# Bilateral Oophorectomy and the Risk of Breast Cancer in *BRCA1* Mutation Carriers: A Reappraisal

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## ABSTRACT

**Background:** The lack of consensus on whether bilateral oophorectomy impacts risk of developing breast cancer among *BRCA1* mutation carriers might be attributed to various biases, specifically, cancer-induced testing bias due to inclusion of prevalent cases. We conducted two complementary matched case–control analyses to evaluate the association of oophorectomy and *BRCA1* breast cancer.

**Methods:** A research questionnaire was administered every two years to collect information on exposures and disease. In the first analysis, we limited the study to prevalent breast cancer cases (diagnosed prior to study entry; $n = 2{,}962$) who were matched to controls on year of birth and country of residence ($n = 4{,}358$). In the second approach, we limited to 330 incident cases (diagnosed in the follow-up period) and 1,548 matched controls. Conditional logistic regression was used to estimate the adjusted odds ratios (OR) and 95% confidence intervals (CI) of invasive breast cancer.

**Results:** In the first approach, there was a significant inverse association between oophorectomy and the risk of developing breast cancer [OR = 0.43; 95% confidence interval (CI), 0.34–0.55; $P < 00001$]. In the second approach, there was no association between oophorectomy and risk (OR = 1.21; 95% CI, 0.87–1.70; $P = 0.26$).

**Conclusions:** The inclusion of women with a personal history of breast cancer prior to ascertainment likely impacts upon the association of oophorectomy and *BRCA1* breast cancer risk.

**Impact:** Oophorectomy is unlikely a determinant of breast cancer risk in *BRCA1* mutation carriers but should be offered at age 35 to reduce the risk of ovarian and fallopian tube cancer.

## Introduction

Several studies have evaluated the potential impact of preventive bilateral salpingo-oophorectomy (referred to as "*oophorectomy*" hereafter) on the risk of breast cancer in women with an inherited pathogenic germline *BRCA1* (or *BRCA2*) mutation, with inconsistent results (1–4). In the most recent study, Choi and colleagues collected data from 876 clinic- and population-based families ($n = 4{,}575$ individuals) with known mutation status in *BRCA1* or *BRCA2*, and applied a novel statistical approach to evaluate the impact of oophorectomy on breast cancer risk (5). They historically followed subjects from age 16 and documented all cases of breast cancer. They concluded that oophorectomy was associated with a large and statistically significant reduction in breast cancer risk in the 5-year period following surgery, but that the impact waned over time. The hazard ratios (HR) were 0.28 [95% confidence interval (CI), 0.10–0.63] for *BRCA1* mutation carriers and 0.19 (95% CI, 0.06–0.71) for *BRCA2* mutation carriers for breast cancer diagnosed within five years of oophorectomy.

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The lifetime risk of developing breast cancer among *BRCA1* mutation carriers is estimated to be 60% to 70% by age 75 (6–8). The annual incidence is approximately 1.8% per year from age 35 to 75 (9, 10). Although preventive bilateral mastectomy is the most effective means of preventing disease, the majority of *BRCA1* mutation carriers rely on screening with yearly MRI and mammography (11–13). Women with a *BRCA1* mutation undergo preventive oophorectomy primarily for the prevention of ovarian and fallopian tube cancer; however, early studies suggested that bilateral oophorectomy also protected against breast cancer in this high-risk population (1). In 2005, we published a case–control study of 3,305 women with a *BRCA1* or *BRCA2* mutation and compared oophorectomy histories in women with and without breast cancer (14). Women were classified as cases or controls based on their disease status on the date of study entry. A previous oophorectomy was associated with a significant reduction in breast cancer risk of 56% for *BRCA1* mutation carriers [odds ratio (OR) = 0.44; 95% CI, 0.29–0.66] and of 43% for *BRCA2* mutation carriers (OR = 0.57; 95% CI, 0.28–1.15). In a 2009 meta-analysis of this and two other studies, Rebbeck and colleagues estimated a 51% reduction in the risk of breast cancer with oophorectomy in carriers of either mutation (1).

In a second (prospective) study from our international consortium, we reported a hazard ratio (HR) of 0.97 (95% CI, 0.73–1.26) for the association of oophorectomy and breast cancer among women with a *BRCA1* mutation (3). Our null finding is in agreement with two recent prospective reports on the same topic (4, 15), whereas two others have suggested a significant protective effect (5, 16). The differing results for the association of oophorectomy and breast cancer reported by the various study groups to date may be attributed to differences in the populations studied or due to methodologic differences in study design (16). We are particularly concerned that the inclusion of prevalent cases (in a case–control or prospective study) may lead to an overestimation of the level of risk reduction with oophorectomy. This is because most women with breast cancer will be unaware of their mutation status at the time of their cancer diagnosis, and thus, very few will have had preventive ovarian surgery prior to cancer development (cancer-induced testing bias). The same argument does not hold true for the controls (i.e., women without disease; refs. 2, 4). To mitigate this bias, it is ideal to include only those women who are aware of their mutation status prior to the time of breast cancer diagnosis.

