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

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IMPORTANCE Preventive bilateral salpingo-oophorectomy is offered to women at high risk of ovarian cancer who carry a pathogenic variant in *BRCA1* or *BRCA2*; however, the association of oophorectomy with all-cause mortality has not been clearly defined.

OBJECTIVE To evaluate the association between bilateral oophorectomy and all-cause mortality among women with a *BRCA1* or *BRCA2* sequence variation.

DESIGN, SETTING, AND PARTICIPANTS In this international, longitudinal cohort study of women with *BRCA* sequence variations, information on bilateral oophorectomy was obtained via biennial questionnaire. Participants were women with a *BRCA1* or *BRCA2* sequence variation, no prior history of cancer, and at least 1 follow-up questionnaire completed. Women were followed up from age 35 to 75 years for incident cancers and deaths. Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% CIs for all-cause mortality associated with a bilateral oophorectomy (time dependent). Data analysis was performed from January 1 to June 1, 2023.

EXPOSURES Self-reported bilateral oophorectomy (with or without salpingectomy).

MAIN OUTCOMES AND MEASURES All-cause mortality, breast cancer–specific mortality, and ovarian cancer–specific mortality.

RESULTS There were 4332 women (mean age, 42.6 years) enrolled in the cohort, of whom 2932 (67.8%) chose to undergo a preventive oophorectomy at a mean (range) age of 45.4 (23.0-77.0) years. After a mean follow-up of 9.0 years, 851 women had developed cancer and 228 had died; 57 died of ovarian or fallopian tube cancer, 58 died of breast cancer, 16 died of peritoneal cancer, and 97 died of other causes. The age-adjusted HR for all-cause mortality associated with oophorectomy was 0.32 (95% CI, 0.24-0.42; $P < .001$). The age-adjusted HR was 0.28 (95% CI, 0.20-0.38; $P < .001$) and 0.43 (95% CI, 0.22-0.90; $P = .03$) for women with *BRCA1* and *BRCA2* sequence variations, respectively. For women with *BRCA1* sequence variations, the estimated cumulative all-cause mortality to age 75 years for women who had an oophorectomy at age 35 years was 25%, compared to 62% for women who did not have an oophorectomy. For women with *BRCA2* sequence variations, the estimated cumulative all-cause mortality to age 75 years was 14% for women who had an oophorectomy at age 35 years compared to 28% for women who did not have an oophorectomy.

CONCLUSIONS AND RELEVANCE In this cohort study among women with a *BRCA1* or *BRCA2* sequence variation, oophorectomy was associated with a significant reduction in all-cause mortality.

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Women with a germline pathogenic (or likely pathogenic) variant in the *BRCA1* or *BRCA2* gene are encouraged to undergo a bilateral salpingo-oophorectomy (ie, oophorectomy) before the ages of 40 and 45 years, respectively, to reduce their risk of developing ovarian and fallopian tube cancer.[1] The surgery is effective[2-4]; however, there is a small risk of developing peritoneal cancer postoophorectomy.[5,6] It is not clear if this represents a primary cancer or a metastatic spread of an occult tubal cancer or precancerous lesion.[7]

Early surgical menopause has unintended consequences, including a decline in cardiovascular and bone health, and has negative impacts on fertility, sexual function, and quality of life.[8-10] In women without sequence variations, premenopausal oophorectomy has been associated with an increase in all-cause mortality, predominantly due to noncancer deaths.[11,12] It is important to accurately measure the risks and benefits of oophorectomy in women found to carry a *BRCA* sequence variation. Some women with a *BRCA* sequence variation choose to postpone surgery until childbearing is complete, while others forgo oophorectomy altogether.

In 2014, we reported a 70% reduction in all-cause mortality among women with a *BRCA1* or *BRCA2* sequence variation following an oophorectomy.[2] The current study is an update of our previous report; we have expanded the size of our international cohort and extended the follow-up period. Further, we excluded women diagnosed with cancer prior to study enrollment to focus solely on the impact of oophorectomy for women without a cancer diagnosis who become aware of their *BRCA* sequence variation status and face the decision of preventive surgery.

