Gynecologic Oncology 152 (2019) 459–464

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

# BRCA mutation testing for first-degree relatives of women with high-grade serous ovarian cancer

Janice S. Kwon [a,*], Anna V. Tinker [b], Gillian E. Hanley [a], Gary Pansegrau [b], Sophie Sun [c], Mark S. Carey [a], Intan Schrader [c]

[a] Department of Obstetrics and Gynecology, University of British Columbia, Vancouver, BC, Canada
[b] Department of Medical Oncology, BC Cancer Agency, Vancouver, BC, Canada
[c] Hereditary Cancer Program, BC Cancer Agency, Vancouver, BC, Canada

## HIGHLIGHTS

- Women with high-grade serous ovarian cancer (HGSC) have a 20% risk of carrying a BRCA mutation.
- Many women with HGSC are untested for BRCA mutations, and their first-degree relatives may be ineligible for BRCA testing.
- BRCA testing for first-degree relatives of women with HGSC is cost-effective when BRCA status is unknown.
- BRCA testing with subsequent risk-reducing surgery is more effective and less costly than surgery alone.

## ARTICLE INFO

*Article history:*
Received 18 July 2018
Received in revised form 25 September 2018
Accepted 15 October 2018

*Keywords:*
Ovarian cancer, high-grade serous carcinoma
BRCA mutation
First-degree relatives
Risk-reducing bilateral salpingo-oophorectomy (RRBSO)

## ABSTRACT

*Background.* Women with high-grade serous ovarian cancer (HGSC) have a 20% chance of carrying a BRCA1 or 2 mutation. Not all undergo genetic testing, and there is a large legacy group of untested patients. Their female first-degree relatives (FDR) may not qualify for testing unless they have specific ethnicity, or personal/family cancer history. We conducted a cost-effectiveness analysis to evaluate risk-reducing strategies for these FDR who are ineligible for testing.

*Methods.* A Markov Monte Carlo simulation model estimated the costs and benefits of 3 strategies for female FDR of HGSC patients whose BRCA status is unknown: (1) no BRCA testing; (2) universal BRCA testing, followed by risk-reducing bilateral salpingo-oophorectomy (RRBSO) for mutation carriers; (3) universal RRBSO, without BRCA testing. Effectiveness was estimated in quality-adjusted life year (QALY) gains over a 50-year time horizon. Sensitivity analyses accounted for uncertainty around various parameters.

*Results.* Universal BRCA testing for female FDR of women with HGSC yielded a higher average QALY gain at acceptable cost compared to no BRCA testing, with an incremental cost-effectiveness ratio of $7888 per QALY. Universal BRCA testing was more effective and less costly than universal RRBSO (19.20 QALYs vs. 18.52 QALYs, and $10,135 vs. $14,231, respectively). Results were stable over wide ranges of plausible costs and estimates. Compliance with hormone replacement therapy had to exceed 79.3% for universal RRBSO to be the most effective strategy.

*Conclusion.* BRCA mutation testing should be offered to all female first-degree relatives of women with high-grade serous ovarian cancer when BRCA mutation status is unknown.



## 1. Introduction

Women with high-grade serous ovarian carcinoma (HGSC), the most common epithelial ovarian cancer, are usually diagnosed at an advanced stage and have a poor prognosis. These women have about a 20% chance of carrying a mutation in BRCA1 or BRCA2 (herein BRCA1/2), irrespective of family history or ethnicity [1,2], and in many jurisdictions around the world, they are all eligible for BRCA mutation testing [3]. When BRCA mutation carriers are identified, genetic counseling and testing can be extended to relatives, with the goal of identifying unaffected carriers and when appropriate, offering them highly effective surgery and other interventions to reduce their cancer risks. However, for a variety of reasons, not all eligible women undergo genetic testing, eliminating the opportunity to identify unaffected carriers. Furthermore,

* Corresponding author at: University of British Columbia, 2775 Laurel Street, 6th Floor, Vancouver, BC V5Z 1M9, Canada.
*E-mail address:* Janice.kwon@vch.ca (J.S. Kwon).

https://doi.org/10.1016/j.ygyno.2018.10.014
0090-8258/

there is a large legacy group of women with HGSC who never had the opportunity to undergo BRCA mutation testing, which translates into thousands of untested ovarian cancer patients who may have surviving first-degree relatives (FDR) at risk of carrying a BRCA1/2 mutation. These FDR are not always eligible for BRCA mutation testing unless they have a personal history of cancer, there are other family members diagnosed with ovarian or breast cancer, or they have Ashkenazi Jewish or other specific heritage [4]. Without genetic testing, some of these FDR of HGSC patients are being referred for elective surgery (bilateral salpingo-oophorectomy) to avert the diagnosis of ovarian cancer. While this may be a sensible decision for an individual, on a population level, elective risk-reducing surgeries are best applied to the highest risk individuals, i.e. those with BRCA1/2 germline mutations, especially when considering the adverse effects of poorly managed surgically-induced early menopause.

It would be valuable to know whether it is cost-effective to offer BRCA mutation testing to all first-degree relatives of women with HGSC, alive or deceased, whose BRCA mutation status is unknown. This question cannot be answered in the context of a clinical trial. The objective of this study was to conduct a cost-effectiveness analysis of BRCA mutation testing for first-degree relatives of women with ovarian cancer (HGSC) whose BRCA mutation status is unknown, and would not otherwise qualify for genetic testing.

