



## GUIDELINE INTERPRETATION

# Interpretation of breast cancer screening guideline for Chinese women

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### ABSTRACT

Breast cancer is the most common malignant tumor in Chinese women. Early screening is the best way to improve the rates of early diagnosis and survival of breast cancer patients. The peak onset age for breast cancer in Chinese women is considerably younger than those in European and American women. It is imperative to develop breast cancer screening guideline that is suitable for Chinese women. By summarizing the current evidence on breast cancer screening in Chinese women, and referring to the latest guidelines and consensus on breast cancer screening in Europe, the United States, and East Asia, the China Anti-Cancer Association and National Clinical Research Center for Cancer (Tianjin Medical University Cancer Institute and Hospital) have formulated population-based guideline for breast cancer screening in Chinese women. The guideline provides recommendations on breast cancer screening for Chinese women at average or high risk of breast cancer according to the following three aspects: age of screening, screening methods, and screening interval. This article provides more detailed information to support the recommendations in this guideline and to provide more direction for current breast cancer screening practices in China.

### KEYWORDS

Breast cancer; screening; ultrasound; mammography; guideline

## The epidemiology of breast cancer in Chinese women

With the increasing prevalence of obesity and overweight, and other dramatic changes in lifestyles and dietary patterns associated with rapid economic, social, and cultural development, breast cancer is the most common malignant tumor in Chinese women and has become a severe threat to their health. During the past half century, many studies in various countries worldwide have confirmed that breast cancer screening is the most effective way to improve the survival rate and quality of life of breast cancer patients. The World Health Organization (WHO) has stated that early breast cancer is a curable disease, and early diagnosis/treatment is the best way to improve the survival rate. The peak onset age for breast cancer in Chinese women is between 40 and 50 years<sup>1,2</sup>, which is 5–10 years younger than

that in women from Western countries. Therefore, it is imperative to develop population-based breast cancer screening guideline suitable for Chinese women.

Data from the Chinese National Central Cancer Registry between 1989 and 2008 indicate that the incidence of breast cancer showed an increasing trend in both urban and rural areas, particularly in rural areas<sup>3</sup>. This incidence continued to increase from 2009 to 2014<sup>1-2,4-8</sup>. At present, breast cancer is the most common malignant tumor in urban Chinese women and the second most common malignant tumor in rural Chinese women<sup>7</sup>. Simultaneously, the mortality of breast cancer between 2010 and 2014 appeared to be stable in both urban women and rural women. The overall 5-year survival rate of breast cancer in Chinese women is only 73% (55.9% for rural women)<sup>9</sup>, whereas it is nearly 89% for American women<sup>8</sup>. Therefore, there is a long way to go in the prevention and control of breast cancer in China<sup>10</sup>.

## Current breast cancer screening programs for Chinese women

There was no nationwide screening programme for breast

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cancer in China before 2008, owing to factors including the large, widely dispersed population, insufficient mammography equipment, and inadequate insurance coverage for mammography in some areas. To obtain convincing data on population-based breast cancer screening for Chinese women and to explore the effectiveness of the breast cancer screening strategy suitable for current Chinese economic conditions, the National Clinical Research Center for Cancer (Tianjin Medical University Cancer Institute and Hospital) and the China Anti-Cancer Association (CACAA) cooperatively organized an interdisciplinary expert group (consisting of clinicians, epidemiologists, biostatisticians, and public-health administrators) to design and implement three large-scale breast cancer screening programs (the Chinese National Breast Cancer Screening Program (CNBCSP), covering 398,184 urban women aged 35–69 years between 2008 and 2009 (CNBCSP-Urban); the CNBCSP-Rural Program, covering 828,530 rural women aged 35–59 years between 2009 and 2011; and the Chinese breast cancer Multi-modality Independent Screening Trial (MIST), covering 33,234 women aged 45–65 years from five areas in China between 2008 and 2010). The MIST project was the only multicenter population-based breast cancer screening cohort study aiming to evaluate the accuracy of three screening methods (mammography, MAM; breast ultrasonography, BUS; and clinical breast examination, CBE) of breast cancer. In MIST, all participants received CBE, BUS, and MAM separately and concurrently. Pathological examination is recommended for any positive or suspicious CBE, BUS, or MAM findings.

