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Real-world health services utilisation and outcomes after *BRCA1* and *BRCA2* testing in Ontario, Canada: the What Comes Next Cohort Study protocol

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ABSTRACT

Introduction Women who have pathogenic mutations in the *BRCA1* and *BRCA2* genes are at greatly increased risks for breast and ovarian cancers. Although risk-reduction strategies can be undertaken by these women, knowledge regarding the uptake of these strategies is limited. Additionally, the healthcare behaviours of women who receive inconclusive test results are not known. This study protocol describes the creation of a retrospective cohort of women who have undergone genetic testing for *BRCA1* and *BRCA2*, linking genetic test results with administrative data to quantify the uptake of risk-reduction strategies and to assess long-term cancer and non-cancer outcomes after genetic testing.

Methods and analysis Approximately two-thirds of *BRCA1* and *BRCA2* testing in Ontario, Canada is performed at North York General Hospital (NYGH) and Mount Sinai Hospital (MSH), Toronto. We will use registries at these sites to assemble a cohort of approximately 17 000 adult women who underwent *BRCA1* and *BRCA2* testing from January 2007 to April 2016. Trained chart abstractors will obtain detailed information for all women tested over this period, including demographics, personal and family cancer histories and genetic test results. We will link these data to provincial administrative databases, enabling assessment of healthcare utilisation and long-term outcomes after testing. Study outcomes will include the uptake of breast cancer screening and prophylactic breast and ovarian surgery, cancer incidence and mortality and incidence of non-cancer health outcomes, including cardiovascular, osteoporotic and neurodegenerative disease.

Ethics and dissemination This study has been approved by the Research Ethics Boards at NYGH (no 16-0035), MSH (no 13-0124) and Sunnybrook Health Sciences Centre (no 275-2016). We plan to disseminate research findings through peer-reviewed publications and presentations at national and international meetings.

Strengths and limitations of this study

- This cohort will be one of the largest to date of women who have undergone *BRCA1* and *BRCA2* testing.
- Whereas previous studies have largely focused on women with pathogenic mutations, our cohort will include all women tested, including those who received negative or inconclusive results, allowing for the comparison of healthcare utilisation and outcomes between all test result subgroups.
- Through linkage with administrative databases, we will be able to more accurately assess healthcare utilisation and cancer and non-cancer outcomes.
- This study will be limited by the inability to account for certain variables relevant to decision-making, including patient preferences, family planning decisions and breast and ovarian cancer risk factors not captured through chart abstraction or in administrative databases.
- While our study will enable evaluation of the impact of *BRCA* testing on health services utilisation, other important outcomes of testing, such as the psychosocial impact of testing, will not be captured by this study.

BACKGROUND

Up to 20% of women with a family history of breast cancer carry pathogenic mutations in known breast cancer susceptibility genes,[1] most commonly in *BRCA1* and *BRCA2*. Mutations in these genes confer cumulative risks of breast cancer of 72% in *BRCA1* mutation carriers and 69% in *BRCA2* mutation carriers by age 80.[2] Additionally, women with *BRCA1* or *BRCA2* mutations who develop breast cancer have an increased risk of developing contralateral disease, with a 20-year cumulative incidence of contralateral breast cancer estimated at 26%–40%. Pathogenic mutations in *BRCA1* and *BRCA2* also account for most hereditary cases of ovarian cancer—the cumulative risk of ovarian cancer in the general population is 1.3% versus 44% by age 80 in *BRCA1* mutation carriers and 17% in *BRCA2* mutation carriers.[2 3]

Genetic testing for *BRCA1* and *BRCA2* mutations can provide guidance to women at high risk of carrying pathogenic mutations. For women who test positive for germline mutations in the *BRCA1* or *BRCA2* genes, the National Comprehensive Cancer Network (NCCN) guidelines recommend various strategies for breast and ovarian cancer risk reduction, including high-risk breast cancer screening with annual mammography and breast MRI, consideration of prophylactic surgery (bilateral salpingo-oophorectomy (BSO), bilateral prophylactic mastectomy (BPM) or contralateral prophylactic mastectomy (CPM)) and possible chemoprevention.[4] Women who receive negative results are recommended to follow screening guidelines akin to the general population. Individualised recommendations are made for women who receive inconclusive results from testing.

