

Projected Benefit of Bilateral Salpingo-Oophorectomy by Age in BRCA Carriers

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IMPORTANCE Women with a *BRCA1* or *BRCA2* variant face a high lifetime risk of ovarian cancer and are often advised to undergo preventive surgery (bilateral salpingo-oophorectomy [BSO]) before cancer develops. The recommended age of BSO is 35 years for *BRCA1* carriers and is 45 years for *BRCA2* carriers, but some women choose to delay surgery until the age of menopause; there is no standard upper age at which surgery is no longer advised.

OBJECTIVE To estimate the residual lifetime risk of ovarian cancer among BRCA carriers by current age and projected age at BSO.

DESIGN, SETTING, AND PARTICIPANTS This was a prospective cohort study in an international cohort of BRCA carriers monitored for incident ovarian cancer. A life table analysis used age-specific ovarian cancer incidence rates and competing mortality rates to estimate lifetime risk of ovarian cancer among women with a *BRCA1* or *BRCA2* pathogenic variant with both ovaries intact and no prior ovarian cancer at baseline. Patients were recruited between 1995 and 2024 across 24 international centers, and the mean (SD) follow-up was 4.4 (3.9) years.

EXPOSURE Timing of BSO, defined as immediate BSO, delayed BSO, or no BSO.

MAIN OUTCOME AND MEASURES Residual lifetime risk of ovarian cancer.

RESULTS The cohort consisted of 4286 *BRCA1* and 1427 *BRCA2* carriers between the ages of 30 and 74 years at baseline (mean [SD] age, 42.0 [10.8] years). There were 249 incident ovarian cancers in the follow-up period. The lifetime risk of ovarian cancer was 55.0% (95% CI, 48.8-61.9) for a *BRCA1* carrier and 24.1% (95% CI, 15.1-36.6) for a *BRCA2* carrier. A 30-year-old *BRCA1* carrier with BSO delayed to age 50 years had a projected residual ovarian cancer risk of 23.9% (95% CI, 20.7-27.4). At age 75 years, the residual risk of ovarian cancer was estimated to be 8.4% (95% CI, 1.7-22.7) for a *BRCA1* carrier and 3.7% (95% CI, 0.1-22.7) for a *BRCA2* carrier.

CONCLUSIONS AND RELEVANCE The residual risk of ovarian cancer for older women in good health is sufficiently high to consider preventive surgery. *BRCA1* carriers who defer BSO until age 50 years may face a substantial risk of developing ovarian cancer.

 [Invited Commentary](#)

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Inherited variants in the *BRCA1* and *BRCA2* genes put a woman at high lifetime risk of ovarian or fallopian tube cancer (hereafter, *ovarian cancer*) which has been estimated to be 40% for *BRCA1* carriers and 20% for *BRCA2* carriers.^{1,2} The case-fatality rate from ovarian cancer in carriers (and non-carriers) is high, and therefore it is ideal to determine the carrier status of a woman before she develops cancer and to offer preventive surgery, which has been shown to reduce the risk of ovarian cancer and all-cause mortality.³⁻⁷ Screening for ovarian cancer through serum CA-125 monitoring or transvaginal ultrasound has not been proven to be effective.⁸

The decision to have bilateral salpingo-oophorectomy (BSO) requires a discussion between the health care professional and the patient, and several considerations need to be raised. Current age is the strongest predictor of lifetime residual risk of ovarian cancer among variant carriers. Competing causes of death also influence lifetime risk, as a woman may die of another cause prior to developing ovarian cancer. The older a woman is, the lower her residual lifetime risk of cancer and, consequently, the expected benefit of BSO diminishes with age. Risk factors for ovarian cancer among variant carriers include a family history of ovarian cancer, use of oral contraceptives and tubal ligation (both are protective), and the location and type of variant.^{2,9-12} Polygenic risk scores can help refine the risk,¹³ but these are not in widespread clinical use.

Based on the published age-specific risks of cancer, the probability of identifying a prevalent occult cancer at surgery, and the postsurgical risk of peritoneal cancer, we and others recommend BSO at age 35 years for *BRCA1* carriers and at age 45 years for *BRCA2* carriers.¹⁴ Many women choose to delay surgery until menopause or completion of their family to preserve fertility or avoid the symptoms of surgically induced menopause. Some will have a salpingectomy followed by BSO at the age of menopause. Many women do not undergo testing until late in life, and they may question the benefit of preventive surgery at an older age.

