衞生防護中心
Centre for Health Protection

Cancer Expert Working Group on Cancer Prevention and Screening

2016 Recommendations on Prevention and Screening for Breast Cancer For Health Professionals

Local epidemiology of female breast cancer

1. Breast cancer has been the most common cancer among women in Hong Kong since the early 1990's. In 2014, there were 3,868 newly registered female breast cancer cases, accounting for 26.6% of all new cancer cases in females. 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.[1]

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 compared with rates reported in the West (e.g. United Kingdom (UK) or Australia), and in Asian countries (e.g. Singapore) in 2012.[3]

Risk factors of female breast cancer

4. There are a range of factors determined a woman's risk of breast cancer. **Positive family history** has been identified as a strong known risk factor for developing breast cancer. 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 high risk for breast cancer. Germline mutations in *BRCA1/2* genes are associated with an approximately 40% to 85% lifetime risk of breast cancer, being 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] The prevalence of *BRCA* mutation in the general population also remains unknown in Hong Kong. According to the latest 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* etc) 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 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) 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]

- **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** which is Group I carcinogen as classified by International Agency for Research on Cancer (IARC), World Health Organization. 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 all-age breast cancer by 10%.

- **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. The 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 doctors promptly if suspicious symptoms appear because delay in seeking medical attention may lead to advanced stage at presentation and poorer survival.[19]

Screening for general female population at average risk

10. Breast self-examination (BSE), clinical breast examination (CBE) and mammography are common breast cancer screening modalities adopted by the medical profession. Ultrasonography and magnetic resonance imaging (MRI) have also been considered as the only screening modality or as supplementary to mammography.

(i) Breast Self-examination (BSE)

11. BSE had 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 increased harm due to increased numbers of benign lesions and biopsies performed.[20] Hence, there is insufficient evidence to recommend regular breast self-examination (i.e. a regular, formally taught and ritual examination of woman's breasts by herself 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 these are detected.

(ii) Clinical breast examination (CBE)

12. There are three randomised controlled trials (RCTs), one conducted in the Philippines[21] and two in India,[22, 23] 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 Philippine study was discontinued due to poor compliance and other two Indian studies are currently underway, no conclusion on the effectiveness of CBE on 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, over-diagnosis (the diagnosis of breast cancer 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 potential complications arising from subsequent invasive investigations or treatment may outweigh benefits.[24-31]

14. A Cochrane review estimated that mammography screening resulted in 15% increase in breast cancer mortality and 30% increase in over-diagnosis and over-treatment. 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 more than 200 women would be falsely alarmed and experience significant psychological distress because of false-positive findings.[32, 33]

15. The UK Independent Breast Review in 2013 showed that mammography screening

leads to a relative risk reduction of 20% in breast cancer mortality and estimated a 11% over-diagnosis rate.[34]

16. The Swiss Medical Board reported that for every 1,000 women with regular mammography screening, 1-2 women's lives could be saved, but around 100 women would 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. On the other hand, the Board recommended thorough medical assessment and comprehensive information about the benefits and harms should be provided to women considering mammography screening. [35, 36]

17. The 25 year follow-up of the Canadian National Breast Screening Study revealed that women aged 40-59 who underwent annual mammography screening received no benefit on breast cancer mortality but resulted in 22% over-diagnosis, suggesting policy makers to reassess the rationale of screening.[24]

18. Recently, the International Agency for Research on Cancer (IARC) of World Health Organization 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, the evaluation supported that there is sufficient evidence that mammography screening led to over-diagnosis 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 potential short-term psychological consequences.[9, 37]

19. On the other hand, some international and local evidence suggested that reduction in breast cancer mortality could be attributable to improved survival due to treatment advancement and improved health service delivery rather than screening.[29, 31, 38, 39]

20. In Hong Kong, the age-standardised incidence rate of breast cancer is relatively lower than those in Western countries. Therefore the positive predictive value of mammography is lower, generating more false-positive results and the ensuing unnecessary follow-up investigations which may cause complications and psychological distress.[40, 41] Furthermore, local modeling studies showed that population-based mammography screening is not a cost-effective public health intervention among other strategies to prevent and control breast

cancer.[42, 43]

(iv) Ultrasonography

21. Ultrasonography, used as an adjunct to mammography in women with radiologically dense breasts, has the potential of depicting small, node-negative breast cancers not seen on mammography.[44, 45] Both Cochrane review in 2013[46] and the recent IARC review[9] 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

