ICARE NEWSLETTER

•WINTER 2014•

What's Inside?

ICARE Recruitment and Participation Update

Participation in the ICARE initiative continues to expand through referrals, events and active outreach efforts. There are almost 1400 participants, including almost 900 individuals from families with *BRCA* mutations. Participants in ICARE represent 46 U.S. states and 10 countries worldwide. We continue to foster relationships with healthcare providers across the country and beyond, and hope to maintain our rapid pace of registry growth. We are continually completing research files on our participants 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, which helps us learn how to identify, evaluate and manage those with inherited cancer. We have updated our software to make the online ICARE questionnaires more user friendly and visually pleasing. If you have not completed your initial or follow-up questionnaire and would like to be sent an additional paper copy or electronic link, please contact the study team via phone (813-745-6446) or email (ICARE@InheritedCancer.net).

Welcome

As part of our bi-annual update through the ICARE newsletter, we wanted to inform you of a number of exciting developments that have taken place over the last 6 months. We continue to use the information contributed by ICARE participants to further knowledge about those with inherited cancer predisposition.[1-3] Additionally, the U.S. Preventive Services Task Force (USPSTF) issued guidelines for risk assessment and *BRCA* testing in December 2013.[4] This updated document requires insurance companies to cover *BRCA* testing (i.e., "preventive services") without a co-pay or deductible in those with a family history. This is because the USPSTF guidelines were incorporated into the Affordable Care Act (ACA), which states that health plans must cover services (without deductible or co-pay) that the task force has rated as a Grade A or B recommendation (i.e. which reflects strength of evidence and magnitude of benefit). However there remain serious gaps in these guidelines, as they omit: 1) men, 2) risk assessment and testing for Lynch syndrome, 3) assigning letter grade for screening and prevention (which would document strength of evidence for each available option), and 4) continues not to include cancer survivors with a *BRCA* mutation (who are at risk for other new cancers and could benefit from cancer prevention options). Therefore, although these guidelines represent an improvement over the ones issued in 2005, there remain some gaps in coverage.

A number of other recent events including the Supreme Court overturning gene patents, Hollywood's release of Decoding Annie Parker and Angelina Jolie's announcement, have led to heightened awareness of the *BRCA* genes. However a recent study suggests that awareness has not resulted in improved understanding to accurately interpret cancer risks and health implications.[5] Thus there remains a tremendous need to continue educational and outreach efforts.

As we continue to expand our efforts, we sincerely thank you for your continued support for the ICARE initiative – together, we strive to achieve our mission to "*end the cycle of inherited cancer through research, education and outreach*."

Sincerely,

Tuya Pal, MD, FACMG

1. Senst N et al. Clin Genet. 2013 Jul;84(1):43-6. PMID: 23066998.
2. Semple J et al. Ann Surg Oncol. 2013 Jun 6. PMID: 23740344.
3. Cragun et al. J Genet Counsel (2013) 22:932, available at http://link.springer.com/article/10.1007/s10897-013-9650-y
4. Moyer, V.A et al. Ann Intern Med 2013 Dec 24: PMID:24366376.
5. Borzekowski, D.L et al. Genet Med (2013) Dec 19: PMID:24357847.

Research and Clinical Updates

Contralateral Mastectomy may improve survival in BRCA mutation carriers

It has been established that women who carry a germline *BRCA* mutation face breast cancer risks of 60-70% in their lifetime. After an initial breast cancer diagnosis, these women face a high risk for contralateral breast cancer. Some women with *BRCA* mutations move forward with contralateral mastectomy when they develop their first breast cancer diagnosis (as part of their breast cancer treatment); however it remains unclear whether contralateral mastectomy reduced the breast cancer-related mortality in these women. Recently, Dr. Kelly Metcalfe published a study[1] based on 390 women with stage I or II breast cancer and a *BRCA* mutation followed for up to 20 years from diagnosis. Of these women, 209 were treated with unilateral mastectomy compared to 181 treated with bilateral mastectomy. Results indicated that women with *BRCA*-associated breast cancer treated with bilateral mastectomy were 48% less likely to die of breast cancer within 20 years of diagnosis than women treated with unilateral mastectomy (even after controlling for age). This is among the largest and longest running studies to evaluate long-term survival of *BRCA*-associated breast cancers, comparing type of surgery at initial diagnosis. Study findings suggest that bilateral mastectomy should be discussed as an option for young women with a *BRCA* mutation and early stage breast cancer. However, despite the long follow-up and large sample size, further research is needed to confirm these findings given the small numbers of "events" (i.e., second breast cancers) in participants. Ultimately, emerging data on personalized chemotherapeutic and biologic treatments for *BRCA*-related breast cancers coupled with study findings suggest that women with newly-diagnosed breast cancer might benefit from the knowledge that they carry a *BRCA* mutation.

