

Perspective

# Current status of breast cancer prevention in China

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Breast cancer is the most common malignancy and the fourth leading cause of cancer-related death among Chinese females. And in the past two decades, there has been an ever-increasing incidence of breast cancer in both urban and rural areas in China, resulting in a great social and economic burden. Prevention has been proved to be one of the most important ways to control disease burden. However, because of the national condition, currently the prevention of breast cancer in China is far away from being satisfactory or effective. Here, we reviewed the epidemiology characteristics, the risk factors, and the current screening efforts of breast cancer in China. Also, we discuss alternative ways to improve the prevention work of breast cancer in China.

Breast cancer is the second most common cancer in the world and the most frequent cancer among women

with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers).<sup>1</sup> Traditionally, China was believed to be among low-incidence areas of breast cancer.<sup>2</sup> However, in the past two decades, China experienced an ever-increasing incidence of breast cancer, twice as fast as global rates.<sup>2</sup> According to the latest Chinese Cancer Registry Annual Report,<sup>3</sup> breast cancer has become the most common cancer among Chinese women and ranked the fifth leading cause of cancer-related deaths. In consideration of the huge population base of 1.34 billion,<sup>4</sup> China is facing increasing enormous social and economic burden of breast cancer. Prevention has been proved to be one of the most effective methods to hold the increasing chronic disease burden. However, because of the socioeconomic disparities and insufficient financial resources, by far, prevention of breast cancer has not been well carried out in China.<sup>5,6</sup> Health ministry and health-care systems are facing many challenges caring for patients with breast cancer and population at increased risk of breast cancer: inadequate funding; inequitable distribution of resources and services; inadequate numbers, training, and distribution of health-care personnel and equipment; lack of adequate care for many populations based on socioeconomic, geographic and other factors.

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Here, we review the epidemiology characteristics, the risk factors, and the current screening efforts of breast cancer in China. Also, we discuss alternative ways to improve the prevention work of breast cancer in China.

### **Disease burden of breast cancer**

According to Globocan 2012 by WHO,<sup>1</sup> an estimated 187,000 new breast cancer cases were diagnosed in China in 2012, accounting for nearly 12% of the whole world new breast cancer cases, with an age-standardized rate (ASR) of 22.1 cases per 100,000 women, while 48,000 females died from breast cancer, accounting for about 9% of the whole world, with an ASR of 5.4 cases per 100,000 women. The Chinese Cancer Registry Annual Report 2013<sup>3</sup> showed that breast cancer is the most common malignancy among Chinese females, with an estimated incidence of 25.89 cases per 100,000 women. On the other hand, breast cancer is the fourth leading cause of cancer-related death among Chinese females, after lung cancer, gastric cancer, and liver cancer, with an estimated mortality of 6.56 cases per 100,000 women. Similar to other regions, there was an obvious urban–rural difference in incidence of breast cancer. The incidence in urban areas (47.79 cases per 100,000 women) is nearly twice as high as that in rural areas (27.72 cases per 100,000 women). And this urban–rural difference pattern was also observed in local cancer registry report, such as Jiangsu Province.<sup>7</sup> In the past 15 years between 1993 and 2008, there has been a sharp increase in breast cancer incidence in both urban and rural areas, with an estimated annual increase rate of 3.7% and 8.9%, respectively.<sup>8,9</sup> As a result, the gap in breast cancer incidence between rural and urban areas has been narrowing, especially in some developed areas such as Beijing.<sup>10</sup> And a cross-sectional study covering Shandong Province, Jiangsu Province, Hebei Province, and Tianjin also demonstrated a similar prevalence of breast cancer between urban and rural areas.<sup>11</sup> This narrowing trend may be related to the national urbanization. And at the above increase rate, it was expected that there would be more than 2.5 million breast cancer cases by 2021.<sup>12</sup>

