BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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How to Manage Patients With Moderate-Risk Germline Mutations

Nadine M. Tung, MD
Associate Professor of Medicine
Harvard Medical School
Director of the Cancer Risk Evaluation Program
Beth Israel Deaconess Medical Center
Boston, Massachusetts

H&O Which germline mutations are associated with a high risk for breast cancer?

NT Mutations in *BRCA1* and *BRCA2*, *TP53*, *PTEN*, *CDH1*, and *STK11* are considered high-risk mutations insofar as they are associated with a more than 5-fold increase in breast cancer risk. Mutations in *BRCA1* and *BRCA2* are the most common of these high-risk mutations, and confer a greater than 11-fold increase in breast cancer risk and a lifetime risk for breast cancer of 66% to 76% by age 80 years. Mutations in *TP53* are associated with Li-Fraumeni syndrome, those in *PTEN* with Cowden syndrome, those in *CDH1* with both invasive lobular carcinoma and diffuse gastric cancer syndrome, and those in *STK11* with Peutz-Jeghers syndrome. Compared with *BRCA1* and *BRCA2*, mutations in these other genes are much rarer. *PALB2* is a more recently identified high-risk breast cancer susceptibility gene. As with all of these genes, family history can modify risk. For women with a *PALB2* mutation, the lifetime risk of breast cancer is 33% for those with no family history compared with 58% for those with a strong family history.[1]

H&O What germline mutations are associated with a moderate risk for breast cancer?

NT Moderate-risk mutations are associated with a 2- to 5-fold increase in breast cancer risk and include those in *ATM*, *CHEK2*, and *NBN*. The lifetime risk for breast cancer among women with one of these mutations is 20% to 30%, and higher if there is a family history of breast cancer. For example, a significant family history of breast cancer could increase the relative risk (RR) from 2 or 3 to 4 or 5, which would represent a 45% risk for breast cancer by age 80 years.

BRIP1, RAD51C, and *RAD51D* are more recently identified ovarian cancer susceptibility genes. However, a large case-control study has demonstrated no increased risk of breast cancer with *BRIP1* mutations.[2] Likewise, there are not sufficient data to classify *RAD51C/D* or *BARD1* as breast cancer susceptibility genes.

> Prophylactic mastectomy is not likely to translate into a survival advantage in patients with moderate-risk mutations.

H&O Could you discuss your 2016 study published in the *Journal of Clinical Oncology*, along with any other relevant studies?

NT We conducted a study to evaluate the prevalence of breast cancer susceptibility genes in patients with breast

cancer seen at the Dana Farber Cancer Institute (DFCI). Although there may be some selection for younger patients or those with more aggressive disease at academic cancer centers, this study was the first to evaluate the frequency of these mutations in patients with breast cancer that were unselected for family history. Previous studies had evaluated selected patients who had a family history or were referred for genetic testing.

We found that in nearly 500 unselected patients with breast cancer seen at DFCI who agreed to bank blood for research, 10.7% had a germline mutation in 1 of the 23 cancer susceptibility genes that were analyzed. Of the non-Jewish patients, 5.1% had a mutation in *BRCA1/2* and 4.6% had a germline mutation in another cancer risk gene, with almost all the mutations in moderate-risk breast cancer genes.[3] Our results were consistent with those from The Cancer Genome Atlas, which found that in 500 patients who had breast cancer, 5.5% had a germline *BRCA1/2* mutation and 4.3% had a mutation in another cancer predisposition gene. The mutation distribution was almost identical to that found in our study.[4]

H&O Why have some studies found different results regarding which genes are significant, and regarding the magnitude of risk?

NT Risk estimates are still emerging for many gene mutations. For case control studies, risk estimates ideally should be based on large studies in which data from breast cancer patients who have not been selected for family history are compared with a population of controls who do not have cancer and are of the same age and ethnicity. The same assay for determining variants should be used in both groups. What we see instead is that many studies are based on data from women with familial breast cancer who have been referred to high-risk clinics or for genetic testing. This approach, of course, can result in an overestimation of risk.