Key Points

Question Is bilateral oophorectomy associated with a decreased risk of death among women with a *BRCA1* or *BRCA2* sequence variation?

Findings In this cohort study of 4332 women, after a mean follow-up of 9.0 years, 901 incident cancers were noted in 851 women, and 228 women had died (57 of ovarian or fallopian tube cancer, 58 of breast cancer, 16 of peritoneal cancer, and 97 of other causes). The age-adjusted hazard ratio was 0.32 for all-cause mortality associated with oophorectomy, 0.28 for women with *BRCA1* sequence variations, and 0.43 for women with *BRCA2* sequence variations.

Meaning Results suggest that among women with a *BRCA1* or *BRCA2* sequence variation, oophorectomy is associated with a significant reduction in all-cause mortality.

Methods

Study Population

Eligible study participants were identified from a longitudinal study of 17 947 women with a pathogenic or likely pathogenic germline variant in the *BRCA1* or *BRCA2* gene, which was initiated in 1995 and includes 83 participating centers from 16 countries.[2,13-16] The women underwent genetic testing over an extended period of time (1994-2019). These women sought genetic testing because of a personal or family history of breast and/or ovarian cancer. The criteria for genetic testing were not standardized and varied from center to center. Sequence variation detection was performed using a range of techniques, and all abnormal nucleotide sequences were confirmed by direct DNA sequencing. All participants provided written informed consent, and the institutional ethics committees of all the participating centers approved the study.

Data Collection

Participants completed a baseline questionnaire at the time of enrollment and a follow-up questionnaire every 2 years thereafter to update exposures and ascertain incident cancers and deaths. Questionnaires were mailed to the study participant or were administered over the telephone by a genetic counselor or research assistant. The questionnaires requested information regarding surgery (eg, oophorectomy, hysterectomy), and exogenous hormone use (eg, hormone replacement therapy [HRT], oral contraceptives [OCs]). For the current study, oophorectomy was defined as a bilateral oophorectomy, with or without a concomitant hysterectomy or salpingectomy. Prior to 2012, the questionnaires did not distinguish between oophorectomy and salpingo-oophorectomy. An oophorectomy performed for the treatment of clinically or screen-detected ovarian cancer was not considered as an exposure for this analysis (patients were considered unexposed). In contrast, an oophorectomy performed with preventive intent, but for which an invasive cancer was detected in the fallopian tubes or ovaries at the time of surgery (occult), was considered as a preventive oophorectomy (exposed). Women who underwent a unilateral oophorectomy were considered unexposed (no oophorectomy); however, they were reclassified to the exposed group if the second ovary was removed later. In the subanalysis of breast cancer–specific mortality, a woman who had an oophorectomy following the diagnosis of breast cancer was included as exposed.

Incident Cancer Diagnoses, Vital Status, and Cause of Death

Pathology reports and medical records were requested for all women who reported incident breast, ovarian, or endometrial cancer, and information regarding histologic type, stage, site of origin, and other pathologic features was abstracted. Serous peritoneal cancer diagnosed 6 or more months after a preventive oophorectomy was considered a primary peritoneal cancer, whereas ovarian, fallopian tube, or peritoneal cancer diagnosed in women with 2 ovaries intact was classified as ovarian or fallopian tube cancer.

For women who died, the cause and date of death were obtained from the collaborating investigator at each site. This was determined by review of patient records, by correspondence with the treating physician, or from next of kin. Furthermore, for women from Ontario, Canada, cause and date of death were determined by record linkage to the Ontario Cancer Registry (Ontario Health). For the participants from Poland, vital status and date of death were determined by record linkage to the Vital Statistics Database of the Polish Ministry of Administration and Internal Affairs. In some cases, women

were diagnosed with cancer but died before completion of a follow-up questionnaire. These diagnoses were reported by the study center or by next of kin and were confirmed through pathology or medical record review. In some cases, the cause of death was listed as cancer, but no incident cancer was reported prior to the death. For these cases, we considered the date of diagnosis to be 1 year prior to the date of death.

