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Overview of breast cancer prevention: what's the next?

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Breast cancer is the leading cause of death among women at the ages of 20 – 59 years[1]. The incidence of breast cancer in Asia is also shown to be increasing recently, especially in the more affluent cities, and the peak incidence of breast cancer is at the age of 45–50 years[2]. Breast cancer prevention has started from secondary prevention strategy of early detection of the disease with different modalities in Asia[3-5] despite the absence of unified nationwide screening program. There are a lot of discussion about the benefits and harms of breast cancer screening[6-8] and still a lot of controversial issues such as stratification of breast cancer risk, choice of screening modalities, ways of information dissemination, different culturo-religious beliefs, and various levels of medical resources, especially in Asia, remain unresolved. In no doubt, a cost-effective prevention method should be more widely accepted.

The recent hot topic on primary prevention of breast cancer is prophylactic mastectomy in women with BRCA1/2 mutation which accounts for 5% – 10% of breast cancer only[9-11]. Previously, we discussed about the importance of early detection for breast cancer as a preventive measure considering that genetic mutation contributes only a small proportion of breast cancer and the heterogeneous disease involves multistep and multifactorial process[3]. Preventive therapy should be considered given the promising results of prevention trials and will be discussed further in this mini-review.

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1 Cancer prevention studies

Tamoxifen was approved for breast cancer risk reduction by U. S. Food and Drug Administration (FDA) in 1998 and further endorsed the use in specified population[12-14]. The four major prevention trials of tamoxifen for primary prevention of breast cancer have completed[12,15-17] (Table 1). A significant reduction in risk of invasive and noninvasive breast cancers was observed in patients treated with tamoxifen compared with placebo. Despite the significant risk reduction of breast cancer, tamoxifen is not widely accepted due to the concerned side effects, especially the drug-induced thromboembolic event and endometrial cancer. It is therefore important to select subjects with high risk of breast cancer to be given tamoxifen at doses of 5 mg/d or 10 mg on alternate days or 20 mg per week which are adequately effective and adopted by European Institute of Oncology in 2004[18], but further prospective studies are warranted.

Raloxifene is also a selective estrogen receptor modulator (SERM) being recognized as another possible option for breast cancer prevention. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial[19] evaluated 7705 postmenopausal women with osteoporosis randomized to receive raloxifene 60 mg/d, 120 mg/d, or placebo from 1994 to 1998. A significant reduction of ER-positive invasive breast cancer by 84% ($RR = 0.16$; 95% CI: 0.09 – 0.30) was observed after 4 years of treatment. Although raloxifene increased the risk of venous thromboembolic disease ($RR = 3.1$; 95% CI: 1.5 – 6.2), it did not increase the risk of endometrial cancer ($RR = 0.8$; 95% CI: 0.2–2.7) as with tamoxifen[20]. The extended MORE study to Continuing Outcomes Relevant to Evista (CORE) study enrolled 4011 postmenopausal women to be randomly assigned to receive additional 4 years ofraloxifene 60 mg/d or placebo. Over the 8 years of MORE and CORE trials, the incidences of invasive

Table 1 Tamoxifen prevention trials for breast cancer

Trial	Study duration	*n*	Age (range)	Median follow-up (months)	Invasive breast cancer			Noninvasive breast cancer		
					Tamoxifen (*n*)	Placebo (*n*)	Risk ratio (95% *CI*)	Tamoxifen (*n*)	Placebo (*n*)	Risk ratio (95% *CI*)
Royal Marsden[15]	1986–1996	2494	30–70	158	82	104	0.78 (0.58–1.04)	14	9	N/A
NSABP P1[12]	1992–1997	13 388	≥ 35	84	145	250	0.57 (0.46–0.70)	60	93	0.63 (0.45–0.89)
Italian[16]	1992–1997	5408	35–70	132	62	74	0.84 (0.60–1.17)	9	6	N/A
IBIS-I[17]	1992–2001	7144	35–70	96	124	168	0.74 (0.58–0.94)	17	27	0.63 (0.32–1.20)