## 2. Materials and methods

We developed a Markov Monte Carlo simulation model to estimate the costs and benefits of BRCA mutation testing in a hypothetical cohort of unaffected female first-degree relatives (FDR) of women with ovarian, fallopian tube or peritoneal high-grade serous carcinoma (HGSC). In this model, testing was offered to unaffected female FDR only, recognizing that these women could undergo risk-reducing interventions if proven to be BRCA mutation carriers. Although male relatives could have daughters who would benefit from testing and risk-reducing strategies, the benefit was measured in terms of life expectancy gain for the FDR being tested, and not second-degree relatives. This project was exempt from Research Ethics Board review, as no individual level data were used for this study. The model was populated with data from published sources, including the estimated BRCA mutation rate in HGSC patients, breast and ovarian cancer risks according to BRCA mutation status, uptake of risk-reducing surgery, and use of hormone replacement therapy after surgery [5–9]. We applied Canadian health care costs from the Canadian Institute for Health Information [10], and the BC Medical Services Plan schedule for physician services [11]. We assumed that the female FDR in this model were currently ineligible for genetic testing, because they had no personal or family history of cancer, apart from the index case with ovarian cancer, and they were not of Ashkenazi Jewish ethnicity. Three strategies were compared: (1) no testing (reference strategy); (2) BRCA mutation testing for all, followed by risk-reducing surgery (bilateral salpingo-oophorectomy, with or without mastectomy and reconstruction) for confirmed mutation carriers ("universal BRCA testing"); and (3) risk-reducing bilateral salpingo-oophorectomy for all, without BRCA testing ("universal RRBSO").

The benefits of each risk-reducing strategy were calculated in terms of average discounted quality-adjusted life expectancy. Average discounted lifetime costs were estimated in Canadian dollars (CAD$) in the year 2018. The primary outcome measure was the incremental cost-effectiveness ratio (ICER), defined as the additional cost divided by the incremental health benefit compared to an alternate strategy. If the ICER was less than $100,000 per year of life gained, the strategy would be considered cost-effective. According to the Panel on Cost-effectiveness in Health and Medicine, all costs and benefits were discounted at a rate of 3% per year. The model was programmed using decision analytic software from TreeAge Pro 2014 (Williamstown, MA).

We assumed that women entered the model at an average age of 40, they had not yet undergone a mastectomy or oophorectomy, and they had not yet been diagnosed with breast or ovarian cancer. Those who had BRCA mutation testing and were confirmed mutation carriers did not necessarily have immediate risk-reducing surgery, and they could choose to undergo risk-reducing bilateral salpingo-oophorectomy (RRBSO), with or without bilateral mastectomy and reconstruction. Those who underwent universal RRBSO had surgery upfront, which was accomplished as an outpatient laparoscopic procedure. Women would be advised of the risks of premature menopause after RRBSO, and the potential risks and benefits of hormone replacement therapy (HRT). Based on current estimates of compliance with HRT, 35% of those undergoing RRBSO would use HRT for up to 5 years after this procedure [12–14]. The Markov model has various health states (at risk, undergoing risk-reducing surgery, being diagnosed with breast or ovarian cancer, dying of these cancers or other age-associated causes according to national Life Tables [15]). The basic framework for this model is illustrated in Fig. 1. Women transition from one health state to another according to probabilities governed by age, BRCA mutation status, and risk-reducing interventions. To calculate quality-adjusted life expectancy, utilities for various health states were included for post-surgery (RRBSO with or without mastectomy), depending on intraoperative and postoperative complications (including injury to bowel, bladder, ureters, hemorrhage, wound infection, bowel obstruction or ileus) [16], the use of HRT, as well as breast cancer and ovarian cancer, which were derived from published sources [17–24]. For those who undergo premenopausal RRBSO but do not use HRT, it was assumed there was an increased risk of mortality secondary to events from osteoporosis, coronary heart disease and stroke, based on estimates from the Nurses' Health Study [25]. The time horizon for this model was 50 years. Data for the base case of the model are provided in Table 1.

To account for uncertainty in the risk of carrying a BRCA mutation, and variability in the uptake of risk-reducing surgery and subsequent use of HRT, we conducted sensitivity analyses on these rates, as well as costs to approximate those applicable to the United States, and indirect opportunity costs, which could range from as little as a few weeks to a few months, depending on postoperative recovery [26–28]. We conducted a Monte Carlo simulation to estimate the number of women who would be diagnosed with ovarian and breast cancer according to each strategy, as well as deaths secondary to premenopausal BSO without HRT.

## 3. Results

BRCA mutation testing for female first-degree relatives of women with HGSC yielded a higher average quality-adjusted life expectancy at acceptable cost compared to no testing, with an ICER of $7888 (CAD) per QALY gained. BRCA mutation testing of first-degree relatives was more effective and less costly than universal RRBSO in the absence of testing (19.20 QALYs vs. 18.52 QALYs, and $10,135 and $14,231, respectively), and therefore BRCA mutation testing is the dominant strategy. Table 2 summarizes the average discounted quality-adjusted life expectancy gains and costs associated with each strategy.

Our results were stable over a wide range of costs, to estimate those in the United States health care system, and variables such as BRCA mutation rates among women with HGSC, and the proportion having risk-reducing surgery in the context of a known BRCA mutation. Compliance with HRT must be very high in order to mitigate the downstream consequences known to be associated with premenopausal BSO. Fig. 2 illustrates that the proportion using HRT must be higher than 79.3% for universal RRBSO to be a more effective strategy than BRCA mutation testing first for these women. The utility associated with premenopausal BSO in the absence of HRT must also be very high for this strategy to be more effective than BRCA mutation testing. Sensitivity analysis revealed that when this utility is greater than 0.956, universal RRBSO (without BRCA mutation testing) is preferable to BRCA mutation testing

