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Managing *BRCA* Mutation Carriers in China: Reply

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The reply from Kalogerakos [1] to our article has highlighted the importance of the need to understand the risk conferred by *BRCA* mutation carriers in Chinese and other ethnic groups in order to achieve personalized medicine. Guidelines for prophylactic interventions and intensive surveillance are based on studies performed mainly in Caucasian cohorts. *BRCA1* and *BRCA2* mutation carriers have a 4.5-fold and 3.4-fold increased risk of getting contralateral breast cancer. The relative risk of contralateral breast cancer in *BRCA1* mutation carriers increases as the age at first diagnosis decreases, and can be as high as 11-fold if the age at first diagnosis of breast cancer is under 35 [2]. Occult invasive cancers found in prophylactic mastectomy specimens ranges from 0.7 to 10.7%. Prophylactic mastectomy is found to be effective in preventing invasive breast cancer in *BRCA* mutation carriers as the remaining risk is less than 0.2% per woman-year [3]. Similarly, salpingo-oophorectomy significantly reduces the risk of breast cancer (hazard ratio [HR] = 0.36-0.63) and ovarian or fallopian tube cancer (HR = 0.14-0.28) in *BRCA* mutation carriers. There is also reduction in breast cancer (HR = 0.44) and ovarian cancer-specific mortality (HR = 0.21) [4]. However, there is limited information on *BRCA2* mutation carriers since it is less common in Caucasian cohorts. Because of a lower incidence of breast cancer in Chinese (1 in 20) and also a higher *BRCA2* detection rate found in our study, risk in this group is likely to be different. Therefore, it is important to have more precise ethnicity-specific estimates of specific risks so that more accurate guidelines based on the efficacy of risk-reducing interventions, surveillance, and use of novel drugs such PARP inhibitors can be made.

Next-generation sequencing technology (also known as massive parallel sequencing) allows the development of studies unachievable a few years ago. Nowadays, next-generation sequencing technology provides an unprecedented ability to search for mutations, copy number aberrations, and somatic rearrangements in an entire cancer genome at base pair resolution which can be performed in a matter of weeks. By comparing *BRCA* mutations carriers who do not develop cancer with those who do, it may be possible to identify novel genetics changes associated with development of *BRCA*-related breast/ovarian and related cancers. As sequencing capacity improves, scientists will move forward from one genome per individual to multiple genomes per individual from sources including precancerous cells and cancer cells. Furthermore, recent genome-wide association studies using high-throughput human SNP arrays also identified new breast cancer susceptibility genes which can increase cancer risk prediction [5, 6]. As the complexity of assessing cancer risk genetically increases in technology and knowledge of ethnic differences, clinical recommendations will need to be standardized and personalized accordingly.

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