22. Locally, there is no consensus on how to identify women at increased risk of breast cancer among the female population. In 2010, the Cancer Expert Working Group on Cancer Prevention and Screening (CEWG), based on international studies and overseas practices, derived a local definition of increased risk by adopting a set of qualitative risk stratification criteria that includes *BRCA1/2* deleterious mutation carrier status; characteristics of family history and personal risk factors (refer to paragraphs 4-6). Women at increased risk is categorized as having 'high risk' or at 'moderate risk' as shown in Table 1.[47]

(i) Mammography

23. Enhanced surveillance for early detection of breast cancer has been suggested as secondary preventive measures for women at increased risk. Although there have not been any RCTs of mammography screening specifically on women at increased risk, previous observational studies have concluded that mammography screening in high risk population is effective, despite the differences in their study populations, criteria for risk stratification, screening protocols and measures of effectiveness.[48-54] However, mammography has lower sensitivity in younger women and those with genetic predisposition to breast cancer due to increased mammographic density and higher likelihood of obscuring the radiological features of early breast cancer.[55]

(ii) Magnetic resonance imaging (MRI)

24. MRI has been recommended as an adjunct to routine mammography for the surveillance of women at high risk in some countries (e.g. US[56], UK[57]). MRI is more sensitive than mammography for detection of breast cancer among *BRCA1/2* mutation carriers.[58, 59] IARC review found improved sensitivity but lower specificity of MRI plus mammography of about 95% and 80% respectively, as compared with mammography only

(about 40% and 95% respectively).[9]

25. 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, as compared with other common screening modalities (e.g. CBE, mammography and ultrasonography).[60-62]

26. A modeling study of three large *BRCA1/2* screening projects in UK,[63] Canada[64] and the Netherlands[65, 66] demonstrated that screening with mammography and MRI (combined screening) detected relatively more ductal carcinoma *in situ* (DCIS) and smaller invasive cancers in *BRCA2* mutation carriers than *BRCA1* mutation carriers, resulting in larger reductions in breast cancer mortality from 41.9% (for mammography only) to 50.1% (combined screening) for *BRCA1;* from 46.8% (for mammography only) to 61.6% (combined screening) for *BRCA2*.[67]

27. 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 to 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.[68] IARC review also found variable all-cause survival results among the reviewed cohort studies in women with *BRCA1/2* mutation.[9]

28. Notwithstanding the above studies showed that MRI is superior to mammography in detecting breast cancer among women at high risk, the higher radiation risk due to MRI and acceptance of more false-positive results for mammography should be considered in making individual screening decisions.[69] Regarding the effectiveness of screening Chinese women at higher breast cancer risk, there is lack of local studies on the role and effectiveness of MRI and/mammography.

(iii) Local research

29. To bridge the knowledge gap for prediction and assessment of risk of breast cancer in the local female population, the Research Office of Food and Health Bureau commissioned The University of Hong Kong a large scale research in October 2015 to develop a locally-validated, evidence-driven quantitative risk prediction tool for breast cancer screening. This study is ongoing and the findings will facilitate the CEWG to formulate evidence-based

recommendations on criteria for breast cancer screening especially for those at higher risk.

30. After taking into consideration local epidemiology, emerging scientific evidence, local and overseas screening practices, the CEWG has fine-tuned the recommendations on breast cancer screening in June 2016 as shown in Table 1.

