ICARE Newsletter

SUMMER 2017

What's Inside?

ICARE Recruitment & Participation Update

Participation in ICARE continues to expand through referrals, events, and active engagement efforts. As of August 2017, there are 2333 participants enrolled in our registry, including 1062 individuals from families with *BRCA* mutations and 352 carriers of other inherited cancer genes. Participants in ICARE represent 46 U.S. states, the District of Columbia, and 13 countries worldwide. Individuals interested in joining ICARE may enroll in the registry online through the ICARE website (InheritedCancer.net) or request a paper enrollment packet by contacting the study team via phone (615-875-2444) or email (ICARE@InheritedCancer.net).

Welcome Message

As we send you our first ICARE newsletter since our relocation earlier this year from Moffitt Cancer Center to Vanderbilt-Ingram Cancer Center, we are pleased to be completely up and running again at our new home in Nashville, where we have been joined by prior and new team members. In setting up our registry at Vanderbilt, we have added features you have requested, including the option to complete everything online. As always, we value your feedback and want to make enrolling and participating in ICARE as easy as possible.

In acclimating to the culture at Vanderbilt and drawing upon the wisdom of our new colleagues, we have come to recognize that "engagement" rather than "outreach" more accurately reflects the bi-directional nature of our efforts. Consequently, we have updated our mission statement as follows: "To end the cycle of inherited cancer through research, education, and engagement".

Within the current newsletter, we have highlighted some of the recent clinical and research advances which demonstrate the rapid pace of scientific developments in the realm of inherited cancer predisposition. These include additional studies about cancer risks among individuals with mutations in inherited cancer genes (including *BRCA* and other genes), as well as recently published data about optimizing cancer risk management among various groups of *BRCA* carriers. Additionally, with the tremendous advances in new oncology treatments, we want to share some recent studies that have demonstrated the benefits of specific targeted treatments among *BRCA* carriers and those with Lynch Syndrome.

We hope this year has treated you well, and we remain grateful to you for partnering with us to end the cycle of inherited cancer through research, education, and engagement.

Sincerely,

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

Breast and Ovarian cancer risks among BRCA carriers followed over time

Findings from an international study of over 6000 women with a *BRCA1* mutation and almost 4000 women with a *BRCA2* mutation followed for an average of 5 years were recently published.[1] Results showed the risk of breast cancer by age 80 was ~70% for both *BRCA1* and *BRCA2* carriers. Rates of breast cancer increased until age 30-40 in *BRCA1* carriers and 40-50 in *BRCA2* carriers, after which they remained constant over time to age 80. Risk of ovarian cancer by age 80 was 44% among *BRCA1* carriers and 17% among *BRCA2* carriers. Among women with a prior breast cancer diagnosis, the risk of developing another new breast cancer in the other breast (called "contralateral breast cancer") after 20 years was 40% for *BRCA1* carriers and 26% for *BRCA2* carriers. Overall, the risk of breast cancer was higher in individuals who had more relatives with breast cancer. Consistent with findings published by Rebbeck et al. in 2015 in JAMA, there were certain locations of the gene mutation that presented a higher risk for breast cancer[2] – specifically, risks of breast cancer were higher for: 1) *BRCA1* if the mutation was outside the region between c.2282-c.4071 and 2) *BRCA2* if the mutation was outside the region between c.2831-c.6401. Ultimately, findings from the current study provide information to better predict cancer risks based on family history and mutation location, which may contribute to developing and improving personalized cancer risk management for women with mutations in these genes.

[1]*Kuchenbaecker et al. JAMA. 2017 Jun 20;317(23):2402-2416. PMID: 28632866.* [2]*Rebbeck et al. JAMA 2015 Apr 7;313(13):1347-61. PMID: 25849179.*

Breast and Ovarian Cancer Associations for Genes Tested through Multi-Gene Panels

As testing for multiple genes at the same time ("multi-gene panel testing") has become increasingly available with tremendous advances in genetic testing technology, it has become critical to evaluate and refine cancer associations and levels of risk for many of these genes now tested. Through a commercial laboratory database of almost 100,000 results of multi-gene panel testing, associations between mutations in specific genes with breast and ovarian cancers were evaluated.[1] Findings indicated that 8 genes were associated with breast cancer and 11 genes were associated with ovarian cancer. Most of the genes associated with breast cancer have previously been confirmed in association with breast cancer, including *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *PTEN*, and *TP53*. An additional newer gene, *BARD1*, was also found to be associated with breast cancer in this dataset, but remains a gene for which data continues to emerge to help determine whether a true association with breast cancer exists. Similarly, for ovarian cancer, most genes identified to have an association were consistent with data from prior studies, including *BRCA1*, *BRCA2*, *BRIP1*, *MLH1*, *MSH2*, *MSH6*, *STK11*, *RAD51C*, and *RAD51D*. Additional genes that were shown to have an association with ovarian cancer in this dataset included *ATM* and *NBN*, however additional research is needed to determine if an association with ovarian cancer truly exists. Ultimately, there remains a great need to continue to evaluate cancer risks for inherited genes for which we have limited information about level of risk and types of associated cancer.