It may therefore be helpful to have a measure of the individual's lifetime residual risk of ovarian cancer, based on the patient's current age and, should the patient choose to delay prophylactic surgery, the projected age at BSO. It is also pertinent to ask at what age preventive BSO may no longer be advisable. The answers to these questions depend on a woman's health status, including breast cancer history, personal preferences, the potential complications of surgery, residual risk of ovarian cancer, and life expectancy. With this in mind, we estimated the age-specific incidence of ovarian cancer among carriers of *BRCA1* and *BRCA2* pathogenic variants and applied these incidence rates with competing causes of death to theoretical cohorts of women to estimate a residual lifetime risk of being diagnosed with ovarian cancer according to current age and age at planned BSO.

Methods

Study Design and Setting

Study participants were identified from a prospective, international cohort study across 24 centers including women

Key Points

Question What is the residual lifetime risk of ovarian cancer for BRCA carriers according to age at the time of bilateral salpingo-oophorectomy (BSO)?

Findings In this study, we analyzed prospective data from 5713 BRCA carriers and applied the life table approach to estimate the residual ovarian cancer risk according to variant type, current age, and projected age at BSO.

Meaning Clinical decision support tools can help personalize the risk of ovarian cancer and inform decisions regarding the timing and projected benefit of BSO in BRCA carriers.

carrying a pathogenic germline variant in the *BRCA1* or *BRCA2* genes. Genetic testing was conducted based on a known family variant or due to a suggestive personal or family history. Variant detection was done using a range of validated techniques, and all variants were confirmed by direct DNA sequencing. All centers received approval from their institutional review board, and each participant provided written informed consent. Recruitment took place between 1995 and 2024, and the mean (SD) follow-up was 4.4 (3.9) years.

Data Collection

Each participant filled out a baseline questionnaire at study entry and a follow-up questionnaire every 2 years thereafter to update information on the incidence of all newly diagnosed cancers. Ovarian cancer diagnoses were based on self-report (by the patient or next of kin) and included epithelial (serous, endometrioid, mucinous, and other) cancers originating in the ovary and/or fallopian tubes. In the event of a cancer diagnosis or death from cancer, pathology and/or medical records were requested to confirm the primary site and the histological type of tumor.

Study Population

Eligible participants consisted of *BRCA1* or *BRCA2* carriers, aged 30 to 74 years at baseline, with no personal history of ovarian cancer at or before study entry, and who had not undergone BSO prior to enrollment. Participants must have completed a baseline questionnaire and at least 1 follow-up questionnaire in the accrual period. The eligible cohort consisted of 5713 BRCA variant carriers; 4286 with a *BRCA1* variant and 1427 with a *BRCA2* variant.

Statistical Analysis

Empirical Ovarian Cancer Risks

In the first part of the study, we estimated age-specific ovarian cancer incidence rates and cumulative ovarian cancer risk in *BRCA1* and *BRCA2* variant carriers. Participants were monitored from the date of study accrual until the first of either (1) date of ovarian cancer diagnosis, (2) date of BSO, (3) date of completion of a last follow-up questionnaire, or (4) date of death from any cause. Age-specific ovarian cancer incidence rates were estimated in 5-year age intervals by dividing the number of ovarian cancers observed in each interval by the

number of person-years at risk. Rates were expressed as percentages per year. We estimated the actuarial cumulative risk of ovarian cancer from age 30 years to age 80 years as 1 minus the left-truncated Kaplan-Meier survival estimate. Analysis was done separately for *BRCA1* and *BRCA2* carriers, and we stratified by personal history of breast cancer and family history of ovarian cancer. We obtained 95% CIs for incidence rates using 1000 individual-level bootstrap resamples of the analytic cohort. Analyses were performed using SAS Software version 9.4 (SAS Institute).

