Hong Kong J Radiol. 2023;26:260-5. Epub 12 Dec 2023 | https://doi.org/10.12809/hkjr2217565

PERSPECTIVE

Optimising Risk-based Breast Cancer Screening in Hong Kong

CPY Chien, G Ho, TPW Lam

Department of Radiology, Queen Mary Hospital, Hong Kong SAR, China

ABSTRACT

In Hong Kong, breast cancer is the most common cancer and the third leading cause of cancer mortality in women. The incidence has been increasing substantially over the past decades. In 2021, the Hong Kong Government launched a risk-based pilot screening programme with reference to the revised recommendations of the Cancer Expert Working Group on Cancer Prevention and Screening. The mortality rate reduction has yet to be assessed. This article provides an overview of breast cancer screening, briefly discusses the background and updated recommendations, and focuses on the supplementary screening tools and future directions in risk-based screening in Hong Kong.

Key Words: *Breast density; Breast neoplasms; Mammography; Mass screening*

中文摘要

優化香港基於風險的乳癌篩查

錢珮恩、何潔明、林培榮

在香港，乳癌是最常見的癌症，也是女性癌症死亡的第三大原因。過去幾十年來，乳癌發病率大幅增加。2021年，香港政府參考癌症預防及普查專家工作小組的修訂建議，推出基於風險的篩查先導計劃，而其死亡率降低程度尚待評估。本文概述乳癌篩查，簡要討論其背景和最新建議，並重點介紹香港基於風險篩查的補充篩查工具和未來方向。

INTRODUCTION

Female breast cancer had the highest incidence among all cancers diagnosed in women in 2020, with an estimated 2.3 million new cases (11.7%). It accounted for one in four cancer cases and for one in six cancer deaths.[1] The aim of breast cancer screening programme is to reduce breast cancer mortality through early detection and treatment. The World Health Organization recommends

Correspondence: *Dr CPY Chien, Department of Radiology, Queen Mary Hospital, Hong Kong SAR, China*
Email: cpy658@ha.org.hk

Submitted: 13 Apr 2022; Accepted: 5 Sep 2022.

Contributors: All authors designed the study. CPYC acquired and analysed the data and drafted the manuscript. All authors critically revised 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: All authors have disclosed no conflicts of interest.

Funding/Support: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability: All data generated or analysed during the present study are available from the corresponding author on reasonable request.

© 2023 Hong Kong College of Radiologists. CC BY-NC-ND 4.0

population-based mammography screening biennially for women aged 50 to 69 years at average risk for breast cancer in countries with adequate resources.[2]

Although breast cancer is less common in Asian countries compared to the United States and Europe, its incidence has been increasing substantially over the past decades.[1,3,4] In Hong Kong, breast cancer is the most common cancer and the third leading cause of cancer mortality in women, with age-standardised incidence and mortality rates of 65.5 and 10.2 per 100,000 population, respectively, in 2019.[5] Most Western countries have well-established population-based mammogram screening programmes based on age.[6,7] Our Asian counterparts (i.e., South Korea, Singapore, Taiwan, and Japan) have also introduced screening programmes in the past two decades.[8] In 2021, the Hong Kong Government launched a risk-based pilot screening programme based on the revised recommendations of the Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) under the Centre for Health Protection.[9]

This article provides an overview of breast cancer screening, briefly discusses the background and updated recommendations, and focuses on the supplementary screening tools and future directions in risk-based screening in Hong Kong.

BACKGROUND AND PRINCIPLES OF BREAST CANCER SCREENING

The goal of breast cancer screening is to detect breast cancer at its pre-clinical stage, so that it can be treated early to reduce disease- and treatment-related morbidity and mortality. Evidence has shown that detecting breast cancers at this early stage is associated with better outcomes.[10] The risk of metastasis and death increases with tumour size and number of involved axillary lymph nodes at detection.[11,12]

The 5-year survival rate drops from 86% to 99% in localised and regional disease to 29% in distant disease.[13] Treatment of early cancers requires less extensive breast tissue resection and axillary lymph node dissection, and hence fewer complications and side-effects. It also reduces overall treatment costs and financial burden on the healthcare system. Potential harms, which lead to controversies of effectiveness of screening programmes, include false-positives, overdiagnosis, overtreatment, psychological stress of participants; and lead-time bias which leads to seemingly increased survival.

