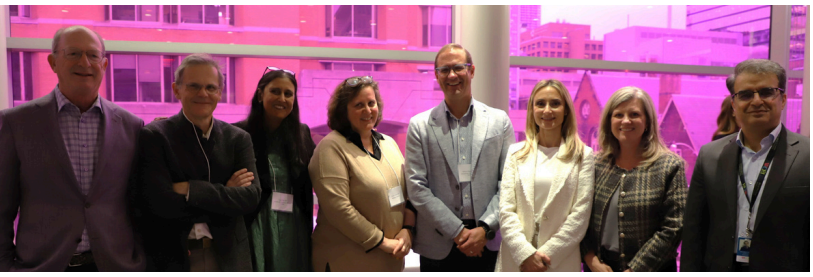
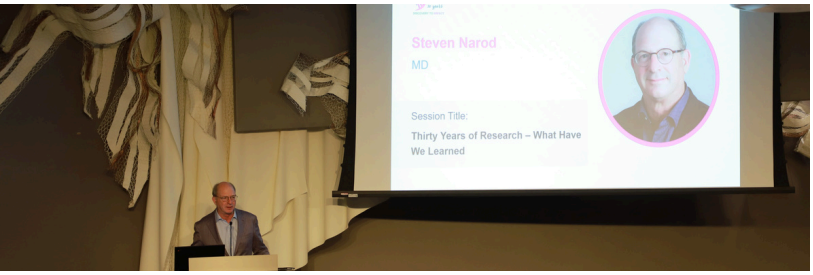
WOMEN'S COLLEGE HOSPITAL HEREDITARY CANCER NEWSLETTER





SPRING 2025 ISSUE

Welcome Message

Dear Research Community,

It's hard to believe that it has been 30 years since the discovery of the *BRCA1* and *BRCA2* genes. In case you were not aware, Dr. Steven Narod was part of the team that made this important medical breakthrough and has continued to make a significant impact on the management of high-risk populations. Since 1994, there have been countless findings stemming from our team, including establishing the effectiveness of cancer risk reduction surgeries and treatment of *BRCA*-associated breast cancer, among many others. Our research has made an enormous impact on cancer prevention, screening and the treatment of women with a *BRCA1* or *BRCA2* mutation and is included in national and international guidelines that inform the care of mutation carriers across the globe. This has all been possible because of your participation in our research. We would like to take this opportunity to thank all of you who continue to contribute to our international program of research. It is because of your ongoing commitment that our team has been able to impact how we can best manage individuals at high risk of cancer.

On November 4 and 5, 2024, we hosted the two-day event From Discovery to Impact: Celebrating 30 Years of *BRCA1* & *BRCA2*. The first day was geared towards researchers & health professionals, while the second day was for patients and the public. Thanks to the support of our distinguished speakers, Women's College Hospital Foundation, our sponsors, AstraZeneca and the Peter Gilgan Centre, and of course, our attendees, the event was a huge success. For more information and to watch event recordings, please visit this page.

Paperless data collection!

In a bid to simplify data collection, we will begin using REDCAP, an online survey and database tool instead of the paper questionnaire you may have filled out in the past. Of course, paper versions will remain available for those who prefer this method. Please make sure the email address we have on file for you is current and keep an eye out for messages from our team.

Medical records requests

Our team will likely continue contacting you for additional information beyond what is collected by our usual research questionnaire. This may include requests to sign a medical release form so that we can better review details collected in pathology records and treatment. Such requests are typical for studies that require us to review medical charts. Many of you have access to these charts making collecting this critical information easier.