Modeling Residual Risks of Ovarian Cancer

In the second part of the study, we conducted a model-based analysis to estimate the residual lifetime risk of ovarian cancer among BRCA carriers according to their current age and planned age at BSO. Analyses were performed separately for *BRCA1* and *BRCA2* carriers. For each current age, we estimated the cumulative ovarian cancer risk at which BSO was performed immediately (at current age), or delayed BSO until a later age, and no BSO. This life table model was reported in accordance with relevant ISPOR-SMDM Modeling Good Research Practices, including model conceptualization, data inputs, transparency, and uncertainty analysis.¹⁵

The life table analysis was conducted for current ages ranging from 30 to 75 years in 5-year increments. We considered BSO at 5-year increments from a current age to age 75 years, as well as no BSO. For each scenario, women were monitored from their current age until an ovarian cancer diagnosis, death, or age 110 years. The analysis included 130 scenarios in total, defined by all possible combinations of variant type, current age, and age at BSO. Age-specific ovarian cancer incidence rates were derived from the empirical analysis described above. We used Poisson regression with smoothing splines and an offset for person-time to estimate ovarian cancer incidence rates from ages 30 years to 80 years. A spline with 3 degrees of freedom was used to capture nonlinear associations between age and ovarian cancer incidence while minimizing the risk of overfitting. Because estimates beyond this age were not available from the original data, the age-specific ovarian cancer rate was truncated at age 80 years and carried forward to age 110 years. Age-specific mortality rates for females in the US were obtained from the Surveillance, Epidemiology, and End Results (SEER) 17 database.¹⁶ Mortality rates included deaths from all causes excluding deaths from ovarian and breast cancer (eTable 1 in Supplement 1). Linear interpolation of the log-transformed 5-year mortality rates was used to estimate mortality rates to age 110 years.

For each scenario, a life table analysis was done on weekly intervals from the current age to age 110 years. At each interval, women were assigned probabilities of an ovarian cancer diagnosis and death according to their attained age-specific ovarian cancer incidence rate and mortality rate. Death was treated as a competing event, such that women who died were no longer at risk for ovarian cancer. We assumed that BSO eliminated the risk of ovarian cancer from the age at BSO onward. We assumed no occult cancers were identified at the time of BSO, though occult cancers were included in the empirical incidence rates derived above. The analysis output was a residual

risk of ovarian cancer. 95% CIs were obtained using 1000 individual-level bootstrap resamples of the empirical BRCA cohort data, with the age-specific rates, modeled rates, and life table estimates recalculated for each bootstrap sample. We examined empirical differences in cumulative ovarian cancer risk according to personal history of breast cancer and family history of ovarian cancer to determine if residual risk estimates should be adjusted for these factors. Where meaningful differences in ovarian cancer risks were observed, the model-based life table analysis was repeated for these strata. Modeling analyses were performed in R version 4.3.1 (R Foundation).

Results

In this prospective cohort study, 5713 women aged 30 to 74 years at baseline (mean [SD] age, 42.0 [10.8] years), 4286 carrying a *BRCA1* variant and 1427 carrying a *BRCA2* variant, were monitored for a mean (range) of 4.4 (0.0-15.0) years (eTable 2 in Supplement 1). Among women with available data, 2165 (37.9%) had a personal history of breast cancer at baseline, and 912 (22.1%) reported a family history of 1 or more first-degree relatives with ovarian cancer. During the follow-up period, 249 incident cases of ovarian cancer were diagnosed, 225 in *BRCA1* carriers (5.2%) and 24 in *BRCA2* carriers (1.7%). The median (IQR) age at diagnosis of ovarian cancer was 50.3 (45.0-57.1) years for *BRCA1* carriers and 57.5 (53.3-64.8) years for *BRCA2* carriers.

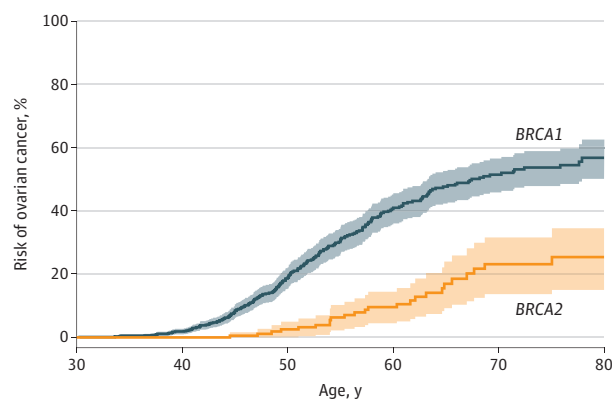
Age-specific ovarian cancer incidence rates for *BRCA1* and *BRCA2* carriers are presented in Table 1. Overall, annual incidence rates were 1.18% (95% CI, 1.04-1.34) per person-year for *BRCA1* carriers and 0.40% (95% CI, 0.25-0.57) per person-year for *BRCA2* carriers. From the Kaplan-Meier analysis, we estimated the actuarial risk of ovarian cancer from age 30 years to age 80 years to be 56.8% (95% CI, 50.1-62.6) for *BRCA1* carriers and 25.4% (95% CI 15.0-34.5) for *BRCA2* carriers (Figure). In these analyses, the follow-up is censored at death from any cause. Cumulative risk of ovarian cancer is reported according to a personal history of breast cancer (eFigures 1-3 in Supplement 1), and a family history of ovarian cancer (eFigures 4-6 in Supplement 1).