In an attempt to evaluate the effect of oophorectomy on breast cancer risk and to assess the potential impact of cancer-induced testing bias on risk estimates, we revisited our international cohort and conducted two complementary matched case–control analyses of oophorectomy and breast cancer in *BRCA1* mutation carriers. In the first approach, we limited the analysis to prevalent breast cancer cases (i.e., those diagnosed before the baseline questionnaire), whereas in the second approach, we limited the analysis to incident cases (i.e., those diagnosed in the follow-up period). In both settings, we employed a matched case–control design whereby cases and controls were matched on age and other important baseline characteristics. Because of the small number of *BRCA2* mutations carriers with incident cancer, we limited the study to women with a *BRCA1* mutation.

## Materials and Methods

### Study population

Women who were enrolled in a multicenter, longitudinal study of women with an inherited pathogenic *BRCA1* or *BRCA2* mutation from 85 participating centers in 16 countries were eligible for inclusion. For the current study, we focused only on women with a mutation in the *BRCA1* gene who had sought genetic testing because of a personal and/or family history of breast and/or ovarian cancer. Mutation detection was conducted using a variety of techniques; however, all nucleotide sequences were confirmed by direct sequencing of DNA. All participating institutions received ethics review board approvals of the host institutions and all the study participants provided written informed consent.

### Data collection

A baseline questionnaire was completed at enrollment which was either administered at the time of a clinic appointment or at their home at a later date. The baseline questionnaire collected detailed information on family and personal history of breast cancer (and other cancers), reproductive and medical histories (including preventive oophorectomy and mastectomy), as well as medication use.

A follow-up questionnaire was administered every two years thereafter to update exposure information and to identify incident breast cancers. These were either administered over the phone by a genetic counsellor or research assistant, or alternatively, mailed to each participant to complete and return. Of the women who completed a baseline questionnaire, 81% completed one or more follow up questionnaires

Women were classified as having a bilateral oophorectomy if both ovaries were removed (with or without fallopian tubes or uterus intact) prior to the diagnosis of breast cancer (for cases) or at date of last follow-up for women without breast cancer (for controls). Women with a unilateral oophorectomy were included as unexposed (i.e., no oophorectomy). We did not consider salpingectomy in the exposure classification.

### Breast cancer cases

For this analysis, the outcome of interest was the diagnosis of a first primary invasive breast cancer. Ductal carcinoma *in situ* was not included as an outcome. Information on breast cancer was self-reported and included date of diagnosis and treatment. There were 4,460 women with breast cancer in the study, including 4,072 prevalent cases and 388 incident cases. Prevalent cases were defined as those diagnosed before the date of completion of the baseline questionnaire. Incident cases were those that were diagnosed in the follow-up period (i.e., after study enrollment). To qualify as an incident case, the subject would have reported no personal history of breast cancer in the baseline questionnaire but a diagnosis of cancer in one of the follow-up questionnaires. **Figure 1** provides an overview of the study population for each statistical approach.

### Statistical approach 1: Prevalent cases only

In the first analytic approach, women were eligible if they had a diagnosis of a first primary invasive breast cancer at or prior to study enrollment (i.e., at or prior to the time of completion of the baseline questionnaire; **Fig. 1**). Of the 11,950 women who were initially eligible, we excluded women who had a prior diagnosis of ovarian cancer ($n = 1,707$), who were missing information on oophorectomy status ($n = 223$), who had undergone a prophylactic bilateral mastectomy prior to oophorectomy ($n = 179$), who were missing relevant information on ovarian cancer ($n = 87$) or breast cancer status ($n = 74$) such as date of diagnosis) or who were missing information on date of birth or date of baseline questionnaire completion ($n = 2$). After these exclusions, a total of 9,678 subjects qualified for inclusion in the analysis including 4,072 women with breast cancer (potential cases) and 5,676 women without breast cancer (potential controls).