Careful consideration of the cost-benefit balance, and adherence to the World Health Organization principles outlined by Wilson and Jungner,[14] are important when implementing breast cancer screening programme With numerous randomised controlled trials demonstrating a 20% to 30% decrease in mortality from breast cancer, numerous countries have implemented population-based screening programmes.[15] Most well-established population-based breast cancer screening programmes offer biennial mammography to women aged 40 to 50 years to 69 to 74 years.[16] Subsequent studies with data generated from screening programmes have provided further evidence that screening mammography is beneficial.[17]

UPDATES ON HONG KONG BREAST CANCER SCREENING

In 2010, the CEWG had adopted a simple and rather restrictive set of risk stratification criteria based on the presence of *BRCA1* or *BRCA2* genes, family history, and selected personal risk factors that led to only a small group of high-risk eligible women being screened.[18] For the last few decades, elective screening has been practised in Hong Kong in the private sector. Women attending such screening services are self-referred. The largest self-financed and self-referred mammography screening programme was organised by the Tung Wah Group of Hospitals, which has been offering mammography screening since 1993 with the number of examinations continuing to increase throughout the years.[19]

Recently, there has been a transition from elective screening to a broader risk-based approach. Based on the revised recommendations of the CEWG, the Hong Kong Government has rolled out a risk-based breast cancer screening pilot programme to provide screening services for eligible women over a period of 2 years. A local breast cancer risk stratification model for the Hong Kong Chinese population, developed by The University of Hong Kong based on the identified local risk factors for breast cancer, is employed.[9]

The new CEWG recommendations result in two additional groups of women being recommended for mammographic screening every 2 years. These groups are made up of women at moderate risk with a relevant defined family history, and women aged 44 to 69 with certain combinations of personal risk factors (including a history of breast cancer among first-degree relatives, a prior diagnosis of benign breast disease, nulliparity and late age of first live birth, early age at menarche, high

body mass index, and physical inactivity) putting them at increased risk of breast cancer.[9]

RISK-BASED SCREENING PROGRAMME

Population-based screening programmes based on different age groups have long been implemented in Western countries. They have proven to reduce breast cancer–related mortality effectively.[20] On the other hand, there was increasing evidence in favour of advocating for risk-based breast cancer screening due to potential higher cost-effectiveness in concentrating the resources on screening women with increased risk.[21,22] Some Western countries are also transitioning to risk-based screening approaches that do not rely on age alone.[23,24]

Risk-based programmes are aimed at women who are more likely to benefit, thus reducing the risk of causing harm to women at lower risk, and allow resources to be used more efficiently. In Hong Kong, although the age-standardised incidence rate of breast cancer is rising, it still remains relatively low when compared to Western countries. It is known that performing screening mammography in populations with relatively low disease prevalence would lead to higher false-positive rates and hence unnecessary biopsies, creating potential complications and psychological distress.[25] Therefore, under these circumstances, a personalised risk-based approach may be more cost-effective than universal age-based screening for Hong Kong Chinese women.[26]

The effectiveness of a risk-based screening programme depends much on the accuracy of individual risk estimation. In terms of risk stratification, the Gail model is one of the earliest breast cancer risk assessment tools that has been developed, validated and calibrated to be deployed in different populations.[27,28] More recently, the Breast Cancer Surveillance Consortium model and the Tyrer-Cuzick model have included breast density in risk assessment, which demonstrated modest performance improvement.[29,30] Histories of hyperplasia and lobular carcinoma in situ are also included.[29,30] With more local radiological and biomarker data available, the Hong Kong breast cancer risk stratification model can be improved to cover additional risk factors and identify women with increased risks effectively in the future.