To estimate the actual expected lifetime risk of developing ovarian cancer, we generated results from a series of life table analyses as described above, incorporating age-specific ovarian cancer incidence rates (eFigure 7 in Supplement 1) and competing causes of death (eFigure 8 in Supplement 1). Based on SEER data, approximately 34% of 30-year-old women will die of another cause before reaching age 80 years, and therefore the actual risk is lower than this actuarial risk. The remaining 66% of women who are alive at age 80 years continue to be at risk of ovarian cancer. The life expectancy and residual lifetime risks of ovarian cancer by current age are presented in Table 2. We assume BSO to be fully protective and, consequently, the potential benefit of BSO at the current age is equivalent to the lifetime residual risk of ovarian cancer. The expected benefit of BSO declined from age 30 years to age 75 years. For *BRCA1* carriers, the residual lifetime risk at age 35 years was 54.8% (95% CI, 48.4-62.0), at age 50 years was 42.7% (95% CI, 34.8-51.4), and at age 75 years was 8.4% (95% CI, 1.7-22.7). For *BRCA2* carriers, the

Table 1. Age-Specific Ovarian Cancer Incidence Rates for *BRCA1* and *BRCA2* Carriers

Age group, y	<i>BRCA1</i>			<i>BRCA2</i>		
	Person-years	Ovarian cancer events, No.	Rate per 100 person-years, % (95% CI) ^a	Person-years	Ovarian cancer events, No.	Rate per 100 person-years, % (95% CI) ^a
30-34	4684.4	5	0.11 (0.02-0.21)	944.1	0	0
35-39	4529.2	12	0.26 (0.13-0.43)	1154.1	0	0
40-44	3133.5	40	1.28 (0.91-1.70)	1004.5	1	0.10 (0.00-0.31)
45-49	2072.6	49	2.36 (1.74-3.03)	779.7	3	0.38 (0.00-0.84)
50-54	1484.2	47	3.17 (2.28-4.07)	667.9	5	0.75 (0.15-1.49)
55-59	1157.7	37	3.20 (2.21-4.20)	546.3	4	0.73 (0.00-1.57)
60-64	752.7	19	2.52 (1.45-3.77)	375.9	6	1.60 (0.50-3.08)
65-69	588.2	9	1.53 (0.59-2.63)	253.7	4	1.58 (0.34-3.43)
70-74	395.3	4	1.01 (0.23-2.17)	211.6	0	0
75-79	213.0	3	1.41 (0.00-2.97)	114.4	1	0.87 (0.00-3.37)
Overall	19 010.8	225	1.18 (1.04-1.34)	6052.2	24	0.40 (0.25-0.57)

^a 95% confidence intervals were estimated using 1000 individual-level bootstrap resamples; limits correspond to the 2.5th and 97.5th percentiles of the bootstrap sample distribution.

Figure. Line Graph Showing Cumulative Risk of Ovarian Cancer by Age Among *BRCA1* and *BRCA2* Carriers

residual lifetime risk at age 35 years was 24.2% (95% CI, 15.2-36.7), at age 50 years was 22.2% (95% CI, 12.3-35.3), and at age 75 years was 3.7% (95% CI, 0.1-22.7).