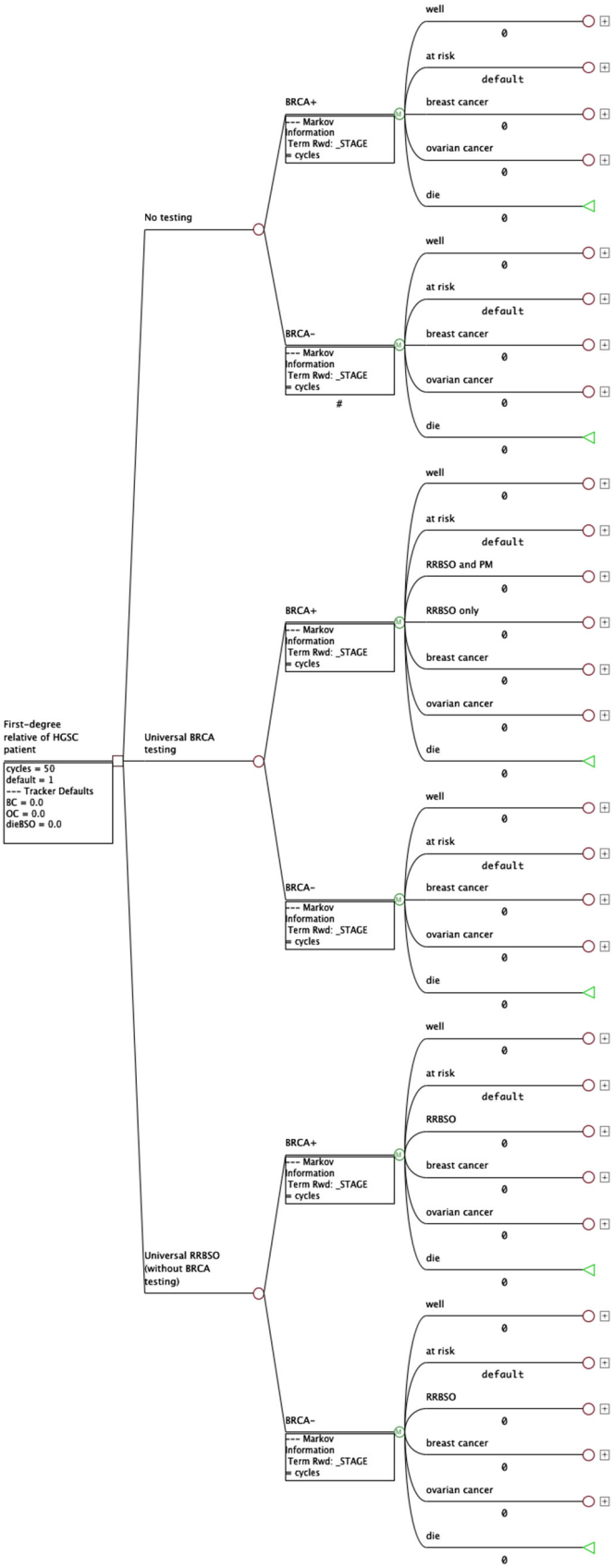


**Fig. 1.** Framework for Markov decision-analytic model.

**Table 1**
Selected data for base case.

| Variables | Estimate for base case | Range |
|---|---|---|
| Probabilities | | |
| Lifetime risk breast cancer with BRCA mutation [5,6] | 57% BRCA1; 49% BRCA2 | 47–66%; 40–57% |
| Lifetime risk ovarian cancer with BRCA mutation [5,6] | 40% BRCA1; 18% BRCA2 | 35–46%; 13–23% |
| Lifetime risk breast cancer, no mutation [8] | 12% | 10–13% |
| Lifetime risk ovarian cancer, no mutation [7] | 1.4% | 1–2% |
| Lifetime mortality risk, premenopausal RRBSO without HRT [25] | 12.5% | 10–15% |
| Risk-reducing surgery in first 10 years after BRCA testing [49] | 54% | 40–70% |
| Proportion having risk-reducing surgery with both mastectomy and RRBSO [49,50] | 33% | 30–50% |
| Proportion using HRT up to 5 years after premenopausal RRBSO [12–14] | 35% | 18–63% |
| Proportion with intraoperative or postoperative complications from RRBSO [16] | 6% | 2–6% |
| Utilities | | |
| Well [18] | 0.79–1.0 | 0.79–1.0 |
| Breast cancer [17,21,51] | 0.75 | 0.65–0.85 |
| Ovarian cancer [17,22,51,52] | 0.58 | 0.50–0.70 |
| Mastectomy with reconstruction [23,24] | 0.82 | 0.44–0.87 |
| Premenopausal RRBSO [19,22,24] | 0.68 | 0.50–0.82 |
| Costs* | | |
| BRCA mutation testing [53] | 1806 | 1000–3000 |
| Genetic counseling [11,53] | 506 | 100–1000 |
| Breast cancer first line treatment [10,11,26,28] | 55,776 | 30,000–100,000 |
| Ovarian cancer first line treatment [10,11,27,28] | 46,359 | 40,000–100,000 |
| Outpatient laparoscopic RRBSO [10,11,27,28] | 10,038 | 4000–20,000 |
| Prophylactic mastectomy with reconstruction [10,11,26,28] | 16,155 | 10,000–30,000 |
| Annual cost of HRT (estrogen and progestin) [54] | 164 | 164–1000 |

* Costs are expressed in Canadian dollars (CAD).

first. If we estimate life expectancy gain (unadjusted for quality of life), and assume 100% compliance with HRT for those undergoing premenopausal BSO, then universal RRBSO without BRCA mutation testing is the most effective strategy. Although universal RRBSO without BRCA mutation testing is more costly in this scenario, it has a favorable ICER of $10,057 relative to BRCA mutation testing first.

