ICARE NEWSLETTER

WINTER 2016

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 2016, there are 1830 participants, including 979 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. In our efforts to complete participant research files we appreciate the time our participants have taken to facilitate collection of initial and follow-up questionnaires, three-generation family trees, and documentation of genetic test results (as applicable).

The information you provide to the registry helps 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

Over the last six months, new information that is highly relevant to individuals with or at risk for inherited cancer predisposition has been generated. In this newsletter, we review the latest data about cancer risks in newer and established inherited cancer genes, highlight new information of relevance when considering treatment for inherited cancer, and go over some of the reasons it is important to share genetic test results with family members. We are always looking for feedback, so please let us know if you have other topics you would like to see in future editions. We remain grateful for your participation in our efforts as we strive to meet our mission to "end the cycle of inherited cancer through research, education, and outreach."

Sincerely,

Tuya Pal

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

The importance of sharing genetic test results with family members…

Once an individual has had genetic testing for inherited cancer predisposition this information could help their close family members. For example, when a *BRCA* mutation or a mutation in another inherited cancer gene is found, it is important for close family members (with or without a diagnosis of cancer) to know so they too can be proactive with cancer risk management and prevention options if they are identified to also have the familial mutation. It is usually up to the first individual in the family identified with a mutation to share their positive genetic test result with their relatives. Unfortunately, prior US-based studies suggest low rates of testing among at-risk family members[1] the reasons for which are unclear, although higher rates of testing among family members were reported in a study conducted in Spain.[2]

It is also important for individuals who are the first person in their family to have genetic testing for inherited cancer and receive a negative result to share their results with family members. This may help to prevent unnecessary testing in the family and/or clarify the meaning of their negative result.

Tools exist to help facilitate sharing of positive test results among family members. These tools include creating a 'family sharing letter' to briefly describe the mutation that was found, what it means, and where relatives can access more information. At the Moffitt Cancer Center, a family sharing letter is given to all patients who are found to carry a mutation seen through our Genetic Risk Assessment Service.

[1]*Barsevick AM et al. J Fam Psychol. 2008 Apr;22(2):303-12. PMID: 18410217.*

[2]*Sanz J et al. Fam Cancer. 2010 Sep;9(3):297-304. PMID: 20091130.*

As an ICARE participant, if you think having this type of letter may help you to share your genetic test results with close family members, please contact our team by email (ICARE@inheritedcancer.net) or phone (813-745-6446) and we would be happy to create a letter for you.

As you already know, sharing up-to-date information about inherited cancers is very important, so we have included some self-addressed postage paid postcards for you to share with your family members, in case they want to learn more about or participate in ICARE.

What is the risk for ovarian cancer among women with mutations in newer ovarian cancer genes?

The most common form of inherited ovarian cancer is due to mutations in the *BRCA1* and *BRCA2* genes, which are present in 10-15% of women with ovarian cancer and lead to an ovarian cancer risk of up to 44% and 27%, respectively. Another set of genes known to raise ovarian cancer risks are the mismatch repair genes (i.e., *MLH1, MSH2, MSH6, PMS2, EPCAM*) which lead to Lynch Syndrome. Mutations in these genes result in a lifetime risk of ovarian cancer in the range of 10-12%.

Technological advances that make it possible to test for multiple inherited cancer genes at the same time have led to the suggestion that 20-25% of women with ovarian cancer may have an inherited mutation in a cancer predisposing gene.[1] There have been several inherited cancer genes identified among women with ovarian cancer (e.g., *RAD51C, RAD51D, BRIP1*), however it has only recently become possible to gather enough information to tell us how high the lifetime ovarian cancer risk may be for women with mutations in some of these genes.

It is important to figure out the level of ovarian cancer risk to determine whether removal of the ovaries for risk reduction is appropriate. Generally, a lifetime risk in the range of ~10% is reasonable to consider risk-reducing salpingo-oophorectomy (i.e., removal of the ovaries and fallopian tubes). The lifetime risk for developing ovarian cancer among women in the general population is between 1-2%.