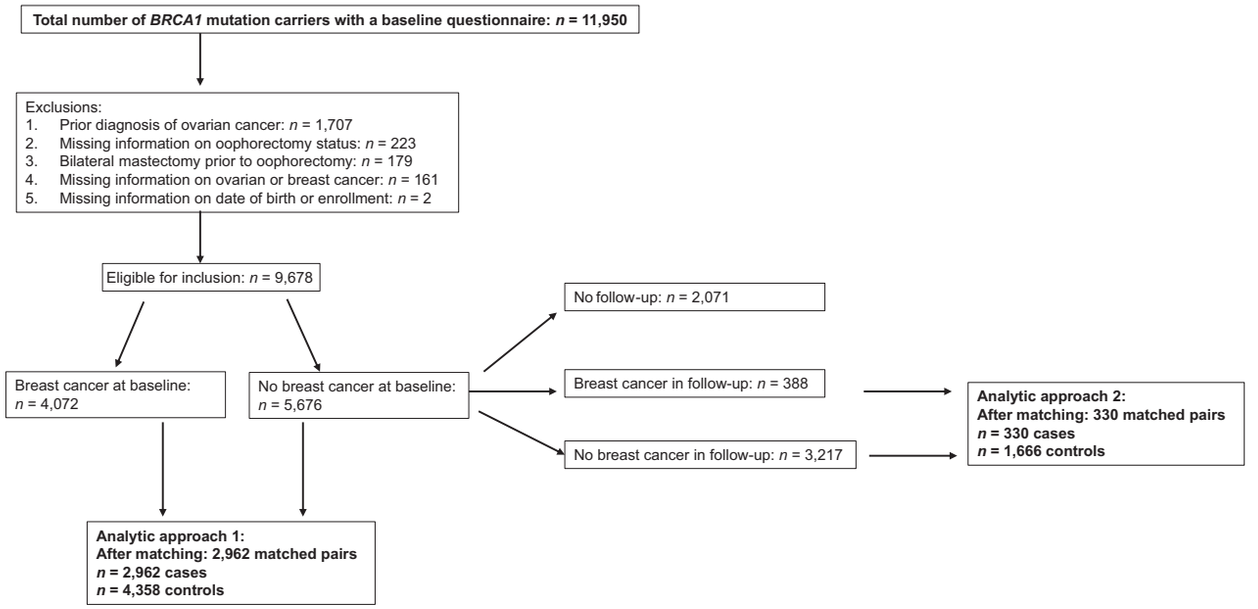


**Figure 1.**
Overview of study population included in each statistical approach.

### Matching

One or more control subjects were selected for each case subject and matched according to year of birth (within one year) and country of residence. A control was eligible to be matched to a given case if the date of interview or date of prophylactic bilateral mastectomy in the matched control occurred at or after the year of breast cancer diagnosis of the case. Each case matched to at least one control (range one to four). Of the 4,072 women with breast cancer, we were able to identify one or matched controls for 2,962 (73%).

### Statistical approach 2: Incident cases only

#### Study subjects available for analysis

A total of 6,840 women with a *BRCA1* mutation were potentially eligible for inclusion in the second analytic approach (**Fig. 1**). These women had no previous diagnosis of breast, ovarian, fallopian tube, or other cancer diagnosis prior to study entry (baseline questionnaire). Women who had no follow-up information were excluded ($n = 1{,}555$). Subjects were not eligible for inclusion if they had undergone a prophylactic bilateral mastectomy at enrollment ($n = 228$) or who were missing information on mastectomy ($n = 150$) or oophorectomy status ($n = 30$). We also excluded women who were greater than age 85 at baseline ($n = 4$), had a unilateral oophorectomy prior to baseline and a second unilateral oophorectomy in the follow-up period ($n = 19$), or had missing information on date of birth or vital status ($n = 12$). After applying these exclusions, 3,515 subjects qualified for inclusion in the final analysis. Among these, 388 women developed an invasive breast cancer in the follow-up period (potential cases) and 3,127 did not develop breast cancer (potential controls).

#### Matching

One or more control subjects were selected for each case subject and matched according to year of birth (within one year), date of baseline questionnaire (within two years) and country of residence. A control was eligible to be matched to a given case if her date of last follow-up was after the date of diagnosis of breast cancer of the case, and if the control did not have a preventive mastectomy prior to the date of diagnosis of the matched case. Among the 388 eligible incident cases, we were able to identify one or more matched controls for 330 (85.1%). Each case was matched to at least one control (range 1 to 13) for a total of 1,666 controls.

### Statistical analyses

For each data set, a matched case–control analysis was performed to evaluate the association between oophorectomy and the risk of breast cancer. Continuous variables were compared between cases and controls were compared using the Student $t$ test, while categorical variables were compared using a $\chi^2$ test. Conditional logistic regression was used to estimate the ORs and 95% CIs for breast cancer associated with oophorectomy. The following covariates were included in the multivariate model: parity (0, 1, 2, ≥3) and oral contraceptive use (ever, never). For the controls, we only considered exposures that took place prior to the date of diagnosis of the matched case. We performed subgroup analyses to evaluate the relationship between oophorectomy and risk by age at oophorectomy, age at diagnosis, years (or time) since oophorectomy, and country of residence.

The SAS statistical package, version 9.1.3 (SAS Institute, Cary, NC) was used to conduct the analyses. $P$ values were based on two-sided tests and were considered statistically significant if $P < 0.05$.