## Recommendations on breast cancer screening for Chinese women

### Recommendations for women at average risk of breast cancer

#### Screening age

- Women aged 45–69 years and with an average risk of breast cancer should undergo regular screening (level A recommendation).
- Women aged 40–44 years and with an average risk of breast cancer should have the opportunity to receive screening. They are encouraged to fully understand the potential benefits, risks and limitations of breast cancer screening, and then consult with their doctors to make individualized decisions on screening (level B recommendation).
- Women aged 69 years and older and with an average risk

of breast cancer should have the opportunity to continue screening as long as their overall health is good and they have a life expectancy of 10 years or longer (level B recommendation).

According to the latest data from the Chinese National Central Cancer Registry<sup>1-2,4-7</sup>, the incidence of breast cancer in women aged 25 years and younger is relatively low, then begins to increase in women aged 35–45 years. The peak onset age for breast cancer is 45–69 years, and the incidence decreases in women aged 70 years and older. As shown in GLOBOCAN 2018<sup>11-12</sup>, similar age distributions of breast cancer incidence have been observed in women from Japan, South Korea, North Korea, and other East Asian countries. However, the incidence of breast cancer in the United Kingdom, Sweden, United States, Canada, and other western countries shows a continuously increasing trend with age. The peak onset ages for breast cancer in Chinese women are nearly 5–10 years younger than those in American women. The difference in the distributions of age-specific incidences of breast cancer between Chinese women and European-American women may be associated with various factors, such as environmental factors, genetic factors, and different use of hormone replacement therapy<sup>11-12</sup>. These differences suggest that Chinese women should begin and stop breast cancer screening at different ages than European-American women.

In the CNBCSP-Urban and CNBCSP-Rural programs<sup>13</sup>, both the detection rates of breast cancer in women aged 40–44 years from the two programs were significantly higher than those in women aged 35–39 years. No significant difference was found in the detection rates between urban women aged 45–49 years (60.5/100,000) and 40–44 years (45.2/100,000); however, a significantly higher detection rate was found in rural women aged 45–49 years (70.2/100,000) than those aged 40–44 years (39.8/100,000). These results suggested that Chinese urban and rural women should begin regular screening at different ages.

Given the younger peak onset age for breast cancer in Chinese women than European-American women, the similar peak onset age for breast cancer between Chinese women and other East-Asian women, and the detection rates from CNBCSP-Urban and CNBCSP-Rural, the guideline development group (GDG) suggests that women aged 45–69 years with an average risk of breast cancer should undergo regular screening (level A recommendation).

#### Screening methods

- MAM has been proven to be effective in reducing breast cancer mortality. It is recommended as the primary breast

cancer screening method for women with an average risk of breast cancer (level A recommendation).

- BUS can effectively increase the detection rate of breast cancer among women with dense breasts after negative results of mammography. It is recommended as a supplementary screening method after mammography in women with dense breasts (level B recommendation).

- CBE is not recommended as a primary screening method due to insufficient evidence. However, CBE might increase the detection rate of breast cancer in women who have never been screened. Therefore, CBE is recommended as a preliminary screening method before imaging screening (level B recommendation).

- BUS is recommended as the primary screening method for women aged 40–44 years with a high risk of breast cancer but without a family history of early onset breast cancer or pathogenic genetic mutations. MAM combined with BUS is recommended for women 45 years and older with the same high risk of breast cancer (level B recommendation).