Expanding our research interests

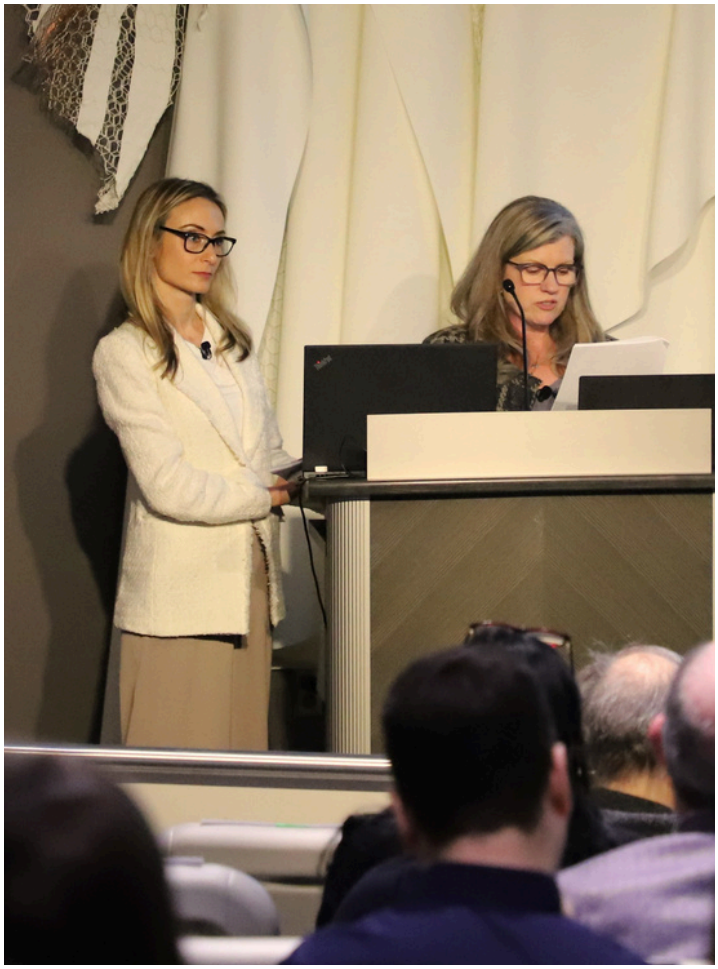
Along with studying *BRCA1* and *BRCA2*, other genes are associated with high cancer risks, such as *ATM* and *PALB2*. We are working to integrate such genes into our established research program to conduct additional studies to better understand the best way to screen, prevent or treat cancers.

As always, we are extremely grateful to our study participants and collaborators for continuing to provide important information through questionnaires and medical record reviews.

This is a critical part of our research program. With this information, we are dedicated to ongoing research to help improve the lives of individuals at high risk of breast and ovarian cancer due to a mutation in a cancer predisposition gene.

Sincerely, and on behalf of our entire team at Women's College Hospital,

Joanne Kotsopoulos & Kelly Metcalfe



MRI Surveillance and Breast Cancer Mortality in Women With *BRCA1* and *BRCA2* Sequence Variations

Breast MRI Screening Reduces Risk of Breast Cancer Death

J Lubinski , J Kotsopoulos, P Moller, T Pal, A Eisen, L Peck, BY Karlan, A Aeilts, C Eng, L Bordeleau, WD Foulkes, N Tung, FJ Couch, R Fruscio, T Ramon Y Cajal, CF Singer, SL Neuhausen, D Zakalik, C Cybulski, J Gronwald, T Huzarski, K Stempa, J Dungan, C Cullinane, OI Olopade, K Metcalfe, P Sun, SA Narod; Hereditary Breast Cancer Clinical Study Group JAMA Oncology 2024 Apr 1;10(4):493-499.

Magnetic resonance imaging (MRI) surveillance is offered to women with a *BRCA1* or *BRCA2* mutation who face a high lifetime risk of breast cancer. Surveillance with MRI is effective at detecting cancers at an earlier stage, but prior to this study, the association of MRI surveillance with breast cancer death had not been well defined. In this study, we compared deaths from breast cancer in women with a *BRCA1* or *BRCA2* mutation who were being screened with breast MRI compared to those who were not having breast MRI. After an average of 9.2 years of follow-up, 14% of the women developed breast cancer, and 1.4% died of breast cancer. For women with a *BRCA1* mutation, having breast MRI significantly reduced the risk of dying of breast cancer by approx. 80%. There was no statistically significant benefit for women with a *BRCA2* mutation. For those who did not have MRI, the risk of dying of breast cancer up to age 75 was 20.5%, compared to 5.5% for those who had MRI surveillance. Results of this study suggest that among women with a *BRCA1* mutation, MRI surveillance was associated with a significant reduction in breast cancer death compared with no MRI surveillance. Further studies of women with *BRCA2* mutations are needed to determine if these women obtain the same benefits associated with MRI surveillance.