The conditional nature of the lifetime risk estimates for ovarian cancer does not allow for probabilities to be subtracted between current ages to derive residual risk from a delayed BSO. For example, to estimate residual ovarian cancer risk for a 35-year-old woman who chooses to delay BSO to age 50 years, one cannot use the difference in residual lifetime risk between ages 35 and 50 years. To derive accurate probabilities for these scenarios, we generated residual risk estimates obtained from our life table analysis for *BRCA1* carriers (Table 3) and *BRCA2* carriers (Table 4). The ovarian cancer risk of a 30-year-old *BRCA1* individual, should she wish to delay BSO to age 50 years, is estimated to be 23.9% (95% CI, 20.7-27.4). A 30-year-old *BRCA2* individual who delays BSO age until age 50 years will have a projected 3.5% (95% CI, 1.1-6.2) risk of ovarian cancer.

To support the clinical counseling of patients, we present estimates of their residual lifetime risk of ovarian cancer by current age, projected age at BSO, and gene variant in Tables 3 and

Table 2. Life Expectancy and Residual Lifetime Risk of Ovarian Cancer Among *BRCA1* and *BRCA2* Carriers

Current age, y	Life expectancy, y	Residual risk of ovarian cancer (95% CI)	
		<i>BRCA1</i>	<i>BRCA2</i>
30	53.1	55.0% (48.8-61.9)	24.1% (15.1-36.6)
35	48.2	54.8% (48.4-62.0)	24.2% (15.2-36.7)
40	43.3	53.7% (47.1-61.1)	24.3% (15.2-36.9)
45	38.5	50.0% (42.9-57.8)	23.8% (14.7-36.6)
50	33.6	42.7% (34.8-51.4)	22.2% (12.3-35.3)
55	28.9	33.4% (24.3-44.1)	18.9% (8.8-32.5)
60	24.3	24.7% (14.0-37.4)	14.3% (5.0-29.8)
65	19.8	17.7% (7.3-32.1)	9.7% (1.7-27.6)
70	15.6	12.3% (3.5-27.6)	6.0% (0.4-25.8)
75	11.6	8.4% (1.7-22.7)	3.7% (0.1-22.7)

4, and graphically in eFigures 9 and 10 in Supplement 1. We observed notable differences in ovarian cancer risk among *BRCA1* carriers according to family history of ovarian cancer (eFigure 4 in Supplement 1). In turn, we also provide residual lifetime risk estimates separately for *BRCA1* carriers with and without a family history of ovarian cancer in eTables 3 and 4 in Supplement 1. There was only a modest difference in the risk of ovarian cancer according to a personal history of breast cancer at baseline (eFigure 1 in Supplement 1).

Discussion

In this study, we estimated the age-specific incidence and lifetime risks of ovarian cancer in a prospective cohort of 5713 BRCA carriers. Our calculated actuarial risks of ovarian cancer to age 80 years were 56.8% (95% CI, 50.1-62.6) for *BRCA1* carriers and 25.4% (95% CI, 15.0-34.5) for *BRCA2* carriers, which are higher than those previously reported; for example, Kuchenbaecker et al² estimated the cumulative ovarian cancer risk to age 80 years to be 44% (95% CI, 36-53) for *BRCA1* carriers and 17% (95% CI, 11-25) for *BRCA2* carriers. Our data

Table 3. Residual Lifetime Risk of Ovarian Cancer Among *BRCA1* Carriers

Current age, y	Risk estimate by projected age at BSO in y, % (95% CI)										No BSO
	30	35	40	45	50	55	60	65	70	75	
30	0	0.9 (0.6-1.4)	4.2 (3.1-5.2)	12.1 (10.0-14.2)	23.9 (20.7-27.4)	34.7 (30.9-38.8)	42.3 (37.8-46.7)	47.1 (42.2-51.8)	50.2 (45.1-54.9)	52.2 (47.0-57.3)	55.0 (48.8-61.9)
35	NA	0	3.3 (2.5-4.0)	11.3 (9.4-13.3)	23.3 (20.0-26.8)	34.3 (30.4-38.4)	41.9 (37.4-46.5)	46.9 (41.9-51.6)	50.0 (44.8-54.8)	52.1 (46.8-57.2)	54.8 (48.4-62.0)
40	NA	NA	0	8.4 (6.9-10.0)	20.9 (17.9-24.2)	32.3 (28.4-36.3)	40.3 (35.6-45.0)	45.4 (40.2-50.2)	48.7 (43.4-53.6)	50.8 (45.5-56.1)	53.7 (47.1-61.1)
45	NA	NA	NA	0	13.7 (11.6-16.1)	26.4 (22.8-30.2)	35.2 (30.4-39.9)	40.8 (35.5-45.9)	44.5 (38.9-49.8)	46.8 (41.1-52.3)	50.0 (42.9-57.8)
50	NA	NA	NA	NA	0	14.9 (12.4-17.5)	25.2 (21.1-29.6)	31.9 (26.6-37.3)	36.2 (30.6-41.8)	38.9 (32.9-44.7)	42.7 (34.8-51.4)
55	NA	NA	NA	NA	NA	0	12.4 (9.7-15.5)	20.4 (16.1-25.0)	25.6 (20.3-31.0)	28.9 (22.7-35.1)	33.4 (24.3-44.1)
60	NA	NA	NA	NA	NA	NA	0	9.4 (7.0-11.9)	15.5 (11.1-19.8)	19.4 (12.9-25.7)	24.7 (14.0-37.4)
65	NA	NA	NA	NA	NA	NA	NA	0	7.1 (4.1-9.8)	11.6 (5.9-17.6)	17.7 (7.3-32.1)
70	NA	NA	NA	NA	NA	NA	NA	NA	0	5.2 (1.9-9.4)	12.3 (3.5-27.6)
75	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	8.4 (1.7-22.7)