Inclusions and Exclusions

Participants were excluded if they had been diagnosed with any cancer (except for thyroid or nonmelanoma skin cancer) prior to completion of the baseline questionnaire or if they did not complete at least 1 follow-up questionnaire. Women were also excluded if they (1) completed the most recent follow-up questionnaire before age 35 years; (2) completed the baseline questionnaire after age 74 years; (3) had follow-up time less than 1 year; or (4) were missing data on key variables (eg, date of birth). After these exclusions, there were 4332 women eligible for the analysis. See eFigure 1 in Supplement 1 for a detailed summary of the exclusions.

Statistical Analysis

In the primary analysis, we estimated the extent of risk reduction (hazard ratio [HR]) for all-cause mortality associated with bilateral oophorectomy using a Cox proportional hazards model. We included oophorectomy as a time-dependent variable (women who underwent bilateral oophorectomy during the follow-up were transferred from unexposed to exposed at that time). Women who had an oophorectomy prior to the baseline questionnaire were considered exposed from the date of completion of the baseline questionnaire. Participants were followed up from the date of the baseline questionnaire or age 35 years (whichever was later) until either death, age 75 years, or date of completion of the last follow-up questionnaire. All HRs were adjusted for age at study entry and country of residence (Canada, US, Poland, other). We conducted an additional multivariate analysis and included smoking (ever/never), OC use (ever/never), parity, HRT (yes/no), and bilateral preventive mastectomy (yes/no; time dependent) as covariates. A second analysis was conducted with death from ovarian, fallopian tube, or peritoneal cancer as the composite end point. A third analysis was conducted with death from breast cancer as the end point; here, we censored the participants at the time of preventive mastectomy, and we considered oophorectomies that occurred both before and after the diagnosis of breast cancer as exposed.

Annual mortality rates were calculated by age, gene sequence variation, and oophorectomy status. These rates were based on the ratio of the number of events (deaths) and the number of person-years of risk accumulated in that specific age interval. We used the annual mortality rates to construct cumulative mortality curves (from age 35 to 75 years) for 4 theoretical cohorts of women who (1) had an oophorectomy at age 35 years and (2) did not have an oophorectomy before age 75 years, and subdivided by gene.

The SAS statistical package, version 9.4 (SAS Institute), was used to conduct the analyses. *P* values were based on 2-sided tests and were considered statistically significant if $P < .05$.

Results

In this prospective study, we observed 4332 women (mean age, 42.6 years; 3177 with a *BRCA1* sequence variation and 1155 with a *BRCA2* sequence variation) for up to 24 years (mean, 9.0 years) for incident cancers and death from all causes. The characteristics of the study participants are presented in **Table 1**. There were 901 incident cancers diagnosed (among 851 women) in the cohort: 582 breast (496 invasive and 86 ductal carcinoma in situ), 140 ovarian or fallopian tube (94 clinically detected through symptoms or screening and 46 occult diagnosed at oophorectomy), and 35 primary peritoneal cancers diagnosed after oophorectomy, as well as 24 melanomas; 17 pancreatic, 16 endometrial, 13 colorectal, and 12 lung cancers; and 62 cancers of other sites (**Table 2**). **Table 3** summarizes the 228 deaths reported in the cohort. Of these, 182 (80.0%) were from cancer, 28 (12.3%) were from other causes, and for 18 deaths (7.9%), the cause of death was unknown.

A total of 2932 women underwent a preventive oophorectomy: 2106 of the 3177 women with *BRCA1* sequence variations (66.3%) and 826 of the 1155 women with *BRCA2* sequence variations (71.5%). We included women who had an oophorectomy prior to or following study enrollment in the latter group; the mean time from baseline to surgery was 4.3 years. Among the 2932 women who had an oophorectomy, 112 died (3.8%). Among the 1400 women who did not have an oophorectomy, 116 died (8.3%). The age-adjusted HR for all-cause mortality associated with oophorectomy (time dependent) was 0.32 (95% CI, 0.24-0.42; $P < .001$) (**Table 4**). The age-adjusted HR was 0.28 (95% CI, 0.20-0.38; $P < .001$) for women with *BRCA1* sequence variations and 0.43 (95% CI, 0.22-0.90; $P = .03$) for women with *BRCA2* sequence variations. After adjustment, the HR for all-cause mortality associated with oophorectomy was 0.31 (95% CI, 0.23-0.44; $P < .001$).