Almost all current breast cancer screening guidelines recommend MAM as the primary method for breast cancer screening. To date, eight high-quality randomized controlled trials (RCTs) have evaluated the effectiveness of MAM screening for breast cancer: the Health Insurance Plan (HIP) study (USA)<sup>14-17</sup>, Canadian National Breast Cancer Screening (CNBSS) phase I (CNBSS-I) and phase II (CNBSS-II) (Canada)<sup>18-22</sup>, Age Study (UK)<sup>23-25</sup>, Stockholm Study (Sweden)<sup>26-29</sup>, Malmo Mammographic Screening Trial (MMST-I/MMST-II)<sup>30-35</sup>, Gothenburg Study<sup>36-39</sup>, and Swedish Two-county Study<sup>40-45</sup>. Among these RCTs, the first RCT was initiated in 1963, and the last was initiated in 1991. The youngest age of beginning screening was 39 years, and the oldest age of stopping screening was 70 years. A total of 327,393 women were initially recruited in the screening group, and the control group included 343,953 women. MAM combined with CBE was used in the screening groups of the HIP and CNBSS-I study, and usual care was used in the control group of the above two studies. The CNBSS-II study compared the screening effectiveness between MAM plus CBE and CBE alone. Other studies compared the effectiveness between MAM alone and CBE alone. The screening intervals ranged from 12 months to 33 months, and the number of rounds of screening varied from two to nine. MAM examination generally required one or two positions. The durations of these screening programs ranged from 4 years to 10 years. The shortest follow-up was more than 10 years, whereas the longest follow-up was 25 years.

On basis of the results from the eight RCTs, MAM screening was found to decrease overall breast cancer

mortality 18–20%. Conclusions from different studies and different periods have been relatively consistent. For women aged 50–69 years, GDG found nearly consistent conclusions that MAM screening decreases breast cancer mortality 13–34%, whereas the benefits appear to increase with age. However, for women aged 50 years and younger and women aged 70–74 years, GDG found that only a fraction of women can benefit from screening. In summary, these results clearly demonstrate that regular MAM screening can definitely decrease the breast cancer mortality in women aged 50–69 years.

To date, no RCT has evaluated the long-term benefit of MAM screening in Chinese women. However, results from CNBCSP-Urban, CNBCSP-Rural, and MIST have provided very important preliminary support for this guideline. The detection rates of breast cancer were 56.0/100,000, 52.0/100,000, and 306.9/100,000 for CNBCSP-Urban, CNBCSP-Rural, and MIST, respectively<sup>13</sup>. Higher detection rates of breast cancer were associated with family history of breast cancer, obesity, being unmarried (including single, divorced, separated, and widowed status), a marriage age >25 years, a lower education level, having no occupation, and having no insurance. The difference in the detection rates of breast cancer among CNBCSP-Urban, CNBCSP-Rural, and MIST may be due to several reasons, such as the different incidence rates of breast cancer between Chinese urban and rural areas and the exposure to different risk factors. However, the screening strategy used in these three programs may also have been one major reason leading to the difference. Urban women received MAM and BUS in series after positive CBE findings in CNBCSP-Urban, whereas rural women received BUS and MAM in series after positive CBE findings in CNBCSP-Rural<sup>13</sup>. In MIST, women received three screening methods separately and concurrently. This difference in the detection rates also suggests that CBE cannot be used as the primary screening method, owing to missed diagnosis.

Moreover, the detection rates of early stage (AJCC TNM stage 0+I) breast cancer in CNBCSP-Urban, CNBCSP-Rural and MIST were 46.15%, 38.76% and 55.56%, respectively. Compared with breast cancer cases clinically diagnosed in the same period, three screening programs detected more early stage breast cancer, smaller tumors, less lymph node metastasis, and more carcinoma in situ<sup>13,46-47</sup>. In MIST, the sensitivity of MAM (85.86%) was significantly higher than that of BUS (62.75%) and CBE (42.16%), whereas the sensitivity of MAM was very similar to that reported in the early HIP. These results support that conducting population-based MAM screening for breast cancer would be feasible in

the future in China. After referring to the current evidence on MAM, GDG recommends MAM as the major screening method for Chinese women at average risk of breast cancer. The recommendation level is A.

Compared with MAM screening, the advantages of BUS screening include higher sensitivity in women with dense or small breasts, no radiation exposure, lower cost, and easier access in China; the disadvantages of BUS screening include lower sensitivity in early breast cancer with microcalcifications, the time required, a lack of standardized techniques, operator dependence, and a lack of reproducibility<sup>48</sup>. Therefore, most current guidelines do not recommend BUS as a major screening method for women at average risk of breast cancer.