Another explanation for differences among studies is that specific gene mutations may be associated with different risks. For example, in the *CHEK2* gene, truncating/frameshift mutations such as 1100delC confer a higher risk for breast cancer than do the common missense variants, such as c.470T>C (p.IIe157Thr) and c.1283C>T (p.Ser428Phe). In fact, some commercial testing companies report these missense changes as variants of unknown significance and others report them as pathogenic mutations, which can lead to a lot of confusion among clinicians.

H&O What is the effect of heterozygous mutations?

NT The effect is to confer a potential risk for cancer. Cancer presumably develops when the normal, wild-type allele for the gene in question is lost in the cancer cell of origin.

Data suggest that inheriting homozygous mutations (eg, the *CHEK2* mutation 1100delC) significantly elevates the risk for breast and other cancers, but this is rare in the United States. In the Netherlands, *CHEK2* mutations are much more common because 1.2% of the population is heterozygous for the 1100delC mutation. A single germline 1100delC mutation in *CHEK2* is seen in 5% of Dutch women with breast cancer and homozygous mutations are found in 0.3%.[5]

Our group conducted a study of more than 2000 patients with breast cancer referred for *BRCA* testing. Only 4 of the women had 2 distinct germline mutations, and in all mutations were in different genes.[6] We did not find any women with a homozygous mutation in a single gene.

H&O Are there any other inherited genetic changes that play a role in susceptibility to breast cancer?

NT Single-nucleotide polymorphisms (SNPs) are low-risk genetic changes associated with an RR for breast cancer that is less than 2. Researchers have identified 160 to 170 SNPs associated with increased breast cancer risk. Although the risks associated with these SNPs can be combined to determine a polygenic risk score (PRS), it is not yet clear how to incorporate the score into models that include other risk factors.[7] Women whose PRS is in the highest 1% of scores because of their risk alleles have an RR of 3.5 for breast cancer.

H&O Does the finding of specific mutations in women with breast cancer affect treatment decisions?

NT Regarding local treatment, there is no evidence that any of the mutations other than *TP53* should prevent a woman from having breast-conserving therapy that includes radiation. Radiation should be avoided if possible in patients who have breast cancer with germline *TP53* mutations because these mutations increase the chance of radiation-induced cancers, including angiosarcoma.

Another concern has been that mutations in DNA repair genes may result in increased local toxicity or risk of future contralateral breast cancer (CBC) after radiation. That has not been shown to be the case for *BRCA1/2*, and there is no evidence that it is true for other genes, including *ATM*. WeCare (The Women's

Environment, Cancer, and Radiation Epidemiology Study), which evaluated risk factors for CBC, did not find an increase in CBC after the use of radiation in patients with breast cancer who had the most common germline mutations in *ATM*.[8]

Regarding the risk for CBC, the data are emerging. Some evidence does support an increase in CBC among patients with germline mutations in *CHEK2* or *PALB2*. For example, one study reported a 5-year risk for CBC of 10% in *PALB2* mutation carriers, vs 17% in *BRCA1* carriers and 3% in women with neither mutation.[9] Likewise, for *CHEK2* mutation carriers in whom hormone receptor–positive breast cancer develops—the most common type in these carriers—the RR for a CBC is 3.5, and the chance of CBC in the next 5 years is approximately 12%.[10]

It is extremely important, however, to realize that the risk for CBC in carriers of moderate-risk mutations such as *CHEK2* is lower than that for carriers of *BRCA* or other high-risk mutations. Thus, the discussions regarding prophylactic mastectomy that we routinely have with *BRCA* carriers are *not* usually appropriate for carriers of moderate-risk mutations. There are always exceptions for women with a very strong family history of breast cancer. Prophylactic mastectomy is not likely to translate into a survival advantage in patients with moderate-risk mutations.

H&O How about systemic treatment?