Bilateral Oophorectomy and All-Cause Mortality in Women With *BRCA1* and *BRCA2* Sequence Variations

Oophorectomy Reduces Risk of Death

J Kotsopoulos, J Gronwald, T Huzarski, P Møller, T Pal, JM McCuaig, CF Singer, BY Karlan, A Aeilts, C Eng, A Eisen, L Bordeleau, WD Foulkes, N Tung, FJ Couch, R Fruscio, SL Neuhausen, D Zakalik, C Cybulski, K Metcalfe, OI Olopade, P Sun, J Lubinkski , SA Narod, Hereditary Breast Cancer Clinical Study Group JAMA Oncol. 2024 Apr 1;10(4):484-492

Removal of both the ovaries and fallopian tubes (oophorectomy) is strongly recommended at age 35 for *BRCA1* and age 40 for *BRCA2* mutation carriers to prevent cancers of the ovary and fallopian tube and to reduce all-cause mortality. In this study, we compared death rates of women with a *BRCA1* or *BRCA2* mutation who had an oophorectomy compared to those who did not have an oophorectomy. Overall, women with an oophorectomy had a 68% reduction in death compared to those who didn't have an oophorectomy. We also estimated the risk of death from any cause to age 75. For women with a *BRCA1* mutation, the risk of death to age 75 for those with an oophorectomy at age 35 years was 25% compared to 62% for those without an oophorectomy.

For women with a *BRCA2* mutation, the risk of death to age 75 for those with an oophorectomy at age 35 was 14% compared to 28% for those without an oophorectomy. The results of this study demonstrate a profound impact of this surgery on the risk of dying in these women. This research confirms the critical role of this surgery in the care of this high-risk population. Our team will continue to study the short and long-term impact of early surgical menopause in *BRCA* mutation carriers and to ensure safe and effective post-surgical management to reduce comorbidities and improve quality of life.

Risk-reducing Mastectomy and Breast Cancer Mortality in Women with a *BRCA1* or *BRCA2* Pathogenic Variant: An International Analysis

Low Risk of Death after Risk Reducing Mastectomy

K Metcalfe, T Huzarski, J Gronwald, J Kotsopoulos, R Kim, P Moller, T Pal, A Aeilts, A Eisen, B Karlan, L Bordeleau, N Tung, O Olopade, D Zakalik, CF Singer, W Foulkes, F Couch, SL Neuhausen, C Eng, P Sun, J Lubinski, SA Narod ; Hereditary Breast Cancer Clinical Study Group British Journal of Cancer 2024 Feb;130(2):269-274.

Risk-reducing mastectomy (RRM) is offered to women with a *BRCA1* or *BRCA2* pathogenic variant. Previous research has shown that this preventive surgery reduces the risk of developing breast cancer However, there was limited evidence that this surgery reduces the risk of dying of breast cancer. In this study, we followed 1654 women with a *BRCA1* or *BRCA2* mutation for an average of six years. Half of these women had RRM, and half did not. Of the 827 women who did not have a risk-reducing mastectomy, 100 (12.1%) were diagnosed with breast cancer, and of these, 7 died of breast cancer. Of the 827 women who had a risk-reducing mastectomy, 20 women (2.4%) were diagnosed with breast cancer (15 of these cancers were found at time of preventive surgery), and two died of breast cancer. For women who had a risk-reducing mastectomy, the probability of dying of breast cancer within 15 years of having the operation was less than one percent. The results of this study confirmed that in women with a *BRCA1* or *BRCA2* pathogenic variant, RRM reduces the risk of breast cancer, and the probability of dying of breast cancer is very low after the surgery.

Incidence of Endometrial Cancer in *BRCA* Mutation Carriers

No Significant Increased Risk of Endometrial Cancer

J Kotsopoulos, J Lubinski, T Huzarski, T Pal, Bychovsky, RH Kim, N Tung, A Eisen, WD Foulkes, CF Singer, A Aeilts, SL Neuhausen, L Bordeleau, B Karlan, R Fruscio, C Eng, O Olopade, D Zakalik, F Couch, RY Cajal, P Sun, J Gronwald, SA Narod. Gynecologic Oncology 2024 Aug 21:189:148-155.

It is important to understand whether an inherited *BRCA* mutation also increases the risk of endometrial cancer as this may have implications regarding surgical prevention, in particular including hysterectomy (removal of the uterus) at the time of preventive salpingo-oophorectomy. There is some evidence to suggest that women with a *BRCA1* mutation may be more susceptible of uterine papillary serous cancer, a less common but more aggressive subtype of endometrial cancer.

