ICARE NEWSLETTER

WINTER 2015

What's Inside?

ICARE Recruitment and Participation Update

Participation in the ICARE initiative continues to expand through referrals, events and active outreach efforts. As of January 2015, there are 1584 participants, including 915 individuals from families with *BRCA* mutations, enrolled in the registry. Participants in ICARE represent 46 U.S. states and the District of Columbia, and 10 countries worldwide. We continue to foster relationships with healthcare providers across the country and hope to maintain our rapid pace of registry growth. We are completing participant research files through the collection of initial and follow-up questionnaires, three-generation family trees, and documentation of genetic test results (as applicable). We appreciate the time our participants have taken to facilitate collection of these materials. The information you provide to the registry is critical to answer important questions about issues faced by those at risk for inherited cancer predisposition. These efforts help us learn how to identify, evaluate and manage those with inherited cancer. If you have not completed your initial or follow-up questionnaire and would like to be sent an additional paper copy or electronic link, contact the study team via phone (813-745-6446) or email ICARE@InheritedCancer.net.

Welcome Message

Upon publication of the 8th issue of our bi-annual ICARE newsletter, we would like to highlight our achievements over the last 5 years, which include: 1) recruitment of almost 1600 individuals to our registry, including nearly 1000 *BRCA* carriers; 2) outreach to approximately 250 healthcare providers across the country; and 3) publication of 18 articles in which data from ICARE participants was included. These articles have contributed to furthering the knowledge about inherited cancer predisposition. The expansion of our efforts has only been possible due to the ongoing involvement of our ICARE participants, for which we are grateful. We strive to "end the cycle of inherited cancer through research, education, and outreach," through this partnership.

Several important advances have been realized over the last few months, including FDA-approval of the first PARP-Inhibitor for select *BRCA* carriers with ovarian cancer (see page 3 for more details), characterization of another important inherited breast cancer gene, *PALB2* (see page 2 for more details), and continued discovery of additional genes associated with inherited colorectal cancer (see page 4 for more details).

Many thanks for partnering with us and continuing to contribute to our efforts. We wish you all the very best in 2015!

Sincerely,

Tuya Pal, MD, FACMG on behalf of the ICARE Team

A New Study Recruiting PALB2 Mutation Carriers

Together with Dr. Marc Tischkowitz, lead author on a recent *New England Journal of Medicine* paper on *PALB2*, Drs. Steven Narod, Kelly Metcalfe and Tuya Pal are in the process of recruiting 500 *PALB2* mutation carriers to determine breast cancer characteristics and outcomes. Only through these types of research efforts will we be able to learn more about this gene and figure out how to help those with mutations.

Please contact us through our website (inheritedcancer.net), email (ICARE@inheritedcancer.net), or phone (813-745-6446) if you have a patient or know someone with a *PALB2* mutation who may be interested in participating in this effort.

PALB2: A Third Important Gene for Inherited Breast Cancer

Marc Tischkowitz, MD

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.

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.

"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'."

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.

"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.

Research and Clinical Updates

The first PARP-Inhibitor to be approved for clinical use in BRCA carriers

More frequently, cancer drugs are being developed to treat tumors based on their molecular make-up. PARP inhibitors are the first class of drugs specifically developed to treat *BRCA*-related tumors through targeting the DNA repair pathway. The PARP Inhibitors target this pathway and cause cancer cells to die while healthy cells are spared.

Although PARP inhibitors were developed almost a decade ago, they were only recently approved for clinical use through the U.S. Food and Drug Administration (FDA) after extensive evaluation through clinical trials. Specifically, the PARP inhibitor called Olaparib (Lynparza) was approved for use in *BRCA* carriers with advanced ovarian cancer treated with three or more prior lines of chemotherapy.

The effectiveness of this PARP inhibitor, Olaparib, was examined in a study of 137 women with *BRCA* mutations and advanced ovarian cancer. Results showed that about a third of patients had partial shrinkage or complete disappearance of their ovarian tumor for an average of 8 months. These findings led the FDA to grant accelerated approval of this drug to treat life-threatening disease (because results of the clinical trial showed likely clinical benefit to patients).