## Results

### Statistical approach 1: Prevalent cases only

For the first analytic approach, we only included women who had a diagnosis of breast cancer at or prior to the time of enrollment into our longitudinal study (i.e., prevalent cases) and matched controls (**Table 1**). Few women had a bilateral oophorectomy (3.7% in the cases and 5.7% in the controls). Otherwise, the cases and controls were well-matched. There was a significant inverse association between oophorectomy and the risk of developing breast cancer (**Table 2**). The adjusted OR was 0.43 (95% CI, 0.34–0.55; $P < 0.0001$). The association

**Table 1.** Characteristics of breast cancer cases and controls, by analytic approach.

| Variables | Analytic approach 1 *Prevalent cases only* Cases ($n = 2,962$) | Analytic approach 1 *Prevalent cases only* Controls ($n = 4,358$ in 2,962 sets) | Analytic approach 2 *Incident cases only* Cases ($n = 330$) | Analytic approach 2 *Incident cases only* Controls ($n = 1,548$ in 330 sets) |
|---|---|---|---|---|
| Year of birth (SD) | 1,958.8 (11.6) | 1,959.2 (11.3) | 1,965.2 (11.5) | 1,965.0 (11.5) |
| Mean (SD) age at baseline years | 46.4 (10.1) | 46.3 (10.4) | 39.6 (11.0) | 40.1 (10.8) |
| Age at breast diagnosis (SD) years | 40.5 (8.4) | n/a[a] | 44.8 (10.2) | n/a |
| Oophorectomy, *n* (%)[b] | | | | |
| No | 2,854 (96.4%) | 4,109 (94.3%) | 217 (65.8%) | 1,161 (75.0%) |
| Yes | 108 (3.7%) | 249 (5.7%) | 113 (34.6%) | 387 (25.1%) |
| Before baseline | 108 | 249 | 32 | 124 |
| After/at baseline | 0 | 0 | 81 | 263 |
| Age at oophorectomy (SD) | 42.7 (7.6) | 41.8 (7.7) | 45.2 (6.1) | 45.3 (6.6) |
| Parity, *n* (%)[b] | | | | |
| No parity | 548 (18.9%) | 1,074 (25.3%) | 91 (28.1%) | 417 (27.1%) |
| Yes | 2,354 (81.2%) | 3,167 (74.7%) | 233 (71.9%) | 1,124 (72.9%) |
| Mean (SD) | 1.8 (1.3) | 1.6 (1.3) | 1.5 (1.3) | 1.5 (1.2) |
| Missing | 60 | 117 | 6 | 7 |
| Family history of breast cancer | | | | |
| Number of first-degree relatives affected | | | | |
| All relatives | | | | |
| 0 | 1,016 (50.3%) | 1,250 (44.3%) | 110 (36.8%) | 658 (42.3%) |
| 1 | 741 (36.7%) | 1,227 (43.4%) | 157 (52.2%) | 588 (43.1%) |
| 2 or more | 265 (13.0%) | 348 (12.3%) | 32 (10.6%) | 117 (8.6%) |
| Missing | 940 | 1,533 | 31 | 185 |
| Relatives diagnosed under age 50 | | | | |
| 0 | 1,421 (61.6%) | 1,573 (55.9%) | 143 (48.0%) | 796 (58.8%) |
| 1 | 603 (29.9%) | 1,015 (36.0%) | 127 (42.6%) | 498 (36.6%) |
| 2 or more | 172 (8.5%) | 228 (8.0%) | 28 (9.4%) | 66 (4.8%) |
| Missing | 946 | 1,542 | 32 | 188 |
| Hormone replacement therapy[b], *n* (%) | | | | |
| Yes | 150 (5.1%) | 254 (5.9%) | 66 (20.1%) | 246 (16.1%) |
| No | 2,786 (94.9%) | 4,053 (94.1%) | 262 (79.9%) | 1,278 (83.9%) |
| Missing | 26 | 51 | 2 | 24 |
| Screening MRI[b], *n* (%) | | | | |
| Yes | 129 (6.1%) | 250 (7.2%) | 163 (52.8%) | 682 (46.2%) |
| No | 1,980 (93.9%) | 3,237 (92.8%) | 146 (47.2%) | 793 (53.8%) |
| Missing | 853 | 871 | 21 | 73 |
| Oral contraceptive use[b], *n* (%) | | | | |
| Ever use | 1,708 (58.5%) | 2,573 (59.5%) | 176 (53.3%) | 791 (51.2%) |
| Never | 1,212 (41.5%) | 1,721 (40.1%) | 154 (46.7%) | 755 (48.8%) |
| Mean used years (SD) | 3.7 (5.2) | 3.4 (4.7) | 3.3 (4.4) | 2.8 (3.9) |
| Missing, *n* | 42 | 64 | 0 | 2 |
| Ethnicity, *n* (%) | | | | |
| Jewish | 385 (13.0%) | 578 (13.3%) | 25 (7.6%) | 85 (5.5%) |
| French Canadian | 116 (3.9%) | 133 (3.1%) | 8 (2.4%) | 39 (2.5%) |
| Other white | 2,400 (81.0%) | 3,589 (82.4%) | 290 (87.9%) | 1,416 (91.5%) |
| Other | 61 (2.1%) | 58 (1.3%) | 7 (2.1%) | 8 (0.5%) |
| Country of residence, *n* (%) | | | | |
| Poland | 1,114 (37.6%) | 1,770 (40.6%) | 221 (67.0%) | 1,192 (77.0%) |
| USA | 867 (29.3%) | 1,055 (24.2%) | 54 (16.4%) | 153 (9.9%) |
| Canada | 599 (20.2%) | 892 (20.5%) | 52 (15.8%) | 199 (12.9%) |
| Norway | 119 (4.0%) | 299 (6.9%) | — | — |
| Netherlands | 79 (2.7%) | 116 (2.7%) | — | — |
| Israel | 81 (2.7%) | 97 (2.2%) | — | — |
| Austria | 50 (1.7%) | 64 (1.5%) | 3 (0.9%) | 4 (0.3%) |
| Italy | 40 (1.4%) | 51 (1.2%) | — | — |
| Bahamas | 9 (0.3%) | 10 (0.2%) | — | — |
| China | 2 (0.1%) | 2 (0.1%) | — | — |
| Spain | 1 (0.0%) | 1 (0.0%) | — | — |
| Caribbean | 1 (0.0%) | 1 (0.0%) | — | — |