After systematic searching and review of the current studies in which BUS was used to screen for breast cancer, we identified nine studies evaluating the effectiveness of supplementary BUS after negative MAM<sup>49-57</sup> and seven studies evaluating the effectiveness of BUS in combination with MAM<sup>58-64</sup>. The sensitivity of supplementary BUS after negative MAM ranged from 62% to 100%, the specificity ranged from 69% to 100%, the positive predictive value ranged from 1% to 26%, and all negative predictive values were close to 100%. The detection rate of breast cancer by supplementary BUS after negative MAM ranged from 0.4/1,000 to 22.4/1,000, the recall rate ranged from 0.4% to 31.1%, and the biopsy rate ranged from 0.4% to 5.5%<sup>49-57</sup>. The Chinese MIST study showed that supplementary BUS after negative MAM additionally identified ten breast cancer patients, representing an 11.9% increase in the detection rate. These results suggest that BUS, used as a supplement to negative MAM, could improve the cancer detection rate. Moreover, the Chinese MIST study showed that supplemental BUS screening would be more suitable for women with dense breasts or benign breast diseases after MAM with a diagnosis of BI-RADS classified as 0-2<sup>65</sup>.

In studies in which BUS was used in combined with MAM, the sensitivity of BUS alone ranged from 1% to 71%, and the negative predictive value ranged from 99% to 100%. The detection rate of breast cancer by BUS alone ranged from 1.9/1,000 to 8.6/1,000, the recall rate ranged from 0.3% to 18.0%, and the biopsy rate ranged from 0.2% to 5.5%<sup>58-64</sup>. Moreover, some studies showed that the cancer detection rate with BUS alone is comparable with MAM alone among women at high risk of breast cancer<sup>58,60</sup>. To investigate whether there were differences in the accuracy and effectiveness between BUS alone and MAM alone among Chinese women at relatively high risk of breast cancer, the GDG first defined Chinese women at relatively high risk of

breast cancer as women with one or more pre-defined risk factors, including early age at menarche ( $\leq 12$  years), late age at menopause ( $\geq 55$  years), late age at first pregnancy ( $> 30$  years), having ever taken oral contraceptives, obesity (body mass index  $\geq 28$  kg/m<sup>2</sup>), and a family history of breast cancer. In MIST, the cancer detection rate among Chinese women at relatively high risk of breast cancer was significantly higher than that among women without any of the above six risk factors [4.34‰ (48/11,066) vs. 2.23‰ (46/20,654),  $P = 0.001$ ]. Among 11,066 Chinese women at relatively high risk of breast cancer, further analysis showed that the cancer detection rate by BUS alone was 3.09‰ (33/10,694), which was significantly higher than that by CBE alone [1.73‰ (19/10,959),  $P = 0.002$ ] but similar to that by MAM alone [3.18‰ (34/10,696),  $P = 0.663$ ]. Compared with MAM alone, BUS alone had a significantly higher specificity [98.6% (10,501/10,646) vs. 98.1% (10,443/10,650),  $P = 0.001$ ] but a similar sensitivity [68.8% (33/48) vs. 73.9% (34/46),  $P = 0.663$ ], positive predictive value [18.5% (33/178) vs. 14.1% (34/241),  $P = 0.221$ ], and negative predictive value [99.9% (10,501/10,516) vs. 99.9% (10,443/10,455),  $P = 0.574$ ]. These results were relatively consistent with findings from another Chinese multicenter prospective screening trial in which BUS alone had a significantly higher sensitivity than that of MAM alone (100% vs. 57.1%,  $P = 0.04$ ), but a similar specificity (100% vs. 99.9%,  $P = 0.51$ ) and a positive predictive value (72.7% vs. 70.0%,  $P = 0.87$ )<sup>66</sup>.

