



# Prediction of carrying a *BRCA1* or *BRCA2* mutation

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Breast Cancer Susceptibility Genes 1 and 2 (*BRCA1* and *BRCA2*, collectively termed herein as *BRCA*) are tumor suppressor genes responsible for DNA repair. Hereditary breast and ovarian cancer syndrome (HBOC) due to *BRCA1* and *BRCA2* pathogenic variants accounts for approximately 5–10% of all breast cancers, and 15% of ovarian cancers (1). For women who carry a pathogenic *BRCA* mutation, the cumulative risk for developing breast or ovarian cancer by age 70 years is 45–66% and 11–41%, respectively, in European populations (2), and the mutations are also related to increased likelihood of prostate cancer, pancreatic cancer, melanoma, and so on. Detection of germline *BRCA* pathogenic variants has implications on cancer surveillance and risk-reducing strategies for affected individuals and their family members, and on clinical management in patients with related cancers. Risk-reducing salpingo-oophorectomy (RRSO), which decreases risks of both breast and ovarian cancer, is recommended for affected individuals after childbearing and bilateral mastectomy can be considered to prevent breast cancer (3). Tamoxifen substantially reduces breast cancer risk for women at high-risk for breast cancer and can be used a chemo-preventive measure in affected individuals (4). The clinical impact of *BRCA* mutations is highlighted for the use of PARP inhibitors, as their benefit for breast cancer is mainly limited to the patients with *BRCA* mutations (5,6).

Prevalence of *BRCA* pathogenic variants is estimated to be 0.33–0.13% in the general population, with the exception of populations with high frequency founder mutations, such

as the Ashkenazi Jewish population (7). The prevalence is thought to be highly ethnic-specific, especially between Caucasian and non-Caucasian populations (8), but data on the prevalence in Asian population is limited compared to those in Caucasian population. The contributions of *BRCA* mutations to breast cancer incidence are expected to differ between Asians and Caucasians, considering the lower but continuous increasing incidence and younger age of developing breast cancer compared to the Caucasian population (9).

In the article entitled “Predicting the Likelihood of Carrying a *BRCA1* or *BRCA2* Mutation in Asian Patients With Breast Cancer”, published on *Journal of Clinical Oncology* (10), the authors built a new model (Asian Risk Calculator) for estimating the likelihood of carrying a pathogenic variant in *BRCA1* or *BRCA2* gene, using germline *BRCA* genetic testing results of Asian patients with breast cancer. A total of 8,162 patients were recruited to two cross-sectional population-based studies in Malaysia and Singapore from 2 hospitals and 6 hospitals, respectively. Of them, 75.4% were Chinese, 14.8% Malay, and 9.9% Indian by ethnicity. Germline DNA was sequenced to detect *BRCA1* or *BRCA2* mutations, and 323 (4.0%) patients had germline pathogenic variants. The final prediction model for *BRCA* pathogenic variant (PV) carrier status (Asian Risk Calculator, ARiCa) included younger age of diagnosis, Indian ethnicity, bilateral breast cancer, estrogen receptor (ER)-negativity, human epidermal growth factor receptor 2 (HER2)-negativity, higher grade, and

presence of first-degree family history of breast or ovarian cancer. ARiCa model outperformed, with the highest area under the curve (AUC) (0.80), other genetic risk models such as BOADICEA (AUC 0.73) developed using data on European-ancestry populations and the empirical models (PENNII and KOHCal) developed using patients with breast cancer with early-onset or familial breast cancer (AUC 0.74 and 0.71, respectively). The outperformance of ARiCa was pronounced in the prediction for BRCA2 pathogenic variants, as all the models were similar for BRCA1. Applying representative clinical genetic testing criteria, such as National Comprehensive Cancer Network (NCCN) and Mainstreaming Cancer Genetics (MCG; UK), to Asian population required high screening rate (72% and 69%, respectively) for relatively low identification rate (37% and 39%). The authors report that ARiCa outperformed even the modified NCCN or MCG criteria with family history, age, and grade.

What are the implications of this study and how can the calculator be applied to the daily practice for Asian patients? As many Asian countries are with limited resources and many Asian patients are with breast cancer are younger, it is not always feasible or practical to apply the current guidelines such as NCCN. Moreover, many Asian countries have national health insurance system with strict payer policy and have their own reimbursement policy for BRCA testing. For example, in Korea where National Health Insurance is the single payer, testing for germline *BRCA1* or *BRCA2* mutations are reimbursed for (I) patients with breast cancer and family history of breast cancer, epithelial ovarian cancer, metastatic prostate cancer, or pancreatic cancer within third-degree relatives; (II) breast cancer diagnosed at 40 years of age or less; (III) triple-negative breast cancer diagnosed at 60 years of age or less; (IV) bilateral breast cancer; (V) diagnosis of breast cancer with epithelial ovarian or pancreatic cancer; (VI) male breast cancer; (VII) epithelial ovarian cancer. These criteria are different from any other guidelines and should be interpreted and analyzed for efficacy and effectiveness in the context of the specific population applied.

The authors should be commended for the successful development of the prediction tool. To be applied to and to be helpful for patients with breast cancer, these kinds of tools should also be validated in various contexts and in various populations. Moreover, the performance should be interpreted with the feasibility and applicability for each country in different situations. These efforts, together with development of more efficient and cost-effective detection

techniques, are warranted for better identification and better outcome of patients with *BRCA* mutations.

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