ICARE NEWSLETTER

SUMMER 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 over 1400 participants, including almost 900 individuals from families with *BRCA* mutations, enrolled in the registry. 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. These efforts help 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. 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

As part of the updates we provide through our bi-annual ICARE newsletter, we wanted to outline some exciting recent advances. We continue to use the information provided by ICARE participants to further our knowledge about inherited cancer predisposition.[1,2,3,4,5] An article which included ICARE participants published earlier this year suggested that in *BRCA1* carriers, the risk of breast cancer at an early age may be influenced by the age and duration of use of oral contraceptive pills (further details of that study are included on page 2).[2] Another study which included ICARE participant data reported that removal of the ovaries in *BRCA* carriers results in an 80% reduction in ovarian cancer risk as well as a 77% reduction in overall mortality (further details of study are included on page 3).[3]

As our efforts continue to expand, together we will meet our mission to "end the cycle of inherited cancer through research, education, and outreach." Again, we thank our ICARE participants for contributing to our research efforts, and helping to advance our knowledge about inherited cancer predisposition.

Sincerely,

Tuya Pal, MD, FACMG

1. Phelan CM et al. Br J Cancer. 2014 Jan 21;110(2):530-4. PMID:24292448.
2. Kotsopoulos J et al. Breast Cancer Res Treat. 2014 Feb;143(3):579-86. PMID: 24458845.
3. Finch AP et al. J Clin Oncol. 2014 May 20;32(15):1547-53. PMID: 24567435
4. Cragun D et al. Genet Med. 2014 Jun 12. PMID: 24922460.
5. Gronwald J et al. Breast Cancer Res Treat. 2014 Jun 21. PMID: 24951267.

Welcome Back!

We are excited to welcome back Courtney Lewis to the ICARE team. Before she left to pursue her master's degree in genetic counseling at the University of Cincinnati in 2012, Courtney was the lead study coordinator for ICARE. Upon her recent graduation, she returned to the Moffitt Cancer Center where she has taken over as the Outreach Coordinator for ICARE, and is also one of the genetic counselors in the Moffitt Genetic Risk Assessment Service.

Courtney is interested in public health genetics and enhancing the provision of high quality genetic counseling and testing services for inherited cancer susceptibility. As part of her role as ICARE Outreach Coordinator, she helps to develop and sustain partnerships with our many ICARE Partners involved in cancer risk assessment practices. She also assists in the development of ICARE educational tools for our participants and partnering providers.

Research and Clinical Updates

Early results to suggest that PSA screening may help to detect prostate cancer early in men with BRCA mutations

Over the last few years, there have been a number of studies to suggest that men with *BRCA* mutations, particularly *BRCA2*, have a higher risk of developing aggressive prostate cancer. It remains uncertain whether these men might benefit from screening through the prostate-specific antigen (PSA) test. Within the last few years, PSA screening guidelines in the United States were revised, and no longer recommend screening for all men in the general population.[1] However, use of the PSA test in targeted screening for high risk men remains under active study. The initial results from an international study suggested PSA screening may be useful in detecting prostate cancer early among *BRCA* carriers.[2] Specifically, the investigators recruited almost 2500 men, of whom 59 were subsequently diagnosed with prostate cancer (including 18 *BRCA1* carriers and 24 *BRCA2* carriers). Based on a PSA threshold of 3.0 ng/ml, almost half of *BRCA2* carriers who had a biopsy were diagnosed with prostate cancer, which is much higher than the proportions reported when screening the general population for prostate cancer. Most of the men with a *BRCA2* mutation who developed prostate cancer had intermediate- or high-risk disease, which is considered to be clinically important and requires treatment. These preliminary results suggest that targeted PSA screening in *BRCA* carriers may be useful to detect a high proportion of those who develop aggressive prostate cancer.

> ***Most of the men with a BRCA2 mutation who developed prostate cancer had intermediate- or high-risk disease, which is considered to be clinically important and requires treatment.***

1.http://www.uspreventiveservicestaskforce.org/prostatecancerscreening/prostatefinalrs.htm
2. Bancroft et al.Eur Urol. 2014 Jan 15. pii: S0302-2838(14)00004-9. PMID: 24484606

Is breast cancer risk affected by timing of oral contraceptives in BRCA1 carriers?