[a]n/a, not applicable.

[b]Among the cases, if an oophorectomy was performed following or at the time of a breast cancer diagnosis, then it was included as 'no oophorectomy'; among the controls, if the age at oophorectomy was at or following the breast cancer diagnosis of the matched case then it was included as 'no oophorectomy'. Similar criteria were applied for parity, use of hormone replacement therapy or oral contraceptives, and MRI screening.

**Table 2.** Association between oophorectomy and risk of breast cancer in *BRCA1* mutation carriers, by analytic approach. Matched analysis.

| | Analytic approach 1 *Prevalent cases only* | | | Analytic approach 2 *Incident cases only* | | |
|---|---|---|---|---|---|---|
| | Number of cases/controls | Adjusted OR (95% CI)[a] | *P* | Number of cases/controls | Adjusted OR (95% CI)[a] | *P* |
| No oophorectomy | 2,854/4,109 | 1.00 (reference) | | 217/1,161 | 1.00 (reference) | |
| Oophorectomy | 108/249 | 0.43 (0.34–0.55) | <0.0001 | 113/387 | 1.21 (0.87–1.70) | 0.26 |
| No oophorectomy | 2,854/4,109 | 1.00 (reference) | | 217/1,161 | 1.00 (reference) | |
| Oophorectomy prior to baseline | 108/249 | 0.43 (0.34–0.55) | <0.0001 | 32/124 | 0.94 (0.58–1.55) | 0.82 |
| Oophorectomy after baseline | NA | NA | | 81/263 | 1.37 (0.94–2.00) | 0.10 |
| No oophorectomy | 2,854/4,109 | 1.00 (reference) | | 217/1,161 | 1.00 (reference) | |
| ≤40 years | 40/113 | 0.37 (0.25–0.54) | <0.0001 | 25/97 | 1.11 (0.66–1.86) | 0.69 |
| 41–50 years | 51/105 | 0.48 (0.34–0.69 | <0.0001 | 70/213 | 1.55 (1.02–2.37) | 0.04 |
| >50 years | 17/31 | 0.50 (0.27–0.94) | 0.03 | 18/77 | 0.73 (0.37–1.42) | 0.35 |
| By country | | | | | | |
| United States | (867 matched sets) | | | (54 matched sets) | | |
| No oophorectomy | 829/963 | 1.00 (reference) | | 27/95 | 1.00 (reference) | |
| Had oophorectomy | 46/92 | 0.48 (0.33–0.71) | 0.0002 | 27/58 | 1.97 (0.85–4.79) | 0.11 |
| Canada | (599 matched sets) | | | (52 matched sets) | | |
| No oophorectomy | 575/837 | 1.00 (reference) | | 29/125 | 1.00 (reference) | |
| Had oophorectomy | 24/55 | 0.40 (0.24–0.68) | 0.0006 | 23/74 | 1.08 (0.48–2.44) | |
| Poland | (1,114 matched sets) | | | (221 matched sets) | | 0.85 |
| No oophorectomy | 1,089/1,707 | 1.00 (reference) | | 158/937 | 1.00 (reference) | |
| Had oophorectomy | 25/63 | 0.37 (0.22–0.61) | 0.0001 | 63/255 | 1.02 (0.66–1.56) | |
| Others | (382 matched sets) | | | (3 matched sets) | | 0.94 |
| No oophorectomy | 369/602 | 1.00 (reference) | | 3/4 | 1.00 (reference) | |
| Had oophorectomy | 13/39 | 0.46 (0.23–0.94) | 0.03 | 0/0 | Na | |