N/A: not available

breast cancer and ER-positive invasive breast cancer were reduced by 66% (*HR* = 0.34; 95% *CI*: 0.22–0.50) and 76% (*HR* = 0.24; 95% *CI*: 0.15–0.40), respectively, in the raloxifene group compared with the placebo group without any new safety concern[21]. The Raloxifene Use for the Heart (RUTH) trial was another randomized, placebo-controlled study which evaluated 10 101 postmenopausal women with coronary heart disease (CHD) or multiple risk factors for CHD from 1998 to 2000[22]. Women randomized to receive the raloxifene 60 mg/d have significantly reduced risk of invasive breast cancer by 44% (*HR* = 0.56; 95% *CI*: 0.38–0.83) compared with placebo, but not in ER-negative or noninvasive breast cancer[23]. Nevertheless, caution should be taken with raloxifene associated with an increased risk of fatal stroke (*HR* = 1.49; 95% *CI*: 1.00–2.24) and venous thromboembolism (*HR* = 1.44; 95% *CI*: 1.06–1.95)[22].

Following the success, a Study of Tamoxifen And Raloxifene (STAR) prevention was established to compare tamoxifen and raloxifen in 19 747 high-risk women recruited according to modified Gail model[24-25] from 1999 to 2004. The study has drawn attention following the tamoxifen prevention study. Raloxifen is as effective as tamoxifen in the prevention of invasive breast cancer, but not in noninvasive one. Lower incidences of uterine cancer (*RR* = 0.62; 95% *CI*: 0.35–1.08), venous thrombolic events (*RR* = 0.70; 95% *CI*: 0.54–0.91), and cataracts (*RR* = 0.79; 95% *CI*: 0.68–0.92) were observed in raloxifen-treated women, but there were no significant differences in ischemic heart disease events (*RR* = 1.10; 95% *CI*: 0.85–1.43), strokes (*RR* = 0.96; 95% *CI*: 0.64–1.43), or fractures (*RR* = 0.92; 95% *CI*: 0.69–1.22) when compared with tamoxifen[26]. This further highlights the use of SERM in women at high risk of breast cancer and low risk for adverse events. The promising results of MORE, CORE, RUTH and STAR trials have driven U. S. FDA to make the approval of raloxifene for reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer in 2007.

With the evolution of endocrine therapy following the impressive reduction in disease recurrence for adjuvant use of aromatase inhibitors[27-29], aromatase inhibition was also investigated as one of the possible prevention strategies against breast cancer. NCIC Clinical Trials Group Mammary Prevention. 3 (NCIC CTG MAP. 3) trial enrolled 4560 postmenopausal women with Gail risk score greater than 1.66% from 2004 to 2010[30]. The NCIC CTG MAP. 3 trial has demonstrated significant reductions in the annual incidence of invasive breast cancer by 65% (*HR* = 0.35; 95% *CI*: 0.18–0.7) and the annual incidence of invasive plus noninvasive breast cancer by 53% (*HR* = 0.47; 95% *CI*: 0.27–0.79) in those treated with exemestane 25 mg/d compared with placebo. Most of the tumors were ER-positive in this study. Certainly a longer follow-up is necessary and the subsequent study on mammographic findings, concurrent bisphosphonate use, and ethnicity[31] may help to outline a full picture of who could benefit from the use of exemestane therapy. Another phase 3 IBIS 2 study[32] exploring the use of anastrozole in preventing breast cancer has also finished recruitment. In the near future, the feasibility of using aromatase inhibitors for breast cancer prevention will be displayed.

At present, approved cancer prevention therapies focus mainly on the prevention of estrogen-dependent breast cancer. A recent systematic review of reduced risk of primary breast cancer for the U. S. Preventive Services Task Force has demonstrated the use of SERM to reduce incidence of invasive breast cancer by 7 to 9 cases in 1000 women over 5 years compared with placebo, but increase the incidence of thromboembolic events with tamoxifen causing 4 more events per 1000 women than raloxifene[33].

The review also emphasized the data limitation on mortality and adherence measures and for women who were nonwhite, premenopausal, or have comorbid conditions. In addition, it is important to pay heed to heterogeneity of the disease as such different subtypes in molecular level was found[34] and tumor heterogeneity was noted in molecular subtypes[35]. The preventive therapies only highlight the prevention of ER-positive breast cancer. The changing epidemiology with more young patients and aggressive diseases will create the unmet need to look for other preventive agents.