In conclusion, on the basis of the above results of supplementary BUS after negative MAM among women with dense breasts or benign breast diseases, the GDG recommends supplementary BUS after MAM in women with dense breasts (level B recommendation). According to the results of BUS alone among women at relatively high risk of breast cancer, the GDG recommends BUS as the primary screening method for women aged 40-44 years and with a high risk of breast cancer but without a family history of early onset breast cancer or pathogenic genetic mutations. For women 45 years and older with a high risk of breast cancer, in view of the complementarity between breast BUS and MAM, the GDG recommends MAM combined with BUS screening for breast cancer (level B recommendation).

The value of CBE screening for breast cancer remains inconclusive. Guideline from the American Cancer Society (ACS) recommend against CBE alone for breast cancer screening. However, according to the WHO position on mammography screening, in limited resource settings with weak health systems, CBE appears to be a promising approach and could be implemented among women aged 50-69 years when the necessary evidence from ongoing

studies becomes available. The National Cancer Comprehensive Network (NCCN) recommends that women aged  $\geq 25$  but  $< 40$  years at average risk of breast cancer should receive clinical encounter every 1–3 years. Moreover, a few guidelines, such as the CACA and the Japanese Breast Cancer Society, recommend that CBE could be used as a supplement to MAM<sup>67,68</sup>. An RCT comparing the effectiveness of MAM combined with or without CBE has shown that MAM combined with BUS does not significantly improve the accuracy and cancer detection rate as compared with MAM alone<sup>69</sup>. In the MIST, the sensitivity, specificity, positive predictive value, and negative predictive value of CBE were 42.16%, 99.52%, 21.29%, and 99.82%, respectively. The sensitivity of CBE was significantly lower than that of MAM (85.86%) or BUS (62.75%). Although few studies have suggested that CBE alone could increase the cancer detection rate, there is no adequate evidence supporting that CBE decreases breast cancer mortality. Therefore, CBE is recommended only as a preliminary screening method before imaging screening (level B recommendation).

In addition to MAM, BUS, CBE, researchers are exploring the potential value of other imaging examinations for breast cancer screening, including digital breast tomosynthesis (DBT), breast magnetic resonance imaging (MRI), and automatic breast ultrasound (ABUS). Compared with traditional MAM, DBT can decrease the rate of missing diagnosis of breast cancer among women with dense breasts. For instance, an Italian study has shown that DBT with 3D images can improve breast-cancer detection and has the potential to reduce false positive recalls<sup>70</sup>. Although DBT brings improvements, it also brings some new problems, including longer imaging times, longer reading times, higher radiation doses, and higher cost. In three small studies of MRI screening among women with dense breasts, breast MRI was able to detect breast cancers missed by MAM and BUS (with sensitivity ranging from 75% to 100%); however, it may also increase the recall rate (8.6%–23.4%) and have low positive predictive value (3.0–33.3%)<sup>71–73</sup>. To date, no high-quality studies have investigated the effectiveness of these new methods in screening for breast cancer among Chinese women at average risk of breast cancer. Therefore, in view of the very limited evidence and the clear risks of above-mentioned new screening methods, the GDG does not make a clear recommendation on these screening methods.

### **Screening interval**

- Women with an average risk of breast cancer should undergo biennial mammography (level A recommendation).

Different agencies recommend different breast cancer screening intervals for women with average risk of breast cancer. For instance, the U. S. Preventive Services Task Force (USPSTF) recommends biennial screening mammography for women aged 50–74 years. The ACS recommends that women aged 45–54 years should be screened annually, whereas women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. Both the NCCN and Korean National Cancer Centre recommend annual screening for women aged 40 years and older. The International Agency for Research on Cancer (IARC) has not made a definite recommendation for screening interval, owing to insufficient evidence. The Committee of Breast Cancer in the CACA recommends annual opportunistic screening for women aged 40–49 years and women aged 70 years and older, whereas it recommends annual or biennial opportunistic or population-based screening for women aged 50–69 years<sup>68</sup>. On the basis of the above recommendations and limited resources in China, the GDG recommends biennial screening for Chinese women with average risk of breast cancer, and the recommendation level is A.