NT Regarding systemic treatment with chemotherapy or targeted therapy, data show that platinum chemotherapy is an effective agent in *BRCA* carriers, particularly in those with triple-negative breast cancer.[11-13] The OlympiAD study (Assessment of the Efficacy and Safety of Olaparib Monotherapy Versus Physicians Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients With Germline BRCA1/2 Mutations) and the EMBRACA study (A Study Evaluating Talazoparib, a PARP Inhibitor, in Advanced and/or Metastatic Breast Cancer Patients With BRCA Mutation) demonstrated that the poly(ADP-ribose) polymerase (PARP) inhibitors olaparib (Lynparza, AstraZeneca) and talazoparib (experimental) are more effective than non-platinum chemotherapy in *BRCA* carriers with advanced human epidermal growth factor receptor 2 (HER2)–negative breast cancer.[14,15]

There is currently no evidence to support the use of different systemic therapies in patients with breast cancer who have moderate-risk mutations. The use of olaparib in such patients with metastatic breast cancer is now being evaluated, based on a study that demonstrated responses to olaparib in patients with metastatic prostate cancer who had germline or somatic mutations in DNA damage response genes, such as *ATM*.[16] This study is being initiated through the Translational Breast Cancer Research Consortium (NCT03344965).

H&O What is your advice regarding cancer screening for women with moderate-risk mutations?

NT I recommend translating the RR into a 5-year risk to guide screening; this was the approach my colleagues and I used in our paper establishing recommendations for surveillance in individuals with germline moderate-risk mutations.[17] The 2015 review article by Easton and colleagues[13] provides information about the breast cancer risks associated with mutations in each gene.

Currently, eligibility for surveillance with breast magnetic resonance imaging (MRI) is based on determination of the lifetime risk for breast cancer. However, risk assessment models vary a great deal in their lifetime risk estimates and were not validated for lifetime risk. Using short-term (eg, 5- or 10-year) risk, as we do for considering breast cancer risk reducing medications, might be more appropriate. Of course, there needs to be agreement regarding the appropriate thresholds for initiating mammography and using breast MRI for surveillance. In our article published in *Nature Reviews: Clinical Oncology*, we used a 5-year breast cancer risk threshold of 1% or greater to initiate mammography because that is the risk for an average 45- or 50-year-old woman. Currently, all guidelines recommend mammography by the age of 45 or 50 years. We used a 5-year threshold of 2.5% to initiate breast MRI because that risk exceeds the highest risk experienced by women in the general population.

H&O Which patients with breast cancer should be tested for germline mutations? Do most physicians follow these recommendations?

NT Guidelines such as those by the National Comprehensive Cancer Network (NCCN)[19] specify which patients should receive *BRCA* testing, and additional guidelines exist for patients with other high-risk breast cancer susceptibility genes (eg, *TP53* and *PTEN*). Underutilization still occurs; not all the women who meet the criteria for testing receive a referral and testing.

Recently, the NCCN added a "test-to-treat" indication for *BRCA* testing, stating that *BRCA* testing is appropriate for any patient with HER2-negative metastatic breast cancer for whom treatment with a PARP inhibitor would be considered. Several studies have demonstrated that the NCCN criteria are very sensitive for identifying

Table. Breast Cancer Screening Recommendations for Patients With Moderate-Risk Germline Mutations

Gene(s)	Tung et al (NRCO)[a,17]	NCCN v1.2018[19]	WISDOM Trial[20]
PALB2	Annual mammography and MRI starting at age 30 y	Annual mammography starting at age 30 y Consider MRI	Annual mammography and MRI starting at age 30 y
ATM *CHEK2* (truncating)	Annual mammography and MRI starting at age 40 y[b]	Annual mammography starting at age 40 y Consider MRI	Annual mammography starting at age 40 y MRI only if significant family history[b]

MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NRCO, *Nature Reviews: Clinical Oncology*; y, years.

[a] Age at which to initiate surveillance may be younger if family history is strong.

[b] Tung et al used a 5-year risk above 2.5% for MRI; WISDOM used a 5-year risk above 6.0%.

Sources: Tung N et al. *Nat Rev Clin Oncol.* 2016[17]; NCCN Clinical Practice Guidelines in Oncology[19]; Shieh Y et al. *J Natl Cancer Inst.* 2017;109(5).[20]

early-stage breast cancer patients with germline *BRCA* mutations. In women with metastatic breast cancer who may be eligible for a PARP inhibitor and who do not meet NCCN criteria for testing, the prevalence of *BRCA* mutations is not known.