RELATIONSHIP BETWEEN BREAST DENSITY AND BREAST CANCER

Increased mammographic breast density is an independent moderate risk factor for breast cancer. Women with extreme density are 4 to 6 times more likely to develop breast cancer than those with fatty breasts. Furthermore, extreme breast density is a solitary risk factor that puts women into higher lifetime and 10-year risk categories for breast cancer.[31] It is regarded as the same risk category (relative risk of 2.1 to 4) with ductal carcinoma in situ, high endogenous postmenopausal hormonal levels, high-dose radiation to the chest, and two or more first-degree relatives with breast cancer.[32]

Mammography is known to have lower sensitivity in women with dense breasts, including the Chinese population, younger and premenopausal women, and those with genetic predispositions to breast cancer, due to the increased mammographic density masking the radiological features of early breast cancer.[33] Therefore, it leads to more interval cancers and higher cancer stages at diagnosis. In addition, superimposed glandular tissue can also mimic the presence of a lesion, resulting in reduced specificity, increased recall rates, and unnecessary investigations.

SUPPLEMENTARY SCREENING TOOLS IN WOMEN WITH INCREASED RISK OF BREAST CANCER

In view of the associated increased cancer risk and mammographic masking effect in the relatively denser breast tissue in Chinese women, some recommend the use of supplementary screening tools to increase screening sensitivity and specificity.[34] Digital breast tomosynthesis (DBT) generates pseudo–three-dimensional images, which can resolve superimposition of breast tissue, thus increasing lesion visibility and reducing unnecessary recalls due to summation artifacts. It has been shown to have higher sensitivity and specificity compared to traditional digital mammography.[35] Ultrasound has been shown to reduce interval cancer rates for women with dense breasts when added to mammography. However, it is only suggested to be considered as a supplementary tool on a case-by-case basis due to its high false-positive rate.[36]

Breast contrast-enhanced magnetic resonance imaging (MRI) provides physiological parameters related to tumour angiogenesis in addition to anatomical assessment. It has been widely accepted for screening women who are at high risk for breast cancer, such as confirmed carriers of *BRCA1* or *BRCA2* deleterious mutations in genetic testing and those who had radiation therapy to the chest between 10 to 30 years of age for

Hodgkin lymphoma.[9] Kuhl et al[37] found that MRI could identify an additional 15.5 cancers per 1,000 cases in women at average risk of breast cancer. The DENSE (Dense Tissue and Early Breast Neoplasm Screening) trial has shown that using supplemental MRI screening in women with extremely dense breasts resulted in significantly fewer interval cancers than mammography alone.[34] However, due to long imaging time and limited availability, MRI is restricted to screening a limited number of high-risk women. Abbreviated MRI (AB-MRI) is a shortened version of the standard MRI protocol. By retaining a dynamic contrast-enhanced MRI sequence and one to two other sequences (depending on individual institutions), the examination time is shortened to 10 minutes. According to the American College of Radiology Imaging Network EA1141 trial,[38] AB-MRI was superior to DBT in detection of both invasive breast cancer and ductal carcinoma in situ, with 2.4 times higher detection rate in women with dense breasts. The positive predictive values of AB-MRI and DBT were shown to be similar.[38] Current evidence demonstrates that this technique has the potential to supplement mammography screening in women with dense breast tissue and increased risk of breast cancer. The shortened AB-MRI protocol and examination time increase the availability of MRI, allowing more women to be screened. It may potentially be included in the future screening programme.