### **Recommendations for women at high risk of breast cancer**

The definition of women at high risk of breast cancer varies across countries, organizations, and institutions. On the basis of the breast characteristics of Chinese women, we define women at high risk of breast cancer as those who meet at least one of the following criteria: (1) women with at least two first/second-degree relatives ever diagnosed with breast cancer; (2) women with at least one first-degree relative carrying known BRCA1/2 pathogenic genetic mutations; (3) women with at least one first-degree relative ever diagnosed with breast cancer and with at least one of the following: (a) one first-degree relative with age at diagnosis of breast cancer of 45 years or younger; (b) one first-degree relative with age at diagnosis of breast cancer ranging from 45 to 50 years, and at least one first-degree relative ever diagnosed with ovarian epithelial cancer, fallopian tube cancer, or primary peritoneal cancer at any age; (c) one first-degree relative with two primary breast cancers, and age at diagnosis of first primary breast cancer 50 years or younger; (d) two first-degree relatives ever diagnosed with ovarian epithelial cancer, fallopian tube cancer, or primary peritoneal cancer at any age; (e) one male first-degree relative with breast cancer; (4) women carrying known pathogenic genetic mutations associated with breast cancer; (5) women with at

least one first-degree relatives ever diagnosed with hereditary tumor syndrome, such as hereditary breast and ovarian syndrome, Cowden syndrome, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, or Lynch syndrome; (6) women ever diagnosed with moderate to severe dysplasia in breast duct/lobular or lobular carcinoma *in situ* (LCIS); or (7) women ever received chest radiotherapy.

### **Recommendations for screening**

- Women with a high risk of breast cancer such as a family history of early onset breast cancer and pathogenic genetic mutations should start regular screening at 35 years of age. Women with a high risk of breast cancer but without a family history of early onset breast cancer or pathogenic genetic mutations should start regular screening at 40 years of age (level C recommendation).

- Breast MRI is recommended as a primary screening method for women at high risk of breast cancer such as a family history of early onset breast cancer and pathogenic genetic mutations. Breast MRI is also recommended as a supplementary screening method after negative findings of MAM and BUS for women with a high risk of breast cancer but without a family history of early onset breast cancer or pathogenic genetic mutations (level C recommendation).

- Women with a high risk of breast cancer such as a family history of early onset breast cancer and pathogenic genetic mutations should undergo annual breast MRI (level B recommendation).

For women at high risk of breast cancer, the ACS recommends MRI screening for women with an approximately 20%–25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women treated for Hodgkin disease. Both the USPSTF and the IARC do not give clear screening recommendations. The Committee of Breast Cancer in the CACA recommends that women at high risk of breast cancer could start annual screening younger than 40 years of age with MAM and breast MRI<sup>68</sup>. To provide more explicit screening recommendations for women at high risk of breast cancer, we have classified the high-risk women into two groups on the basis of their genetic risk: women with a family history of early onset breast cancer and pathogenic genetic mutations, and other high-risk women. For the first group of high-risk women, the GDG recommends stronger screening measures, including an earlier age of starting screening and a more sensitive screening method.

### **Genetic test**

The breast cancer susceptibility genes BRCA1 and BRCA2 act

as tumor suppressor genes and play a role in the maintenance of genome integrity. BRCA1/2 mutations can explain nearly 80% breast cancer caused by pathogenic germline mutations<sup>74</sup>. Germline mutations in the BRCA1 and BRCA2 genes lead to an increased susceptibility to breast, ovarian, and other cancers. Three studies in Chinese populations have shown that the mutation rates of BRCA1/2 in healthy populations, patients with sporadic breast cancer, patients with familial breast cancer, patients younger than 40 years and with familial breast cancer, and patients with bilateral breast cancer and with a family history of breast cancer were 0.4%, 3.5%, 12.7%, 27.0%, and 30.0%, respectively<sup>75-77</sup>. Healthy women carrying BRCA1/2 mutations have an estimated 37.9% and 36.5% cumulative risk of breast cancer at 70 years of age, and the corresponding risk in women without these mutations is only 3.6%<sup>77</sup>. Therefore, detection of susceptible gene mutations would be important in identifying women with a high genetic risk of breast cancer. According to the classification system of the IACR, the American College of Medical Genetics and Genomics (ACMG), and the Evidence-based Network Interpretation of Germline Mutant Alleles (ENIGMA), BRCA gene variants can be classified into five grades from high risk to low risk. Chinese researchers' first consensus on the interpretation of BRCA gene mutation in 2017 promoted the clinical application of BRCA testing in China<sup>78</sup>.