The mean age at diagnosis of breast cancer in China is 45–55 years, much more younger than 65 years in the United States and as well as other western countries.<sup>13</sup> Traditionally, there is an interesting double-peak pattern in age-specific incidence curve of breast cancer in the mainland of China, one peak at about 45–55 years and another at 70–74 years.<sup>2,14</sup> Similarly in Taiwan of China and Hong Kong of China, such double-peak

pattern was reported.<sup>15–17</sup> The unique peak in age-specific incidence at 45–55 years might be due to shifts in risk factor profiles such as menstrual and reproductive characteristics.<sup>18</sup> However, data from Beijing<sup>10</sup> showed that during 2004 and 2008, the peak age group of the female breast cancer incidence in urban areas was 60–64 years, whereas in rural areas the peak was, respectively, at 50–54 and 80–84 years. This result indicated a shift trend to western patterns with an older median age at diagnosis, especially in developed areas. It was estimated that by 2030, 27.0% of breast cancer cases would be diagnosed at age older than 65 years, while in 2008 this number is only 16.6%.<sup>19</sup>

Data from 16 population-based cancer registries during 2003–2005<sup>20</sup> showed that the 5-year survival rate of female breast cancer cases in China was 73.0%, ranking the first in all cancers. And survival for rural patients was about half that of their urban counterparts. Compared to 89.0% of the United States,<sup>21</sup> there is still quite a lot to be improved.

However, it is not possible to describe the accurate incidence and mortality of breast cancer in China, because the cancer registry system is not well established.<sup>22,23</sup> By 2013, there were only 249 cancer registries in China, covering 31 provinces with about 200 million people, accounting for about 15.42% of Chinese population.<sup>22</sup> While in the United States, about 96% patients were included in health-care system such as National Program of Cancer Registries (NPCR) by Centers for Disease Control<sup>23</sup> and Surveillance, Epidemiology, and End Results (SEER) Program by National Cancer Institute.<sup>24</sup> This deficiency of data has become a big bottleneck for the development of cancer control policy. Since 2012, cancer registry programs based on hospitals have been carried out in several provinces in China, but still not well developed. And there are some shortcomings in the above programs, such as insufficient extensions and integrity, distribution disproportion, lacking of necessary quality control and like.<sup>25</sup> With the expansion of China's cancer registry, anyhow, the accuracy of breast cancer burden estimates would be improved and more representative.

### **Risk factors of breast cancer in China**

A number of case–control studies have been conducted to explore the risk factors of breast cancer in different areas, but resulted in a relatively consistent conclusion.<sup>26</sup> Traditional risk factors such as a long menstrual life, nulliparity, later age at first birth, and limited breastfeeding are associated with increased risk of breast cancer in the Chinese population,<sup>11,27,28</sup>

despite the different regional distributions. But as to the numbers of birth, different results were reported. Bao et al<sup>29</sup> found that increased numbers of births per woman were associated with a reduced risk of breast cancer ( $OR = 0.69$ , 95%  $CI$ : 0.52–0.91) for postmenopausal women. While in Yu's study,<sup>11</sup> no association between numbers of birth and risk of breast cancer was observed. This may be related to the one-child policy. Most population, especially younger women, have no more than one child, and affected by traditional family views, especially in rural areas, childless families are rare.

Diabetes mellitus was reported to be associated with a 10–20% excessive risk of breast cancer,<sup>30</sup> and a meta-analysis by Hardefeldt<sup>31</sup> showed that type 2 diabetes mellitus could increase female breast cancer risk by 22% ( $OR = 1.22$ , 95%  $CI$ : 1.07–1.40). However, in China, little attention has been paid to diabetes mellitus, and only one study by Wang et al<sup>32</sup> showed a similar association in Chinese population ( $OR = 3.35$ , 95%  $CI$  1.02–11.01). Similar to breast cancer, diabetes mellitus is another public health focus. With the increased life expectancy and changing lifestyles, the incidence of diabetes mellitus in China has increased four fold in the last two decades.<sup>33</sup> By 2008, there were 92.4 million adults with diabetes (50.2 million men and 42.2 million women) and 148.2 million adults with prediabetes (76.1 million men and 72.1 million women).<sup>34</sup> So it is vital to know whether there is any association between the increase in diabetes mellitus and breast cancer.