"This research highlights the importance of a woman knowing her BRCA status at the time she is diagnosed with breast cancer," says Dr. Kelly Metcalfe, the study's lead author.

1. Metcalfe et al. 2014 BMJ. 2014 Feb 11;348:g226. PMID: 24519767

Tamoxifen may reduce contralateral breast cancer risk in BRCA carriers

There have been suggestions that Tamoxifen may reduce risks for contralateral breast cancer (i.e., breast cancer in the other breast) in *BRCA* carriers if taken after the initial breast cancer diagnosis, based mainly on retrospective studies. Only one prospective study has looked at this question, and showed that Tamoxifen may be useful in *BRCA2*, but did not find an association in *BRCA1* (however there were less than 20 *BRCA* carriers in this study, which is limiting).[1] More recently, a study led by Australian researchers investigated almost 2500 women based on combined prospective and retrospective data.[2] Although this was a nonrandomized design, the study was able to demonstrate that Tamoxifen use was significantly associated with a reduction in contralateral breast cancer risk in both *BRCA1* and *BRCA2* mutation carriers. These findings suggest that Tamoxifen may be considered for breast cancer prevention in *BRCA* carriers with breast tissue, particularly those who are pre-menopausal and have their ovaries. A balanced discussion of the potential benefits and harms of Tamoxifen enables these women to make an informed decision as to whether they may wish to consider this medication.

"…Tamoxifen use was significantly associated with a reduction in contralateral breast cancer risk in both BRCA1 and BRCA2 mutation carriers."

1. King MC et al. JAMA. 2001 Nov 14;286(18):2251-6. PMID: 11710890.
2. Phillips KA et al. J Clin Oncol. 2013 Sep 1;31(25):3091-9. PMID: 23918944.

Recent evidence to suggest that individuals with germline mutations in the PTEN gene (which leads to Cowden Syndrome) may have higher renal cancer risks

Cowden Syndrome is an inherited condition that leads to higher risks for breast and thyroid cancer, and possibly other cancers.[1] There have been a few recent studies that suggest that this condition also puts individuals at a higher risk for kidney cancer. Specifically, Tan et al[2] reported a lifetime risk of 30.6% (95% CI: 17.8-49.4) for kidney cancer. More recently, two additional studies also suggested higher risks of kidney cancer,[3,4] although not as high as reported in the Tan study. Based on this data, authors of these studies have suggested individuals with Cowden Syndrome might consider yearly renal ultrasounds around the age of 40 (or alternatively, 10 years earlier than the earliest diagnosis in the family).

1. Pilarski R. J Genet Couns. 2009 Feb;18(1):13-27. PMID: 18972196. *2. Bubien V et al. J Med Genet. 2013 Apr;50(4):255-63. PMID: 23335809.*
3. Tan MH et al. Clin Cancer Res. 2012 Jan 15;18(2):400-7. PMID: 2225225 *4. Nieuwenhuis MH et al. Fam Cancer.2013 Aug 11. PMID: 23934601.*

Research and Clinical Updates

We need to improve awareness about clinical trials for Hereditary Cancer!

The process for new drugs to be developed and used takes place over many years (i.e., from discovery of the drug to when it is approved for use by the FDA). Before it can be approved, these drugs need to be tested through clinical trials to make sure that new treatments work as well or better than current treatments. But for this to happen, clinical trials must recruit enough people to make sure that these new drugs work. This issue is particularly important when considering research focused on very specific populations, such as *BRCA* carriers. PARP inhibitor research is a prime example of the long process from discovery to use. This exciting new class of drugs was first discovered in 2005 to target weaknesses of cancer cells in individuals with *BRCA* mutations. Early PARP inhibitor clinical trials were small but promising; however almost nine years later, there remain no FDA-approved PARP inhibitors available for standard clinical use outside of clinical trials. Over the past couple of years, there have been renewed efforts to study these drugs. Currently, a number of large PARP inhibitor clinical trials are accruing patients. However, because these trials are based at a select number of centers, it has become critical to raise awareness for all patients who may be eligible (including *BRCA* carriers treated for cancer at centers that may not have a PARP trial for which they may be eligible). To address this issue, FORCE (the *BRCA* Patient Advocacy and Support Organization) is developing a clinical trials tool to aid *BRCA* carriers in searching for PARP trials for which they may be eligible, which is anticipated to be completed in March. In the meantime, FORCE lists many of these trials on their website (available at: http://www.facingourrisk.org/information_research/other_studies.php).