Despite these recommendations, little is known about the health-related behaviours of women after *BRCA1* and *BRCA2* testing. Many studies evaluating the uptake of risk-reducing strategies among women with *BRCA1* and *BRCA2* mutations report results from small cohorts of women or include patients from selected genetics or familial cancer clinics and rely on self-report to ascertain uptake of screening and prophylactic surgery. These methods are prone to selection and recall biases and do not enable a true appreciation for the uptake of risk-reducing strategies. A better understanding of the uptake of breast cancer screening and prophylactic surgery is important because risk-reducing strategies can potentially decrease cancer-related mortality among women with pathogenic *BRCA1* and *BRCA2* mutations. Previous studies have shown that BSO reduces the incidence of ovarian cancer by 80% and the hazard for all-cause mortality by 77%.[5–7] BPM has been demonstrated to reduce breast cancer incidence by 90%–95%.[8] By understanding the real-world uptake of risk-reducing strategies and the factors associated with their use, targeted strategies can be developed to improve uptake among women most likely to benefit from their use.

In addition to a limited understanding of healthcare utilisation after *BRCA1* and *BRCA2* testing, relatively little is known about how prophylactic surgery affects long-term cancer and non-cancer outcomes. Evidence of an overall survival benefit attributable to prophylactic breast surgery is lacking.[8] Quantifying the survival benefit is important in understanding the implications of not undertaking prophylactic surgery and would provide information helpful to patients and providers faced with decision-making after the receipt of a positive *BRCA1* or *BRCA2* test result. Women with *BRCA1* and *BRCA2* mutations who choose to undergo BSO also face specific risks related to the premature oestrogen deficiency induced by surgical menopause. In studies of women in the general population, oophorectomy before age 50 has been linked to cardiovascular and neurodegenerative disease, osteoporosis and increased all-cause mortality.[9–14] These risks may be augmented in women with *BRCA1* and *BRCA2* mutations as they tend to undergo BSO at a young age,[15] often do not receive hormone replacement therapy (HRT)[16] and may be exposed to cardiotoxic chemotherapy.[17] Women with *BRCA1* mutations may also be especially susceptible to the cardiovascular and neurodegenerative effects of early menopause as animal studies suggest roles of *BRCA1* in cardiac remodelling[18] and cognitive function.[19] No previous studies have assessed non-oncologic health outcomes of *BRCA1* and *BRCA2* mutation carriers who undergo BSO.

In Ontario, genetic testing for *BRCA1* and *BRCA2* mutations has been offered since 2001 to women who meet personal or family cancer history criteria. By linking genetic testing data to administrative health data, we can evaluate the uptake of risk-reducing strategies and long-term cancer and non-cancer health outcomes. We, therefore, aim to:

1. develop a cohort of women who underwent *BRCA1* and *BRCA2* testing in Ontario, Canada among whom healthcare utilisation and long-term outcomes can be assessed by linking their genetic testing data with health administrative databases;
2. assess the uptake of breast cancer screening after *BRCA1* and *BRCA2* testing and determine the factors associated with its use;
3. assess the uptake of prophylactic surgical procedures after *BRCA1* and *BRCA2* testing;
4. determine the effects of screening and prophylactic surgery on cancer incidence and mortality, as well as on non-cancer health outcomes.

METHODS AND ANALYSIS

Aim 1: develop a cohort of women who underwent *BRCA1* and *BRCA2* testing in Ontario, Canada

Overview

Beginning in 2001, the Ontario Ministry of Health (MOH) made genetic testing for *BRCA1* and *BRCA2* available to individuals who meet at least 1 of 13 personal or family cancer history criteria (box 1). Additionally, in 2007, Cancer Care Ontario (CCO) developed provincial guidelines recommending that all women with genetic mutations that increase their risk of breast cancer be offered high-risk screening with annual mammography and breast MRI.[20]

Although genetic counselling is geographically distributed, genetic testing is performed at seven designated centres in the province. Approximately two-thirds of all testing in Ontario occurs at two sites: North York General Hospital (NYGH) and Mount Sinai Hospital (MSH), Toronto. This study will use registries at NYGH and MSH to identify all adult women (≥18 years old) who underwent *BRCA1* and *BRCA2* testing between 1 January 2007 and 30 April 2016. We expect to capture approximately 17 000 women tested at NYGH or MSH over this period. We will conduct chart abstraction at testing sites to obtain detailed genetic testing and cancer history data. Information obtained through chart review will be linked to health administrative databases to enable collection