At present, there is no sufficient evidence that genetic testing can decrease the mortality rate associated with breast cancer. The GDG recommends genetic tests only for women with hereditary breast cancer and with a strong willingness to receive BRCA1/2 gene testing. When more than one gene can explain inherited breast cancer, if appropriate, multi-gene testing may be more efficient and/or cost-effective. On the basis of the NCCN guideline, genes associated with hereditary breast cancer, such as CDH1, PTEN, STK11, TP53, ATM, CHEK2, PALB2, NBN, and NF1, could potentially be included in a multi-gene test. However, cancer risk assessment and genetic counseling are highly recommended to fully understand the potential benefits, risks, and limitations when genetic testing is offered (ie, pre-test counseling) and after results are disclosed (ie, post-test counseling).

### **Preventive intervention**

The WHO has proposed four basic recommendations for disease prevention: a reasonable diet, moderate exercise, smoking cessation and alcohol restriction, and healthy psychology. These healthful lifestyle recommendations are also suitable for cancer prevention in high-risk women.

In addition to above lifestyle interventions, high-risk women would also benefit from chemoprevention to decrease the incidence risk of breast cancer<sup>79</sup>. Drugs for chemoprevention of breast cancer mainly include selective estrogen receptor modulators (SERM) and aromatase inhibitors. Tamoxifen was the first SERM approved by the US Food and Drug Administration for the chemoprevention of breast cancer. Several RCTs have shown that among women aged 30–70 years with a high risk of breast cancer, tamoxifen can decrease the risk of developing breast cancer by 38% and the risk of developing ER-positive breast cancer by 48%<sup>80–83</sup>. Aromatase inhibitors, new drugs used for endocrine therapy, have also been used in chemoprevention of breast cancer. A RCT has suggested that exemestane significantly decreases the risk of developing invasive breast cancers (0.19% vs. 0.55%,  $P = 0.002$ ) and ductal carcinoma in situ (0.35% vs. 0.77%,  $P = 0.004$ ) in postmenopausal women at moderately increased risk of breast cancer<sup>84</sup>. Another study has shown that anastrozole effectively decreases the 5-year incidence of breast cancer (2% vs. 4%,  $P < 0.000,1$ ) and decreases the predicted cumulative 7-year incidence of breast cancers (2.8% vs. 5.6%) in high-risk postmenopausal women<sup>85</sup>. Although use of aromatase inhibitors is debatable for chemoprevention of breast cancer, owing to potential side-effects and low compliance, high-risk women meeting the above inclusion and exclusion criteria would benefit from the prophylactic use of aromatase inhibitors.

On the basis of the NCCN guideline, risk-reducing surgery should generally be considered only in women with a genetic mutation conferring a high risk for breast cancer, a compelling family history, LCIS, or possibly prior thoracic radiotherapy at < 30 years of age<sup>86</sup>. Risk-reducing surgery includes risk-reducing mastectomy and risk-reducing bilateral salpingo-oophorectomy. Retrospective analyses with median follow-up periods of 13 to 14 years have indicated that risk-reduction bilateral mastectomy decreases the risk of developing breast cancer by at least 90% in moderate- and high-risk women and in known BRCA1/2 mutation carriers<sup>87</sup>, and risk-reducing bilateral salpingo-oophorectomy decreases the risk of developing breast cancer in BRCA1/2 mutation carriers by 50%<sup>88</sup>. There is no conclusive evidence to support extensive use of the risk-reducing bilateral salpingo-oophorectomy, and no adequate evidence to support risk-reducing surgery in China at present. The GDG recommends personalized decisions on risk-reducing surgery after comprehensive consideration of the benefits and risks of the surgery as well as genetic background, personal willingness, physical conditions, and economic status. Whether prophylactic surgery can provide benefits remains

to be confirmed in the future.