However, to date, findings have not been clear. Our team evaluated the lifetime risk of developing endometrial cancer in almost 5,000 women who had a uterus. After following these women for 6.7 years, there were 38 cases of diagnosed and most were the common endometrioid subtype which have a favorable prognosis. The lifetime risk of developing endometrial cancer was similar to estimates observed in the general population. Women with prior tamoxifen use were at a significantly increased risk, but this was expected and is also observed in women without a *BRCA* mutation. These findings were based on a small number of incident cases and require confirmation with additional follow-up of our aging cohort.

Clinical Showcase - Psychosocial Support

The Peter Gilgan Centre for Women's Cancers is a virtual program at Women's College Hospital (WCH), which supports patient-centred cancer care in partnership with the Genetics and Hereditary Breast and Ovarian Cancer Clinic. The Centre draws together excellence in research, clinical care, innovation and education for women's cancers. The psychosocial team includes social worker Luana Pereira and Peer Support and Information Specialist Kate Mlodzik.

Luana Pereira, MA Clin. Psych, MSW, RSW is a registered social worker and experienced psychotherapist specializing in psychosocial oncology. At WCH, she provides counselling and brief therapy to patients at high risk of developing breast or ovarian cancer, newly diagnosed patients, and cancer survivors. She works collaboratively with patients to improve coping with cancer-related stress, including decision-making support, adjusting to a new diagnosis and treatment, managing associated anxiety and depression symptoms, processing changes and navigating challenges that come with a genetic mutation status.

Kate Mlodzik is the Canadian Cancer Society peer support and information specialist. Through her training and lived experience, she supports patients navigating their personal path with a breast cancer diagnosis, genetic mutation discovery and those considering breast reconstruction.

Luana and Kate collaborate to support patients and facilitate several psychosocial support initiatives together. Their virtual programs are award-winning and have received excellent participant feedback. These programs include a virtual peer support group for genetic mutation carriers (SPARK), a bi-annual breast reconstruction workshop, and an annual breast reconstruction conference. For more information on our program, please see our website: https://www.womenscollegehospital.ca/care-programs/peter-gilgan-centre-for-womens-cancers/

Ask a Genetic Counsellor Q&A with Aletta Poll, GC

Aletta was been working in the field of hereditary breast and ovarian cancer genetics for over 20 years. With a specialized Master's in Genetic Counselling from the University of Manchester, she is part of the hereditary breast cancer research team at Women's College Hospital, where she sees patients both clinically and on a research basis. Her focus is on the rapid identification and optimal management of women who carry high-risk mutations.

Why is it important to know if you carry a mutation in a gene like BRCA1 or BRCA2?

Some people (both men and women) are born with a mutation in a cancer protection gene like *BRCA1* or *BRCA2*. These individuals are at higher risk of developing certain cancers in their lifetime, like breast, ovarian, pancreatic, or prostate cancer and can potentially get these cancers at younger ages. In some cases, the cancers can also be of a more aggressive type, like triple-negative breast cancers for female *BRCA1* mutation carriers. Knowing about these risks means that individuals can access better screening, starting at a younger age than the general population. They can also consider options to reduce their cancer risk, either through medications or surgery. If a mutation carrier develops cancer, there may also be targeted therapies they can avail of to help treat their cancer, like *PARP1* inhibitors for breast and ovarian cancers in *BRCA1/2* carriers.

If a mutation is found in an individual, are their family members likely to be carriers?

In most cases, an individual inherits a mutation from one of their parents. This means if someone is found to carry a mutation, typically, their siblings and biological children have a 50/50 chance of having it as well. Predictive genetic testing can be done in adults to find out if they inherited the mutation or not and, consequently, if they are at higher risk of cancer as adults. We call this cascade testing. Both men and women can carry mutations, though men may have a lower chance of developing cancer, depending on the gene. Whether a person develops cancer or not, if they genetically carry a mutation, they can pass it on. Not only are immediate family members at risk of being carriers, but so are more distant relatives - like aunts, uncles, cousins etc. It is also helpful to know whether a person inherited the mutation from their father or mother, as that lets us know which side of the family may have the same mutation. If it is not possible to know which side of the family the mutation came from, then we recommend predictive cascade testing on both sides.

How can relatives access genetic testing?

In Canada, any adult who is at risk of carrying a hereditary cancer gene mutation due to the detection of such a gene in a blood relative is **eligible to have predictive genetic testing for free**. To get tested, they simply need to be referred by their family doctor to their local genetics clinic. A list of cancer genetics clinics in Canada can be found here: https://www.cagc-accg.ca/

How do I tell my relatives that I'm a mutation carrier?