Box 1 The Ontario Ministry of Health criteria for *BRCA1* and *BRCA2* testing. Any individual who meets at least one of the following criteria is eligible for *BRCA1* and *BRCA2* mutation testing

Affected individuals (breast or ovarian cancer)

At least one case of cancer:

- Ashkenazi Jewish and breast cancer <50 years or ovarian cancer* at any age
- Breast cancer <35 years
- Male breast cancer
- Invasive serous ovarian cancer at any age*

At least 2 cases of cancer on the same side of the family:

- Breast cancer <60 years and a first-degree or second-degree relative with ovarian cancer* or male breast cancer
- Breast and ovarian cancer* in the same individual or bilateral breast cancer with the first case <50 years
- Two cases of breast cancer, both <50 years, in first-degree or second-degree relatives
- Two cases of ovarian cancer*, any age, in first-degree or second-degree relatives
- Ashkenazi Jewish and breast cancer at any age and any family history of breast or ovarian cancer*

At least 3 cases of cancer on the same side of the family:

- Three or more cases of breast or ovarian cancer* at any age

Testing for unaffected individuals

- Relative of an individual with a known *BRCA1* or *BRCA2* mutation
- Ashkenazi Jewish and first-degree or second-degree relative of individual with: breast cancer <50 years or ovarian cancer at any age* or male breast cancer or breast cancer at any age, with a positive family history of breast or ovarian cancer*
- A pedigree strongly suggestive of hereditary breast/ovarian cancer, that is, risk of carrying a mutation for the individual being tested is >10%

*Including cancer of the fallopian tubes and primary peritoneal cancer.

of demographic, healthcare utilisation and long-term outcome variables.

Requisition forms and pedigrees

To request *BRCA1* and *BRCA2* testing, genetic counsellors provide a requisition form with testing indication plus a detailed pedigree to the genetic testing site. Chart abstractors will extract demographics, including age at testing and detailed information on race and ethnicity, as well as genetic counselling centre, reason for testing (MOH criterion) and the type of testing ordered, from requisition forms. Test type can include: (1) sequencing of the entire coding region and splice sites of the *BRCA1* and *BRCA2* genes using capillary-based Sanger sequencing, next-generation sequencing or analysis by denaturing high-performance liquid chromatography (DHPLC) and deletion or duplication detection by multiplex ligation-dependent probe amplification (MLPA); (2) familial testing (if a known mutation was previously found in a relative); or (3) founder mutation testing (for three specific mutations most commonly found among individuals of Ashkenazi Jewish descent).

Abstractors will use pedigrees to determine the number and ages of first-degree and second-degree relatives affected by cancer and the types of cancers diagnosed in these relatives. For patients who underwent counselling and cancer treatment at the genetic testing site, additional cancer-related variables may also be available. Where obtainable, pathology reports will be used to extract details on stage, grade, breast cancer laterality and hormone receptor status.

Coding conventions have been developed with a robust plan for abstractor training, including the use of mock charts prior to beginning abstraction. Data will be audited at random intervals to ensure quality and completeness.

Genetic testing reports

Abstractors will use test result reports to determine whether variants were identified in the *BRCA1* and/or *BRCA2* genes. From 2007 to 2016, variants were categorised using the American College of Medical Genetics and Genomics (ACMG) 2007 guidelines,[21] which classify variants into: pathogenic (category 1), likely pathogenic (category 2), variants of uncertain significance (VUS; category 3), likely benign (category 4) and benign (category 5) categories. Abstractors will record the ACMG category of the variant identified. For women who underwent familial testing, variants will be classified as positive (found to carry a known familial risk-increasing variant) and true negative (not found to carry a known familial variant). For women who underwent sequencing or DHPLC/MLPA, variants will be grouped based on an accepted three-tier classification system[22]: (1) positive (a pathogenic or likely pathogenic variant was identified), (2) inconclusive (a VUS was identified) or (3) negative (a likely benign or benign variant was identified). In this context, a negative test result is non-informative as these women may still harbour a risk-increasing mutation in an untested gene. Therefore, both women who receive inconclusive and those who receive non-informative negative test results can have uncertain future cancer risks.