Among women who had an oophorectomy prior to baseline, the age-adjusted HR for all-cause mortality was 0.38 (95% CI, 0.21-0.56; $P < .001$). Among women who had an oophorectomy the same year as the baseline or thereafter, the HR for all-cause mortality to age 75 years was 0.33 (95% CI, 0.22-0.49; $P < .001$). The magnitude of the risk reduction was similar irrespective of age at surgery (Table 4).

The age-adjusted HR associated with bilateral oophorectomy was 0.19 (95% CI, 0.12-0.33; $P < .001$) for ovarian, fallopian tube, or peritoneal cancer mortality. The age-adjusted HR for death from any cancer to age 75 years associated with oophorectomy was 0.31 (95% CI, 0.22-0.42; $P < .001$).

There were 582 incident breast cancers in the follow-up period. The HR for breast cancer incidence associated with oophorectomy was 0.72 (95% CI, 0.60-0.88; $P < .001$). The HR was 0.79 (95% CI, 0.63-0.99; $P = .04$) for women with *BRCA1* sequence variations and 0.55 (95% CI, 0.38-0.81; $P = .003$) for women with *BRCA2* sequence variations. Among these patients with breast cancer, 58 (10%) died in the follow-up. The overall HR for death from breast cancer associated with oophorectomy was 0.44 (95% CI, 0.25-0.78; $P = .005$) and was 0.50 (95% CI, 0.27-0.95; $P = .03$) for women with *BRCA1* sequence variations and 0.22 (95% CI, 0.06-0.84; $P = .03$) for women

Table 1. Characteristics of the 4332 Women With *BRCA1* and *BRCA2* Sequence Variations, Overall and According to Preventive Oophorectomy Status (Ever/Never)

Variable	Participants, No. (%)		
	No oophorectomy (n = 1400)	Oophorectomy (n = 2932)	*P* value[a]
Year of birth, mean (range)	1968 (1922-1986)	1962 (1924-1985)	<.001
Year of baseline, mean (range)	2006 (1992-2019)	2006 (1993-2019)	.32
Age at baseline, mean, y	37.8	44.9	<.001
Years of follow-up from baseline, mean (range)	8.2 (1.0-24.3)	9.4 (1.0-24.5)	<.001
Years of follow-up from oophorectomy, for those who had surgery after baseline, mean	NA	6.7	NA
BRCA sequence variation			
BRCA1	1071 (76.5)	2106 (71.8)	.001
BRCA2	329 (23.5)	826 (28.2)	
Age at oophorectomy, mean (range), y	NA	45.4 (23.0-77.0)	NA
Bilateral mastectomy			
No	1141 (85.5)	1182 (66.6)	<.001
Yes	193 (14.5)	945 (33.4)	
Missing	66	105	
Hysterectomy			
No	1305 (94.0)	1240 (45.4)	<.001
Yes	82 (5.9)	1590 (54.6)	
Missing	13	92	
Parity			
Mean (range)	1.5 (0-10)	1.9 (0-8)	<.001
Nulliparous	425 (31.3)	428 (14.9)	<.001
Parous	933 (68.7)	2454 (85.2)	
Missing	42	50	
Breastfeeding[b]			
Mean (range), mo	13.0 (0-96)	12.6 (0-147)	.50
Never	124 (15.4)	341 (16.0)	.72
Ever	680 (84.6)	1796 (84.0)	
Missing	129	317	
Smoking			
Never	769 (57.8)	1600 (57.3)	.73
Ever	561 (42.2)	1195 (42.8)	
Missing	70	137	
Oral contraceptive use			
Never	439 (31.3)	750 (26.0)	<.001
Ever	939 (68.7)	2130 (74.0)	
Missing	22	52	
HRT use			
Never	1273 (90.9)	1392 (47.5)	<.001
Ever	127 (9.1)	1540 (52.5)	
Country of residence[b]			
Canada	277 (24)	882 (76)	.01
Poland	625 (44)	786 (56)	
US	252 (24)	806 (76)	
Other	246 (35)	458 (65)	

Abbreviations: HRT, hormone replacement therapy; NA, not applicable.