Cancer Expert Working Group on Cancer Prevention and Screening
March 2017

Table 1 2016 CEWG recommendations on breast cancer screening

<table>
<tr><th colspan="2">Breast cancer screening</th></tr>
<tr><th colspan="2">For asymptomatic population at average risk</th></tr>
<tr><td colspan="2">1. There is insufficient evidence to recommend for or against population-based mammography screening for asymptomatic women at average risk in Hong Kong.
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.
3. There is insufficient evidence to recommend clinical breast examination.
4. Individuals considering breast cancer screening should be adequately informed by doctors about benefits and harms.</td></tr>
<tr><th colspan="2">For women at high risk</th></tr>
<tr><td>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 (BC)/ovarian cancer, such as
● any 1° female relative being a confirmed carrier of BRCA1/2 deleterious mutations;
● any 1° or 2° female relative with both BC and ovarian cancer;
● any 1° female relative with bilateral BC;
● any male relative with history of BC;
● two 1° female relatives with breast cancer AND one of them being diagnosed age ≤50;
● two or more 1° or 2° female relatives with ovarian cancer;
● three or more 1° or 2° female relatives with breast cancer OR a combination of BC and ovarian cancer
3. Personal risk factors
● history of radiation 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</td><td>Recommendation on screening
● Should see a cancer specialist; 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 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
● 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.</td></tr>
<tr><th colspan="2">For women at moderate risk</th></tr>
<tr><td>Local definition – with any one of the risk factors:
1. Family history of only 1 first-degree female relative with breast cancer diagnosed at or below 50 years of age; <u>or</u>
2. 2 first-degree female relatives diagnosed to have breast cancer after theage of 50</td><td>● Should discuss with their doctors about the pros and cons of breast cancer screening before deciding whether to start screening by mammography every two to three years.
● MRI is not recommended for women at moderate risk.</td></tr>
</table>

References

1. Hong Kong Cancer Registry, Hospital Authority. Female Breast Cancer in 2014. Available from: https://www3.ha.org.hk/cancereg/pdf/factsheet/2014/breast_2014.pdf.
2. Department of Health and Census and Statistics Department, HKSAR. Mortality Statistics, 2015.
3. Ervik M, Lam F, Ferlay J, Mery L, Soerjomataram I, Bray F.(2016). Cancer Today. Lyon, France: International Agency for Research on Cancer. Cancer Today. Available from: http://gco.iarc.fr/today.
4. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer.* May 29 1997;71(5):800-809.
5. PDQ® Cancer Genetics Editorial Board. PDQ Genetics of Breast and Gynecologic Cancers. Bethesda, MD: National Cancer Institute. Updated 20 January 2017. Available at: http://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq.
6. Kharazmi E, Chen T, Narod S, Sundquist K, Hemminki K. Effect of multiplicity, laterality, and age at onset of breast cancer on familial risk of breast cancer: a nationwide prospective cohort study. *Breast Cancer Res Treat.* Feb 2014;144(1):185-192.
7. Bevier M, Sundquist K, Hemminki K. Risk of breast cancer in families of multiple affected women and men. *Breast Cancer Res Treat.* Apr 2012;132(2):723-728.
8. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. 1998 Sep 4 [Updated 2016 Dec 15]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1247/.
9. IARC Handbooks of Cancer Prevention; Volume 15. *Breast Cancer Screening.* 2016. France: International Agency for Research on Cancer, World Health Organization. .
10. Shiovitz S, Korde LA. Genetics of breast cancer: a topic in evolution. *Ann Oncol.* Jul 2015;26(7):1291-1299.
11. Kwong A, Chen JW and Shin VY. A new paradigm of genetic testing for hereditary breast/ovarian cancer. *Hong Kong Med J*. 2016;22:171-7.
12. National Cancer Institute: BRCA1 and BRCA2: Cancer Risk and Genetic Testing. Bethesda, MD: National Cancer Institute. Date last rerviewed 1 April 2015. Available at: http://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet.
13. Hong Kong Hereditary Breast Cancer Registry. *Our Statistics* (Analysis of Participants recruited into research study till September 2016). Available from: http://www.asiabreastregistry.com/en/hereditary-cancers/our-statistics.
14. World Cancer Research Fund / American Institute for Cancer Research. Continuous Update Project Report. *Food, Nutrition, Physical Activity, and the Prevention of Breast Cancer*. 2010. Available at: http://www.wcrf.org/sites/default/files/Breast-Cancer-2010-Report.pdf.
15. Stewart BW and Wild CP (eds.). *World Cancer Report 2014*. Lyon, France: International

Agency for Research on Cancer, WHO. 2014. Available from: http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014.