Administrative data

Cancer history and genetic testing data will be linked to health services databases at the Institute for Clinical Evaluative Sciences (ICES). ICES is a not-for-profit research institute that houses Ontario's health-related data, including clinical and administrative data, with records on publicly funded health services for all Ontario residents eligible for universal health coverage since 1986.

Demographics

We will obtain demographic data through various ICES holdings. Vital statistics and postal codes for all Ontario residents who have been insured since 1990 are available through the Registered Persons Database (RPDB). Geographic location will be determined from postal codes and linked to census data to derive socioeconomic

status (in quintiles). The Rurality Index of Ontario, a validated scale (0–100) with 10 components related to population size and density and distance to treatment centres, will be used to classify individuals into quintiles with higher values reflective of more rural communities.[23] The Ontario Marginalization Index (ONMARG), which focuses on both health and social well-being, will also be used. The ONMARG is a validated measure that considers four elements: material deprivation, residential instability, ethnic concentration and dependency.[24] Immigration status is available through the Citizenship and Immigration Canada database.

Comorbidity burden will be ascertained using the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), a repository of data on inpatient hospital stays since 1988, the CIHI National Ambulatory Care Reporting System (NACRS), which provides data on ambulatory and outpatient care received since 2002, and the Same Day Surgery (SDS) database, a collection of records of patients who underwent same day procedures since 1991. Comorbidity burden will be categorised according to the Aggregated Diagnosis Groups of the Johns Hopkins Adjusted Clinical Groups system,[25] which uses both inpatient and outpatient healthcare data and physicians' billings to divide patients into 32 groups; individuals within each group are expected to demonstrate similar levels of healthcare utilisation. Additionally, we will link with the Ontario Mother–Baby Dataset to determine the number of children delivered by women in our cohort.

Cancer history

Cancer history prior to genetic testing will be confirmed using the Ontario Cancer Registry (OCR). The Ontario Cancer Act provides a mandate for CCO to maintain a provincial cancer registry. OCR captures data on all incident cancers, excluding non-melanoma skin cancers, diagnosed in Ontario since 1964, using hospital discharge and day surgery records, pathology reports, records of patients referred to regional cancer centres and death certificates where cancer has been identified as a contributing cause of death. OCR is over 95% complete.[26] OCR will be used to capture cancer diagnoses missed through chart abstraction and diagnoses made after genetic testing.

Healthcare utilisation

Physician services in Ontario are provided through the government-run Ontario Health Insurance Plan (OHIP), which is available to all residents of Ontario. OHIP covers the cost of visits to doctors and other select health-related services. Physician compensation for the provision of OHIP-covered services requires the submission of claims; the OHIP database contains records of all billings since 1991. Uptake of breast cancer screening will be determined by evaluating the frequency and timing of OHIP codes for physician-referred breast MRI and mammography in screen-eligible women without a history of breast cancer. Mailed reminders for screening mammography, which do not require physician referral, may also be provided to women through the Ontario Breast Cancer Screening Program (OBSP), an organised provincial screening programme available to women aged 50–74 years. We will use the OBSP database, which has captured these data since 1990, to supplement screening data ascertained through the OHIP database. In combination with CIHI-DAD/NACRS and SDS, the OHIP database will also be used to assess uptake of prophylactic breast and ovarian surgery.

Characteristics of treating physicians will be extracted from the ICES Physician Database, which has captured data on physicians in Ontario, including demographics, physician specialty, practice type and practice location since 1992.

The New Drug Funding Program (NDFP) database will be used to obtain information on chemotherapy use. The NDFP funds cancer drugs and covers over 90% of adjuvant chemotherapy regimens for breast cancer. The Cancer Activity Level Reporting database, which records patient-level indicators of the quality, cost and performance of cancer treatment systems, will also be used to obtain data on outpatient oncology visits and systemic and radiation treatments.

Cancer and non-cancer health outcomes

Incident cancers occurring during the follow-up period after *BRCA1* and *BRCA2* testing and staging information will be determined through linkage with OCR. Vital statistics for all insured Ontario residents are available through RPDB, enabling determination of overall survival. Cause of death is available through the database of the Office of the Registrar General, which contains data on all registered deaths since 1990, enabling determination of cancer-specific survival.

