Hereditary Cancer Research Updates

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Welcome Message

The Risk Factor Study, which involves more than 17,000 international participants, is the largest long-term study of women who carry a BRCA1 or BRCA2 genetic mutation.

The study, which began more than 20 years ago, has significantly increased our understanding of the prevention and management of cancers associated with a BRCA1 or BRCA2 mutation. This has been possible due to the continuing participation of women around the world who complete a questionnaire every two years. With this information, we are now better able to advise women on the effectiveness of various cancer prevention options for breast and ovarian cancer, and we have a better understanding of how to treat BRCA-associated breast cancer to maximize the chance of survival.

More recently, newer cancer causing genes have been discovered including PALB2, CHEK2, and ATM. We recognize the importance of studying the clinical aspects of inheriting mutations in these genes, expanding our research accordingly.

As part of this update, we would like to share some of the most recent research findings that have come from the Risk Factor Study. We thank you for your ongoing participation and look forward to continuing our work with you.

Sincerely,
Dr. Steven Narod, Dr. Kelly Metcalfe, Dr. Joanne Kotsopoulos and Dr. Mohammad Akbari

Dr. Narod, Dr. Metcalfe, Dr. Kotsopoulos, Dr. Akbari

Virtual Hereditary Cancer Series

Join us to connect with and learn from leaders in hereditary breast and ovarian cancer research and treatment.

Register Here.

WITH THE PETER GILGAN CENTRE FOR WOMEN'S CANCERS AT WOMEN'S COLLEGE HOSPITAL, IN PARTNERSHIP WITH THE CANADIAN CANCER SOCIETY

Ultrasound Screening for Ovarian Cancer: Not Effective for Women with a BRCA1 Mutation

A comparison of ovarian cancer mortality in women with BRCA1 mutations undergoing annual ultrasound screening or preventive oophorectomy.

Gynecol Oncol 2019 Nov;155(2):270-274.| *Jacek Gronwald, Jan Lubinski, Tomasz Huzarski, Cezary Cybulski, Janusz Menkiszak, Monika Siołek,Małgorzata Stawicka, Ping Sun, Shana J Kim, Joanne Kotsopoulos, Steven A Narod*

We recently collaborated with our colleagues in Poland to determine if there was a difference in survival for BRCA1 mutation carriers who elected for ovarian cancer screening with ultrasound compared to those women who opted for preventive oophorectomy (removal of both fallopian tubes and ovaries). This study included 1,964 women with a BRCA1 mutation who still had their ovaries. During the follow-up time, 659 had a preventive oophorectomy, and among these women, 1.8% were diagnosed with ovarian cancer either at the time of preventive surgery or after, and there were two deaths. This can be compared to the the 1,196 women who elected for ovarian cancer screening and no preventive surgery, where 6.1% were diagnosed with cancer, and 27 died. There was a 77% reduction in death associated with preventive surgery compared to ovarian cancer screening. Based on the results of this study, we concluded that ovarian cancer screening is not a viable alternative to preventive surgery. **To reduce the risk of death from ovarian cancer, women with a BRCA1 mutation should follow the guidelines to have a preventive oophorectomy between the ages of 35 and 40 years or when childbearing is complete.**

Oophorectomy and its Impact on Depression

Does preventive oophorectomy increase the risk of depression in BRCA mutation carriers?

Menopause 2020 Feb;27(2):156-161.| *Joanne Kotsopoulos, Jacek Gronwald, Jan Lubinski, Jeanna McCuaig, Henry T Lynch, Susan L Neuhausen, William D Foulkes, Jeffrey N Weitzel, Leigha Senter, Nadine Tung, Charis Eng, Beth Karlan, Ping Sun, Steven A Narod, Hereditary Breast Cancer Clinical Study Group*

Early surgical menopause due to removal of the ovaries has been shown to increase the risk of depression and anxiety among women in the general population; however, the impact in women with a BRCA1 or BRCA2 mutation is not known. In a recent study, we compared anti-depressant use among 1,012 women from the "Risk Factor Study" who had no previous diagnosis of cancer. We reported that there was no increase in use of anti-depressants after undergoing preventive oophorectomy. In fact, we found that among women who underwent preventive surgery before the age of 50 years, there was a reduction in anti-depressant use. There was also a decrease in use of anti-depressants among women who started using hormone replacement therapy (HRT) after oophorectomy. Our results were similar when the analysis evaluated the impact of surgery on self-reported depression (rather than antidepressant medication use). **While based on a small number of women, these findings suggest that oophorectomy likely does not increase psychological distress among women at an elevated risk of ovarian cancer.**

International Differences in the Uptake of Cancer Prevention Options

International trends in the uptake of cancer risk reduction strategies in women with a BRCA1 or BRCA2 mutation.

