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EDITORIAL – BREAST ONCOLOGY

Breast Cancer Genes and Contralateral Prophylactic Mastectomy: Beyond BRCA

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Multigene panel germline testing is one of the most useful and cost-effective tools for counseling patients with a newly diagnosed breast cancer. Genetic testing provides relevant information regarding the risks of associated malignancies, informs family members of their potential risks, and identifies patients who may be candidates for specific systemic therapies. Moreover, multigene panel testing can provide patients with a unilateral breast cancer information about their risk of a contralateral breast cancer (CBC). This information can then be used to guide management of the contralateral breast.

The cumulative risk of CBC is relatively low (approximately 0.4% per year) among patients with unilateral breast cancer without known germline pathogenic variants (PVs).[1] In contrast, the cumulative, 10-year risk of CBC is approximately 30% among patients with unilateral breast cancer and a *BRCA1* or *BRCA2* PV.[2] Many choose to undergo contralateral prophylactic mastectomy (CPM) to reduce that risk. However, the risk of CBC among patients with PVs in moderate-risk genes, such as *ATM*, *PALB2*, and *CHEK2*, is less clear. Additionally, the use of CPM among these women is largely unknown.

The publication of the current study by Zhang et al., evaluating the association of moderate-risk breast cancer genes and CPM, is timely. In this retrospective, single-center study from the Memorial Sloan Kettering Cancer Center, the authors reported that the overall CPM rate among patients with *ATM*, *PALB2*, and *CHEK2* gene mutations was 39%.[3] For patients with PVs in these genes, the CPM rate was 54% compared with 30% for patients with variants of unknown significance (VUS). The authors did not report the use of CPM at their institution during this same time interval for women without genetic mutations or for those who did not undergo genetic testing. Importantly, the findings of this study from a renowned cancer center in New York City may not be generalizable to other breast cancer patients in the United States.

The use of CPM has dramatically increased in the United States and other countries over the past several decades.[4,5] The most common reason cited by patients for CPM is fear and anxiety regarding a future CBC.[6,7] Data regarding the cumulative risk of CBC for moderate-risk genetic mutations are just now emerging. Bilateral breast cancer was identified in 16% of patients in the study by Zhang *et al.* with pooling of data amongst the three moderate-risk genes (*ATM, CHEK2,* and *PALB2*).[3] However, risks of CBC appear to differ depending on the gene involved, age at diagnosis, and primary tumor estrogen receptor status. In the CARRIERS consortium study of 15,104 women with unilateral breast cancer, *CHEK2* PV carriers had a 10-year, cumulative CBC incidence of 7.9%.[8] Patients with a *PALB2* PV did not have a significantly overall increased risk of CBC; however, among patients with estrogen receptor-negative primary cancers, a *PALB2* PV was significantly associated with increased risk of CBC, with a 10-year, cumulative incidence similar to that of *BRCA1* PV carriers (20% vs. 23%). *ATM* PV carriers were not at significantly elevated risk of CBC with a 10-year, cumulative incidence of 4%. In a cohort of Dutch patients with CHEK2 PVs, the 10-year, cumulative incidence of CBC was 28.9%,[9] which is markedly higher than that reported in the CARRIERS study. So, the data regarding CBC risk among patients with moderate-risk genetic mutations are still evolving.

Presently, there are no established thresholds of CBC risk for recommending CPM. The American Society of Breast Surgeons published a consensus statement in 2016

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concluding that CPM should be "discouraged" for women with an average risk of CBC and that CPM "should be considered primarily for women at the highest risk for CBC," including those with PVs in *BRCA1* or *BRCA2*.[10] Of note, the guideline also commented that there is insufficient evidence regarding CBC risk to recommend for or against CPM among patients with PVs in *CHEK2*, *PALB2*, or *CDH1*.

Given our limited information to date, how do physicians advise patients with unilateral breast cancer and moderate-risk genetic mutations about management strategies of the contralateral breast? First, physicians need to understand that the risk of CBC is not the same for all moderate-risk genetic mutations: e.g., the risk is for *CHEK2* is considerably higher than for *ATM*. Additionally, physicians need to emphasize that CBC risk among patients with VUS is indeed *unknown*. A small proportion of VUS ultimately get reclassified; amongst those, the majority are reclassified as benign variants.[11] Nevertheless, nearly a third of the patients with VUS in the cohort by Zhang et al. received CPM.[3] Moreover, other factors, such as the estrogen receptor status of the primary tumor, age at diagnosis, and family history, also contribute to CBC risk. Patients should be advised that CPM is associated with increased postoperative complications and longer recovery, which can lead to delays in adjuvant therapy for the known cancer.[12] Finally, whereas CPM likely reduces the risk of CBC for patients with moderate-risk PVs, the impact on disease-specific survival is probably minimal, although currently unknown. Shared decision-making with a thorough discussion of CBC risks versus CPM risks therefore can be challenging. More data to guide these discussions are needed.

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