Advances in preventive and treatment approaches for individuals with Lynch Syndrome

A study of over 1800 individuals with a mutation in one of the Lynch Syndrome genes was recently completed to assess whether aspirin and ibuprofen use may reduce colon cancer risk.[1] Results showed that in those who took aspirin or ibuprofen for between 1 month and 4.9 years, the colon cancer risks were lower than those with less than one month of use. This study provides additional evidence that both aspirin and ibuprofen may be an effective strategy to help reduce colorectal cancer risk among those with Lynch syndrome, where individuals currently rely solely on frequent colonoscopies for risk reduction. We encourage patients to speak with their healthcare provider about this study to determine if the addition of these medications would be right for them.

Pertaining to treatment of colorectal cancers, a new class of drugs that target the immune system (called PD-1 Inhibitors) has been shown to have potential efficacy in colorectal cancers with the MSI-H phenotype. Given that most colorectal cancers in individuals with Lynch syndrome are MSI-H, this drug could potentially represent a targeted treatment for these individuals. However, prior to becoming standard treatment in the clinical setting, clinical trials are needed. These are currently being conducted to evaluate PD-1 inhibitors in individuals with MSI-H colorectal cancers. As clinical trials continue, we will monitor this exciting advancement for individuals with Lynch Syndrome.

"Given that most colorectal cancers in individuals with Lynch syndrome are MSI-H, PD-1 inhibitors could potentially represent a targeted treatment for these individuals."

1. *Ait Ouakrim D et al. Aspirin, Ibuprofen, and the Risk of Colorectal Cancer in Lynch Syndrome. J Natl Cancer Inst. 2015 Jun 24;107(9). PMID: 26109217.*

2. *Xiao Y, et al. The microsatellite instable subset of colorectal cancer is a particularly good candidate for checkpoint blockade immunotherapy. Cancer Discov. 2015 Jan;5(1):16-8. PMID:25583798.*

The PREVENT Trial: A Follow-up Genetic Counseling Intervention

In collaboration with Dr. Kelly Metcalfe at the University of Toronto, we are inviting women with a *BRCA1/2* mutation to participate in a clinical trial which will provide up-to-date follow-up information for cancer risk management through a genetic counselor. For those who meet eligibility criteria, participation involves completion of two questionnaires and a scheduled session over the phone with a genetic counselor.

Please contact Courtney Lewis (the genetic counselor leading enrollment efforts through ICARE) by email (ICARE@inheritedcancer.net) or phone (813-745-6446) if you would like to learn more.

A New Study Recruiting PALB2 Mutation Carriers

Together with Dr. Marc Tischkowitz, senior author on the *New England Journal of Medicine* paper on *PALB2* from August 2014, 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 via 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.

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ICARE NEWSLETTER

• SUMMER 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 August 2015, there are 1738 participants, including 946 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

Tremendous advances continue to be made in the field of inherited cancer predisposition, as we learn more about both established genes such as *BRCA1* and *BRCA2,* as well as newer genes such as *PALB2*. A few of the important advances over the last few months include: 1) how breast and ovarian cancer risks may vary by the location and region of the *BRCA* mutation; 2) further exploration of clinical outcomes of breast cancer among women with *PALB2* mutations; and 3) identification of additional inherited cancer genes. Furthermore, important advances in cancer prevention and treatment among those with inherited cancer predisposition are being made, as illustrated by recently published information relevant for individuals with Lynch Syndrome.

Again, we are grateful to all of you for partnering with us and continuing to contribute to our efforts as we strive to meet our mission to "end the cycle of inherited cancer through research, education, and outreach." Through the ongoing involvement of our ICARE participants and healthcare provider partners, we take part in many regional, national and international efforts to advance the understanding of inherited cancer predisposition.