Olaparib constitutes the first of a new class of drugs (i.e., PARP inhibitors) for treating ovarian cancer. This drug serves as an example of how the understanding of the underlying molecular mechanisms by which cancer develops can lead to more personalized and effective treatments.

There are many open clinical trials that continue to evaluate PARP inhibitors to determine: 1) when to start treatment with these agents in ovarian cancer patients; 2) whether they work in other *BRCA*-associated cancers such as breast cancer, pancreatic cancer and prostate cancer (among others); and 3) whether they may also be of benefit to individuals without germline *BRCA* mutations. Thus it is important to continue evaluating these drugs through clinical trials to determine how they may be best used to treat and perhaps prevent cancer.

Ask the Expert

In each newsletter, we give our participants an opportunity to have their genetics and research questions answered by experts. Please send your questions to ICARE@InheritedCancer.net so that we may include responses in future newsletter editions. The following question was addressed to Dr. Steven Narod who is a Tier I Canada Research Chair in Breast Cancer and a senior scientist at Women's College Research Institute in Toronto, Canada. Dr. Narod is a world-leader in the field of breast and ovarian cancer genetics. Over the course of his career, he has profoundly shaped current knowledge about cancer risks, prevention and screening amongst carriers of *BRCA1* and *BRCA2* mutations.

Q. *As a BRCA mutation carrier, how much does Tamoxifen reduce my chance of developing contralateral breast cancer?*

A. Following an initial breast cancer diagnosis in *BRCA* mutation carriers, the annual risk for developing contralateral breast cancer (i.e., breast cancer in the other breast) is 3%.[1] We have mainly relied on studies evaluating contralateral breast cancer risk reduction with Tamoxifen. These studies have suggested that in women with breast cancer and a *BRCA* mutation, Tamoxifen reduces the lifetime risk of contralateral breast cancer by ~50%, particularly among those who still have their ovaries.[3, 4, 5] Only one study to date with fewer than 20 carriers evaluated Tamoxifen for primary breast cancer prevention and showed risk reduction in *BRCA2*; however, risk reduction was not confirmed in *BRCA1* (but it is important to note that this was a small sample size because there might not have been enough women to find an effect).[2] Consequently, Tamoxifen may be considered in *BRCA* carriers with at risk breast tissue, especially among those who are premenopausal and have their ovaries.

More recently, we evaluated how the duration of Tamoxifen use affected contralateral breast cancer risk.[6] We found that the risk of contralateral breast cancer was reduced by about half in those who used Tamoxifen for a short time (less than one year). These results do not imply any changes to the recommended course of Tamoxifen in the context of a breast cancer diagnosis because the primary goal in this situation would be to reduce risk of recurrence. However these results may be relevant for women without a breast cancer diagnosis who are considering Tamoxifen for primary prevention. In these women, consideration of a short course of Tamoxifen may be preferred over the recommended 5-year course, particularly given that many women are reluctant to take the drug because of the fear of side effects.[7]

Ultimately, we urge women to have a balanced discussion of the potential benefits and harms of Tamoxifen with their healthcare providers to enable them to make an informed decision about using this medication.

1. Metcalfe K, et al. *British Journal of Cancer.* Apr 26 2011;104(9):1384-1392.
2. King MC, et al. *Jama.* Nov 14 2001;286(18):2251-2256.
3. Gronwald J, et al. *International Journal of Cancer.*May 1 2006;118(9):2281-2284.
4. Narod SA, et al. *Lancet.* Dec 2 2000;356(9245):1876-1881.
5. Phillips KA, et al. *J Clin Oncol.* Sep 1 2013;31(25):3091-3099.
6. Gronwald J, et al. *Breast Cancer Res Treat.* Jul 2014;146(2):421-427.
7. Cuzick J, et al. *Lancet.* Mar 22 2014;383(9922):1041-1048.

Discovery of New Colorectal Cancer Genes

New inherited cancer genes continue to be discovered with the exciting advances made possible through next-generation sequencing technologies. Recent studies identified that the *POL* genes predispose to inherited colorectal cancer.[1,2,3] In one study, Niemenen and colleagues studied a four-generation family with Lynch Syndrome with no evidence of mismatch repair deficiency.[2] Through various means (including genetic linkage, exome sequencing, tumor studies, and functional investigations), they were able to identify a new gene called *RPS20* which may be the underlying factor predisposing this family to colorectal cancer.