Using validated algorithms, we will determine the incidence of non-cancer health outcomes that may be associated with early BSO. Specifically, we will assess cardiovascular outcomes, including ischaemic heart disease,[27] congestive heart failure[28] and stroke/transient ischaemic attack[29]; neurodegenerative diseases, such as Alzheimer's disease and/or related dementias[30] and Parkinson's disease[31] and osteoporotic outcomes, including diagnoses of osteoporosis[32] or related fractures (wrist, humerus, hip or vertebral[33]) (online supplementary appendix 1).

Significance

Through the combination of chart abstraction and linkage with administrative databases, we will compile detailed information about women who underwent *BRCA1* and *BRCA2* testing in Ontario. This cohort can then be used to generate more accurate estimates of healthcare utilisation and long-term outcomes following *BRCA1* and *BRCA2* testing, areas in which gaps currently exist in our knowledge. Importantly, our large cohort will allow previously understudied groups, such as those

who receive negative or inconclusive test results, to be followed over time to better understand their healthcare behaviours and outcomes.

Aim 2: assess the uptake of breast cancer screening after *BRCA1* and *BRCA2* testing and determine the factors associated with its use

Breast cancer screening recommendations for women who undergo *BRCA1* and *BRCA2* testing include: (1) annual breast MRI and mammography from age 30 to 69 for women who test positive, (2) biennial mammography beginning at age 50 for women with negative results and (3) individualised screening based on personal and family cancer history for women who receive inconclusive/non-informative negative results.[4 34 35] In an international survey of women with *BRCA1* and *BRCA2* mutations, 30.6% of women without breast cancer reported having undergone at least one MRI and 87.5% reported at least one mammogram; however, wide variation was seen in the use of screening between countries.[36] Other smaller studies evaluating screening practices of women at high risk for breast cancer have relied on interviews conducted on relatively small samples recruited from genetic counselling or testing research programmes.[37 38] The real-world uptake of recommended screening practices among *BRCA1* and *BRCA2* mutation carriers is not known. Additionally, the frequency with which high-risk breast cancer screening regimens are undertaken by women who receive inconclusive or negative results has not been studied.

Analysis plan

We will evaluate screening practices among women without a history of breast cancer at the time of genetic testing. Women who underwent BPM prior to testing will be excluded. Remaining women will be categorised based on test result received (positive, true negative, non-informative negative, inconclusive). We will use the OHIP and OBSP databases to identify breast MRI and mammography. We will then construct multivariable recurrent event regression models to explore the association between rate of screening and test result over time. The mean cumulative function approach will be used to illustrate the mean cumulative number of screens over time for each of the test result groups to assess if uptake varies over follow-up.

Significance

For women at increased risk of breast cancer development, high-risk breast cancer screening can allow for early cancer detection and intervention. Currently, it is unclear how often women with pathogenic mutations in *BRCA1* or *BRCA2* undertake high-risk breast cancer screening. By assessing the frequency of screening, we can determine whether strategies to increase uptake of screening are needed and can also identify subgroups of women with low screening behaviours who would benefit from targeted interventions.

Aim 3: assess the uptake of prophylactic surgical procedures after *BRCA1* and *BRCA2* testing

Owing to the increased risk of ovarian cancer development among women who carry pathogenic *BRCA1* and *BRCA2* mutations, as well as the lack of effective screening strategies, the Canadian and American guidelines currently recommend that BSO be performed by age 35–40 in *BRCA1* mutation carriers and by age 40–45 in *BRCA2* mutation carriers.[4 39 40] Guidelines from the NCCN also recommend that the option of risk-reducing mastectomy be discussed with *BRCA1* and *BRCA2* mutation carriers. The reported uptake of prophylactic surgery among mutation carriers varies widely.[36 41–47] Similar to the literature on screening practices, most studies evaluating the uptake of prophylactic surgery rely on small samples and use surveys to generate estimates, which are prone to biases.

In contrast to recommendations for women with pathogenic *BRCA1* and *BRCA2* mutations, recommendations for women who receive inconclusive/non-informative negative results are made based on personal and family cancer histories; however, recent consensus statements advise against CPM in women with a history of breast cancer who carry a VUS mutation.[48] Prophylactic surgery is not recommended for women who receive true negative results from *BRCA1* and *BRCA2* testing. Previous studies have not evaluated the uptake of prophylactic surgery among these groups in whom the efficacy of prophylactic procedures has not been demonstrated.