Sincerely,

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

2015 NCCN Clinical Practice Guideline Update

Breast and Ovarian Management Based on Genetic Test Results[a]

	Recommend Breast MRI[c] (>20% lifetime risk of breast cancer[d])	Recommend RRSO	Discuss Option of RRM
Intervention warranted based on gene and/or risk level	ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53	BRCA1, BRCA2, Lynch syndrome[e]	BRCA1, BRCA2, CDH1, PTEN, TP53
Insufficient evidence for intervention	BARD1, BRIP1	BARD1, BRIP1, PALB2, RAD51C, RAD51D	ATM, BARD1, CHEK2, PALB2, STK11

RRSO: Risk-reducing salpingo-oophorectomy
RRM: Risk-reducing mastectomy
Note: To access full guidelines document, refer to www.nccn.org

[a]Other genes may be included in mutli-gene testing. [b]Intervention may still be warranted based on family history or other clinical factors. [c]See NCCN Guidelines for Breast Cancer Screening and Diagnosis. [d]May be modified based on family history or specific gene mutation. [e]See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

The rapid pace of discovering more inherited cancer genes continues…

Over the last few months, a number of additional genes associated with inherited cancer predisposition have been identified. A few of these genes include: 1) the *RECQL* gene which appears to be another rare gene involved in inherited breast cancer[1]; 2) the *SMAD9* gene associated with hamartomatous polyposis and ganglioneuromas of the intestinal tract[2]; 3) the *FOCAD* gene associated with polyposis and the development of colorectal cancer[3]; and 4) the *Inositol Polyphosphate Multikinase* gene involved in the development of intestinal carcinoids.[4] These newly discovered genes require further study before they can be added to clinical tests widely offered to patients.

Recently discovered genes that have started to be offered through clinical testing laboratories include those associated with colorectal cancers (*GREM1*, *POLD1,* and *POLE*), rhabdoid tumors (*SMARCA4*), and uveal and skin melanomas, as well as other cancers (*BAP1*).

These genes by no means represent a comprehensive list of new inherited cancer genes; rather they serve to highlight the rapid pace at which new cancer genes continue to be identified. We anticipate that next-generation sequencing technologies and new gene discoveries will continue to result in making new testing options more rapidly available. Consequently, it is important for individuals with personal and/or family histories suggestive of inherited cancer, where an underlying genetic reason has not yet been identified, to periodically check in with their healthcare providers to see if additional genetic testing may be available and/or warranted.

1. *Cybulski C et al. Germline RECQL mutations are associated with breast cancer susceptibility. Nat Genet. 2015 Jun;47(6):643-6. PMID: 25915596.*
2. *Ngeow J et al. Exome Sequencing Reveals Germline SMAD9 Mutation that Reduces PTEN Expression and is Associated with Hamartomatous Polyposis and Gastrointestinal Ganglioneuromas. Gastroenterology. 2015 Jun 26. PMID: 26122142.*
3. *Weren RD et al. Germline deletions in the tumour suppressor gene FOCAD are associated with polyposis and colorectal cancer development. J Pathol. 2015 Jun;236(2):155-164. PMID: 25712196.*
4. *Sei Y et al. A Hereditary Form of Small Intestinal Carcinoid Associated With a Germline Mutation in Inositol Polyphosphate Multikinase. Gastroenterology. 2015 Jul;149(1):67-78. PMID: 25865046.*

Breast cancer risks and outcomes among women with a PALB2 mutation

Through a recent study of over 12,000 Polish women with breast cancer, *PALB2* mutations were detected in almost 1%. In this study, about one third of those with a *PALB2* mutation had triple negative (lacking estrogen, progesterone and HER2 receptors) breast cancer and the average age at breast cancer diagnosis was 53.3 years. Breast tumors of 2 cm or larger had substantially worse outcomes (i.e., 32.4% 10-year survival) compared with tumors smaller than 2 cm (i.e., 82.4% 10-year survival).

Overall, the study findings confirm a substantially elevated risk of breast cancer (24-40%) among women with a *PALB2* mutation up to age 75. The five-year cumulative incidence of contralateral breast cancer was 10% among those with a *PALB2* mutation, compared to 17% among those with a *BRCA1* mutation and 3% among those without a mutation in either gene. Survival at 10 years was also worse in women with a *PALB2* mutation at just under 50%, compared to 72.0% among those with a *BRCA1* mutation, and 74.7% among those without a mutation in either gene.