16. International Agency for Research on Cancer, World Health Organization. *List of Classifications by cancer sites with sufficient or limited evidence in humans, Volumes 1 to 117**. Last update: 24 October 2016. Available at: http://monographs.iarc.fr/ENG/Classification/Table4.pdf.
17. Lee H, Li JY, Fan JH, et al. Risk factors for breast cancer among Chinese women: A 10-year nationwide multicenter cross sectional study. *J Epidemiol*. 2014;24(1):67-76.
18. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet.* Jul 20 2002;360(9328):187-195.
19. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. *The Lancet.* Apr 03 1999;353(9159):1119-1126.
20. Kösters JP, Gøtzsche PC. Regular self-examination or clinical examination for early detection of breast cancer (Review). *The Cochrane Library*. 2008, Issue 4.
21. Pisani P, Parkin DM, Ngelangel C, et al. Outcome of screening by clinical examination of the breast in a trial in the Philippines. *Int J Cancer.* Jan 01 2006;118(1):149-154.
22. Mittra I, Mishra GA, Singh S, et al. A cluster randomized, controlled trial of breast and cervix cancer screening in Mumbai, India: methodology and interim results after three rounds of screening. *Int J Cancer.* Feb 15 2010;126(4):976-984.
23. Sankaranarayanan R, Ramadas K, Thara S, et al. Clinical breast examination: preliminary results from a cluster randomized controlled trial in India. *J Natl Cancer Inst.* Oct 05 2011;103(19):1476-1480.
24. Miller AB, Wall C, Baines CJ, Sun P, To T, Narod SA. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. *BMJ.* Feb 11 2014;348:g366.
25. Siu AL. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med.* Feb 16 2016;164(4):279-296.
26. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med.* Nov 22 2012;367(21):1998-2005.
27. Kalager M, Adami HO, Bretthauer M, Tamimi RM. Overdiagnosis of invasive breast cancer due to mammography screening: results from the Norwegian screening program. *Ann Intern Med.* Apr 03 2012;156(7):491-499.
28. Jorgensen KJ, Zahl PH, Gotzsche PC. Overdiagnosis in organised mammography screening in Denmark. A comparative study. *BMC Womens Health.* Dec 22 2009;9:36.
29. Jorgensen KJ, Zahl PH, Gotzsche PC. Breast cancer mortality in organised mammography

screening in Denmark: comparative study. *BMJ.* Mar 23 2010;340:c1241.

30. Ong MS, Mandl KD. National expenditure for false-positive mammograms and breast cancer overdiagnoses estimated at $4 billion a year. *Health Aff (Millwood).* Apr 2015;34(4):576-583.

31. Autier P, Boniol M, Gavin A, Vatten LJ. Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database. *BMJ.* Jul 28 2011;343:d4411.

32. Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database Syst Rev*. 2011(1):CD001877.

33. Gotzsche PC, Jorgensen KJ. Screening for breast cancer with mammography. *The Cochrane database of systematic reviews*. 2013;6:CD001877.

34. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. *Br J Cancer.* Jun 11 2013;108(11):2205-2240.

35. Swiss Medical Board. *Systematic mammography screening*. Report Dated 15 December 2013. Available at: http://www.medical-board.ch/fileadmin/docs/public/mb/fachberichte/2013-12-15_bericht_mammographie_final_kurzfassung_e.pdf.

36. Biller-Andorno N, Juni P. Abolishing mammography screening programs? A view from the Swiss Medical Board. *N Engl J Med.* May 22 2014;370(21):1965-1967.

37. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Breast-cancer screening--viewpoint of the IARC Working Group. *N Engl J Med.* Jun 11 2015;372(24):2353-2358.

38. 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.* Jan 06 2015;112(1):167-170.

39. Kalager M, Zelen M, Langmark F, Adami HO. Effect of screening mammography on breast-cancer mortality in Norway. *N Engl J Med.* Sep 23 2010;363(13):1203-1210.

40. Lui CY, Lam HS, Chan LK, et al. Opportunistic breast cancer screening in Hong Kong; a revisit of the Kwong Wah Hospital experience. *Hong Kong Med J.* Apr 2007;13(2):106-113.

41. Kwong A, Cheung PS, Wong AY, et al. The acceptance and feasibility of breast cancer screening in the East. *Breast.* Feb 2008;17(1):42-50.

42. Wong IO, Kuntz KM, Cowling BJ, Lam CL, Leung GM. Cost-effectiveness analysis of mammography screening in Hong Kong Chinese using state-transition Markov modelling. *Hong Kong Med J.* Jun 2010;16 Suppl 3:38-41.

43. Wong IO, Tsang JW, Cowling BJ, Leung GM. Optimizing resource allocation for breast cancer prevention and care among Hong Kong Chinese women. *Cancer.* Sep 15 2012;118(18):4394-4403.

44. Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA.*

May 14 2008;299(18):2151-2163.

45. Ohuchi N, Suzuki A, Sobue T, et al. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial. *Lancet.* Jan 23 2016;387(10016):341-348.