"It is important to figure out the level of ovarian cancer risk to determine whether removal of the ovaries for risk reduction is appropriate."

Recently published data has provided some clarification of risks for mutations in the ovarian cancer genes outlined in the table, where an association with ovarian cancer has been suspected:

Gene	Risk	Estimated Lifetime Risk by age 80
RAD51C	5-6 fold[2,3,4] to 16 fold[5]	~9%[3]
RAD51D	6-12 fold[4,5,6,7]	10%[7]
BRIP1	3-9 fold[6,8,9]	5.8%[8]
PALB2	Current data fails to clearly support a high risk for ovarian cancer[6,8,10,11]	

This new information will help individuals with mutations in these genes and their providers determine an individualized cancer risk management plan.

[1] *Walsh T et al. Proc Natl Acad Sci U S A. 2011 Nov 1;108(44):18032-7. PMID: 22006311*
[2] *Pelttari LM et al. Hum Mol Genet. 2011 Aug 15;20(16):3278-88. PMID: 21616938*
[3] *Loveday C. Nat Genet. 2012 Apr 26; 44(5):475-6 PMID: 22538716*
[4] *Song H et al. J Clin Oncol. 2015 Sep 10;33(26):2901-7. Epub 2015 Aug 10. PMID: 26261251*
[5] *Pelttari LM et al. J Med Genet. 2012 Jul;49(7):429-32. PMID: 22652533*
[6] *Norquist BM et al. JAMA Oncol. 2015 Dec 30:1-9. PMID: 26720728*
[7] *Loveday C. Nat Genet. 2011 Aug 7;43(9):879-82. PMID: 21822267*
[8] *Ramus SJ et al. J Natl Cancer Inst. 2015 Aug 27;107(11). PMID: 26315354*
[9] *Rafnar T et al. Nat Genet. 2011 Oct 2;43(11):1104-7. PMID: 21964575*
[10] *Kanchi KL et al. Nat Commun. 2014;5:3156. PMID: 24448499*
[11] *Antoniou AC et al. N Engl J Med. 2014 Aug 7;371(6):497-506. PMID: 25099575.*

How much does age at first breast cancer affect the risk of contralateral breast cancer risk in BRCA carriers?

A recently published study of Dutch patients (including 200 *BRCA1* carriers, 71 *BRCA2* carriers, and 6023 non-carriers) showed that the contralateral breast cancer (breast cancer in the opposite breast) risks at 10 years was 21.1% for *BRCA1*, 10.8% for *BRCA2*, and 5.1% for non-carriers.[1] Among *BRCA* mutation carriers, it was important to take age at diagnosis of the first breast cancer into account to refine the 10-year risk of a second breast cancer diagnosis as follows: for those diagnosed at age 40 or younger, risks were 25.5% for *BRCA1* and 17.2% for *BRCA2*; for those diagnosed between 41-49 years, risks were 15.6% for *BRCA1* and 7.2% for *BRCA2*. These findings show that it is important to provide age-specific risk estimates to *BRCA* mutation carriers as part of the counseling process in order for patients to make informed decisions about their cancer risk management.

"…it is important to provide age-specific risk estimates to BRCA mutation carriers as part of the counseling process…"

[1] *van den Broek AJ, et al. J Clin Oncol. 2015 Dec 23.PMID: 26700119.*

Potential Use of PARP-Inhibitors Among Men with Prostate Cancer who Carry a a mutation in BRCA or other DNA-Repair Gene

A recent study published in the New England Journal of Medicine suggests that PARP-Inhibitors may be of potential use in men who are no longer responding to standard treatments and carry either somatic (i.e., tumor) and/or germline (inherited) mutations in DNA-repair genes (i.e., *BRCA1/2*, *ATM*, Fanconi Anemia genes and *CHEK2*).[1] Of 49 men with prostate cancer evaluated through the study, 16 (33%) had somatic mutations in DNA-repair genes. Of these 16 patients, 14 (88%) responded to the PARP-inhibitor drug (Olaparib), including all 7 patients with *BRCA2* mutations (3 with germline mutations and the other 4 with somatic mutations only) and 4 of the 5 *ATM* mutation carriers. These findings further demonstrate the potential importance of PARP-inhibitors among men with DNA-repair gene mutations in their prostate cancers; however, further studies are needed before these drugs can be considered for routine clinical use.