[a] *P* value comparing women who did and did not undergo bilateral oophorectomy; *t* test for continuous variables and χ^2 test for categorical variables.

[b] Among parous women only.

with *BRCA2* sequence variations. Among women with a *BRCA1* sequence variation, the 15-year cumulative mortality from breast cancer postoophorectomy was 2.6% (there were too few deaths among women with *BRCA2* sequence variations to estimate this). There were 1138 women who opted to have a bilateral preventive mastectomy; none of these women died of breast cancer.

Only 918 of the 2932 women who had an oophorectomy in the current cohort (31.3%) had an oophorectomy by the recommended age (age 40 years for *BRCA1* and age 45 years for *BRCA2*). Among the 585 women with *BRCA1* sequence variations who had an oophorectomy prior to age 40 years, there were 3 occult cancers (0.5%) diagnosed (compared with 41 occult cancers [2.7%] diagnosed in the 1521 women who had an

Table 2. Incident Cancers Diagnosed in the Follow-Up Period, by Oophorectomy Status

Cancer type	Cancers, No.		
	Total (N = 4332)	Oophorectomy (n = 2932)	No oophorectomy (n = 1400)
Breast (invasive)	496	384	112
Ovarian	121	32	89
DCIS	86	67	19
Peritoneal	35	34	1
Melanoma	24	20	4
Fallopian tube	19	18	1
Pancreatic	17	12	5
Endometrial	16	12	4
Colorectal	13	10	3
Lung	12	8	4
Lymphoma	7	7	0
Brain	6	4	2
Kidney	5	5	0
Liver	4	2	2
Parotid gland	3	3	0
Stomach	3	3	0
Angiosarcoma	2	1	1
Bladder	2	2	0
Bone	2	2	0
Cervical	2	2	0
Leukemia	2	2	0
Vulvar	1	1	0
Multiple myeloma	1	1	0
Sarcoma	1	1	0
Other cancer	18	15	3
Unknown	3	2	0
Total[a]	901	650	251

Abbreviation: DCIS, ductal carcinoma in situ.

[a] There was a total of 901 incident cancers among 851 participants.

oophorectomy after age 40 years), and 11 deaths occurred: 4 from breast cancer, 1 from an (occult) ovarian cancer, 2 from primary peritoneal cancer, 1 from leukemia, 1 from lung cancer, 1 from chronic obstructive pulmonary disease, and 1 with an unknown cause of death. Among the 333 women with *BRCA2* sequence variations who had an oophorectomy prior to age 45 years, there were no occult cancers diagnosed (compared with 2 occult cancers [0.4%] diagnosed in the 493 women who had an oophorectomy after age 45 years), and there were 7 deaths: 2 from breast cancer, 2 from primary peritoneal cancer, 1 from lung cancer, 1 from surgical complications, and 1 with an unknown cause of death. Among the women with *BRCA1* sequence variations, 1538 (48.4%) received their test result after age 40 years, and among women with *BRCA2* sequence variations, 546 (47.3%) received their test result after age 45 years. Among the 2699 women who did not have an oophorectomy by age 45 years, 268 (9.3%) had a child after age 35 years.

The annual all-cause mortality rates by age (in 10-year intervals) according to oophorectomy status are presented in **Table 5**. Based on the age-specific rates, we estimated the all-cause cumulative mortality to age 75 years for women with a *BRCA1* sequence variation and who had oophorectomy at age 35 years to be 25%, vs 62% for women who never had an oophorectomy (eFigure 2 in Supplement 1). We estimated the all-cause cumulative mortality to age 75 years for women with a *BRCA2* sequence variation and who had oophorectomy at age 35 years to be 14%, vs 28% for women who never had an oophorectomy (eFigure 3 in Supplement 1).