It has been proven in many epidemiological studies<sup>35–37</sup> that obesity, especially postmenopausal obesity, is associated with breast cancer, and earlier obesity onset is related to higher breast cancer risk.<sup>38</sup> The study by Sun<sup>38</sup> showed that in China women with a body mass index (BMI) of 24 kg/m<sup>2</sup> or higher had a four-fold increased risk of breast cancer compared with those less than 24 kg/m<sup>2</sup>. And similar association was also reported by Yu<sup>33</sup> ( $OR = 1.696$ ). At present, nearly 30% women were reported as being overweight (BMI  $\geq 25$  kg/m<sup>2</sup>) or obese (BMI  $\geq 30$  kg/m<sup>2</sup>) in China.<sup>39</sup> Besides, obesity is closely associated with type 2 diabetes mellitus, and among type 2 diabetes mellitus patients in China the prevalence of obesity could reach more than 30%. Thus, the potential combined effects of diabetes mellitus and obesity on the increase of breast cancer incidence should be paid attention to.<sup>40</sup>

As to some other factors such as breast density,<sup>41,42</sup> which have been well investigated in western studies, due to lack of attention, no definite association with breast cancer risk among Chinese women could be drawn.

## Current screening of breast cancer in China

In consideration of the high incidence, screening is believed to be one of the most important methods to prevent breast cancer, and it has been proved in both Swedish and the United States trials that mammography screening could reduce breast cancer mortality risk by about 20%.<sup>43,44</sup> In China, there has been no such large-scale or long-term follow-up trial, but data from some local screening programs have proved that screening could help detect early stage breast cancer. In Guangzhou screening program,<sup>45</sup> the early breast cancer detective rate was 84.1%, about 5% higher than that among in-hospital patients (79.3%). While as to 0–I stage diseases, the detective rate was 47.0% and 37.2% among screening and in-hospital populations, respectively. Similar early detective rates were also reported in three Shanghai programs.

However, by now, there has been no nationwide screening program of breast cancer. Once in 2005, China government started a national population-based screening program of breast cancer.<sup>46</sup> This program was aimed to screen 100,000 women with both mammography and breast ultrasonography, but stopped 2 years later due to the insufficient financial funding support and the concern about false-positive. In fact, there are several barriers for large-scale population-based screening for breast cancer in China. First, China bears an enormous population of more than 652 million females,<sup>4</sup> and substantial external financial resources are needed to cover such large-scale screening. More importantly, there are insufficient convincing cost-effectiveness data by far. Cost-effectiveness analysis of local breast cancer screening in Shanghai showed that it costs about RMB Yuan 120,000 through screening to detect one breast cancer case, while RMB Yuan 211,000 for each early stage cases. In Guangdong Province,<sup>45</sup> at least 1339 females should be screened to detect one new breast cancer case. And in Shanghai, the cost for each early detective breast cancer was at least RMB Yuan 90,000 or at most RMB Yuan 284,000, depending on different age groups, nearly equal to one or three times of the real GDP per capita of Guangzhou in 2010 (RMB Yuan 88,000).<sup>45</sup> Whereas among Hong Kong Chinese females,<sup>47</sup> the incremental cost-effectiveness ratio (ICER) of mammography screening was US \$ 61,600 per QALY saved, and the probability of the ICER being below a threshold of US\$ 50,000 per QALY was only 15.3%. Obviously, population-based breast cancer screening is not financially worthwhile in all the above three areas. Second, even though the health education

has greatly improved in the past several years, the public awareness of breast cancer is still quite low. A cross-sectional epidemiology survey covering more than 120,000 females<sup>48</sup> showed that 81.4% of participants were poorly aware of breast cancer. As a result, few females would like to spend money on mammography or ultrasonography screening, and the screening rates were quite low from 11.38% to 19.2% in different areas,<sup>49</sup> far below that of 301.0/1000 in the United States.<sup>50</sup> And third, because of the large, widely dispersed population and the huge urban–rural gap, there is quite a shortage of mammography and ultrasonography equipments, especially in rural areas.

As to the screening rationale, different screening patterns have been employed in different screening programs. Compared to the well-accepted benefit of mammography screening in western countries,<sup>43,51</sup> it has been a long time since the controversy of mammography screening, ultrasonography screening, and clinical breast examination screening was raised in China. Following national guidelines,<sup>52</sup> annual mammography for women aged 40–49 years and every 1–2 years for those aged 50–69 years is recommended. However, in view of the earlier diagnosis age and the higher breast density of Chinese women, mammography was traditionally supposed to be not as sensitive as that among European or American women. A meta-analysis by Kang<sup>53</sup> showed that among Asian females, the sensitivity of mammography screening was 0.845 (95% *CI*: 0.821–0.870), much lower than that among western countries (0.95, 95% *CI*: 0.93–0.96). And findings from a study in Beijing<sup>54</sup> showed that only 5.2% of new breast cancer cases were detected by routine mammographic screening, whereas 82.1% of cases experienced obvious symptoms at diagnosis, while the proportion of breast cancers detected through mammography screening is about 60% in the United States.<sup>55</sup> However, a population-based randomized trial<sup>56</sup> demonstrated that among women aged 40–49, mammography showed a higher sensitivity of invasive breast cancer detection than ultrasonography (96% vs. 75%) and suggested that alternating ultrasonography screening was an effective complement to mammography screening among young women. At present, there is no methodologically sound evidence available justifying the routine use of ultrasonography as an adjunct screening tool in women at average risk for breast cancer.<sup>57</sup> In Beijing breast cancer screening program covering 568,000 women,<sup>58</sup> ultrasonography was employed as the only screening tool, and the detective rate was only 47.83/100,000, whereas the incidence of breast cancer

