Research and Clinical Updates

PALB2: A Third Important Gene for Inherited Breast Cancer

Following the publication of an important article in the *New England Journal of Medicine* (*NEJM*) in August 2014, germline *PALB2* gene mutations were confirmed as the third most important gene for inherited breast cancer, following *BRCA1* and *BRCA2*.[1] *PALB2* stands for "partner and localizer of *BRCA2*" and is located on chromosome 16. Studies suggest that *PALB2* mutations may account for ~2-3% of inherited breast cancer, highlighting its importance as a breast cancer predisposition gene. In those with *PALB2* mutations, prior studies suggest: 1) breast cancer risks in women range from two to six-fold; 2) breast cancer risks in men appear to be 8-fold or higher; and 3) risk of pancreatic cancer, although poorly defined, may also be elevated.

Marc Tischkowitz, MD

While the increased risk of breast cancer in those with a *PALB2* mutation has been known for years, genetic testing was not routinely performed because mutations were thought to be rare and cancer risks were unclear. However, declining genetic testing costs due to next-generation sequencing (NGS) technology have revolutionized genetic testing practices through development of multi-gene tests that include *BRCA*, *PALB2*, and multiple other genes in one test. As a result, individuals are increasingly being identified with *PALB2* mutations.

The recent *NEJM* article is the first to broadly address the absolute risk of breast cancer in *PALB2* carriers. This international study was based on 154 families with *PALB2* mutations, including 311 women and 51 men. In this study, breast cancer risk estimates in those with *PALB2* mutations: 1) ranged from 33-58% by age 70 in women depending on family history; and 2) were just over 8-fold in men (although results did not reach statistical significance). Results also suggested that women with a *PALB2* mutation were slightly more likely to develop triple negative breast cancer, which is an aggressive type of breast cancer resistant to hormone treatment with a higher chance of recurrence.

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"Since the *BRCA1* and *BRCA2* genes were discovered in the mid-90s, no other genes of similar importance have been found. *PALB2* is a potential candidate to be '*BRCA3*'. As mutations in this gene are uncommon, obtaining accurate risk figures is only possible through large international collaborations like this" said lead author of the study, Dr. Marc Tischkowitz from the Department of Medical Genetics at the University of Cambridge, "Now that we have identified this gene, we are in a position to provide genetic counseling and advice. If a woman is found to carry this mutation, we would recommend additional surveillance, such as MRI breast screening."

PALB2 stands for "partner and localizer of BRCA2" and is located on chromosome 16.

Interestingly, *PALB2*-associated cancers may be sensitive to a new class of drugs known as PARP inhibitors, which are currently under investigation for *BRCA*-associated cancers. Thus it is possible that these drugs may also work in *PALB2*-associated cancers.

There are early suggestions that women with *PALB2*-associated breast cancer may develop more aggressive disease.[2] However, most studies are based on small numbers, thus it remains important to study breast cancer characteristics and outcomes in *PALB2* carriers through larger studies. Only through these types of research efforts will we be able to learn more about this important gene and figure out how to better help those with mutations. As outlined on page 1 of this newsletter, we are currently recruiting 500 *PALB2* mutation carriers to determine breast cancer characteristics and outcomes.

1. Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. New England Journal of Medicine. Aug 7 2014; 371(6):497-506.

2. Heikkinen T, Karkkainen H, Aaltonen K, et al. The breast cancer susceptibility mutation PALB2 1592delT is associated with an aggressive tumor phenotype. Clinical Cancer Research. May 1 2009; 15(9):3214-3222.

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Breast cancer risks and outcomes among women with a PALB2 mutation

Through a recent study of over 12,000 Polish women with breast cancer, *PALB2* mutations were detected in almost 1%. In this study, about one third of those with a *PALB2* mutation had triple negative (lacking estrogen, progesterone and HER2 receptors) breast cancer and the average age at breast cancer diagnosis was 53.3 years. Breast tumors of 2 cm or larger had substantially worse outcomes (i.e., 32.4% 10-year survival) compared with tumors smaller than 2 cm (i.e., 82.4% 10-year survival).

Overall, the study findings confirm a substantially elevated risk of breast cancer (24-40%) among women with a *PALB2* mutation up to age 75. The five-year cumulative incidence of contralateral breast cancer was 10% among those with a *PALB2* mutation, compared to 17% among those with a *BRCA1* mutation and 3% among those without a mutation in either gene. Survival at 10 years was also worse in women with a *PALB2* mutation at just under 50%, compared to 72.0% among those with a *BRCA1* mutation, and 74.7% among those without a mutation in either gene.

Given a possible association of poorer outcomes among women with breast cancers larger than 2 cm, focused efforts should be made to detect small cancers among women with a *PALB2* mutation through various screening procedures.

Furthermore, as early data suggests women with *PALB2*-associated breast cancer may develop more aggressive disease, it is important to study breast cancer characteristics and outcomes in *PALB2* carriers through larger studies.

"It is important to study breast cancer characteristics and outcomes in PALB2 carriers through larger studies."

Ultimately, personalized treatments may be important for these women, thus it is vital to collect details about pathological features (receptor status), treatment (including chemotherapy regimen) and follow-up. Only through these types of research efforts will we be able to learn more about this important gene and figure out how to better care for those with mutations. As outlined on the last page of this newsletter, we are currently recruiting 500 *PALB2* mutation carriers to determine breast cancer characteristics and outcomes.

3. Cybulski C,et al. Clinical outcomes in women with breast cancer and a PALB2 mutation: a prospective cohort analysis. Lancet Oncol. 2015 Jun;16(6):638-44. PMID: 25959805.