[1] *Mateo J, et al. NEJM. 2015 Oct 29;373(18):1697-708. PMID: 26510020.*

Clinical and Research Updates •

Improving our understanding of cancer risks among individuals with Li-Fraumeni Syndrome

A recent study from France included over 400 patients with Li-Fraumeni Syndrome (all of whom had an inherited *TP53* gene mutation). Cancer types among children and adults differed, with the main cancer types among children being osteosarcomas, adrenocortical carcinomas, central nervous system (CNS) tumors and soft tissue sarcomas; whereas among adults, the main cancer types were breast cancer and soft tissue sarcomas.

The study also evaluated whether the type of mutation was associated with a specific presentation of cancer. What they found was that average age at which cancer presented was substantially lower among those who had a 'dominant negative' missense mutation (21.3 years) compared to those with all types of loss-of-function mutations (28.5 years) or genomic rearrangements (35.8 years). With the exception of children with adrenocortical carcinoma, most affected children had dominant-negative missense mutations.

Among women ages 30 or younger with breast cancer, *TP53* mutations were detected in 6%. Breast cancer pathology reports were evaluated in a group of *TP53* carriers, and showed that 55% were HER2 receptor positive and 37% were triple positive (i.e., ER, PR and HER2 receptor positive). Among women with breast cancer and a *TP53* mutation, the development of contralateral breast cancer (cancer in the opposite breast) was very high at 31% compared to an estimated 10% contralateral breast cancer risk among women in the general population.

"…mutations in TP53 are unexpectedly being identified in individuals without a family history characteristic of Li-Fraumeni Syndrome."

There was a high rate (43%) of multiple primary cancers among *TP53* mutation carriers, the majority of which were cancers that developed following an initial cancer diagnosis. Treatment records were available on a subset of patients who received radiation treatment for their first tumor which showed that 30% developed secondary tumors in the radiation field, within 2-26 years (mean, 10.7 years) following their initial cancer treatment.

With the increasing use of multi-gene tests, mutations in *TP53* are unexpectedly being identified in individuals without a family history characteristic of Li-Fraumeni Syndrome.[2]

Consequently, clinicians and researchers are pursuing efforts to better understand the expanding cancer risks and how cancer presents among some of these individuals who are unexpectedly found to have a *TP53* mutation, which is needed to further tailor their medical care.

[1]Bougeard G et al. J Clin Oncol. 2015 Jul 20;33(21):2345-52. PMID: 26014290; [2]Kamihara J,et al. Hum Mutat. 2014 Jun;35(6):654-62. PMID: 24706533

Ask the Expert

Through 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 by Dr. Christine Laronga at the Moffitt Cancer Center:

Q. *As a BRCA carrier, is it reasonable for me to consider nipple-sparing mastectomy (compared to total mastectomy) to reduce my future risks of breast cancer?*

A. One strategy to manage the high (60-70%) lifetime breast cancer risk among women with a *BRCA* mutation is risk-reducing bilateral total mastectomy (not subcutaneous mastectomy where a rim of breast tissue is intentionally left on the underside of the breast skin to afford a more natural feel to the reconstructed breast). This procedure reduces the risk of developing breast cancer by 90% or more. In the past, the entire breast with the overlying nipple and areolar disk was removed when performing this surgery, but more recently there has been an increase interest in preserving the nipple ("nipple-sparing" mastectomy). For many women, the nipple is what defines the breast as a breast. Prior studies have shown that some patients have psychosocial benefit when the nipple-areolar complex is spared, and for some, the inability to preserve the nipple may be a barrier to even consider mastectomy.