"Findings indicated that 8 genes were associated with breast cancer and 11 genes were associated with ovarian cancer."

"Additional genes that were shown to have an association with ovarian cancer in this dataset included ATM and NBN…"

[1]*Kurian et al. JCO Precision Oncology. 2017 :1, 1-12*

What are new and subsequent cancer risks among patients with Li-Fraumeni Syndrome?

Although individuals with Li-Fraumeni Syndrome (LFS), due to mutations in the *TP53* gene, have a very high lifetime risk of cancer, risks of initial and subsequent cancers are not well defined. Through a group of patients with the classic form of LFS, researchers at the National Cancer Institute estimated their cancer risks.[1] They evaluated a total of 286 individuals with *TP53* mutations from 107 families, and found of women 50% had developed cancer by age 31 and of men 50% had developed cancer by age 46. This suggests that on average women with LFS tend to develop cancer earlier than their male counterparts. For women, cancer risk was the highest after age 20, mainly due to high risks of breast cancer. This differed in men, where the risk was highest in childhood and later adulthood. Among both sexes, almost 100% of individuals had developed cancer by age 70. Cancer risks outlined by type of cancer developed by age 70 among women and men with LFS are shown in the table below.

"This suggests that on average women with LFS tend to develop cancer earlier than their male counterparts."

Cancer Type	Cancer Risks by Age 70	
	Women	Men
Breast cancer	54%	~
Soft tissue sarcoma	15%	22%
Brain cancer	6%	19%
Osteosarcoma	5%	11%

Of individuals who developed cancer, about half went on to develop at least one more cancer after an average timeframe of 10 years. Furthermore, having been diagnosed with one cancer did not lower their risk of developing a subsequent cancer. The new information from this study helps to refine cancer risk estimates among those with LFS, which is needed to guide their cancer risk management strategies.

[1]*Mai et al. Cancer. 2016 Dec 1;122(23):3673-3681. PMID: 27496084.*

New results of a PARP inhibitor study among BRCA carriers with metastatic breast cancer

Over the last decade, a new class of drugs called "PARP Inhibitors" has been evaluated as a form of targeted treatment among *BRCA* carriers. Results were recently reported from a Phase 3 clinical trial among *BRCA* carriers with HER2-negative metastatic breast cancer who received two or less prior chemotherapy regimens for their metastatic disease.[1] Study participants received either the PARP inhibitor (olaparib) or standard treatment, and the primary outcome measured was progression-free survival (i.e. the length of time during and after the treatment where the cancer does not get worse). Of the 302 women who participated in this study, progression-free survival was ~3 months longer among those who received olaparib compared to standard treatment. Side effects from treatment and treatment discontinuation were also lower in the olaparib group. Furthermore, progression of disease or death was 42% lower among those given olaparib. Although no PARP inhibitor is yet FDA-approved for breast cancer, these results demonstrate the type of evidence needed to move a drug from the clinical trials setting to an FDA-approved treatment and highlight the expansion of personalized treatments among *BRCA* carriers.

[1]*Robson et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017 Jun 4. PMID: 28578601.*

Emerging FDA approvals of immunotherapy among patients with metastatic MSI-H cancers

Over the last few years, immunotherapy has emerged as an exciting new class of drugs. As early as 2015, immunotherapy through PD-1 Inhibitors among patients with MSI-H colorectal cancers was shown to be of potential benefit.[1] As many individuals with Lynch Syndrome have cancers that are MSI-H and mismatch repair deficient, this class of drugs was thought to represent a class of 'targeted treatments' for individuals with this syndrome.

More recently, the FDA granted accelerated approval for the use of a PD-1 Inhibitor (nivolumab) for the treatment of patients with MSI-H or mismatch repair deficient metastatic colorectal cancer that has progressed after standard treatment through fluoropyrimidine, oxaliplatin, and irinotecan.[2] The approval was based on results of the Phase II CheckMate-142 trial, where almost a third of patients who received nivolumab experienced some benefit from it.[3] These exciting advances illustrate the expanded treatment options that are being evaluated and approved for those with inherited forms of cancer.

[1]*Le et al. N Engl J Med. 2015 Jun 25;372(26): 2509-20. PMID:26028255.*
[2]*https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-receives-fda-approval-opdivo-nivolumab-ms.*
[3]*Overman et al. Lancet Oncol. 2017 Jun 19. [Epub ahead of print] PMID: 28734759.*

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 such that we may include responses in future newsletter editions. The following question was addressed by Dr. Steven Narod who is a Tier I Canada Research Chair in Breast Cancer and a senior scientist at the Women's College Research Institute in Toronto, Canada. Dr. Narod is a world-leader in the field of breast and ovarian cancer genetics.

