.89-1.13)
≥30	1.50 (1.33-1.73)
Nulliparous	1.64 (1.44-1.79)
Family history of breast cancer among first-degree relatives	
No	1
Yes	1.96 (1.68-2.25)
Prior diagnosis of benign breast disease	
No	1
Yes	1.61 (1.43-1.79)
Body mass index, kg/m^2	
<18.5	0.95 (0.83-1.00)
18.5-23	1
>23	1.36 (1.30-1.45)
Physical activity†	
No	1
Yes	0.92 (0.85-0.98)

* The area under the receiver operating characteristic curve is 0.60 for Hong Kong

† Physical activity refers to intense exercise (eg, lifting heavy objects, cardiovascular exercise, and rapid bicycling) at least once weekly on average in the past 10 years

TABLE 3. Revised CEWG recommendations on breast cancer screening[40]

(A) For women at 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 aged ≤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, eg, Hodgkin's disease
   - history of breast cancer, including DCIS; lobular carcinoma
   - history of atypical ductal hyperplasia or atypical lobular hyperplasia

Recommendation on screening:

- 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), whichever is earlier, but not earlier than age 30.
  - for confirmed carriers of *BRCA1/2* deleterious mutations or women who had radiation therapy to the chest for treatment between age 10 and 30 years (eg, for Hodgkin's disease), consider additional annual screening by MRI.

Recommendation on genetic testing:

- 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.
- 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. 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

1. Women at moderate risk (ie, 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 2 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

1. Women aged 44 to 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 2 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 (eg, one developed by The University of Hong Kong; 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 in the general population.

Abbreviations: CEWG = Cancer Expert Working Group on Cancer Prevention and Screening; DCIS = ductal carcinoma in situ; MRI = magnetic resonance imaging

follow the respective CEWG recommendations on BC screening (Table 3).[40]

Other imaging techniques

Compared with conventional two-dimensional mammography, digital breast tomosynthesis (also known as three-dimensional mammography) lowers recall rates for false-positives and detects more cancers; however, it exposes women to more radiation.[17,23,24,30,41,42] Thus far, it remains unclear whether digital breast tomosynthesis can provide benefits to patients by detecting clinically significant cancers, rather than causing overdiagnosis. Current international guidelines do not support the use of digital breast tomosynthesis as a screening tool and future research in this area is warranted.[17,23,24,30,33] Ultrasonography, as an adjunct to mammography in women with radiologically dense breasts, may depict small BCs not visible on mammography, while increasing false-positive recall.[43,44] Systematic reviews conducted by Cochrane, IARC, and USPSTF have concluded that there is insufficient evidence to support the use of ultrasonography in asymptomatic

women as a routine screening tool to decrease BC mortality.[17,23,24,45]

Revised recommendation

In accordance with local data and the latest scientific evidence, the CEWG has revised its BC screening recommendations for women in Hong Kong, as summarised below[40]:

1. Breast self-examination is not recommended as a screening tool for BC 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.
2. There is insufficient evidence to recommend clinical breast examination or ultrasonography as a screening tool for BC for asymptomatic women.
3. It is recommended that risk-based approach should be adopted for BC screening.
4. 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 in Table 3.[40]

Author contributions

All authors have made substantial contributions to the concept or design, acquisition of data, analysis or interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As editors of this journal, DVK Chao, HHF Loong, and MCS Wong were not involved in the peer review process of this article. The other authors have no conflicts of interest to disclose.

Declaration

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