Br J Cancer. 2019 Jul;121(1):15-21 | *Metcalfe K, Eisen A, Senter L, Armel S, Bordeleau L, Meschino WS, Pal T, Lynch HT, Tung NM, Kwong A, Ainsworth P, Karlan B, Moller P, Eng C, Weitzel JN, Sun P, Lubinski J, Narod SA; Hereditary Breast Cancer Clinical Study Group.*

In this study, we reported on the uptake of various cancer risk reduction options in women with a BRCA1 or BRCA2 mutation from 10 countries who were enrolled in the Risk Factor Study. Over 6,000 women were followed for 7.5 years on average. We found that there were differences in uptake of cancer prevention and screening options by country. Across all countries, the uptake of preventive oophorectomy was 65%. In Canada, 72% of the women had a preventive oophorectomy. The lowest rate of preventive oophorectomy was in China (37%) and the highest uptake was in France (83%). For women without a previous diagnosis of breast cancer, 28% elected for bilateral prophylactic mastectomy. The lowest uptake of prophylactic mastectomy was in Poland (4%) and the highest was in the United States (50%). In Canada, 38% of women had a bilateral prophylactic mastectomy. For women without a bilateral prophylactic mastectomy, 88%

had a breast MRI. In Canada, 77% of women had a breast MRI for screening. For Canadian women who had genetic testing in 2009 or later, 86% had a breast MRI, compared to 72% of women who had genetic testing earlier than 2009.

When we compared uptake of cancer prevention options by when a woman had her genetic testing, women who had testing and counselling after 2009 were significantly more likely to elect for both prophylactic mastectomy and prophylactic oophorectomy.

These results suggest that uptake of both preventive oophorectomy and breast MRI is not optimal, especially for women who had genetic testing prior to 2009. It is important for women with a BRCA1 or BRCA2 mutation to be aware of the current guidelines for cancer screening and prevention. This may require specialized follow-up care and return visits with a genetic counsellor.

Low Long-Term Distress Rates in Women with a BRCA1 or BRCA2 Mutation

Predictors of long-term cancer-related distress among female BRCA1 and BRCA2 mutation carriers without a cancer diagnosis: An international analysis.

Br J Cancer 2020 Jul;123(2):268-274. Kelly A Metcalfe, Melanie A Price, Carol Mansfield, David C Hallett, Geoffrey J Lindeman, Angie Fairchild, Joshua Posner, Sue Friedman, Carrie Snyder, Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer; Henry T Lynch, D Gareth Evans, Steven A Narod, Alexander Liede

In a recent international study led by our research group, we reported on levels of distress in women who had been identified with a BRCA1 or BRCA2 mutation. This study included 576 women who never had a previous diagnosis of cancer. The women were from the United States, Canada, the United Kingdom, Australia and from a national advocacy group (FORCE). On average, women had received their BRCA result 5 years previously. Overall, 16% of the women reported moderate or severe cancer-related distress. Distress decreased over time; women who received results more recently had higher levels of distress. Women who had undergone risk-reducing breast and ovarian surgery were much less likely to have moderate or severe cancer-related distress compared to women who had not had risk-reduction surgery. Interestingly, women who were recruited through the online support advocacy group had higher levels of distress compared to women recruited through the genetics clinics. This study suggests that some women will experience distress after receiving positive genetic test results. **However, the majority of women have very low levels of distress in the long-term, especially if they elect for cancer risk reducing surgery.**

The Screen Project: Making BRCA Genetic Testing Accessible to All Canadians

The two most commonly mutated genes for hereditary breast and ovarian cancer are BRCA1 and BRCA2. These genes also contribute to prostate and pancreatic cancers.

In March 2017, **we launched the Screen Project, which offers unrestricted genetic testing for BRCA genes to all Canadian women and men who are 18 years of age or older.** Overall, we tested 1,269 individuals between March 2017 and January 2019. There were 30 individuals identified with a BRCA mutation, 14 in BRCA1 and 16 in BRCA2. This represents 2.4% of the tested individuals. Ten (33%) were men and 20 were women (67%). While 23 of the carriers met the provincial criteria for the BRCA testing, they chose to be tested through the Screen Project mostly due to the ease of access. In a survey we did from participants, of the women with a mutation, 94% were satisfied and would recommend the Screen Project to a friend or a family member.

Of the women without a mutation, 89% were satisfied and would recommend the Screen Project.

Based on the success of the first phase of the Screen Project, we launched the second phase of the project in this summer through the Familial Breast Cancer Research Unit of Women's College Hospital. For Phase II of the study, patients will have access to BRCA1 & BRCA2 testing via Invitae for $250 USD. Upon receipt of results, all patients will have the option to reflex to a larger panel of an additional 43 hereditary cancer predisposition genes. These additional genes come at no additional charge to the patient.