[a]Adjusted for oral contraceptive use (ever/never) and parity (0, 1, 2, ≥3) and estimated using conditional logistic regression.

remained significant in the analysis stratified by age at oophorectomy and country of residence (**Table 2**). The level of risk reduction was significant both for women diagnosed with breast cancer prior to age 50 (OR = 0.38; 95% CI, 0.28–0.52; $P < 0.0001$ and after age 50 (OR = 0.56; 95% CI, 0.36–0.83; $P = 0.004$; **Table 3**). We also evaluated the association by time since oophorectomy. The OR was 0.44 (95% CI, 0.30–0.62) for those who underwent oophorectomy 1 to 2 years prior to diagnosis, 0.34 (95% CI, 0.21–0.58) for those who underwent oophorectomy 3 to 5 years prior to diagnosis, and 0.33 (95% CI, 0.18–0.59) for those who underwent oophorectomy 6 to 10 years prior

**Table 3.** Association between oophorectomy and risk of breast cancer in *BRCA1* mutation carriers by age at diagnosis and timing since oophorectomy, by analytic approach. Matched analysis.

| | Analytic approach 1 *Prevalent cases only* | | | Analytic approach 2 *Incident cases only* | | |
|---|---|---|---|---|---|---|
| | Number of cases/controls | Adjusted OR (95% CI)[a] | *P* | Number of cases/controls | Adjusted OR (95% CI)[a] | *P* |
| Age at breast cancer diagnosis | | | | | | |
| ≤50 | (2,621 matched sets) | | | (229 matched sets) | | |
| No oophorectomy | 2,559/3,839 | 1.00 (reference) | | 181/1,037 | 1.00 (reference) | |
| Had oophorectomy | 62/170 | 0.38 (0.28–0.52) | <0.0001 | 48/169 | 1.41 (0.89–2.23) | 0.15 |
| >50 | (341 matched sets) | | | (101 matched sets) | | |
| No oophorectomy | 295/270 | 1.00 (reference) | | 36/124 | 1.00 (reference) | |
| Had oophorectomy | 46/79 | 0.56 (0.36–0.83) | 0.004 | 65/218 | 1.06 (0.65–1.73) | 0.83 |
| Interval between oophorectomy and breast cancer, years | | | | | | |
| No oophorectomy | 2,854/4,109 | 1.00 (reference) | <0.0001 | 217/1,161 | 1.00 (reference) | |
| 1–2 | 44/108 | 0.44 (0.30–0.62) | <0.0001 | 35/129 | 1.26 (0.81–1.96) | 0.31 |
| 3–5 | 20/57 | 0.34 (0.21–0.58) | 0.0002 | 38/119 | 1.40 (0.87–2.26) | 0.16 |
| 6–10 | 17/47 | 0.33 (0.18–0.59) | 0.17 | 26/97 | 1.05 (0.59–1.88) | 0.86 |
| 11 and more | 27/32 | 0.69 (0.40–1.18) | | 14/42 | 0.87 (0.40–1.87) | 0.72 |

[a]Adjusted for oral contraceptive use (ever/never) and parity (0, 1, 2, ≥3) and estimated using conditional logistic regression.
[b]For cases, the interval represents the number of years between the age at breast cancer diagnosis and the age at oophorectomy; while for the controls, the interval is the difference between the age at breast cancer diagnosis of the matched case and the age at oophorectomy of the control.

to their breast cancer diagnosis and 0.69 (95% CI, 0.40–1.18) for those who had surgery 11 or more years prior to their diagnosis

### Statistical approach 2: Incident cases only

In the second analytic approach (nested case–control study), cases were women who developed breast cancer in the follow-up period (i.e., incident breast cancer). **Table 1** summarizes the baseline characteristics of the 330 incident breast cancer cases and 1,548 controls included in this analysis. A high proportion of cases and controls had an oophorectomy (34.6% and 25.1%, respectively). There was no overall association between oophorectomy and the risk of developing breast cancer in the follow-up period (OR = 1.21; 95% CI, 0.87–1.70; **Table 2**). The association did not vary significantly by age at oophorectomy, country of residence, or timing of oophorectomy (prior to or following study enrollment). There was no significant association in the analysis stratified by age at diagnosis or time since oophorectomy (**Table 3**).