46. Gartlehner G, Thaler K, Chapman A, et al. Mammography in combination with breast ultrasonography versus mammography for breast cancer screening in women at average risk. *Cochrane Database Syst Rev.* Apr 30 2013(4):CD009632.

47. Recommendations on Breast Cancer Screening. Hong Kong SAR: Cancer Expert Working Group on Cancer Prevention and Screening, 2012.

48. Maurice A, Evans DG, Shenton A, et al. Screening younger women with a family history of breast cancer--does early detection improve outcome? *Eur J Cancer.* Jul 2006;42(10):1385-1390.

49. Lai MS, Yen MF, Kuo HS, Koong SL, Chen TH, Duffy SW. Efficacy of breast-cancer screening for female relatives of breast-cancer-index cases: Taiwan multicentre cancer screening (TAMCAS). *Int J Cancer.* Sep 25 1998;78(1):21-26.

50. Kerlikowske K, Carney PA, Geller B et al. Performance of screening mammography among women with and without a first-degree relative with breast cancer. *Ann Intern Med*. 2000;133(11):855-863.

51. Gui GP, Kadayaprath G, Darhouse N et al. Clinical outcome and service implications of screening women at increased breast cancer risk from a family history. *Eur J Surg Oncol*. 2006;32(7):719-724.

52. Lalloo F, Boggis CR, Evans DG, Shenton A, Threlfall AG, Howell A. Screening by mammography, women with a family history of breast cancer. *Eur J Cancer.* May 1998;34(6):937-940.

53. Cortesi L, Turchetti D, Marchi I et al. Breast cancer screening in women at increased risk according to different family histories: an update of the Modena Study Group experience. *BMC Cancer*. 2006;6:210.

54. Kollias J, Sibbering DM, Blamey RW et al. Screening women aged less than 50 years with a family history of breast cancer. *Eur J Cancer*. 1998;34(6):878-883.

55. Lord SJ, Lei W, Craft P et al. A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer. *Eur J Cancer* 2007;43(13):1905-1917.

56. Saslow D, Boetes C, Burke W et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin*. 2007;57(2):75-89.

57. *Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer.* NICE Clinical Guideline. Published in June 2013 and last updated in August 2015. Available from:

https://www.nice.org.uk/guidance/cg164/chapter/1-Recommendations#surveillance-and-strategies-for-early-detection-of-breast-cancer.

58. Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. *Ann Intern Med.* May 06 2008;148(9):671-679.

59. Passaperuma K, Warner E, Causer PA, et al. Long-term results of screening with magnetic resonance imaging in women with BRCA mutations. *Br J Cancer.* Jun 26 2012;107(1):24-30.

60. Kuhl C, Weigel S, Schrading S, et al. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. *J Clin Oncol*. 2010; 28:1450-1457.

61. Sardanelli F, Podo F, Santoro F, et al. Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the High Breast Cancer Risk Italian 1 Study). *Invest Radiol*. 2011;46:94–105.

62. Warner E, Hill K, Causer P, et al. Prospective study of breast caner incidence in women with a BRCA1 or BRCA2 mutation under surveillance with and without magnetic resonance imaging. *J Clin Oncol*. 2011;29:1664–9.

63. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet.* May 21-27 2005;365(9473):1769-1778.

64. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA.* Sep 15 2004;292(11):1317-1325.

65. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med.* Jul 29 2004;351(5):427-437.

66. Rijnsburger AJ, Obdeijn IM, Kaas R, et al. BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC Screening Study. *J Clin Oncol.* Dec 20 2010;28(36):5265-5273.

67. Heijnsdijk EA, Warner E, Gilbert FJ, et al. Differences in natural history between breast cancers in BRCA1 and BRCA2 mutation carriers and effects of MRI screening - MRISC, MARIBS, and Canadian studies combined. *Cancer Epidemiol Biomarkers Prev*. 2012; 21(9): 1458-68.

68. Evans DG, Kesavan N, Lim Y, et al. MRI breast screening in high-risk women: cancer detection and survival analysis. *Breast Cancer Res Treat.* Jun 2014;145(3):663-672.

69. Lowry KP, Lee JM, Kong CY, et al. Annual screening strategies in BRCA1 and BRCA2 gene mutation carriers: a comparative effectiveness analysis. *Cancer.* Apr 15 2012;118(8):2021-2030.