We conducted a Monte Carlo simulation to estimate the number of breast and ovarian cancer cases that would be diagnosed in a lifetime according to each of the three strategies, as well as the number of deaths secondary to premenopausal BSO in the absence of HRT. In Canada, there are approximately 2800 women diagnosed with ovarian cancer every year, and about 50% ($n = 1400$) of them will have HGSC. These women likely have at least 1 female first-degree relative (assuming 2 generations, such as a sister or daughter, based on total fertility rates ranging from 1.51–2.46 in the last 50 years [29]). By simulating a cohort of 1400 female first-degree relatives of women with HGSC (through 1000 trials) our model estimates breast cancer diagnoses in 179, 146, and 95 women, and ovarian cancer diagnoses in 40, 19, and 2 women, associated with no testing, universal BRCA mutation testing for all female first-degree relatives, and universal RRBSO without BRCA testing, respectively, over a lifetime. However, the model also estimates that

**Table 2**
Average discounted costs and life expectancy gains in base case.

| Strategy | Costs | Effectiveness (QALYs) | ICER |
|---|---|---|---|
| No BRCA testing (reference) | $8524 | 18.99 | – |
| Universal BRCA testing | $10,135 | 19.20 | $7888 |
| Universal RRBSO, no BRCA testing | $14,231 | 18.52 | Dominated* |

* Dominated means that the strategy is more costly and less effective than an alternate (previous) strategy.

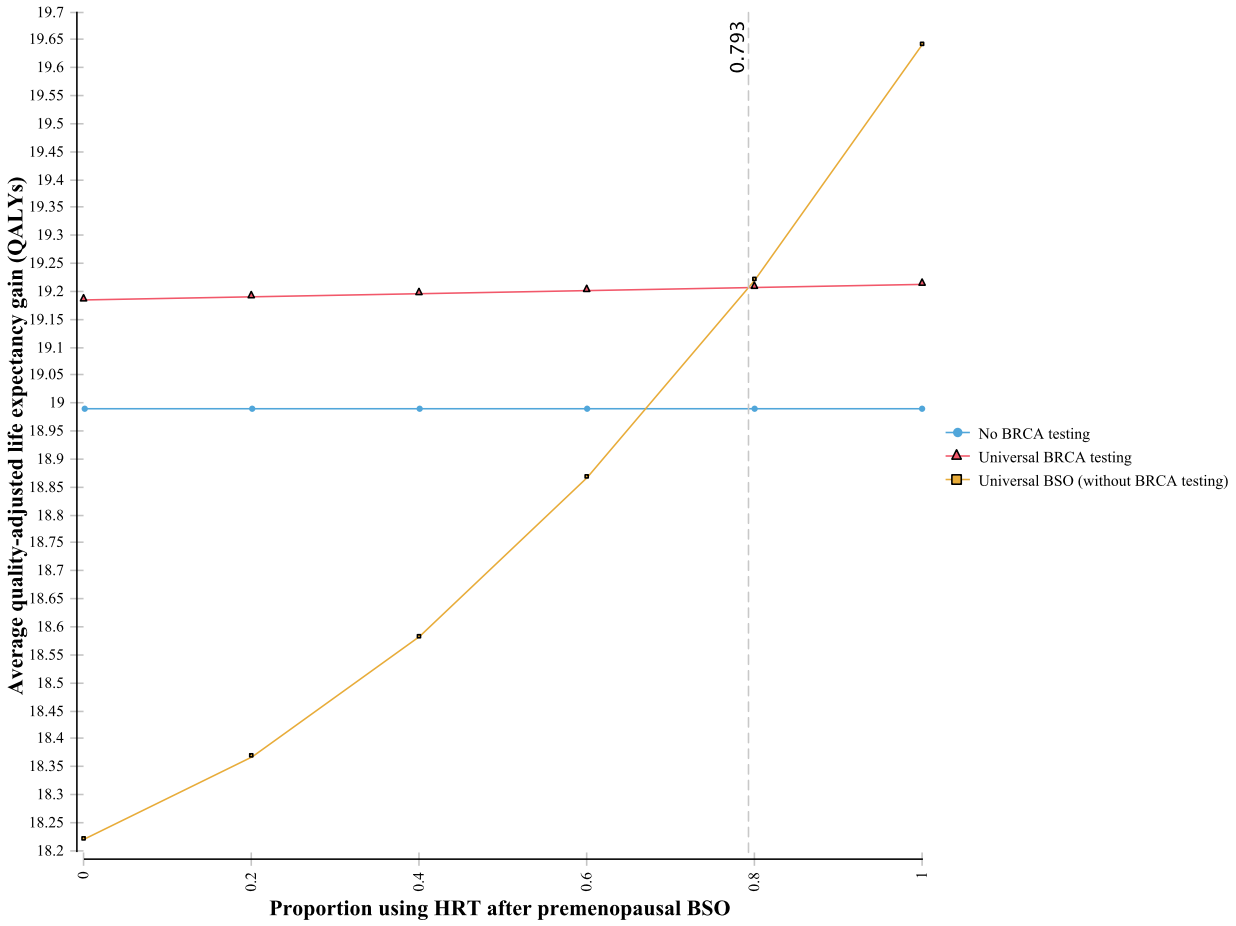


**Fig. 2.** Sensitivity analysis on proportion of women using hormone replacement therapy after premenopausal risk-reducing bilateral salpingo-oophorectomy.

80 women will die as a result of universal RRBSO when offered before menopause because of low use of HRT. These results are summarized in Table 3.

## 4. Discussion

Although women with HGSC have a 1 in 5 chance of carrying a BRCA mutation, many of them do not undergo genetic testing, for a variety of reasons [30–32]. Based on a large cross-sectional study in the United States, it is estimated that only 10% of eligible ovarian cancer patients actually undergo genetic testing [33]. HGSC is associated with a poor prognosis, and many women will die as a result of their disease before being tested for BRCA mutations. Furthermore, there is presumably a large legacy cohort of thousands of women diagnosed with HGSC who never had the opportunity to undergo genetic testing, because they were diagnosed before BRCA testing was routinely offered for HGSC histology, and they had no other risk factors to warrant genetic testing.