Analysis plan

We will evaluate the uptake of BPM among women without a history of breast cancer at the time of genetic testing, uptake of BSO among women without a history of ovarian cancer at the time of testing and CPM among women who develop breast cancer after genetic testing. We will use multivariable regression models to compare the uptake of prophylactic procedures among the various genetic test result groups, adjusting for clustering at the genetic counselling centre level. We will calculate HRs for multivariable regression analyses to determine the independent effects of variables that may be associated with uptake of prophylactic procedures, such as age and parity.

Significance

A better understanding of the proportion of women who use prophylactic surgery, particularly within the *BRCA1* and *BRCA2* negative and inconclusive test result groups, is a vital first step in ensuring that care provided is concordant with current recommendations. There have been no studies demonstrating a survival benefit to prophylactic surgery in women with negative or inconclusive *BRCA1* and *BRCA2* test results. Despite this, some studies have demonstrated a significant uptake of prophylactic surgery in these populations.[42 46 47 49] Surgery carries both immediate risks, as well as potential for long-term complications, including possible detriments to body image and quality of life. Understanding how women use prophylactic

surgery can identify potential targets for counselling and communication to reduce the rate of interventions with limited efficacy in this population.

Aim 4: determine the effect of prophylactic surgery on cancer and non-cancer health outcomes

Prophylactic breast and ovarian surgery are known to reduce cancer incidence. Additionally, two large studies of *BRCA*-positive women have demonstrated significant reductions in all-cause mortality among women who undergo BSO.[7 50] However, the effect of BPM on survival is less clear. Ingham *et al*, the only group to compare overall survival between women who did and did not undergo BPM, were unable to demonstrate a statistically significant improvement in overall survival associated with prophylactic breast surgery (HR 0.25; 95% CI 0.03 to 1.81).[51] Similarly, in a separate study, BPM was not found to significantly improve breast cancer-specific survival (HR 0.29; 95% CI 0.02 to 2.61).[52] Although the point estimates from both studies suggest a potential survival benefit to BPM, the inability to find statistically significant differences is likely attributable to the lack of precision due to small sample sizes.

Additionally, despite the known negative effects of oophorectomy on cardiac,[10] neurological[11 12] and bone health,[13] as well as data from animal studies suggesting a role of *BRCA1* in cardiomyocyte and neuronal function,[18 19] the incidence of cardiovascular, neurodegenerative and osteoporotic disease after BSO has not been studied among the *BRCA* mutation positive population. Given that women with *BRCA1* and *BRCA2* mutations who undergo BSO have surgical menopause induced at a young age relative to natural menopause, the long-term effects of oestrogen deficiency may be especially pronounced in this population, putting these women at high risk for the development of cardiovascular, neurodegenerative and osteoporotic disease. Although women without a history of breast cancer may take HRT to mitigate these effects, uptake is less than 50%,[53] and long-term compliance is likely variable. Women with a history of breast cancer are even less likely to be treated with HRT, as current clinical practice guidelines recommend against its use in this setting.[54]

Analysis

To examine the effect of prophylactic surgery on survival, we will use time-to-event models to compare breast and ovarian cancer-specific and overall survival between women who did and did not undergo prophylactic procedures. For each woman who underwent prophylactic surgery, a matched control will be selected and assigned a dummy date corresponding to the date of surgery to serve as the time from which observation will begin. We will generate separate Cox proportional hazards models for BSO, BPM and CPM. Analyses will be stratified by mutated gene (*BRCA1* vs *BRCA2*) and by test result (positive, true negative, non-informative negative, inconclusive).

To determine whether BSO is associated with cardiovascular, neurodegenerative or osteoporotic disease among *BRCA1* and *BRCA2* mutation carriers, we will generate unadjusted and adjusted incidence rates of each non-cancer outcome per 100 000 person-years and compare incidence rates between women who did and did not undergo BSO. Owing to the high risk of cancer and cancer-related mortality among *BRCA1* and *BRCA2* mutation carriers, we will use Fine and Gray competing risks models to assess the association between BSO and each non-cancer outcome. Analyses will be stratified by mutated gene (*BRCA1* vs *BRCA2*) and breast cancer history (with vs without prior breast cancer).