Contrast-enhanced digital mammography (CEDM) is one of the latest advances in breast imaging. It uses a dual-energy technique performed after intravenous administration of iodinated contrast to identified enhancing lesions. The underlying principle is based on tumour physiology—tumoral angiogenesis increases vascular permeability, resulting in enhancement. Studies have shown that CEDM can improve diagnostic accuracy in evaluation of screening recalls. Initial findings evaluating the application of CEDM in high-risk screening have shown comparable specificity and positive predictive values with MRI. This suggests that CEDM may be useful as an alternative when MRI cannot be performed because of patient contraindication or inaccessibility.[39]

FEATURES OF AN EFFECTIVE SCREENING PROGRAMME

To improve the effectiveness of a risk-based screening programme, accurate risk stratification is essential. Incorporating mammographic breast density in the Hong Kong risk prediction model when more radiological data are available in the future can further enhance the discriminative power of the model to identify women who would benefit from screening.

Diagnostic accuracy depends on interpreter training, skills, and experience. Regular feedback from outcome of screening through assessment, follow-up results and radiological-pathological correlation can enhance the performance of radiologists. Measures such as regular audits and review of interval cancers should be implemented. Double reading is practised in some screening programmes to increase screening performance. Computer-aided detection algorithms can identify areas of abnormal density, morphology, and calcifications and mark them on an overlay image. It is most frequently used as a prompt to radiologists for special consideration during interpretation. Ongoing studies have evaluated it as a surrogate for a second reader.[40] A meta-analysis of five retrospective studies demonstrated better performance in machine learning mammographic breast cancer detection (area under the curve = 0.89) than radiologists (area under the curve = 0.85).[41] Other applications of artificial intelligence in breast cancer screening include lesion characterisation, determination of lesions' malignant probability, and triage of the worklist to streamline workflow.[42,43] A previous study reported that machine learning reduced the number of mammography reads by radiologists by 17% to 91% with 0% to 7% cancers missed.[41] Local regulations, guidelines, and recommendations should be adopted to ensure the quality assurance of mammography screening.

The level of participation and compliance in screening are influenced by personal, socio-economic, and cultural factors. Informed decision-making is important since screening has both positive and negative impact for individuals. Women should be fully informed about the benefits, limitations, and harms under both ethical and legal considerations. Measures can be taken to address the psychological consequences of mammography screening (such as hotlines, follow-up clinics, etc.) to alleviate patients' psychological distress and anxiety. Finally, participation can be influenced by how the screening invitation is made, how access to screening is organised, and how effectively breast cancer awareness is promoted, which are all amendable.

CONCLUSION

The Hong Kong risk-based breast screening programme is in its early phase. Its cost-effectiveness, which depends