**Table 3**
Monte Carlo simulation of 1400 female first-degree relatives of women with high-grade serous ovarian cancer diagnosed every year.

| Strategy | Expected events over time horizon of 50 years | | |
|---|---|---|---|
| | Breast cancer | Ovarian cancer | Deaths from RRBSO |
| No BRCA testing (reference) | 179 | 40 | 0 |
| Universal BRCA testing | 146 | 19 | 7 |
| Universal RRBSO, no BRCA testing | 95 | 2 | 80 |

With at least 2000 and 20,000 women diagnosed with ovarian cancer per year in Canada and the United States respectively in the 1990's [34,35], there may be a comparable number of surviving female first-degree relatives (daughters, sisters), who would benefit from the knowledge of carrying a BRCA mutation, by subsequently undergoing risk-reducing interventions to avoid the diagnoses of ovarian and breast cancer.

The latest NCCN Guidelines (Version 1.2019) recommend BRCA mutation testing for "an individual with no personal history of cancer but with a close relative (first or second degree) with ovarian (epithelial, non-mucinous, including fallopian tube and primary peritoneal) cancer" [36]. However, in many jurisdictions, particularly in Canada, many first-degree relatives of HGSC patients whose BRCA mutation status is unknown still do not qualify for BRCA mutation testing, nor are they eligible for coverage through Medicaid in the United States.

Overall, female first-degree relatives of HGSC patients have an estimated risk of ovarian cancer that is 2–3-fold higher than the general population risk, which translates into a lifetime risk of 3–4% [37–40]. This estimate can also be derived by assuming a 20% risk of a BRCA mutation in HGSC patients, 50% chance of inheritance in 1st degree relatives, and 40% lifetime risk of ovarian cancer if BRCA1 mutation. Some of these women are being referred for RRBSO, without genetic testing, to avert the diagnosis of ovarian cancer. According to guidelines from the United Kingdom National Institute for Health and Care Excellence (NICE), RRBSO is only available to high-risk women with greater than a 10% lifetime risk of ovarian cancer, but Manchanda et al. assert that women with a 4% lifetime risk of ovarian cancer should be offered this procedure [41]. The caveat is that compliance with HRT must be high. Our model also demonstrates effectiveness with RRBSO among women with a comparable increased risk of ovarian cancer, but only if

compliance with HRT is greater than 79.3%. This is an unrealistic assumption based on available data on HRT rates post-oophorectomy in premenopausal women. Approximately 60% of women who undergo RRBSO will ever use HRT, but the mean duration of use is only about 3 years, and only 35% of women use HRT for 5 years post-RRBSO [12–14].

Our model predicts that universal RRBSO for all female first-degree relatives of HGSC patients will yield a lower number of breast and ovarian cancer cases over a lifetime, compared to BRCA mutation testing first (and RRBSO reserved only for mutation carriers). This seems plausible, because premenopausal BSO reduces breast and ovarian cancer risks, even among non-mutation carriers [42], and therefore universal RRBSO for these women will yield the greatest risk reduction against these cancers. However, universal RRBSO without BRCA testing is not the ideal intervention for female first-degree relatives of HGSC patients for 2 reasons. Firstly, most of these women are never destined to develop breast or ovarian cancer, and therefore the majority of women will have surgery unnecessarily. Yet, these women who have surgery are at increased risk of mortality from downstream health consequences, given known compliance rates with HRT [25,43]. Secondly, without genetic testing, family members will remain uninformed about mutation status. Their first-degree relatives, both female and male, need to know that they could still carry a mutation. Men who inherit a BRCA mutation have an increased risk of prostate cancer [44], and many of them will have female descendants who could have increased lifetime risks of breast and ovarian cancer. It is intuitive that offering BRCA testing to male first-degree relatives could reduce cancer rates and costs among them and their descendants. However, even if all male first-degree relatives were tested, they do not have risk-reducing interventions comparable to those for women that would substantially alter their own life expectancy. The average lifetime benefit (life expectancy gain) for men is expected to be much lower, which in turn would increase the ICER. On the other hand, if female first-degree relatives are tested first and are confirmed mutation carriers, then male first-degree relatives can undergo targeted testing, which is much less costly and time-consuming, given the known mutation and the 50% probability of carrying that mutation.

There are several limitations of our study. Firstly, our results are only generalizable to those without additional risk factors for carrying a BRCA mutation. We recognize that this may be an oversimplified model, as there are many other scenarios in which there are first-degree relatives of HGSC patients with an unknown BRCA mutation status, such as a family history of more than one HGSC, a family history of both HGSC and premenopausal breast cancer, or Ashkenazi Jewish ethnicity. However, all of these scenarios increase the pre-test probability of a BRCA mutation, and these women should currently be eligible for genetic testing. Furthermore, we did not consider other germline mutations that are associated with ovarian cancer such as RAD51C or BRIP1, therefore panel testing instead of BRCA mutation testing alone would be more comprehensive and identify a greater number of first-degree relatives at risk for an inherited predisposition to cancer. However, one of the main objectives of this model was to highlight the importance of genetic testing first, rather than pursuing risk-reducing surgery in the absence of this information.

Secondly, although women with a personal history of breast cancer were excluded from this analysis, they should still be eligible for BRCA testing if they have a first-degree relative with HGSC; moreover their pre-test probability of a BRCA mutation is expected to be higher. These women are probably less likely to use HRT given their breast cancer history, and therefore RRBSO should only be offered if truly indicated for a confirmed BRCA mutation, or metastatic or recurrent ER+ breast cancer for which an aromatase inhibitor may be indicated. RRBSO has the potential to be harmful if offered to premenopausal women with early ER+ breast cancer in the absence of a known BRCA mutation, who are subsequently unable to use HRT [45]. We did not include non-hormonal interventions for premature menopause after RRBSO in this model, as there are limited data on their efficacy in this context.