Abbreviations: BSO, bilateral salpingo-oophorectomy; NA, not applicable.

Table 4. Residual Lifetime Risk of Ovarian Cancer Among *BRCA2* Carriers

Current age, y	Risk estimate by projected age at BSO in y, % (95% CI)										No BSO
	30	35	40	45	50	55	60	65	70	75	
30	0	0.0 (0.0-0.2)	0.2 (0.0-0.7)	1.1 (0.2-2.3)	3.5 (1.1-6.2)	7.7 (3.7-12.0)	12.8 (7.7-18.3)	17.2 (10.9-24.1)	20.3 (12.7-28.0)	22.1 (13.7-30.1)	24.1 (15.1-36.6)
35	NA	0	0.2 (0.0-0.5)	1.1 (0.2-2.2)	3.5 (1.0-6.2)	7.7 (3.7-11.9)	12.8 (7.7-18.4)	17.3 (10.9-24.2)	20.4 (12.8-28.1)	22.2 (13.7-30.3)	24.2 (15.2-36.7)
40	NA	NA	0	0.9 (0.1-1.8)	3.3 (1.0-5.9)	7.6 (3.6-11.7)	12.7 (7.7-18.3)	17.3 (10.7-24.2)	20.4 (12.7-28.0)	22.2 (13.7-30.4)	24.3 (15.2-36.9)
45	NA	NA	NA	0	2.5 (0.8-4.4)	6.8 (3.4-10.5)	12.1 (7.5-17.5)	16.7 (10.2-23.7)	19.9 (12.2-27.6)	21.7 (13.2-29.7)	23.8 (14.7-36.6)
50	NA	NA	NA	NA	0	4.5 (2.5-7.0)	10.0 (5.8-14.8)	14.8 (8.3-21.9)	18.1 (10.3-26.1)	20.0 (11.4-28.3)	22.2 (12.3-35.3)
55	NA	NA	NA	NA	NA	0	5.9 (3.0-9.5)	11.0 (5.1-17.6)	14.5 (6.7-22.3)	16.6 (7.9-25.1)	18.9 (8.8-32.5)
60	NA	NA	NA	NA	NA	NA	0	5.6 (2.2-9.7)	9.5 (3.7-15.5)	11.8 (4.5-19.4)	14.3 (5.0-29.8)
65	NA	NA	NA	NA	NA	NA	NA	0	4.3 (1.2-7.5)	6.8 (1.6-12.7)	9.7 (1.7-27.6)
70	NA	NA	NA	NA	NA	NA	NA	NA	0	2.8 (0.3-6.9)	6.0 (0.4-25.8)
75	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	3.7 (0.1-22.7)

Abbreviations: BSO, bilateral salpingo-oophorectomy; NA, not applicable.

were based on 249 incident cases of ovarian cancer, whereas the results of Kuchenbaecker et al were based on 109 incident cases. In both studies, the number of ovarian cancers in *BRCA2* carriers was small (24 in both studies).