## Discussion

Here, we conducted two similar, but complementary, matched analyses of preventive oophorectomy and the risk of breast cancer among women with a pathogenic *BRCA1* mutation. Our goal was to see if, using the same analytic approach, a different selection strategy of study subjects from the same cohort impacted on the results. All subjects were enrolled in our ongoing cohort of *BRCA* mutation carriers. In the first analysis, which included women who reported a history of breast cancer prior to study enrollment (baseline questionnaire), we observed a highly significant protective effect of oophorectomy, conferring a 57% reduction in risk. In the second, prospective approach, we observed no protective association between oophorectomy and the risk of breast cancer (OR = 1.21). The result of the second analysis is in line with our 2017 prospective study on the same topic, which also excluded women with a history of cancer (3).

There are several reasons to accept the results of the second (nested case–control study) over the results over the first (traditional) case–control study. The cases in the first analysis on average, completed the baseline questionnaire 5.9 years after the diagnosis of breast cancer. The majority were aware of their mutation status at the time of breast cancer diagnosis and hence were not aware that they were at increased risk of ovarian cancer prior to the diagnosis and hence the oophorectomy rate was very low. However, the controls in the first study generally were tested after a mutation was found in a family member and most were aware of their mutation status (and their elevated risk of ovarian cancer) before they completed the baseline questionnaire. The breast cancer cases in the second analysis on average, developed breast cancer 5.2 years after completing the baseline questionnaire. The oophorectomy rate in both cases and controls was much higher for the incident subjects than for the prevalent subjects. In particular, among prevalent cases, only 3.7% had an oophorectomy prior to diagnosis, whereas among incident cases, 34.6% of women had an oophorectomy prior to breast cancer diagnosis. Furthermore, for the prevalent cases, only 6.1% had a screening MRI prior to diagnosis, whereas for the incident cases, 52.8% had a screening MRI prior to diagnosis. From this, we can assume that knowledge of mutation status influenced the decision to have an oophorectomy. Also, the consistency of the ORs generated in the prevalence study, across age of oophorectomy, age of diagnosis, and time since diagnosis, collectively suggests the presence of a ubiquitous bias. There is a potential for survivorship bias in case–control studies that is not present in prospective studies, and in our prospective study, the data and pathology information was collected in detail at the time of diagnosis.

Based on the results of this study, we conclude that surgical removal of both the ovaries (with and without fallopian tube removal) likely does not reduce the risk of *BRCA1*-associated breast cancer. These findings emphasize how various sources of bias can influence results in studies involving individuals with either a genetic predisposition or strong family history of disease, and furthermore, may erroneously influence clinical care recommendations (17, 18).

Initial reports on this topic demonstrated an approximately 50% reduction in breast cancer risk with oophorectomy (1). In 2015, Heemskerk-Gerriten and colleagues, raised methodologic concerns of these earlier studies outlining that the most common errors in these initial studies (including our 2005 report) were the inclusion of women with a history of cancer at baseline (cancer-induced testing bias) and not treating oophorectomy as a time-dependent variable (immortal-time bias). Both of these biases inadvertently overestimate the level of breast cancer risk reduction due to oophorectomy. In contrast, the more recent prospective studies that have addressed these issues have generally shown no significant association (2–4, 15).

In a large multi-center study, Mavvadat and colleagues reported no association between oophorectomy and *BRCA1* breast cancer risk ($n = 2{,}272$, 269 incident cases and 5.4 years of follow-up), irrespective of age at surgery (HR = 1.23; 95% CI, 0.94–1.61; ref. 4). Similarly, Mai and colleagues reported no association in their (smaller) report of oophorectomy and breast cancer risk reduction in the Gynecologic Oncology Group Protocol-0199 (GOG-0199) where women elected ovarian cancer screening or oophorectomy at enrollment (15). Among 242 women with a *BRCA1* mutation and no prior history of disease HR for breast cancer in the oophorectomy versus screening group was 1.22 (95% CI, 0.50–3.00).

One purely prospective study did show an impact of oophorectomy on breast cancer risk in *BRCA1* carriers (16). In their analysis of 444 *BRCA1* mutation carriers and 54 incident cancers after 4.3 years of follow-up, Stjepanovic and colleagues saw a significant protective effect of premenopausal oophorectomy for *BRCA1* mutation carriers (HR = 0.45; 95% CI, 0.22–0.92). There were three main differences in their analytic approach and ours: (i) they excluded women who had an oophorectomy prior to baseline; (ii) they excluded women diagnosed with breast cancer within 6 months of the follow-up; and (iii) the observation period started 6 months after genetic testing (event-free bias). However, in our study, excluding women who had oophorectomy prior to baseline did not materially affect our results. Only 27 of the 330 incident breast cancers occurred within six months of baseline and if we excluded these women and their matched controls, the hazard ratio becomes 1.31. Perhaps most importantly, our study was based on 330 incident cancers, compared with 54 in the Stjepanovic and colleagues' article. The median age of breast cancer was 41.1 years in the Stjepanovic and colleagues' article versus 43.0 years in the 330 cases in our article. Stjepanovic and colleagues also comprehensively summarized the potential biases of the key studies on the topic (16).