This issue is particularly important when considering research focused on very specific populations, such as BRCA carriers.

Ask the Expert

Through each newsletter, we give our participants an opportunity to have their questions answered by topic experts. Please send your questions to the study team via email (ICARE@inheritedcancer.net) so that we may include responses in future newsletter editions. The following question was addressed by Dr. Laronga who is a breast surgeon based at the Moffitt Cancer Center:

Q. What are the risks of breast cancer after ovarian cancer in BRCA carriers? What risk management options are recommended?

A. *BRCA* carriers remain at a higher risk of breast cancer, even after having ovarian cancer; yet there is little information as to how high this risk might be. Recently, a study of women with ovarian cancer and a *BRCA* mutation who were followed up for an average of almost six years showed that ~10% went on to develop breast cancer.[1] Thus, most women (i.e., ~90% or higher) did not develop breast cancer, even when looking at 10-year survival rates. The risk of breast cancer in women with ovarian cancer was actually lower than in *BRCA* carriers without ovarian cancer. Study authors suggest that non-surgical management of breast cancer risk may be appropriate for these women. At Moffitt, ovarian cancer survivors with *BRCA* mutations are generally offered breast cancer screening recommended by the National Comprehensive Cancer Network (NCCN).[2] In addition, these women are offered consultation with a breast surgical oncologist to discuss prophylactic mastectomy after they are cancer-free five years out from their initial ovarian cancer diagnosis.

1.Domchek SM et al. Risk of metachronous breast cancer after BRCA mutation-associated ovarian cancer. Cancer. 2013 Apr 1;119(7):1344-8. PubMed PMID:23165893.
2. NCCN guidelines, 2013 Genetic/Familial High-risk Assessment: Breast and Ovarian. in NCCN Practice Guidelines V.4.2013 edn Vol. 2013 (National Comprehensive Cancer Network, Fort Washington, PA, 2013).

Community Spotlight

My daughter was diagnosed with breast cancer in 2009. She was tested and found to be a *BRCA2* carrier. I also am a *BRCA2* carrier. In November 2011, I was diagnosed with male breast cancer and had a double mastectomy followed by four chemotherapy sessions, which ended in April 2012. I take 20 mg of Tamoxifen daily for follow-up.

On May 16, 2013, an MRI guided prostate biopsy was performed after I had two high PSA readings of 5.1 and 5.8. Cancer was found in a few areas and I was told that my Gleason score was 8, which means that it was aggressive. I then elected to have a DaVinci Robotic Prostatectomy, which was done in July 2013. The follow-up pathology showed all negative margins and the lymph nodes showed to be negative as well, so my doctors believe that they got all the cancer.

Mr. Taylor (center) with his wife of 47 years and their children and grandchildren

I was prompted to write this because of the recent article in the Summer 2013 ICARE newsletter about male *BRCA* carriers having poorer outcomes from prostate cancer. In my case, as a *BRCA* carrier, I fit your profile of having an aggressive form of prostate cancer when I was first diagnosed. I feel this is an eye-opener for many men with *BRCA* mutations who would never think they could get multiple cancers, especially breast cancer. I want people to know: **you can elect to be a survivor**."

- Gene Taylor, Cancer survivor

Plug-in to ICARE

Check out our new website:
www.InheritedCancer.net

Please check out our new website! Through our website, you can submit questions or request information about the registry by submitting an online contact form. Alternatively, you can always email the ICARE study team if you have any comments or questions.

Our new study team email address is:
ICARE@InheritedCancer.net

Featured Organization

FERTILE ACTION

Helping women touched by cancer become mothers

Fertile Action helps women touched by cancer become mothers through education, advocacy and financial aid for fertility preservation, sperm donation, egg donation, surrogacy and long-term storage of sperm, oocytes, and embryos. - See more at: www.fertileaction.org.

Registration for the 8th annual Joining FORCES conferences is now open and can be accessed at the following link:
http://www.facingourrisk.org/conference

Contributors

Tuya Pal, MD, FACMG
Emily Robinson, MPH
Lucia Camperlengo, MPH
Christine Laronga, MD
Kelly Metcalfe, PhD, RN

Contact Us

Phone: 813-745-6446 *Fax:* 813-449-8403
Toll Free: 1-800-456-3434 ext. 6446
Email: ICARE@InheritedCancer.net
Website: www.InheritedCancer.net
Facebook: www.facebook.com/ICAREatMoffitt