Third, we may have overestimated the mortality associated with RRBSO in the absence of HRT. This risk estimate was extrapolated from the subgroup of women under age 50 who underwent oophorectomy without HRT in the Nurses' Health Study [25]. After a median follow-up of 28 years, the number needed to harm (NNH) was 8, which translates into a mortality risk of 1/8 (12.5%) attributable to oophorectomy without HRT. Although these women are arguably different from female first-degree relatives of HGSC patients, the point is that they are often young when they have this surgical procedure (under age 50) and based on current life expectancy estimates for women in Canada and the United States [46,47], they should survive another 40 years. Unfortunately, some of them will die prematurely as a result of early menopause after RRBSO, because HRT or other interventions are not consistently used. Breast cancer risk appears to be the main reason why these women choose not use HRT post-RRBSO, but a significant proportion also report that they do not discuss HRT concerns with their health care provider [12]. A recent systematic review revealed that these patients benefit from HRT post-RRBSO, without an increased risk of breast cancer [48]. Greater efforts are required to counsel women about the potential harms of premenopausal RRBSO, and the importance of HRT afterwards.

In conclusion, women with high-grade serous ovarian cancer have up to a 20% risk of carrying a BRCA mutation, and their female first-degree relatives are subsequently at risk of carrying a mutation and developing breast and ovarian cancer. When BRCA mutation status is unknown among these ovarian cancer patients, their first-degree relatives should be recognized by their front-line health care providers as being at risk for carrying a mutation. They should be allowed the opportunity for genetic counseling, and BRCA mutation testing, irrespective of personal cancer history, additional family history, or ethnicity. This is cost-effective compared to the current policy (no testing unless specific cancer history and ethnicity), and less costly and more effective than risk-reducing surgery alone without BRCA testing. Confirmation of BRCA mutation status will inform these women and their family members of their cancer risks, and will facilitate personal decisions relating to cancer prevention strategies.

## Disclosures

Dr. Tinker has received funding from Astra Zeneca to conduct research relating to ovarian cancer detection and a Phase I trial in recurrent ovarian cancer. None of the other authors have any potential conflicts of interest to disclose.

## Author contributions

Janice Kwon: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, writing - original draft and writing – review and editing; Anna Tinker: data curation; writing – review and editing; Gillian Hanley: formal analysis, investigation, methodology, writing – review and editing; Gary Pansegrau: data curation, investigation, writing –review and editing; Sophie Sun: investigation, writing – review and editing; Mark Carey: investigation, writing – review and editing; Intan Schrader: formal analysis, investigation, writing – review and editing.

## Financial support

UBC Division of Gynecologic Oncology Research Award.

## References

[1] K. Alsop, S. Fereday, C. Meldrum, A. de Fazio, C. Emmanuel, J. George, et al., BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group, J. Clin. Oncol. 30 (21) (2012 Jul 20) 2654–2663 (PubMed PMID: 22711857. Pubmed Central PMCID: 3413277).

[2] K.A. Schrader, J. Hurlburt, S.E. Kalloger, S. Hansford, S. Young, D.G. Huntsman, et al., Germline BRCA1 and BRCA2 mutations in ovarian cancer: utility of a histology-based referral strategy, Obstet. Gynecol. 120 (2 Pt 1) (2012 Aug) 235–240 (PubMed PMID: 22776961).

[3] Agency BC, Hereditary cancer program referral form 2015, Available from http://www.bccancer.bc.ca/screening/Documents/HCP_Form-ReferralForm.pdf August 29, 2016.

[4] Force USPST, Final recommendation statement: BRCA-related cancer: risk assessment, genetic counseling, and genetic testing 2013, Available from https://http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing July 19, 2017.

[5] A. Antoniou, P.D. Pharoah, S. Narod, H.A. Risch, J.E. Eyfjord, J.L. Hopper, et al., Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies, Am. J. Hum. Genet. 72 (5) (2003 May) 1117–1130 (PubMed PMID: 12677558. eng).

[6] S. Chen, G. Parmigiani, Meta-analysis of BRCA1 and BRCA2 penetrance, J. Clin. Oncol. 25 (11) (2007 Apr 10) 1329–1333 (PubMed PMID: 17416853. eng).

[7] SEER, Probability of developing cancer by cancer site, all ages, all races, female 2003–2005 ovary 2007, Available from http://seer.cancer.gov/faststats/selections.php?run&output=2&data=6&statistic=10&year=200806&race=1&sex=3&age=1&series=cancer&cancer=61 March 8, 2009.

[8] SEER, Probability of developing cancer by cancer site, all ages, all races, female 2003–2005 breast 2007, Available from http://seer.cancer.gov/faststats/selections.php?run&output=2&data=6&statistic=10&year=200806&race=1&sex=3&age=1&series=cancer&cancer=553 March 8, 2009.

[9] K.A. Metcalfe, P. Ghadirian, B. Rosen, W. Foulkes, C. Kim-Sing, A. Eisen, et al., Variation in rates of uptake of preventive options by Canadian women carrying the BRCA1 or BRCA2 genetic mutation, Open Med. Chem. J.. 1 (2) (2007) e92–e98 (PubMed PMID: 20101300. eng).

[10] CIHI, Patient cost estimator 2017, Available from http://www.cihi.ca/en/patient-cost-estimator.

[11] Health BCMo, BC ministry of health medical services commission payment schedule 2017 [updated July 1, 2017; cited 2017 July 7, 2017], Available from http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/msp/physicians/payment-schedules/msc-payment-schedule.

[12] J. Challberg, L. Ashcroft, F. Lalloo, B. Eckersley, R. Clayton, P. Hopwood, et al., Menopausal symptoms and bone health in women undertaking risk reducing bilateral salpingo-oophorectomy: significant bone health issues in those not taking HRT, Br. J. Cancer 105 (1) (2011 Jun 28) 22–27 (PubMed PMID: 21654687. Pubmed Central PMCID: 3137416).