Once a person is found to carry a *BRCA1/2* mutation or any other hereditary cancer gene mutation, we strongly encourage them to tell their relatives, both close and distant. Not all relatives may choose to pursue testing, but we think it is important for them to know about the possible risks. It can seem daunting to share this type of information, but it can be empowering. To help share information about genetic risk, many clinics can provide the carrier with a Family Member letter that explains about the gene and risks. They can send this letter to relatives.

Don't relatives usually know about their chance of having a mutation?

In our experience, relatives – especially distant relatives – often do not know about their risk of carrying a *BRCA1/2* or other gene mutation. To help find ways of making it easier to share this information, we are starting a study called: Facilitating Cascade Genetic Testing Study (Cascade Study). Find out more about this exciting study and how to participate in section V of this newsletter, Active Research Studies. We hope that by making it easier to share mutation risk information we will help save lives.

Active Research Studies

We are currently enrolling participants for the following research initiatives. Please feel free to share this information with others who may be interested in taking part.

Living as a *BRCA* mutation carrier & options for managing your cancer risk

Women with a *BRCA1* or *BRCA2* mutation are at higher risk of developing breast and ovarian cancer compared to women in the general population. There are options available to women to help reduce or manage these risks, including preventive surgery and screening.

To better understand the cancer prevention decisions that women make, we are conducting a study to investigate why women choose the cancer management options they do, and what factors influence their decisions. This information will help in understanding why there are differences in the uptake of cancer preventive and screening options and help improve the clinical care of this high-risk group.

Eligibility criteria:

- You have received genetic testing results indicating an inherited mutation in either the *BRCA1* or *BRCA2* gene
- You must be at least 18 years of age
- You do not have a prior diagnosis of ovarian cancer
- This study is voluntary, and you can withdraw at any time.

What does participation entail?

Participation requires the completion of a short, online, easy-to-use survey. The study survey collects demographic and medical information and may require completion annually. This survey will take 15-20 minutes of your time. Upon completion of the survey, you will receive a gift card to thank you for your participation.

To learn more, please visit https://www.womensacademics.ca/active-studies/living-as-a-brca-carrier-and-the-options-for-managing-your-cancer-risk/

Hereditary Breast Cancer Treatment Study (Treatment Study)

The Treatment Study is an international research study recruiting women with *ATM*, *CHEK2* and *PALB2* mutations who have been diagnosed with breast cancer. Research shows that *ATM*, *CHEK2* and *PALB2* mutations increase the risk of developing breast cancer; however, it is not clear how to best treat or reduce the risk of breast cancer in women with these hereditary mutations. This research study is collecting information about breast cancer diagnosis and treatment using short questionnaires to learn more about breast cancer among women with these mutations. This information will help to determine the best treatment for women with hereditary breast cancer and determine which factors may predict survival. Through a better understanding, we can personalize breast cancer treatment to increase survival and determine how to best manage at-risk family members to detect cancer early or prevent it.

For more information, contact the study team by emailing TreatmentStudy@wchospital.ca or calling 416-323-6400 ext. 2749.

Facilitating Cascade Genetic Testing Study (Cascade Study)

The Cascade Study is recruiting adults with a known *BRCA1* or *BRCA2* mutation and their relatives. The goal of the study is to develop and test a patient-centered digital tool (app) to increase genetic testing in relatives of *BRCA1/2* carriers. Once an individual is confirmed to have a *BRCA* mutation, genetic testing can be offered to their relatives (referred to as cascade testing), where efforts can be targeted at reducing their cancer risks. Participants will be asked to complete a questionnaire and participate in a virtual interview to learn about their needs and preferences for a digital tool to facilitate cascade genetic testing. It's anticipated this digital tool will provide the necessary evidence to create a much-needed resource for patients and their families to identify individuals at a very high risk of developing cancer.

For more information, please check out the study webpage here or contact the study team by emailing CascadeStudy@wchospital.ca or calling 416-323-6400 ext. 2749.

Find more information, including previous newsletters and webinars here:

- https://www.womensacademics.ca/cancer/
- https:/www.womenscollegehospital.ca/care-programs/peter-gilgan-centre-for-womens-cancers/

Find all of our research studies here:

- https://www.womensacademics.ca/active-studies/

Have you moved? Do you have a new phone number or email? Please connect with us to let us know!

narodstudy@wchospital.ca
416-351-3765
@WCHResearch

THE PETER GILGAN CENTRE FOR WOMEN'S CANCERS

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