A recent study measured the amount of breast tissue that remains when the nipple is spared with a standard retroareolar margin of 5 mm, and found that this only encompasses 1.3% less of the total at-risk breast tissue among women with *BRCA* mutations.[1] Additionally, two recent studies showed that among *BRCA* carriers with nipple-sparing mastectomy, fewer than 2% developed subsequent cancers and none were in the nipple-areolar complex.[2,3] Furthermore, there was a low rate of complications and no evidence that safety in the cancer setting was compromised. Although there remains a need for studies with a longer follow-up time, currently available information suggests that it is reasonable for women with a *BRCA* mutation to consider nipple-sparing mastectomy for both breast cancer risk-reduction and treatment.

From a surgical standpoint, there are different ways of reducing the amount of remaining breast tissue when performing this surgery. When choosing this surgery, it is important to go to a surgeon who is experienced in this procedure in order to maximize risk reduction and minimize complication rates.

[1]Baltzer HL et al. Ann Surg Oncol. 2014 May;21(5):1583-8. PMID: 24526546 ; [2]Yao K et al. Ann Surg Oncol. 2015 Feb;22(2):370-6. PMID: 25023546 ; [3]Manning AT et al. Br J Surg. 2015 Oct;102(11):1354-9. PMID: 26313374

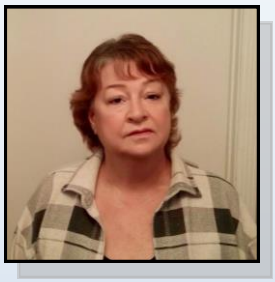
More information about the inherited component of pancreatic cancer…

Although pancreatic cancer is one of the cancer types seen among individuals with mutations in inherited cancer genes (including *BRCA2* and *BRCA1*), the proportion of individuals with pancreatic cancer who have an inherited cause has remained uncertain. To further clarify the role of *BRCA1* and *BRCA2* (*BRCA*), over 300 patients with pancreatic cancer were tested for *BRCA* mutations.[1] *BRCA* mutations were identified in 4.6% of patients, of which almost 80% were in *BRCA2* (with the remainder in *BRCA1*). Many of the patients identified with *BRCA* mutations did not have a strong family history of breast and/or ovarian cancer. Furthermore, individuals of Ashkenazi Jewish ancestry were more likely to have a *BRCA* mutation compared to all others.

More recently, another study tested 96 patients with pancreatic cancer for 22 inherited cancer genes, of which 14 mutations were identified in 13 patients (13.5%).[2] Nine individuals (9.4%) were identified with mutations in established inherited pancreatic cancer genes of varying risks (i.e., *BRCA1*, *BRCA2*, *PALB2*, *MSH6*, and *ATM*). These findings suggest that inherited genes may be a contributing factor in a substantial proportion of individuals with pancreatic cancer. However, more studies are needed to refine the level of pancreatic cancer risk in order to determine who to target for high-risk screening (recognizing that evidence-based screening strategies for the early detection of pancreatic cancer do not currently exist and remain an active area of research). Finally, identification of inherited pancreatic cancer predisposition may contribute to targeted treatment approaches.

[1]*Holter S et al. JCO. 2015 May 4. PMID: 25940717.*
[2]*Hu C,et al. CEBP. 2015 Oct 19. PMID: 26483394.*

Community Spotlight



I was first diagnosed with breast cancer when I was 56 years old. Because of my strong family history of breast cancer, I was referred for genetic counseling and had *BRCA* testing at that time. Recently, I was diagnosed with breast cancer again. When I went to see my surgeon, she advised me to have more genetic testing for inherited breast cancer through multi-gene tests, which were not yet available when I first had my testing. Through this testing, I was found to have a *PALB2* gene mutation, which explains my personal and family history of breast cancer. I recently enrolled in the Inherited Cancer Registry, as I am interested in participating in research in any way that I can to learn more about inherited cancers in people with a *PALB2* mutation.

Mari-Lynn Slayton, ICARE participant

Effort Focused on PALB2 Mutation Carriers through ICARE…

Together with Dr. Marc Tischkowicz, lead author on the recent NEJM 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 are or if you have a patient with a *PALB2* mutation who may be interested in participating in this effort.

Note: For those ICARE participants with a PALB2 mutation, we have already collected much of the information needed from you to contribute to this focused effort. We will inform you of additional information that may be needed for study purposes.

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