The projections in Tables 3 and 4 are intended to help quantify the trade-off associated with delaying BSO, particularly for premenopausal women who are weighing ovarian cancer risk reduction against fertility goals and early menopause. The benefit of BSO was greatest for *BRCA1* carriers and declined sharply with increasing age at surgery, whereas the benefit for *BRCA2* carriers was lower and declined more gradually with age. Among *BRCA1* carriers, cumulative ovarian cancer risk differed by family history of ovarian cancer; therefore, we provide supplementary residual lifetime risk estimates stratified by family history in eTable 3 and eTable 4 in [Supplement 1](#).

These stratified estimates should be interpreted cautiously, particularly in older age groups where the number of events was limited and risk estimates are less stable. Together, these findings support individualized counseling about BSO timing that incorporates residual lifetime ovarian cancer risk in addition to other important factors, including breast cancer history, menopausal harms, fertility goals, and patient preferences. Although these tables quantify residual ovarian cancer risk, they do not estimate the overall net benefit of BSO because factors such as cardiovascular, bone, cognitive, vasomotor, mental health, and quality-of-life outcomes after early menopause were not modeled.

For older women, the discussion about BSO should consider whether the expected reduction in ovarian cancer risk justifies surgery in the context of a patient's comorbidities, life

expectancy, and possible surgical and anesthetic complications. Although ovarian cancer risk persists among older individuals, the absolute benefit of BSO declines as competing mortality increases with age. Table 2, which presents life expectancy and residual lifetime risk of ovarian cancer, may be useful in this setting as a starting point for shared decision-making.

For premenopausal women, BSO induces abrupt and permanent estrogen deprivation, leading to immediate surgically induced menopause. Beyond vasomotor instability and sleep disruption, this hormonal shift has systemic consequences, including adverse effects on neurocognitive function, cardiovascular health, and bone density, impacts on mood, sexual functioning, and overall quality of life.¹⁷ In a study by Hassan et al,¹⁸ the authors reported that BSO in premenopausal variant carriers from the UK did not result in an increase in the incidence of long-term health effects. Recently, we have shown that prescribing menopausal hormonal therapy to BRCA carriers without breast cancer is safe in this situation, and estrogen alone was associated with a lowered risk of breast cancer.¹⁹ In a recent review, Kaunitz et al²⁰ judge the risk of breast cancer associated with menopausal hormonal therapy to be minimal. At present, menopausal hormone therapy is not offered to women with a history of breast cancer, but further studies are under way. Estrogen alone is not given to a woman with an intact uterus; for women who wish to take unopposed estrogen, hysterectomy at the time of BSO should be discussed. Also, some suggest that a bilateral salpingectomy is an alternative to BSO.²¹⁻²⁵ This has been shown to be associated with improved quality of life compared to BSO for women who do not use menopausal hormonal therapy but has not been shown to reduce the risk of ovarian cancer.

Limitations

There are several limitations to our study. First, there were insufficient data for women older than 80 years in this cohort,

which required truncating our modeled ovarian cancer rates at age 80 years. As a result, projected risks at older ages may not reflect real-world ovarian cancer risks in these age groups. Second, we also assumed mortality rates from the general population of the US, and this may be different for women in other countries and for individual patients. Third, the results provided are for women at average risk and, to some extent, ovarian cancer risk may be overestimated in our cohort because participants were more likely to have been ascertained if they had a high-penetrance variant. Fourth, we assume that the women in this study with breast cancer do not die of breast cancer; therefore, for those women with advanced-stage breast cancer or with a breast cancer recurrence, these estimates will overestimate the true risk, and a risk assessment should be done on a personal basis with the oncologist to account for competing causes of death from breast cancer. However, we and others have shown that BSO in women with breast cancer reduces the risk of dying of breast cancer as well as from ovarian cancer^{4,26-28}; therefore, we consider these women to be candidates for BSO. Fifth, there is a small risk of peritoneal cancer following BSO, which we did not take into consideration. In an earlier study of this cohort, the 20-year cumulative risk of peritoneal cancer from the date of BSO was 2.7% for *BRCA1* carriers and 0.9% for *BRCA2* carriers.²⁹

Conclusions

In summary, these risk estimates are intended to support informed decisions between health care providers and patients about the timing of BSO. These results are consistent with the current recommendations for risk-reducing BSO at age 35 years for *BRCA1* and age 45 years for *BRCA2* carriers. These findings further emphasize the importance of timely identification of *BRCA1* and *BRCA2* carriers in young healthy women for whom the expected benefit of BSO is greatest.

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