on multiple modifiable factors, requires continuous evaluation and improvement. The effectiveness of a risk-based screening programme is determined by the discriminative power of the risk stratification model. Inclusion of individual factors such as breast density, histology results of breast biopsy, and biomarkers may modify it to a more comprehensive model. Personalised screening tailored to individuals' risks and preferences maybe the future direction in Hong Kong and worldwide.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-49.
2. World Health Organization. WHO position paper on mammography screening. 2014. Available from: https://www.who.int/publications/i/item/who-position-paper-on-mammography-screening. Accessed 22 Mar 2022.
3. Bray F, McCarron P, Parkin DM. The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res. 2004;6:229-39.
4. Wong IO, Schooling CM, Cowling BJ, Leung GM. Breast cancer incidence and mortality in a transitioning Chinese population: current and future trends. Br J Cancer. 2015;112:167-70.
5. Hong Kong Cancer Registry, Hospital Authority. Female breast cancer in 2019. Available from: https://www3.ha.org.hk/cancereg/pdf/factsheet/2019/breast_2019.pdf. Accessed 22 Mar 2022.
6. Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, et al. Cancer screening in the United States, 2018: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2018;68:297-316.
7. Wübker A. Explaining variations in breast cancer screening across European countries. Eur J Health Econ. 2014;15:497-514.
8. Sitt JC, Lui CY, Sinn LH, Fong JC. Understanding breast cancer screening—past, present, and future. Hong Kong Med J. 2018;24:166-74.
9. Centre for Health Protection, Department of Health, Hong Kong SAR Government. Cancer Expert Working Group on Cancer Prevention and Screening. Recommendations on prevention and screening for breast cancer for health professionals. Available from: https://www.chp.gov.hk/files/pdf/breast_cancer_professional_hp.pdf. Accessed 22 Mar 2022.
10. Eby PR. Evidence to support screening women annually. Radiol Clin North Am. 2017;55:441-56.
11. Colzani E, Liljegren A, Johansson AL, Adolfsson J, Hellborg H, Hall PF, et al. Prognosis of patients with breast cancer: causes of death and effects of time since diagnosis, age, and tumor characteristics. J Clin Oncol. 2011;29:4014-21.
12. Tan LK, Giri D, Hummer AJ, Panageas KS, Brogi E, Norton L, et al. Occult axillary node metastases in breast cancer are prognostically significant: results in 368 node-negative patients with 20-year follow-up. J Clin Oncol. 2008;26:1803-9.
13. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer stat facts: female breast cancer. Available from: https://seer.cancer.gov/statfacts/html/breast.html. Accessed 22 Mar 2022.
14. Wilson JM, Jungner G. Principles and practice of screening for disease. Geneva, Switzerland: World Health Organization. Public Health Papers No. 34. Available from https://apps.who.int/iris/bitstream/handle/10665/37650/WHO_PHP_34.pdf?sequence=17&isAllowed=y. Accessed 2 Apr 2022.
15. Nelson HD, Cantor A, Humphrey L, Fu R, Pappas M, Daeges M, et al. Screening for breast cancer: a systematic review to update the 2009 U.S. Preventive Services Task Force recommendation. Rockville (MD): Agency for Healthcare Research and Quality; 2016.
16. von Karsa L, Qiao YL, Ramadas K, Keita N, Arrossi S, Dean PB, et al. Screening—implementation. In: Stewart BW, Wild CP, editors. World Cancer Report 2014. Lyon, France: International Agency for Research on Cancer; 2014: 330-6.
17. Myers ER, Moorman P, Gierisch JM, Havrilesky LJ, Grimm LJ, Ghate S, et al. Benefits and harms of breast cancer screening: a systematic review. JAMA 2015;314:1615-34.
18. Centre for Health Protection, Department of Health, Hong Kong SAR Government. Cancer Expert Working Group on Cancer Prevention and Screening. Recommendations on breast cancer screening 2010. Available from: http://www.chp.gov.hk/files/pdf/recommendations_on_breast_cancer_screening_2010.pdf. Accessed 2 Apr 2022.
19. Lui CY, Lam HS, Chan LK, Tam KF, Chan CM, Leung TY, et al. Opportunistic breast cancer screening in Hong Kong; a revisit of the Kwong Wah Hospital experience. Hong Kong Med J. 2007;13:106-13.
20. Sardanelli F, Aase HS, Álvarez M, Azavedo E, Baarslag HJ, Balleyguier C, et al. Position paper on screening for breast cancer by the European Society of Breast Imaging (EUSOBI) and 30 national breast radiology bodies from Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Israel, Lithuania, Moldova, The Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Sweden, Switzerland and Turkey. Eur Radiol. 2017;27:2737-43.
21. Pashayan N, Morris S, Gilbert FJ, Pharoah PD. Cost-effectiveness and benefit-to-harm ratio of risk-stratified screening for breast cancer: a life-table model. JAMA Oncol. 2018;4:1504-10.
22. Khan SA, Hernandez-Villafuerte KV, Muchadeyi MT, Schlander M. Cost-effectiveness of risk-based breast cancer screening: a systematic review. Int J Cancer. 2021;149:790-810.
23. Kerlikowske K, O'Kane ME, Esserman LJ. Fifty years of age-based screening: time for a new risk-based screening approach. Evid Based Med. 2014;19:183.
24. Allweis TM, Hermann N, Berenstein-Molho R, Guindy M. Personalized screening for breast cancer: rationale, present practices, and future directions. Ann Surg Oncol. 2021;28:4306-17.
25. Nelson HD, Pappas M, Cantor A, Griffin J, Daeges M, Humphrey L. Harms of breast cancer screening: systematic review to update the 2009 U.S. Preventive Services Task Force recommendation. Ann Intern Med. 2016;164:256-67.
26. Wong IO, Tsang JW, Cowling BJ, Leung GM. Optimizing resource allocation for breast cancer prevention and care among Hong Kong Chinese women. Cancer. 2012;118:4394-403.
27. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81:1879-86.
28. Chay WY, Ong WS, Tan PH, Jie Leo NQ, Ho GH, Wong CS, et al. Validation of the Gail model for predicting individual breast cancer risk in a prospective nationwide study of 28,104 Singapore women. Breast Cancer Res. 2012;14:R19.
29. Brentnall AR, Cuzick J, Buist DS, Bowles EJ. Long-term accuracy