The Screen Project is a Canadian national initiative to make BRCA1 & BRCA2 screening available to all Canadians over 18 years of age at an accessible price. This research study is a great option for patients nationwide who do not meet provincial genetic testing criteria or for recently diagnosed patients who might want to know their BRCA mutation status before starting treatment. **Patients can sign up online at www.thescreenproject.ca and Invitae will ship the saliva kit directly to their address.** The total turnaround time is less than a month and test reports will be available in less than two weeks from the time of receiving saliva samples in the lab. All positive results will be disclosed to the patient via the study genetic counsellor and if appropriate, the patient will be referred to their local genetics clinic for follow-up and management.

ASK A SCIENTIST

Q&A Hormone Replacement Therapy & Breast Cancer

JOANNE KOTSOPOULOS, PHD

Kotsopoulos J, Gronwald J, Karlan BY, et al. Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among BRCA1 Mutation Carriers. JAMA Oncol. 2018;4(8):1059–1065. doi:10.1001/jamaoncol.2018.0211

Dr. Joanne Kotsopoulos is a Scientist with the Familial Breast Cancer Research Unit at Women's College Research Institute, an Associate Professor at the University of Toronto and the Canada Research Chair in Hereditary Breast and Ovarian Cancer Prevention.

Dr. Kotsopoulos directs a wide-range of research initiatives to further our understanding of BRCA-associated breast and ovarian cancer, with the goal of improving health outcomes and identifying risk-reducing strategies.

Q: Is it safe for BRCA1 or BRCA2 mutation carriers to use hormone replacement therapy (HRT) after oophorectomy?

A: Preventive removal of the ovaries and fallopian tubes is strongly recommended to women with a BRCA1 or BRCA2 mutation at a young age to prevent cancer. Unfortunately, this surgery forces many women into surgical menopause, and as a result, many (but not all) will experience various symptoms including hot flashes, sleep disturbances and potentially other health consequences including a decline in bone mineral density. HRT is often recommended to reduce menopausal symptoms associated with oophorectomy among women without a personal history of breast cancer. Among women without a BRCA mutation, HRT has been shown to increase the risk of breast cancer, with a more harmful effect of estrogen+progesterone containing HRT versus estrogen-alone. Given that women with a BRCA mutation also face a very high risk of breast cancer, it is important to evaluate this relationship specifically within this population.

In our study of 872 women with a BRCA1 mutation, we found that overall, use of any type of HRT after preventive oophorectomy did not increase the risk of breast cancer. When we looked at type of HRT, estrogen-only did not increase the risk of breast cancer. There was some evidence that estrogen + progesterone combination HRT may increase the risk of breast cancer; however, the association was not significant and requires additional study in a larger number of women.

Q: Can I use HRT?

A: Whether a woman decides to use HRT is a personal decision and will depend on the severity of her symptoms, age at oophorectomy, whether she has a personal history of breast cancer and if she has also had a hysterectomy (removal of the uterus) or mastectomy. For example, estrogen-only HRT is prescribed to women without a uterus while combination therapy is prescribed to those with a uterus. Importantly, use of HRT or other medications to manage symptoms is something that requires careful clinical management and should be discussed with your doctor. Reassuringly, there are emerging and more novel options for menopause management that are also available that may have less of an impact on breast cancer risk.

Q: What's next?

A: This study only included women with a BRCA1 mutation and we will be conducting a similar analysis among women with a BRCA2 mutation in the near future.

Clinical Showcase – After-Care Clinic

The Familial Ovarian Cancer Clinic (FOCC) and FOCC-Aftercare Clinic at WCH provide expert and evidence-based clinical care for women at elevated risk for hereditary ovarian and fallopian tube cancers. Clinical care includes the full spectrum of gynecologic care: patient-centred contraception counselling, liaison with fertility specialists, counselling on ovarian cancer risk reduction, risk reduction surgery, and menopausal aftercare. Patients seen in the FOCC clinic will be followed until the first post-operative appointment. Any additional follow-up will take place in the FOCC-Aftercare Clinic.

The FOCC-Aftercare Clinic offers services for patients affected by premature menopause or struggling with menopausal symptoms, providing ongoing support for symptom control and health promotion. Patients seen in the FOCC-Aftercare Clinic are monitored for diseases of estrogen deficiency and receive counseling on menopausal expectations. Care plans are catered to individualized needs and built to improve quality of life.

In collaboration with the Department of Gynecologic Oncology at Princess Margaret Hospital, the Women's College Research Institute, and WCH High Risk Breast Clinic, the FOCC-Aftercare Clinic utilizes an interdisciplinary model of care to provide counseling, risk reducing surgery, and comprehensive menopause management to women who are at risk for ovarian or fallopian tube cancer. Our clinic staff currently includes a gynecologic oncologist, two minimally invasive gynecologic surgeons, and a menopause specialist, as well as a full complement of nursing, allied health and administrative support staff. The program is directed by Drs. Bernardini and Jacobson.

Dr. Michelle Jacobson

Dr. Marcus Bernardini

The Risk Factor Study is funded by the Canadian Institutes of Health Research and the Peter Gilgan Centre for Women's Cancers at Women's College Hospital, in partnership with the Canadian Cancer Society.

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