Although oral contraceptives (OC) reduce the risk of ovarian cancer in *BRCA* carriers,[1] it is possible that they may raise breast cancer risk. Thus it is important to understand whether age at OC use is a factor when determining impact on breast cancer risk. To address this question, a recent study (which included data from ICARE participants) of ~5000 women with *BRCA1* mutations suggested that use of OC before age 25 increases the risk of early-onset breast cancer, and that the risk becomes higher when used for longer periods of time. Two groups were compared (one with breast cancer and one without) to determine whether age at which OC was used impacted breast cancer risk. Among *BRCA1* carriers, breast cancer risk was higher in those who started OC use before age 20 (Odds Ratio (OR): 1.45; 95% CI 1.20; p=0.0001), and also possibly higher in those between ages 20-25 (OR 1.19; 95% CI 0.99-1.42; p=0.06).

> ***These findings suggest that OC use for the purpose of preventing ovarian cancer should be avoided prior to the age of 25.***

Higher breast cancer risk was limited to breast cancer diagnosed before the age of 40. Overall, the authors reported that the risk of early-onset breast cancer increased by 11% with each additional year of OC use when it was started before the age of 20. However, in those diagnosed with breast cancer at or after the age of 40, there was no increased risk of breast cancer based on OC use. These findings suggest that OC use for the purpose of preventing ovarian cancer should be avoided prior to the age of 25.

1.Kotsopoulos J, et al. Breast Cancer Res Treat. 2014 Feb;143(3):579-86. PMID: 24458845.

What are factors that modify cancer risk in BRCA carriers?

Since the discovery of the *BRCA* genes about two decades ago, a number of studies have reported on factors that may modify cancer risks in those who carry gene mutations. Recently, results of previously published studies were collected through a comprehensive literature review to estimate the overall effects of various risk modifiers in *BRCA* carriers.[1] Results suggested that giving birth for the first time at an earlier age was likely protective against breast cancer risk. Regarding ovarian cancer, breast feeding and tubal ligation reduced risks in *BRCA1* carriers, and use of oral contraceptives reduced risks in both *BRCA1* and *BRCA2* carriers. Interestingly, smoking raised the risk of breast cancer in only *BRCA2* mutation carriers. These findings suggest that sufficient information exists on some risk factors, which may be useful when counseling patients about cancer risks or lifestyle factors to modify risks in *BRCA* carriers.

1. Friebel TM, et al. J Natl Cancer Inst. 2014 Jun;106(6). PMID: 24824314.

Research and Clinical Updates

New study to suggest benefits of oophorectomy in BRCA mutation carriers

A recent study published in the Journal of Clinical Oncology reported that prophylactic oophorectomy resulted in reducing the risk of ovarian cancer by 80%, and reduced all-cause mortality by 77%.[1] The authors reported results on almost 5800 women, of whom 186 developed either ovarian, fallopian tube or peritoneal cancer. Women who had bilateral oophorectomy had a hazard ratio of 0.2 (95% CI: 0.13-0.39; p<0.001), meaning that their risk of developing ovarian cancer was reduced by 80% following the preventive removal of the ovaries. The hazard ratio for all-cause mortality to age 70 was 0.23 (95% CI: 0.13-0.39; p<0.001), which means that the risk of dying from any cause was substantially reduced by having the oophorectomy. The finding on all-cause mortality is striking and has important clinical implications. Specifically, these findings suggest the age distribution of ovarian cancers should not be the sole criterion for determining the best age at which to advise preventive surgery of the ovaries in *BRCA* mutation carriers. This is because removal of the ovaries may not just prevent ovarian cancer, but there may be additional benefits (particularly the reduction of breast cancer risk). However, there remain important quality of life issues to consider which need to be balanced with the probable gains in life expectancy. It is also important to note that the study did not uniformly collect information on whether the fallopian tubes were removed along with the ovaries. Nevertheless, it is now clearly evident that for the greatest reduction of ovarian cancer risk, removal of the fallopian tubes along with the ovaries is recommended.

"Our study highlights the importance of research which focuses on understanding the long term implications of this preventive surgery on overall health in young women." says lead author, Dr. Amy Finch.