[13] S.M. Domchek, T.M. Friebel, C.F. Singer, D.G. Evans, H.T. Lynch, C. Isaacs, et al., Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality, JAMA 304 (9) (2010 Sep 1) 967–975 (PubMed PMID: 20810374. eng).

[14] J.B. Madalinska, M. van Beurden, E.M. Bleiker, H.B. Valdimarsdottir, J. Hollenstein, L.F. Massuger, et al., The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy, J. Clin. Oncol. 24 (22) (2006 Aug 01) 3576–3582 (PubMed PMID: 16877724).

[15] Canada S, Table 053-0003 - Elements of the Life Table, Canada, Provinces and Territories, Annual, 2011–2013, Female, 2013.

[16] J.D. Wright, A. Kostolias, C.V. Ananth, W.M. Burke, A.I. Tergas, E. Prendergast, et al., Comparative effectiveness of robotically assisted compared with laparoscopic adnexal surgery for benign gynecologic disease, Obstet. Gynecol. 124 (5) (2014 Nov) 886–896 (PubMed PMID: 25437715. Pubmed Central PMCID: 4251548).

[17] K. Anderson, J.S. Jacobson, D.F. Heitjan, J.G. Zivin, D. Hershman, A.I. Neugut, et al., Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation, Ann. Intern. Med. 144 (6) (2006 Mar 21) 397–406 (PubMed PMID: 16549852. eng).

[18] D.G. Fryback, E.J. Dasbach, R. Klein, B.E. Klein, N. Dorn, K. Peterson, et al., The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors, Med. Decis. Mak. 13 (2) (1993 Apr–Jun) 89–102 (PubMed PMID: 8483408. eng).

[19] V.R. Grann, J.S. Jacobson, V. Sundararajan, S.M. Albert, A.B. Troxel, A.I. Neugut, The quality of life associated with prophylactic treatments for women with BRCA1/2 mutations, Cancer J. Sci. Am. 5 (5) (1999 Sep–Oct) 283–292 (PubMed PMID: 10526669. eng).

[20] M.L. Holland, A. Huston, K. Noyes, Cost-effectiveness of testing for breast cancer susceptibility genes, Value Health 12 (2) (2009 Mar-Apr) 207–216 (PubMed PMID: 18647256).

[21] M. Lidgren, N. Wilking, B. Jonsson, C. Rehnberg, Health related quality of life in different states of breast cancer, Qual. Life Res. 16 (6) (2007 Aug) 1073–1081 (PubMed PMID: 17468943. eng).

[22] T.O. Tengs, E.P. Winer, S. Paddock, O. Aguilar-Chavez, D.A. Berry, Testing for the BRCA1 and BRCA2 breast-ovarian cancer susceptibility genes: a decision analysis, Med. Decis. Mak. 18 (4) (1998 Oct–Dec) 365–375 (PubMed PMID: 10372578. eng).

[23] A. Thoma, D. Khuthaila, G. Rockwell, K. Veltri, Cost-utility analysis comparing free and pedicled TRAM flap for breast reconstruction, Microsurgery 23 (4) (2003) 287–295 (PubMed PMID: 12942517. eng).

[24] M.S. van Roosmalen, L.C. Verhoef, P.F. Stalmeier, N. Hoogerbrugge, W.A. van Daal, Decision analysis of prophylactic surgery or screening for BRCA1 mutation carriers: a more prominent role for oophorectomy, J. Clin. Oncol. 20 (8) (2002 Apr 15) 2092–2100 (PubMed PMID: 11956270. eng).

[25] W.H. Parker, D. Feskanich, M.S. Broder, E. Chang, D. Shoupe, C.M. Farquhar, et al., Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study, Obstet. Gynecol. 121 (4) (2013 Apr) 709–716 (PubMed PMID: 23635669. Pubmed Central PMCID: 4254662).

[26] Steiner CAA, Weiss AJTHA, Barrett MLMLB, Inc., Fingar KRTHA, Davis PHA, Trends in bilateral and unilateral mastectomies in hospital inpatient and ambulatory settings, 2005–2013, Rockville, MD 2016 Feburary 2016 (Report No).

[27] AHRQ, Trends in Hysterectomies and Oophorectomies in Hospital Inpatient and Ambulatory Settings, 2005–2013, (Rockville, MD) 2016.

[28] CMS, Physician fee schedule search 2017, Available from http://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx July 7, 2017.

[29] Canada S, Total fertility rate, Canada, 1926 to 2011, Available from https://http://www.statcan.gc.ca/pub/11-630-x/11-630-x2014002-eng.htm January 19, 2018.

[30] M. Arts-de Jong, G.H. de Bock, C.J. van Asperen, M.J. Mourits, J.A. de Hullu, C.M. Kets, Germline BRCA1/2 mutation testing is indicated in every patient with epithelial ovarian cancer: a systematic review, Eur. J. Cancer 61 (2016 Jul) 137–145 (PubMed PMID: 27209246).

[31] H. Hoberg-Vetti, C. Bjorvatn, B.E. Fiane, T. Aas, K. Woie, H. Espelid, et al., BRCA1/2 testing in newly diagnosed breast and ovarian cancer patients without prior genetic counselling: the DNA-BONus study, Eur. J. Hum. Genet. 24 (6) (2016 Jun) 881–888 (PubMed PMID: 26350514. Pubmed Central PMCID: 4867439).

[32] S.V. Petzel, R.I. Vogel, J. McNiel, A. Leininger, P.A. Argenta, M.A. Geller, Improving referral for genetic risk assessment in ovarian cancer using an electronic medical record system, Int. J. Gynecol. Cancer 24 (6) (2014 Jul) 1003–1009 (PubMed PMID: 24887442. Pubmed Central PMCID: 4596256).

