Perspectives

Using Genetic Testing at Cancer Diagnosis for Breast Cancer Control

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BACKGROUND

Breast cancer (BC) is the most common cancer among women globally. The WHO estimates 416,000 women are diagnosed to have BC annually in China, and the numbers of BC cases and deaths in China are predicted to rise by 16% and 48%, respectively, over the next 20 years (*1*). BC can be hereditary, and the most common cause of hereditary BC is an inherited pathogenic or likely pathogenic variant (henceforth called 'pathogenic variant' or 'PV') in the *BRCA1* or *BRCA2* genes. *BRCA1/BRCA2* PV carriers have a 17%–44% risk of developing ovarian cancer (OC) and a 69%–72% risk of developing BC up to the age of 80 (*2*). *PALB2* is a more recently established, high-penetrance BC gene: testing for which is now more widely advocated. *PALB2* carriers have a 53% risk of BC up to the age of 80 (*3*). In addition, *PALB2* has recently been shown to be a moderate-risk OC gene with a 5% lifetime risk of OC (*3*). PV in these three genes accounts for around 4% of BC. Most of these cancers are preventable or can be better mitigated if they are detected earlier.

International Clinical Guidelines on Genetic Testing

The use of genetic testing in women with BC has expanded significantly over the past decades because of the increasing number of laboratories offering testing with lower costs, the increasing public awareness and acceptability of testing, and the growing evidence base of clinical benefit for precision prevention. The current guidelines in the US and UK recommend offering genetic testing to people who fulfill recognized or established family history (FH)-based clinical criteria. These criteria are surrogates for *BRCA* probability, with genetic testing usually offered when someone has approximately a 10% probability threshold of being a *BRCA* carrier. However, people with PV in cancer-susceptibility-genes (CSGs) do not always have a strong FH, and these criteria miss a large proportion (approximately 50%) of PV carriers (*4*–*5*). An alternative option is to offer unselected *BRCA1/BRCA2/PALB2* genetic testing for all BC patients to identify more PV carriers. Unselected, multi-gene testing of BC patients has several benefits for PV carrier patients themselves and also enables genetic testing (cascade testing) to identify relatives of all BC patients carrying the familial PV. These relatives can then benefit from early diagnosis and precision prevention.

Benefits for patients: There are several effective and available risk management options for BC patients with high-risk PVs. For patients that have already been diagnosed with unilateral BC (cancer in one breast), PV carriers can choose contralateral, prophylactic mastectomy (CPM) (preventative mastectomy on the other breast) to reduce their risk of developing contralateral BC. Cancer-affected carriers may become eligible for treatment with novel drugs [like poly ADP ribose polymerase (PARP)] inhibitors] and newer, precision medicine-based therapeutics through clinical trials. They can also undergo surgical prevention for OC as they are at increased risk of OC. Therefore, knowing CSG variant status is important for BC clinical management and overall prognosis.

Benefits for relatives: To reduce BC risk, relatives found to be *BRCA1/BRCA2/PALB2* PV carriers can be offered enhanced MRI/mammography screening, risk-reducing mastectomy (RRM) (*6*), or chemoprevention with selective estrogen-receptor-modulators (*7*). To reduce OC risk, *BRCA1/BRCA2* PV carriers can opt for risk-reducing salpingo-oophorectomy (RRSO) (*8*). RRSO is now also recommended for *PALB2* PV carriers (*9*).

Cost-effectiveness: A study was conducted to estimate the health benefits and costs of multigene testing for all BC-patients compared with the current practice of genetic-testing (*BRCA*) based on FH/clinical criteria in the US and UK settings. We obtained data from 11,836 patients in population-based BC cohorts recruited to four large research studies, showing that unselected *BRCA1/BRCA2/*

PALB2 multigene testing approach for all BC patients is cost-effective compared with *BRCA* testing based on FH/clinical criteria — with incremental cost-effectiveness ratios well below UK and US cost-effectiveness thresholds (*10*). One year's unselected panel genetic testing could prevent 2,101 cases of BC or OC and 633 deaths in the UK, and 9,733 cases of BC or OC and 2,406 deaths in the US (*10*). These findings support changing the current policy to expand genetic testing to all women with BC. This is now recommended by the American Society of Breast Surgeons (*11*). Studies in Spain, the US, and Norway have also shown evidence for the cost-effectiveness of testing women with *BRCA*-related cancers and the cascade testing of relatives of the index cases (*5*,*12*–*13*).

UPTAKE OF RISK-REDUCING STRATEGIES

RRM reduces the risk of developing BC in PV carriers with no history of BC by 91%–95% (*6*). However, significant differences have been seen in the uptake of risk-reducing strategies for *BRCA* carriers across countries. The average RRM uptake is 27.8% based on data from a cohort of 3,413 unaffected women with *BRCA1/BRCA2* PV from ten countries (*14*), with the highest in the US (49.9%) and the lowest in Poland (4.5%). The mean age at RRM is 41.8 years (40.7 years for *BRCA1* carriers and 42.4 years for *BRCA2* carriers), and 3.4% of the mastectomies are done at age 60 and above. Globally, there has been an increasing trend in RRM, with uptake rates of 30.3% post-2009 versus 26.9% pre-2009. However, some countries have persistently low rates (Poland) or decreased rates (from 39.1% to 35.9% in Canada). The RRM uptake among unaffected PV carriers was 37.5% in China, though this was based on a small sample of 30 patients (*14*).