Q. In women with a BRCA mutation and ovarian cancer, who might benefit the most from MRI screening or mastectomy?

A. Although risk-reducing mastectomy (RRM) and MRI screening are routinely offered to unaffected *BRCA* carriers, there are limited studies to guide whether those with a history of ovarian cancer would also benefit from RRM or MRI screening. We recently studied this question among 509 *BRCA* carriers with ovarian cancer through our registry database.[1] We found that twenty (3.9%) patients developed breast cancer within the 10 years following their ovarian cancer diagnosis. Through simulation results, we were able to show limited benefit from MRI screening or RRM among most patients. However, our data suggests that women who had already survived 10 years or more following ovarian cancer or those with early stage ovarian cancer (stage I or II) could benefit from MRI or RRM. Based on these findings, we suggest that *BRCA* carriers with an ovarian cancer diagnosis and no prior history of breast cancer may benefit from MRI or RRM when they are 10 years out from their ovarian cancer diagnosis without a recurrence, or if they were diagnosed with early stage ovarian cancer.

[1]*McGee et al. Gynecol Oncol. 2017 May;145(2):346-351. PMID: 28314588.*

Community Spotlight

After a long rainy summer filled with doctor visits, I was finally diagnosed with triple-negative inflammatory breast cancer (TN IBC) at the age of 49. I completed treatment in June 2008 and was grateful to have a new phase to my vocabulary – NED, 'no evidence of disease'. Since there was no cancer history in my family tree, genetic testing was not offered to me. Fast forward to 2013, with a stronger knowledge base of *BRCA* gene testing, my medical team suggested I be tested and I agreed. My test results revealed that I carried a *BRCA1* mutation, which meant that my children could have the gene as well. I strongly feel that any tool that can be of help to my family to be educated is important, as well as helping medical advancement. This testing could let my children and grandchildren know if they are at risk for breast and ovarian cancers. My three daughters subsequently had testing and my oldest daughter, Natalie, was also found to have this mutation. As Natalie has so eloquently stated after finding out, "I'm glad I'm armed with this knowledge so I can make informed decisions." [https://www.theibcnetwork.org/moms-daughters/]

After my diagnosis of IBC, I was shocked at how little information was available regarding this type of breast cancer, and even more shocked at the lack of research and education considering it was first written about in the 1800's. I formed the IBC Network Foundation, to encourage education and fund research for this orphaned form of breast cancer. I am pleased that we have managed to put almost 1 million dollars to research in five years. Our impact is now global, as we also have a sister charity in the UK funding research.

Vanderbilt is a leading cancer center, but I became familiar with some interest in TN IBC over a chance meeting with some researchers at a conference. I was pleased to see their passion and therefore saw the need for funding. Our foundation has committed to funding TN research at Vanderbilt.

Upon learning about the Inherited Cancer Registry (ICARE) based at Vanderbilt, I was excited to join to contribute to the research mission, as well as being given the opportunity to receive regular research and clinical updates. As much as it might seem frightening to some to join a registry like this, I am grateful for the opportunity to help pay it forward by supporting inherited cancer studies in the hopes we can all live well and have long healthy lives. *–Terry Arnold, ICARE Participant*

What are the benefits of adding a mammogram to MRI for breast cancer screening among women with BRCA mutations?

Recently, researchers evaluated the benefit of adding a mammogram to MRI for breast cancer screening among ~2000 women with a *BRCA1* or *BRCA2* mutation.[1] Results indicated that the addition of mammography to MRI did not substantially raise the chance of detecting breast cancer in the overall group. However, one-third of breast cancer cases diagnosed among women age 40 and below with a *BRCA2* mutation were detected by mammograms alone. Consequently, this study suggests a limited benefit from mammography over and above MRI among *BRCA1* carriers, but a potential benefit among *BRCA2* carriers, particularly those at or below age 40. This type of information may eventually help tailor screening approaches among *BRCA* carriers.

[1]*Phi et al. Br J Cancer. 2016 Mar 15;114(6):631-7. PMID: 26908327.*

PALB2 Effort through ICARE

Dr. Metcalfe, together with Drs. Pal, Narod, and Tischkowicz, are recruiting women with *PALB2* mutations to help determine breast cancer characteristics and outcomes. Only through these types of research efforts will we be able to learn more about this gene and determine how to help those with mutations. If you are a *PALB2* carrier, have a relative with a *PALB2* mutation, or are a healthcare provider with a *PALB2* positive patient, please contact the ICARE study team by phone at 615-875-2444 or email at ICARE@InheritedCancer.net.

*Please note **PALB2 mutation carriers who are already enrolled in ICARE**, we have collected much of the information needed from you to contribute to this focused effort, and will inform you if additional information is needed.*

Tuya Pal, MD, FACMG | Anne Weidner, MPH | Ann Tezak, MA, MPH
Cristi Radford, MS, CGC | Steven Narod, MD, FRCPC, FRSC | Georgia Wiesner, MD, MS

Phone: 615-875-2444 | **Email**: ICARE@InheritedCancer.net | **Website**: InheritedCancer.net