In addition, any breast cancer patient for whom somatic tumor testing reveals a *BRCA* mutation should also have germline *BRCA* testing. Identifying a germline mutation can inform future cancer risks for the patient and family.

Regarding patients with moderate-risk genes, no guidelines currently exist for testing or even which genes should be tested for. Most often, moderate-risk breast cancer susceptibility genes are tested with multigene panels in women who meet the criteria for *BRCA* testing.

H&O What type of testing do you order, and how do you decide on the best approach?

NT Testing is almost always done through a blood draw, which is the most reliable method. Pretest counseling helps the patient decide whether she wants testing only for high-risk genes such as *BRCA1/2,* for which risk estimates and treatment implications are relatively clear, or testing for both high- and moderate-risk mutations.

In a patient with newly diagnosed breast cancer, we may first test for *BRCA* and other high-risk genes that impact immediate treatment decision making. If no mutation is found, we might test for a broader panel of genes that may be used to estimate the risk for future cancers and assess the risk for relatives.

H&O Do any factors exist that predict which women are more likely to have moderate-risk germline mutations?

NT No reliable predictors exist for moderate-risk mutations. Specifically, those factors that increase the risk for *BRCA* mutations—including young age at diagnosis and Ashkenazi Jewish heritage—do not seem to predict for the presence of mutations in most moderate-risk breast cancer susceptibility genes. The examination of larger cohorts of women with mutations in each gene will likely be required to identify gene-specific predictors.

H&O What is the current standard of care for patients with moderate-risk germline mutations who do not have cancer?

NT There is currently no standard of care, but the Table describes breast cancer screening recommendations for these patients from 3 sources: our paper in *Nature Reviews: Clinical Oncology;* the NCCN; and the WISDOM trial (Women Informed to Screen Depending On Measures of Risk).[20] WISDOM is a randomized trial comparing risk-based screening and guidelines-based screening. The authors used a 5-year risk of 6.0% to justify MRI surveillance and recommended MRI for women with moderate-risk germline mutations only if they had a significant family history of breast cancer.

Patients with a *CHEK2* mutation are also at increased risk for colorectal cancer; colonoscopy every 5 years beginning at age 40 years is recommended.

No data exist regarding the use of medications, such

as selective estrogen receptor modulators or aromatase inhibitors, to reduce the risk for breast cancer in women with moderate-risk mutations. However, if the 5-year risk is high enough, it is reasonable to consider medication. This approach is particularly attractive for women with *CHEK2* mutations because these carriers are particularly predisposed to the development of hormone receptor–positive breast cancer.

Prophylactic mastectomy is not typically recommended in patients with mutations in *CHEK2* or *ATM*. In women between the ages of 45 and 50 years, risk-reducing salpingo-oophorectomy should be considered after childbearing is completed in patients who have at least 1 of the more recently discovered ovarian cancer genes: *BRIP1*, *RAD51C*, and *RAD51D*.[17,19]

H&O Should relatives of a woman with moderate-risk germline mutations also be tested?

NT Because it will help with risk assessment and thus the development of appropriate strategies for surveillance and prevention, relatives should be tested. This applies to both first- and second-degree relatives, regardless of whether cancer has developed in the initially identified carrier. Men as well as women should be offered testing if identifying a mutation would alter surveillance or prevention recommendations.

An important point to remember is that if there is a very strong family history of breast cancer, moderate-risk mutations such as *ATM* and *CHEK2* may be responsible for only a portion of the familial risk. This is unlike high-risk mutations such as *BRCA1/2*, which generally account for almost all of the risk.

As a result, a woman in a family with the *ATM* mutation and a very high rate of breast cancer will likely require increased breast cancer surveillance regardless of whether she carries the mutation. In contrast, a woman in a family with *BRCA* mutations who tests negative for the mutation likely has a risk similar to that of a woman in the general population.

Thus, although genetic testing may help to refine risk assessment, it is important to understand the difference between high-risk and moderate-risk genes and not provide false reassurance.

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