in the same year was 58.22/100,000.<sup>59</sup> But as reported by Xu,<sup>45</sup> during 6-year screening based on breast ultrasonography among 8753 women, the proportion of early stage breast cancer detected was 58.33%, much higher than that of the national mammography screening (31.11%). In this study, the detective rate of breast cancer was 77.78/100,000, and when complemented by mammography, the rate could be raised further to 88.89/100,000. In consideration of the lower price of ultrasonography and the denser breast tissue of Chinese women, this study indicated that screening based on ultrasonography may be considered as a preferred pattern of breast cancer screening in China. As to the breast examination, early in the 1980s, the randomized screening trial in Shanghai<sup>60</sup> demonstrated that after 12-year follow-up, breast self-examination failed to neither improve early diagnosis rate nor reduce mortality. Nonetheless, as it could somewhat improve public awareness, self-examination was taken as an important part of health education.<sup>61</sup> At present, there has been no consensus about the role of clinical breast examination for early detection. But in current domestic screening practice, clinical breast examination is always employed in combination with ultrasonography or/and mammography.

### **Risk-based screening: an alternative way**

At present, not only in China, but also around the world, it is not definite which screening pattern is optimized. There are two important factors that we have to take into consideration before the final personalized screening patterns are established. One is the balance between harm and benefit and another one is the ratio of cost to effectiveness.

But on the whole, the one-size-fits-all paradigm in organized screening of breast cancer is shifting toward a personalized approach.<sup>62</sup> It has been proved in a Spanish study that compared to traditional uniform screening pattern, risk-based strategies resulted in a much higher benefit for a specific cost.<sup>62</sup> Enhanced strategies to identify the highest risk population should be research priorities.<sup>63</sup> And as recommended by NCCN guidelines of breast cancer screening and diagnosis,<sup>64</sup> Gail-2 model is advised to be employed for discriminating normal risk and increased risk population, by which different screening follow-ups are conducted. Though well validated and approved in American women, Gail-2 model was not suitable for Chinese women.<sup>65</sup> Thus there is an urgent need to explore and establish a risk assessment tool suitable for Chinese women and China's actual conditions. Based

on a cross-sectional survey covering 120,000 women, Yu et al presented a new risk model including six factors: diabetes mellitus, BMI, family history of breast cancer, personal history of benign breast disease, age at first birth, miscarriages times, and current life satisfactory degree. The area under ROC curve (AUC) for 5-year risk of this model is 0.717, better than Gail model. And worth to mention, this model could work without any assistant examination such as ultrasonography and mammography. So it is particularly well suited for application in community and villages. On this basis, a two-step risk assessment system was proposed. In this system, with the help of an elementary risk tool (for community use), women at suspicious high risk could be selected. And after further screening by another professional risk tool (for hospital use), in which ultrasonography and mammography are included, the women at true high risk are selected finally for long-term follow-up. As described before, a principal challenge to population-based screening of breast cancer in China is the gap between the enormous, widely dispersed population and limited financial funding. So this two-step system is a convenient and economical way for breast cancer screening in China. At present, the critical work is to further optimize the elementary risk tool and to establish the professional tool.

In a word, risk-based strategies are expected to reduce harm and costs. And it is necessary to develop accurate measures of individual risks and to work on how to implement the strategies at the most.

## Conclusion

Breast cancer has been a great social and economical burden for China, but there is still quite a long way to improve the prevention. Breast cancer control efforts should include not only health-care delivery, but also public participation to increase awareness and promotion of early detection.

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