Significance

Although prophylactic breast surgery is recommended for women who carry pathogenic mutations in *BRCA1* and *BRCA2* as it can reduce the incidence of breast cancer, evidence of a breast cancer-specific or an overall survival benefit to BPM has yet to be demonstrated. Previous studies have been limited by small sample sizes. Without an appropriate quantification of the survival benefit attributable to prophylactic surgery, the implications of forgoing prophylactic procedures cannot be well understood by patients or healthcare providers. To allow for truly informed decisions, these data are required.

In making informed decisions related to BSO, patients and providers need to consider the trade-offs required to obtain known survival benefits. By determining the risk of cardiovascular, neurodegenerative and osteoporotic disease in women with *BRCA1* and *BRCA2* mutations who undergo BSO relative to an age-standardised population who did not undergo BSO, we will provide patients and healthcare providers with information important to decision-making and may identify a need for closer surveillance of *BRCA*-positive women for these complications or a need for strategies targeted at prevention of adverse non-cancer conditions in this population.

Sample size and power

We anticipate identifying approximately 17 000 women who underwent *BRCA1* and *BRCA2* testing during the study period. Based on previous reports of a subset of these women[55] and our preliminary analyses, we estimate that 60% of women in our cohort will have a diagnosis of breast cancer, and 10% will have a diagnosis of ovarian cancer at the time of genetic testing. We expect 10%–15% of women tested to carry pathogenic mutations, 20% to be true negatives and 65%–70% to receive inconclusive/non-informative negative results. We will, therefore, be highly powered for all analyses proposed. To demonstrate this, we have calculated the power of our study to find differences in the uptake of BSO and BPM between women who receive positive versus inconclusive/non-informative negative test results. We anticipate having 2295 women without a history of ovarian cancer testing positive and 9945 women receiving inconclusive/non-informative negative results. Assuming the 4-year probability of BSO

is 48.3% among women who tested positive,[41] we will have 80% power to detect a 3.2% difference (95% CI 2.9% to 3.5%) in the uptake of BSO at 4 years between groups based on a two-sided binomial test with alpha of 0.05. Similarly, we anticipate having 1020 women without a history of breast cancer testing positive and 4420 women receiving inconclusive/non-informative negative results. Assuming the probability of BPM is 20% among women who tested positive,[36 41] we will have 80% power to detect a 3.7% difference (95% CI 3.1% to 4.3%) in the uptake of BPM. If 50% of *BRCA1*-positive and *BRCA2*-positive women in our cohort undertook BPM, we will have 80% power to detect a 4.9% difference (95% CI 4.3% to 5.5%).

Patient and public involvement

Patients and the public were not involved in the design of this study. The research questions proposed in this study are specifically designed to explore the patient experience and outcomes after *BRCA* testing.

ETHICS AND DISSEMINATION

Ethics

ICES is a named prescribed entity under section 45(1) of Ontario's Personal Health Information Protection Act (2004), allowing hospitals and other health information custodians to disclose personal health information without individual consent for specific purposes, including for the evaluation of healthcare resources and healthcare system planning. The protocol for this study was approved by the ICES privacy officer. In accordance with ICES policies, we will suppress all cells with <6 patients to prevent reidentification. All research outputs related to this work will undergo a reidentification risk assessment prior to submission for publication.

Dissemination

The findings of this study will be presented at national and international meetings. Manuscripts related to this work will be submitted for publication in peer-reviewed journals. It is expected that study findings will be used to develop educational interventions and recommendations for genetic counsellors and medical and surgical oncologists involved in the care of women at high risk of carrying *BRCA1* or *BRCA2* mutations.

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Contributors FD, MCC, RS, KM and NNB contributed to the design of this study. FD, TL, JL-E, AE and WSM participated in the data acquisition. FD, MCC, RS and NNB contributed to developing the analytic plan proposed for this study. FD, TL, JL-E, AE, WSM and NNB were involved in obtaining the ethics approval for this work. FD prepared the first draft of the manuscript. All authors contributed to and approved the final version of the manuscript.

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Competing interests None declared.

Patient consent Not required.

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