In another study, Palles and colleagues studied three large families with a dominant pattern of inherited colorectal cancer and multiple adenomas through whole genome sequencing.[3] Through these efforts, they identified germline DNA polymerase gene mutations (i.e., *POLE* and *POLD1*) as high penetrance genes predisposing to multiple colorectal adenomas and early onset colorectal cancer. Subsequently, a Dutch study of 1188 patients with familial colorectal cancer and polyposis identified three patients with *POLE* mutations. These patients developed multiple colorectal adenomas, two of whom showed early onset colorectal cancer. Tumors from all three patients were microsatellite unstable and immunohistochemistry showed deficiency of MSH6/MSH2. These findings suggest evaluation of the *POLE* gene in microsatellite unstable colorectal cancers, especially when testing for other established Lynch syndrome gene mutations has not detected a mutation.

These advances serve to highlight the rapid pace at which new cancer genes continue to be identified. In addition to these new discoveries, next-generation sequencing technologies are also expected to make new testing options more quickly available. Consequently, it is important for individuals from high-risk families (particularly those with results that are 'uninformative negative' – i.e., where testing has not yet identified an inherited gene mutation) to periodically ask their healthcare providers whether additional testing options are available for them.

1. Elsayed FA, et al. *European Journal of Human Genetics : EJHG.* Nov 5 2014.
2. Nieminen TT, et al. *Gastroenterology.* Sep 2014;147(3):595-598 e595.
3. Palles C, et al. *Nat Genet.* Feb 2013;45(2):136-144.

Featured Organization

YSC YOUNG SURVIVAL COALITION
Young women facing breast cancer together.

Young Survival Coalition is dedicated to the critical issues unique to young women who are diagnosed with breast cancer. The organization provides resources and support spanning from diagnosis through long-term survivorship, including resource guides to navigate patients through the various stages of a breast cancer diagnosis as follows:

1) Newly Diagnosed Treatment Navigator which helps fight the feelings of fear and isolation that can accompany a diagnosis (www.youngsurvival.org/NDN)

2) What's Next? A Young Woman's Post-Treatment Navigator to help outline what to expect and learn how to manage a "new normal" after initial breast cancer treatment (www.youngsurvival.org/PTN)

3) Beyond 5 Years: A Navigator for Long-Term Survivors, to help manage the issues faced beyond 5 years following diagnosis and treatment (www.youngsurvival.org/LTN)

Highlights of the 2014 NCCN Guidelines Update

Note: To access the full guidelines document, refer to www.nccn.org

A. Genetic/Familial High-Risk Assessment: Breast and Ovarian
   a. For breast cancer screening in *BRCA* carriers, yearly MRI is recommended starting at age 25; mammograms may be considered in instances where MRI is unavailable or individualized based on earliest age of onset in the family. From age 30-75, annual mammogram and breast MRI is recommended. Above age 75, management should be considered on an individual basis.
   b. In male *BRCA* carriers, prostate cancer screening through annual PSA and digital rectal exam starting at age 40 was recommended in *BRCA2* carriers and a consideration in *BRCA1* carriers.
   c. Modifications to TP53 testing and management recommendations
   d. Refinement of screening recommendations in PTEN mutation carriers
   e. Expansion of the multi-gene testing section including considerations when assessing mutations in less characterized genes and general recommendations.

B. Genetic/Familial High-Risk Assessment: Colorectal
   a. Recommendation that tumors from newly diagnosed colorectal cancer patients be screened for Lynch syndrome (called "Universal Tumor Screening").
   b. A new algorithm was created for Routine Tumor Testing Criteria for Lynch Syndrome
   c. Surveillance/Management recommendations were refined by gene for the various Lynch Syndrome genes.
   d. Management recommendations were refined for other inherited colorectal cancers, including Familial Adenomatous Polyposis, Peutz-Jeghers Syndrome, Juvenile Polyposis Syndromes, and Colonic Adenomatous Polyposis of Unknown Etiology.

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