Given a possible association of poorer outcomes among women with breast cancers larger than 2 cm, focused efforts should be made to detect small cancers among women with a *PALB2* mutation through various screening procedures.

Furthermore, as early data suggests women with *PALB2*-associated breast cancer may develop more aggressive disease, it is important to study breast cancer characteristics and outcomes in *PALB2* carriers through larger studies.

"It is important to study breast cancer characteristics and outcomes in PALB2 carriers through larger studies."

Ultimately, personalized treatments may be important for these women, thus it is vital to collect details about pathological features (receptor status), treatment (including chemotherapy regimen) and follow-up. Only through these types of research efforts will we be able to learn more about this important gene and figure out how to better care for those with mutations. As outlined on the last page of this newsletter, we are currently recruiting 500 *PALB2* mutation carriers to determine breast cancer characteristics and outcomes.

Cybulski C,et al. Clinical outcomes in women with breast cancer and a PALB2 mutation: a prospective cohort analysis. Lancet Oncol. 2015 Jun;16(6):638-44. PMID: 25959805.

Location and type of BRCA1/2 mutation may impact breast and ovarian cancer risks

A study of almost 20,000 *BRCA1* carriers and 12,000 *BRCA2* carriers demonstrated differences in breast and ovarian cancer risks depending on the location and type of mutation. Although all regions are associated with increased risk for breast and ovarian cancers among *BRCA1/2* carriers, there were specific regions that were associated with even higher cancer risks. Specifically, within *BRCA1*, there were three breast cancer cluster regions located at: 1) c.179-c.505; 2) c.4328-c.4945; and 3) c.5261-c.5563. There was also an ovarian cancer cluster region from c.1380-c.4062. In *BRCA2*, there were multiple breast cancer cluster regions spanning c.1-c.596, c.772-c.1806 and c.7394-c.8904. There were also ovarian cancer cluster regions located at: 1) c.3249-c.5681, adjacent to c.5946delT (i.e., 6174delT) and 2) c6645-c.7471. Furthermore, nonsense mutations (point mutations resulting in a shorter and unfinished protein product) were associated with earlier age of breast cancer diagnosis and differential breast or ovarian cancer risks for both *BRCA1* and *BRCA2*. Overall, this worldwide effort represents the largest study to date to evaluate breast and ovarian cancer risks by location and type of *BRCA1/2* mutation. Although results suggest variations in risk, these data require validation prior to *BRCA1/2* carriers using the information for cancer prevention decision-making.

"This worldwide effort represents the largest study to date to evaluate breast and ovarian cancer risks by location and type of BRCA1/2 mutation"

Rebbeck TR et al. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. JAMA. 2015 Apr 7;313(13):1347-61. PMID: 25849179.

Ask the Expert

Through each newsletter, we plan to 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, will salpingectomy (removal of the fallopian tubes while keeping the ovaries) lower my risk for developing ovarian cancer?*

A. As many ovarian cancers originate in the fallopian tubes, bilateral salpingectomy has been proposed as a consideration among *BRCA* carriers who are not ready to remove their ovaries.[1] Specifically, bilateral salpingectomy has been suggested as an interim procedure to reduce ovarian cancer risk after childbearing is complete, followed by later oophorectomy (removal of the ovaries). At this time there is no data to prove that salpingectomy reduces ovarian cancer risk among *BRCA* carriers and the benefit is based on theory. In contrast, bilateral salpingo-oophorectomy (i.e., removal of the ovaries and the fallopian tubes) has been shown to reduce the risk of ovarian cancer and of all cause of death dramatically.[2] Bilateral salpingectomy has gained interest because it preserves ovarian function, which prevents premature menopause and its associated adverse effects experienced by some women but it cannot yet be assumed to be equivalent to oophorectomy.

1. *Walker JL et al. Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. Cancer. 2015 Mar 27. PMID: 25820366.*
2. *Finch AP et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014 May 20;32(15):1547-53. PMID: 24567435.*