Furthermore, study findings imply that identifying *BRCA* mutations carriers in countries with limited resources to offer breast MRI screening or bilateral prophylactic mastectomy may still reduce mortality if these patients have access to salpingo-oophorectomy. Ultimately, it remains important to assess the long-term effects of removing the ovaries and fallopian tubes, and continue to work on designing effective treatments and preventive strategies.

1. Finch A et al. J Clin Oncol. 2014 May 20;32(15):1547-53. PMID: 24567435

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. 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, am I at an increased risk for endometrial cancer? Should I have a hysterectomy?

A. Most published studies in *BRCA* mutation carriers have reported that there is not a substantially higher risk of endometrial cancer. In fact, a recent report of 4456 *BRCA* carriers suggested that any increased incidence of uterine cancer among mutation carriers was related to the use of tamoxifen.[1] Results from this study indicated that even with tamoxifen use, the excess risk of endometrial cancer was small, with a 10-year cumulative risk of 2%. It has been suggested that these risks can be further reduced given the option of raloxifene (which does not raise uterine cancer risk) or aromatase inhibitors (which can be used in postmenopausal women for breast cancer prevention). As a result of our current understanding of this topic, I believe that there is no compelling reason to perform a hysterectomy to reduce the risk of uterine cancer in *BRCA* mutation carriers during preventive surgery to remove the ovaries and fallopian tubes. Nevertheless, it is important that the healthcare provider discuss the actual risks with the patients prior to surgery so that they can make a properly informed decision.

1. Segev Y, et al. Gynecol Oncol. 2013 Jul;130(1):127-31. PMID: 23562522.

Is there a higher risk of prostate cancer in individuals with Lynch Syndrome?

Over the last few years, there have been studies to suggest that men with Lynch Syndrome may have a higher risk for developing prostate cancer.[1,2,3,4,5] The results of these studies have differed as to whether there is an association with an aggressive form of disease. For example, some studies report the risk of developing prostate cancer as high as 30% by age 70 with detection of aggressive tumors with a Gleason score of 8 or higher.[3] In contrast, a more recent study suggested a nearly 5-fold increased risk of developing prostate cancer, but these cancers did not appear to occur at an early age nor were they more likely to be the aggressive subtype.[4] Another study found an increased prostate cancer risk, but it was specific to men with *MSH2* mutations,[5] similar to findings of a 10-fold increased risk of prostate cancer in *MSH2* carriers reported in yet another study.[1]

Further studies to clarify the risks of and outcomes from prostate cancer are needed, as the data on prostate cancer risk in men with Lynch Syndrome remain preliminary. Consequently, the 2014 national practice guidelines available through NCCN do not include prostate in the Lynch Syndrome-associated cancers.[6]

1. Barrow PJ et al. Fam Cancer. 2013 Mar;12(1):57-63. PMID: 23054215.
2. Watson P ,et al. Fam Cancer.2005;4(3):245-8. PMID: 16136385.
3. Grindedal EM, et al. Cancer Epidemiol Biomarkers Prev. 2009 Sep;18(9):2460-7. PMID: 19723918.
4: Haraldsdottir S, et al. Genet Med. 2014 Jan 16. PMID: 24434690.
5. Engel C, et al. J Clin Oncol. 2012 Dec 10;30(35):4409-15. PMID: 23091106.
6. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal Cancer. Version 2.2014

Plug-in to ICARE

Remember to visit the ICARE website and Facebook page! Through our website, you can submit questions or request information about the registry by submitting an online contact form, and even see how many participants are enrolled.

Liking ICARE on Facebook will allow you to stay up to date through relevant updates and study progress.

Alternatively, you can always email the ICARE study team if you have any comments or questions.

Website: InheritedCancer.net

Facebook: www.Facebook.com/ICAREatMoffitt

Featured Organization

FORCE
Facing Our Risk of Cancer
EMPOWERED

"New discoveries are made through careful study of different medical options to determine benefits, limitations, and risks compared with current standard care. Participating in research allows people to contribute to medical knowledge and offers the opportunity to receive cutting-edge care."

Use FORCE's new HBOC Study Search Tool to find and participate in research studies focused on hereditary cancers:

http://tinyurl.com/HBOCStudies

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