Although growing evidence has shown that RRM is safe and provides significant benefits from an oncological perspective, decision-making to undergo RRM remains complex and difficult for many. Reconstruction procedures can be complicated and are associated with a not-insignificant morbidity rate. Many women may have associated psychosocial, body image, or sexual concerns and require psychological support. In recent years, modified surgical options, including nipple-sparing mastectomy in which the nipple-areolar complex is preserved, have become available. This has been shown to improve cosmesis, with patients reporting better psychosocial and sexual well-being (*14*).

RRSO reduces OC risk among *BRCA1/BRCA2* PV carriers by 96% (*8*). The RRSO uptake rates can also vary across countries. Uptake rates increase with time and have been reported to be approximately 64.7% among *BRCA* carriers. The mean age at RRSO is 45.6 years (44.7 years for *BRCA1* carriers and 47.7 for *BRCA2* carriers). China was reported to have a low RRSO uptake rate of 36.7% in comparison to a broader cohort of 6,233 *BRCA* PV carriers from ten countries (*14*). There may be many reasons for such differences in uptake rates, including differences in patient preferences, cultural attitudes, health system differences, out-of-pocket costs, counselling, and extent of follow-up.

Other BC prevention options include chemoprevention and breast screening for PV carriers without a history of BC. The uptake rate of chemoprevention ranged from 2% to 15% across countries. As per the National Institute for Health and Care Excellence (NICE) guidelines for familial BC in the UK, annual mammographic surveillance is offered to women aged 40–69 years with a known *BRCA1/BRCA2* PV, and annual MRI surveillance is recommended at even younger ages (30–49 years). The BC screening guideline in China recommends *BRCA1/BRCA2* PV carriers aged 25–75 years undergo breast ultrasound screening every six to twelve months and conduct a breast MRI annually; *BRCA1/BRCA2* PV carriers aged 30–75 years undergo additional mammography annually.

BREAST CANCER GENETIC TESTING IN CHINA

Patient and disease characteristics in Chinese women are different from those in women from western countries. Chinese women's mean age of BC diagnosis is between 45 and 55: about ten years younger than most Caucasian women (*15*). Young BC patients tend to have a higher CSG prevalence. The prevalence of *BRCA* and *PALB2* PV-carriers appears to be higher in Chinese women with BC than in Caucasian women. Therefore, offering genetic testing to all BC patients would likely greatly benefit Chinese women with BC and their families, preventing many more cancer cases and deaths in China. The one-child policy followed by China for many decades (which has now been changed) has also led to smaller family sizes and a

smaller number of female relatives, making the FH-based testing approach potentially even more likely to miss PV carriers and thus overlook huge opportunities for precision prevention in China. As such, the potential impact and benefit of unselected genetic testing at BC diagnosis in China could be even greater than in other Western populations.

In China, there is currently only limited genetic testing available for BC cases. Even FH/criteria-based testing is not uniformly/systematically available as this is not part of the standard state-funded health package. Most patients have no access to genetic testing. Moving to even a FH/clinical-criteria based testing approach is better than the currently-predominant, no-testing approach. However, an alternative would be to move straight to offering testing for all BC cases and cascade testing relatives of index cases. This would have a much greater impact. The cost-effectiveness of these approaches has been evaluated in another research study by the authors (*16*). We examined the incremental lifetime effects, costs, and cost-effectiveness of multigene-testing all BC patients compared with FH/clinical-criteria based genetic (*BRCA*)-testing and no genetic-testing. The findings of this study suggest that unselected, high-risk, multigene-testing for all Chinese BC patients is cost-effective compared with FH/clinical-criteria testing and no genetic-testing in China. Testing all BC patients at diagnosis can identify many more PV carriers for screening/prevention in China, saving many more lives. One year's unselected multigene testing could prevent 7,868 BC or OC cases and 5,164 deaths in China (*16*).

IMPLEMENTATION OF BC GENETIC TESTING

It is important for research evidence to be transitioned to clinical and public health practice for patient/public benefit. In China, there have been some concerns about the current state of genetic testing implementation and oversight. Although unselected, multigene testing for BC patients has been shown to be cost-effective and the price of genetic testing is falling, there remain a number of challenges to overcome in implementing a policy supporting unselected multigene testing for all BC patients.

In China, genetic testing is mainly performed in laboratories at major hospitals affiliated with top-ranked universities or large commercial companies, while many local laboratories are not capable of undertaking/delivering genetic tests. The current laboratory infrastructure lacks the resources and capacity to deliver unselected genetic-testing for all BC patients given the large numbers diagnosed annually. The pool of trained counsellors or clinicians to deliver genetic counselling is also limited. With more genetic-testing conducted, many more PVs and variants of uncertain significance (VUS) carriers will be diagnosed. In addition to expanding laboratory infrastructure, clinicians will need to be trained to increase their understanding of genetics and ability to counsel patients about genetic-testing and its implications for management including that of VUS. Genetic-counselling services should be improved and implementation could be supported by a process of training and education for healthcare professionals to enhance the genetic-counselling workforce. Newer context-specific delivery models will be needed for implementing this approach. 'Mainstreaming' genetic-counselling and testing, which has been successfully implemented across OC treatment pathways, can be an option for successful, large-scale implementation of testing at BC diagnosis too (*11*). There is also a need to expand resources/infrastructure and clinical manpower for downstream management pathways, including screening and prevention. The outcomes of genetic-testing implementation pathways for BC patients need to be evaluated through real-world studies.

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