Prevalence and Clinical Implications of BRCA1/2 Germline Mutations in Chinese Women with Breast Cancer

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Breast cancer susceptibility genes, BRCA1/2, are associated with the development of breast cancer and have been studied extensively in Western societies. The role of BRCA1/2 genes in Chinese women with breast cancer has not been fully elucidated. We determined the prevalence and characteristics of BRCA1/2 germline mutations in a large cohort of 5,931 Chinese women with breast cancer. Further, we conducted a kin-cohort study to investigate the estimated cumulative risks in Chinese women who carry a deleterious BRCA1 or BRCA2 mutation. We also investigated the association between BRCA1 mutation carriers and response to neoadjuvant anthracycline-based chemotherapy among Chinese women with triple-negative breast cancer. Our findings provide guidelines for Chinese women with breast cancer who should undergo BRCA1/2 genetic testing.

BRCA1 and BRCA2 are high penetrance breast cancer susceptibility genes. Both BRCA1 and BRCA2 are tumor suppressor genes that play a crucial role in maintenance of genomic stability through homologous recombination pathway when the double-strand DNA damage occurs. Women with BRCA1/2 mutation confer a high risk of developing breast cancer and other cancers. Genetic testing for BRCA1/2 mutation is more widely applied for high-risk women worldwide to date. Breast cancer patients with BRCA1/2 mutation exhibit different clinico-pathological characteristics compared with those with sporadic breast cancer. This unique profile of BRCA1/2 mutation...
carriers suggests that they have targetable features and are thereby more likely to obtain benefits from intensive surveillance, prophylactic surgery, and chemoprevention, which reduce their risk of developing breast cancer.

Prevalence of BRCA1/2 germline mutations in Chinese women with breast cancer

The prevalence of mutations in BRCA1/2 is different in various ethnic groups and may be affected by founder mutations. Earlier studies of BRCA1/2 mutations were largely based on Caucasian. It has been reported that BRCA1/2 mutations account for 15–20% of familial cases in Caucasian populations. Recently, a number of studies have focused on the Chinese population. We screened for BRCA1/2 germline mutations in 5,931 unselected Chinese women with breast cancer. To our knowledge, this is the largest BRCA1/2 mutation screening undertaken to study breast cancer in Chinese women to date. The overall prevalence of BRCA1/2 mutations was 3.9% in this large cohort. The prevalence of BRCA1/2 mutations in familial breast cancer in our study was 16.9% which was comparable with reports of other series in Chinese women and Caucasian women. In addition, BRCA1/2 mutation rate were 5.2% and 2.0% in early-onset breast cancer (≥40 years) and sporadic breast cancers (>40 years), respectively. A total of 5931 unselected breast cancer patients were screened for BRCA1/2 mutations. It means that the BRCA1/2 mutation rates are 5.2% in early-onset breast cancer (diagnosed with breast cancer at and before age of 40) and 2.0% in sporadic breast cancer (diagnosed with breast cancer above 40). 41.4% of mutations in this cohort were specific for Chinese population. Both BRCA1 and BRCA2 mutation carriers were significantly more likely to be early-onset and bilateral breast cancers, high-grade cancer, and to have a family history of breast cancer compared with non-carriers. BRCA1 mutation carriers were more likely to be triple-negative cancer than BRCA2 mutation carriers and non-carriers.

The breast cancer risk in Chinese women with BRCA1/2 mutations

Caucasian women who carry a BRCA1 or BRCA2 mutation may have a 57–65% or 45–49% breast cancer risk by age 70 years. The life–time risk of breast cancer varies between populations. The spectrum of BRCA1/2 mutations in Chinese women is different to that of Caucasian women. Approximately 50% of BRCA1/2 mutations in Chinese women were not reported in Caucasian women. The breast cancer risk in Chinese women with BRCA1/2 mutations might be different when compared with Caucasian women. We conducted a kin–cohort study to investigate the estimated cumulative risks in Chinese women who carry a deleterious BRCA1 or BRCA2 mutation. Our study included 1,816 unselected Chinese women with breast cancer and 5,549 female first-degree relatives of these probands. We found that the estimated cumulative breast cancer risks in BRCA1 and BRCA2 mutation carriers by age 70 years were 37.9% and 36.5% in Chinese women, respectively. Our findings suggested that the cumulative risk of breast cancer in BRCA1/2 mutation carriers is dramatically higher (approximately ten–fold) than that in general population in Chinese women. Based on these high risks of BRCA1/2 mutation carriers, therefore, genetic counseling, individualized prevention, and even prophylactic is a good choice for prevention for Chinese women who carry BRCA1/2 mutations. It should be noted that environmental and lifestyle factors may also influence the final breast cancer risk for an individual.

The National Comprehensive Cancer Network (NCCN) guidelines have recommended detailed criteria for BRCA1/2 testing. Based on our studies, we suggested that Chinese women with breast cancer who meet the following criteria should be recommended to undergo: (i) breast cancer patients diagnosed at any age with family history of breast or ovarian cancer; (ii) bilateral breast cancer patients without family history of breast cancer diagnosed before the age of 50; (iii) triple negative breast cancer patients diagnosed under the age of 50 years regardless of family history of breast cancer.
**BRCA1/2 mutation carriers and response to neoadjuvant chemotherapy**

Neoadjuvant chemotherapy is widely used in operable primary breast cancers. One study suggested that breast cancer patients with *BRCA1* mutation are more sensitive to cisplatin monotherapy than non-carriers in the neoadjuvant setting, revealing a higher pCR (pathologic complete response) rate (pCR rate, range 61-75%) \(^\text{10}\). We also found that *BRCA1* mutated triple-negative breast cancers were significantly more sensitive to anthracycline-based neoadjuvant regimens than non-*BRCA1/2* mutated triple-negative breast cancers (pCR rate, 57.1% versus 29.0%), but this was not case for taxane-based neoadjuvant regimens \(^\text{11}\). Taken together, these studies suggest that *BRCA1* mutation carriers may be more likely to benefit from cisplatin or anthracycline-based neoadjuvant regimens but not from taxane-based regimens.

Currently, the on-going clinical trials of the targeted drugs (i.e., poly (ADP-ribose) polymerase inhibitors) provide treatment promise for advanced breast cancer patients who carry a *BRCA1/2* mutation \(^\text{12}\). PARP inhibitors in combination with adjuvant chemotherapy may further improve the efficacy of treatment for *BRCA1/2*-mutated tumors; therefore, selecting the optimal chemotherapy regimens for the right patients are the challenges for future clinical trials.

**References**