2 Risk prediction model

A large proportion of breast cancer is attributable to multiple risk factors and only limited cases are linked to genetic predisposition. These factors could be roughly classified into modifiable and non-modifiable risk factors. Modifiable risk factors include obesity, sedentary lifestyle, alcohol consumption, high fat diet and lack of physical activity[36-40]. However, it is hard to identify and quantify the contributing factors. The biological mechanisms involved between these modifiable risk factors and the development of breast cancer deserve further investigation. Taking breast density, one of the important biomarkers of breast cancer risk, as an example, some studies found significant association between high alcohol consumption and breast density[41-43], but how alcohol consumption modifies breast density remains unclear biologically. A population-based study showed that the effect of alcohol consumption on breast density was modified by smoking[44]. In general, several lifestyle changes are recommended to prevent breast cancer regardless of risk.

Personalized medicine has driven the provision of individualized treatment and may evolve to the recommendation for individualized prevention measures. Careful and accurate risk assessment and stratification are therefore essential to identify who should be treated with preventive therapy. Several non-modifiable risk factors are identified as possible primary methods for assessing nongenetic breast cancer risk which is currently based on the Gail model[24-25]. The model was developed by Dr. Mitchell Gail from a huge screening study of 280 000 women aged between 35 and 74 years. The risk assessment tool is available online and its algorithm was last updated in 2011[45]. The modified Gail model has taken the history of atypia and race or ethnicity into account[46]. However, the model could not predict precisely which woman will develop breast cancer, but it could correctly predict the average risk of developing invasive breast cancer in a group of women with the same risk factors and age.

The difference in epidemiology of breast cancer between western and eastern countries[2,47] may be attributed to the different exposure to risk factors and biological differences. In addition to the risk factors in the Gail model, there might be some other factors contributing to the ethnic differences[48]. Breast density is widely recognized as one of the ethnically different risk factors of breast cancer. Premenopausal women in Asia has dense breast which can hardly be assessed by mammography. A review of NSABP-STAR trial however only demonstrate a slight improvement of the prediction model by adding BI-RADS breast composition into Gail model from the AUC of 0.63 to 0.64[44]. A validation study of 28 104 women aged 50 to 64 years who participated in the Singapore Breast Cancer Screening Project was conducted and showed that the Gail model overestimated the breast cancer risk especially for older women aged 60 – 64 years[49]. Further validation of the Gail model in the local population is necessary.

3 Future perspectives

Currently available evidence has demonstrated the benefit of SERM for breast cancer prevention but its clinical application is limited to the group at risk of developing ER-positive invasive breast cancer. Here comes to questions on how to select women at risk of developing the hormone-dependent breast cancer, how to balance the risk and drug-emergent side effects, and whether ethnic differences exist between Asians and Caucasians in this aspect. Prior to exploring any biomarkers of determining who could truly benefit from the preventive therapy, a large-scale prospective study is necessary to investigate whether the use of SERM could have the similar protective effects among Asians with different tumor biology and pharmacogenomics. The study could also help to establish a platform to collect the tumor tissue from breast cancer patients for subsequent analysis of the biological differences.

Breast cancer risk model development is another important area to be studied. The present Gail model is widely used. Nevertheless, in view of the different

epidemiology of breast cancer between eastern and western population, it remains unclear about the accuracy of estimating risk of breast cancer among Asian women. Despite ethnicity of an individual woman including Asian is taken into account in the model, further validation study is still recommended for local population and possibly a modified model specific for the local population is required.

It is still questionable whether cancer vaccine could be employed for prevention of breast cancer following the success of other types of cancer such as virus-induced liver and ovarian cancers. The development of therapeutic vaccine against breast cancer is now based on the tumor antigens present on the cancer cells such as p53, HER-2, carcino-embryonic antigen, mucin 1 and cancer testis antigens which are therapeutic targets[50]. However, the vaccine-induced immune response might stress the tumor to down-modulate the antigen resulting in antigen loss variants[51]. Although vaccine should be tumor-specific in no doubt, it will also become an obstacle to overcome the heterogeneous disease. It is noteworthy that several viral infections are possibly associated with breast cancer such as Epstein-Barr virus[52], mouse mammary tumor virus[53], and human papilloma virus[54]. More observational studies should be carefully conducted especially on the selection of study population to identify the true casual relationship.

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