## Health economic evaluation of breast cancer screening

Cancer screening, especially population-based cancer screening, is a task requiring the coordination of various social resources and collaboration among different healthcare divisions and institutions. As a developing country, China has uneven regional economic development. The input-output ratio should particularly be taken into account when planning and implementing cancer screening projects. Therefore, it is important to conduct related health economic evaluation of breast cancer screening among Chinese women.

During 2008–2010, we collected the stage distribution of breast cancers detected from the CNBCSP-Urban<sup>13</sup>, and the accuracy (sensitivity and specificity) of different screening modalities from the MIST. We also collected the clinical parameters of breast cancers diagnosed in hospitals at the same time. Combining the data on screening cost, diagnosis cost, project management cost, and other social costs, we developed a state-transition Markov model to analysis the cost and effectiveness of breast cancer screening among Chinese urban women<sup>89</sup>. After verifying the rationality of the basic model, we systematically evaluated the incremental costs, the quality-adjusted life years, and cost-effectiveness ratios for 132 breast cancer screening strategies consisting of different screening start and stop ages, screening intervals, and screening modalities, compared with those for no screening.

In 2010 (when China's per capita GDP was 30,876 RMB), compared with no screening, among 132 breast cancer screening strategies, the most effective breast cancer screening strategy under the current Chinese economic conditions was biennial screening with clinical breast examination and breast ultrasound in parallel for women aged 40–64 years. This screening strategy would save 1,394 quality-adjusted life years (QALYs) per 100,000 women, and the social cost for saving a breast-related QALY was found to be 91,944 RMB. Sensitivity analysis showed that in 2016 (when China's per capita GDP was 53,935 RMB), the most effective breast cancer screening strategy under the current Chinese economic conditions was biennial screening with clinical breast examination and mammography in parallel for women aged 40–64 years. Under this screening strategy, the social cost for saving a breast-related QALY was 159,637 RMB. A well-designed RCT with larger sample size and longer follow-up would be required to validate these results in the future.

## Conclusions and outlook

Domestic and foreign studies have shown that population-based breast cancer screening and early diagnosis/treatment after screening are the most effective ways to improve the survival rate of breast cancer. It is imperative to develop a population-based breast cancer screening scheme suitable for Chinese women. In the past 10 years, the CACA and the National Cancer Clinical Medical Research Center (Tianjin) have cooperatively designed and completed three breast cancer screening projects for urban and rural women in China. By analyzing the results of these projects, referring to breast cancer screening guidelines issued in other countries, and reviewing the current high-quality evidence in breast cancer screening, the GDG has developed the present Breast Cancer Screening Guideline for Chinese Women.

The guideline provide specific recommendations for breast cancer screening regarding the ages to begin and stop screening, methods of screening, screening intervals, and cost-effectiveness of screening. The guideline was formulated through consideration of the breast characteristics of Chinese women and the current Chinese economic level. It would be of great importance to standardize population-based breast cancer screening in China, to improve the long-term survival rate of Chinese breast cancer patients more effectively. Moreover, on the basis of the previous studies, the GDG proposes the concept of breast cancer risk-related women and redefines high-risk women with more stringent criteria. The GDG provides differentiated screening recommendations for women with different risk of breast cancer, and provides preliminary suggestions for genetic testing and preventive measures for breast cancer.

China is a multi-ethnic developing country where geographical, economic, social, and cultural differences exist ubiquitously. Evidence to support more detailed recommendations may be insufficient. Therefore, as the first breast cancer screening guideline for Chinese women, this guideline will inevitably have some limitations. Further RCTs with more sophisticated design and analyses are needed to update the guideline in the future.

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## Conflict of interest statement

No potential conflicts of interest are disclosed.

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