On the basis of these studies, our principal concern with bias is the inclusion of women with a past history of breast cancer. Choi and colleagues concluded that among *BRCA1* mutation carriers, oophorectomy was associated with a significantly reduced risk of breast cancer, that decays (or wanes) over time and reaches a threshold five years after surgery (5). The HR was 0.28 (95% CI, 0.10–0.63) within five years and was 0.64 (95% CI, 0.38–0.97) five or

more years after surgery. The cumulative incidence was 49.7% women with an oophorectomy prior to age 40 and 61% and for those without an oophorectomy. In this study, the authors included women with unknown *BRCA1* mutation status as well as women who tested positive for a mutation. Notably, there was low proportion of oophorectomy in the women in their study (3%), similar to what we observed with our first analytic approach (4%–6%). Choi and colleagues initiated follow-up at age 16, well before the family was ascertained and the subjects had genetic testing. Their study is therefore also susceptible to cancer-induced testing bias. In contrast, we only included women with a known pathogenic mutation and excluded women with breast cancer prior to study entry. In our nested case–control study, all the women were aware of their mutation status at the outset.

There are several explanations to reconcile the lack of an association between ovary removal (the predominant source of sex hormones in premenopausal women) and risk of breast cancer in women with a *BRCA1* mutation. *BRCA1* mutation carriers have a propensity to develop hormone receptor–negative disease, and thus, are less likely to be influenced by estrogen deprivation (19). We have recently published that oophorectomy was not associated with the risk of developing a contralateral breast cancer (OR = 0.98; 95% CI, 0.71–1.36), although there was some evidence of risk reduction among those diagnosed with hormone receptor–positive disease and those diagnosed prior to age 50 (20). Whether primary prevention with tamoxifen impacts risk is not yet known.

There are several strengths and limitations of the current study. We included a large number of women with a known *BRCA1* mutation, and thus, we were able to match on important characteristics such as year of birth and country of residence. The longitudinal nature of our study allowed for the collection of detailed information on various important exposures and covariates. We relied on self-reported exposure and outcome information, the accuracy and validity of both self-reported oophorectomy and breast cancer have studied (21, 22). Furthermore, 87.6% (289 of the 330) of the incident breast cancer cases were confirmed by review of pathology reports or medical records. We did not routinely collect pathology reports on the prevalent cases. We did not differentiate between oophorectomy and salpingo-oophorectomy, although there is no reason to suspect a differential effect of tubal removal on risk of breast cancer. Finally, we did not consider the use of progesterone-containing hormone replacement therapy after oophorectomy, a possible risk factor for *BRCA1* breast cancer (23).

In summary, two distinct analyses of the same dataset illustrate how the inclusion of women who are unaware of their mutation status (and with prevalent breast cancer) may unduly influence the risk estimate for the association of oophorectomy and breast cancer. On the basis of our findings and those of others, we conclude that oophorectomy is unlikely to be a strong determinant of *BRCA1* breast cancer development. Nevertheless, we endorse the recommendation that preventive bilateral salpingo-oophorectomy should be recommended to women with a *BRCA1* mutation at age 35 to reduce the risk of ovarian and fallopian tube cancer.

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## Authors' Contributions

**J. Kotsopoulos:** Conceptualization, formal analysis, supervision, methodology, writing–original draft, writing–review and editing. **J. Lubinski:** Writing–review and editing. **J. Gronwald:** Writing–review and editing. **J. Menkiszak:** Writing–review and editing. **J. McCuaig:** Writing–review and editing. **K. Metcalfe:** Writing–review and editing. **W.D. Foulkes:** Writing–review and editing. **S.L. Neuhausen:** Writing–review and editing. **S. Sun:** Writing–review and editing. **B.Y. Karlan:** Writing–review and editing. **A. Eisen:** Writing–review and editing. **N. Tung:** Writing–review and editing. **O.I. Olopade:** Writing–review and editing. **F.J. Couch:** Writing–review and editing. **T. Huzarski:** Writing–review and editing. **L. Senter:** Writing–review and editing. **L. Bordeleau:** Writing–review and editing. **C.F. Singer:** Writing–review and editing. **C. Eng:** Writing–review and editing. **R. Fruscio:** Writing–review and editing. **T. Pal:** Writing–review and editing. **P. Sun:** Formal analysis. **S.A. Narod:** Conceptualization, formal analysis, supervision, funding acquisition, methodology, writing–original draft, writing–review and editing.

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