Editorial Commentary

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

Kyung-Hun Lee[1,2]

[1]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [2]Cancer Research Institute, Seoul National University, Seoul, Republic of Korea

Correspondence to: Kyung-Hun Lee. 101, Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea. Email: kyunghunlee@snu.ac.kr.

Comment on: Ang BH, Ho WK, Wijaya E, *et al.* Predicting the Likelihood of Carrying a BRCA1 or BRCA2 Mutation in Asian Patients With Breast Cancer. J Clin Oncol 2022;40:1542-51.

Keywords: Breast cancer; *BRCA1*; *BRCA2*; Asian

Submitted Jan 10, 2023. Accepted for publication Jan 29, 2023. Published online Feb 13, 2023.
doi: 10.21037/atm-23-162
View this article at: https://dx.doi.org/10.21037/atm-23-162

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.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-162/coif). KHL received payment or honoraria from AstraZeneca, Pfizer and Novartis.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. US Preventive Services Task Force, Owens DK, Davidson KW, et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2019;322:652-65.
2. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA 2017;317:2402-16.
3. Li X, You R, Wang X, et al. Effectiveness of Prophylactic Surgeries in BRCA1 or BRCA2 Mutation Carriers: A Meta-analysis and Systematic Review. Clin Cancer Res

2016;22:3971-81.
4. Visvanathan K, Chlebowski RT, Hurley P, et al. American society of clinical oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. J Clin Oncol 2009;27:3235-58.
5. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med 2017;377:523-33.
6. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med 2018;379:753-63.
7. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br J Cancer 2000;83:1301-8.
8. Bhaskaran SP, Chandratre K, Gupta H, et al. Germline variation in BRCA1/2 is highly ethnic-specific: Evidence from over 30,000 Chinese hereditary breast and ovarian cancer patients. Int J Cancer 2019;145:962-73.
9. Kim EK, Park SY, Kim SW. Clinicopathological characteristics of BRCA-associated breast cancer in Asian patients. J Pathol Transl Med 2020;54:265-75.
10. Ang BH, Ho WK, Wijaya E, et al. Predicting the Likelihood of Carrying a BRCA1 or BRCA2 Mutation in Asian Patients With Breast Cancer. J Clin Oncol 2022;40:1542-51.

Cite this article as: Lee KH. Prediction of carrying a *BRCA1* or *BRCA2* mutation. Ann Transl Med 2023;11(6):271. doi: 10.21037/atm-23-162