of breast cancer risk assessment combining classic risk factors and breast density. JAMA Oncol. 2018;4:e180174.
30. Brentnall AR, Harkness EF, Astley SM, Donnelly LS, Stavrinos P, Sampson S, et al. Mammographic density adds accuracy to both the Tyrer-Cuzick and Gail breast cancer risk models in a prospective UK screening cohort. Breast Cancer Res. 2015;17:147.
31. Harvey JA, Bovbjerg VE. Quantitative assessment of mammographic breast density: relationship with breast cancer risk. Radiology. 2004;230:29-41.
32. American Cancer Society. Breast cancer facts & figures 2019-2020. Atlanta: American Cancer Society, Inc. 2019. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf. Accessed 2 Apr 2022.
33. Checka CM, Chun JE, Schnabel FR, Lee J, Toth H. The relationship of mammographic density and age: implications for breast cancer screening. AJR Am J Roentgenol. 2012;198:W292-5.
34. Bakker MF, de Lange SV, Pijnappel RM, Mann RM, Peeters PH, Monninkhof EM, et al. Supplemental MRI screening for women with extremely dense breast tissue. N Engl J Med. 2019;381:2091-102.
35. Østerås BH, Martinsen AC, Gullien R, Skaane P. Digital mammography versus breast tomosynthesis: impact of breast density on diagnostic performance in population-based screening. Radiology. 2019;293:60-8.
36. Berg WA, Rafferty EA, Friedewald SM, Hruska CB, Rahbar H. Screening algorithms in dense breasts: *AJR* Expert Panel Narrative Review. AJR Am J Roentgenol. 2021;216:275-94.
37. Kuhl CK, Strobel K, Bieling H, Leutner C, Schild HH, Schrading S. Supplemental breast MR imaging screening of women with average risk of breast cancer. Radiology. 2017;283:361-70.
38. US National Library of Medicine. Abbreviated breast MRI and digital tomosynthesis mammography in screening women with dense breasts. Available from: https://clinicaltrials.gov/ct2/show/NCT02933489. Accessed 2 Apr 2022.
39. Jochelson MS, Pinker K, Dershaw DD, Hughes M, Gibbons GF, Rahbar K, et al. Comparison of screening CEDM and MRI for women at increased risk for breast cancer: a pilot study. Eur J Radiol. 2017;97:37-43.
40. Gilbert FJ, Astley SM, Gillan MG, Agbaje OF, Wallis MG, James J, et al. Single reading with computer-aided detection for screening mammography. N Engl J Med. 2008;359:1675-84.
41. Hickman SE, Woitek R, Le EP, Im YR, Mouritsen Luxhøj C, Aviles-Rivero AI, et al. Machine learning for workflow applications in screening mammography: systematic review and meta-analysis. Radiology. 2022;302:88-104.
42. Mendelson EB. Artificial intelligence in breast imaging: potentials and limitations. AJR Am J Roentgenol. 2019;212:293-9.
43. Wallis MG. Artificial intelligence for the real world of breast screening. Eur J Radiol. 2021;144:109661.