[33] C.P. Childers, K.K. Childers, M. Maggard-Gibbons, J. Macinko, National estimates of genetic testing in women with a history of breast or ovarian cancer, J. Clin. Oncol. 35 (34) (2017 Dec 1) 3800–3806 (PubMed PMID: 28820644. Pubmed Central PMCID: 5707208).

[34] J.T. Quirk, N. Natarajan, Ovarian cancer incidence in the United States, 1992–1999, Gynecol. Oncol. 97 (2) (2005 May) 519–523 (PubMed PMID: 15863154).

[35] Canadian Cancer Society PHAoC, Statistics Canada, Canadian cancer statistics 2016, Available from http://www.cancer.ca/~/media/cancer.ca/CW/cancerinformation/cancer 101/Canadian cancer statistics/Canadian-Cancer-Statistics-2016-EN.pdf?la=en.

[36] NCCN, Genetic/familial high-risk assessment: breast and ovarian 2018 [updated July 11, 2018; cited 2018]. Version 1.2019, Available from http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf.

[37] S. Jervis, H. Song, A. Lee, E. Dicks, J. Tyrer, P. Harrington, et al., Ovarian cancer familial relative risks by tumour subtypes and by known ovarian cancer genetic susceptibility variants, J. Med. Genet. 51 (2) (2014 Feb) 108–113 (PubMed PMID: 24277755).

[38] D.F. Easton, F.E. Matthews, D. Ford, A.J. Swerdlow, J. Peto, Cancer mortality in relatives of women with ovarian cancer: the OPCS Study. Office of Population Censuses and Surveys, Int. J. Cancer 65 (3) (1996 Jan 26) 284–294 (PubMed PMID: 8575846).

[39] K. Hemminki, J. Sundquist, A. Brandt, Incidence and mortality in epithelial ovarian cancer by family history of any cancer, Cancer 117 (17) (2011 Sep 01) 3972–3980 (PubMed PMID: 21365633).

[40] J. Lorenzo Bermejo, R. Rawal, K. Hemminki, Familial association of specific histologic types of ovarian malignancy with other malignancies, Cancer 100 (7) (2004 Apr 01) 1507–1514 (PubMed PMID: 15042686).

[41] R. Manchanda, R. Legood, A.C. Antoniou, V.S. Gordeev, U. Menon, Specifying the ovarian cancer risk threshold of 'premenopausal risk-reducing salpingo-oophorectomy' for ovarian cancer prevention: a cost-effectiveness analysis, J. Med. Genet. 53 (9) (2016 Sep) 591–599 (PubMed PMID: 27354448).

[42] W.H. Parker, M.S. Broder, E. Chang, D. Feskanich, C. Farquhar, Z. Liu, et al., Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study, Obstet. Gynecol. 113 (5) (2009 May) 1027–1037 (PubMed PMID: 19384117. eng).

[43] W.A. Rocca, B.R. Grossardt, M. de Andrade, G.D. Malkasian, L.J. Melton 3rd., Survival patterns after oophorectomy in premenopausal women: a population-based cohort study, Lancet Oncol. 7 (10) (2006 Oct) 821–828 (PubMed PMID: 17012044).

[44] J. Lecarpentier, V. Silvestri, K.B. Kuchenbaecker, D. Barrowdale, J. Dennis, L. McGuffog, et al., Prediction of breast and prostate cancer risks in male BRCA1 and BRCA2 mutation carriers using polygenic risk scores, J. Clin. Oncol. 35 (20) (2017 Jul 10) 2240–2250 (PubMed PMID: 28448241. Pubmed Central PMCID: 5501359).

[45] J.S. Kwon, G. Pansegrau, M. Nourmoussavi, G. Hammond, M.S. Carey, Long-term consequences of ovarian ablation for premenopausal breast cancer, Breast Cancer Res. Treat. 157 (3) (2016 Jun) 565–573 (PubMed PMID: 27236562).

[46] Canada S, Life expectancy - statistics Canada 2018, Available from http://www.statcan.gc.ca/pub/89-645-x/.../life-expectancy-esperance-vie-eng.htm January 19, 2018.

[47] Prevention CfDCa, Life expectancy 2018, Available from https://http://www.cdc.gov/nchs/fastats/life-expectancy.htm January 19, 2018.

[48] N. Johansen, A.H. Liavaag, O.E. Iversen, A. Dorum, T. Braaten, T.M. Michelsen, Use of hormone replacement therapy after risk-reducing salpingo-oophorectomy, Acta Obstet. Gynecol. Scand. 96 (5) (2017 May) 547–555 (PubMed PMID: 28236297).

[49] K.A. Metcalfe, D. Birenbaum-Carmeli, J. Lubinski, J. Gronwald, H. Lynch, P. Moller, et al., International variation in rates of uptake of preventive options in BRCA1 and BRCA2 mutation carriers, Int. J. Cancer 122 (9) (2008 May 1) 2017–2022 (PubMed PMID: 18196574. eng).

[50] Program BCAHC, Risk-Reducing Surgery in BRCA Mutation Carriers, 2016.

[51] T.O. Tengs, A. Wallace, One thousand health-related quality-of-life estimates, Med. Care 38 (6) (2000 Jun) 583–637 (PubMed PMID: 10843310. eng).

[52] V.R. Grann, J.S. Jacobson, D. Thomason, D. Hershman, D.F. Heitjan, A.I. Neugut, Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA1/2 mutations: an updated decision analysis, J. Clin. Oncol. 20 (10) (2002 May 15) 2520–2529 (PubMed PMID: 12011131. eng).

[53] BCCA, British Columbia Cancer Agency Hereditary Cancer Program: High Risk Clinic Statistics, 2017.

[54] P. Compass, Pharmacy compass - pacific blue cross 2017, Available from https://http://www.pac.bluecross.ca/pharmacycompass December 5, 2017.