Discussion

In this prospective study of 4332 women with a *BRCA1* or *BRCA2* sequence variation, we calculated age-specific annual mortality rates for women with and without intact ovaries. From these annual rates, we estimated that, among women with *BRCA1* sequence variations, cumulative mortality from all causes to age 75 years fell from 62% to 25% for women who had their ovaries removed at age 35 years, compared to those who retained their ovaries. The reduction for women with a *BRCA2* sequence variation was smaller but substantial (28% to 14%). These findings are consistent with our earlier report and those of others.[2,4,17-19] The current study extends our prior study[2] by including an additional 827 women with *BRCA1* sequence variations and 709 women with *BRCA2* sequence variations and by extending the follow-up time by 2 years. Importantly, we excluded women who had cancer diagnosed prior to baseline, allowing us to focus on women who were healthy at the time they discovered they carry a *BRCA* sequence variation.

In a prospective study of over 350 000 individuals in the UK who underwent whole-exome sequencing, protein-truncating variants in *BRCA1* were associated with a significant decrease in a woman's life span.[20] For those who know their sequence variation status, the opportunity to have an oophorectomy can help mitigate this effect. The impact on mortality was primarily attributed to a reduction in deaths from ovarian and fallopian tube cancer; however, there was also a contribution from reducing deaths from breast cancer.

Our findings contrast with those for women in the general population. For women at average cancer risk, premenopausal oophorectomy is associated with an increased risk of death from cardiovascular disease as well as a decline in quality of life.[8,12,21-23] We also see a decline in quality of life in women with *BRCA* sequence variations with oophorectomy prior to menopause, but this is offset by the prolongation of life expectancy.[9] The members of the current cohort were relatively young (mean age at end of follow-up, 51.7 years), and thus we had limited power to estimate with accuracy the association of oophorectomy with other chronic conditions. Nevertheless, for women between the ages of 55 and 75 years, the all-cause mortality rate was lower in women without ovaries than in those with ovaries (Table 5), suggesting that the benefit of oophorectomy is retained in older women.

Only 31.3% of women who had an oophorectomy in the current cohort had an oophorectomy by the recommended age (age 40 years for *BRCA1* and 45 years for *BRCA2*). It is not clear why some women in this study chose not to have an oophorectomy, and we do not have information in this regard. All

Table 3. Causes of Death in the Cohort, by Oophorectomy Status

Cause of death	Participants, No. (%)		
	Total (N = 4332)	Oophorectomy (n = 2932)	No oophorectomy (n = 1400)
Breast cancer	58 (1.34)	30 (1.02)	28 (2.00)
Ovarian cancer	55 (1.27)	8 (0.27)	47 (3.36)
Pancreatic cancer	16 (0.37)	10 (0.34)	6 (0.43)
Peritoneal cancer	16 (0.37)	16 (0.55)	0
Cardiovascular disease[a]	9 (0.21)	5 (0.17)	4 (0.29)
Lung cancer	8 (0.18)	5 (0.17)	3 (0.21)
Cancer (other)	7 (0.16)	6 (0.20)	1 (0.07)
Brain tumor	4 (0.09)	2 (0.07)	2 (0.14)
Unintentional injury	3 (0.07)	1 (0.03)	2 (0.14)
Colorectal cancer	3 (0.07)	2 (0.07)	1 (0.07)
Liver cancer	3 (0.07)	2 (0.07)	1 (0.07)
Endometrial cancer	2 (0.05)	0	2 (0.14)
Fallopian tube cancer	2 (0.05)	1 (0.03)	1 (0.07)
Leukemia	2 (0.05)	2 (0.07)	0
ALS	2 (0.05)	2 (0.07)	0
Thrombosis	2 (0.05)	1 (0.03)	1 (0.07)
Amyloidosis	1 (0.02)	1 (0.03)	0
Brain aneurysm	1 (0.02)	0	1 (0.07)
COPD	1 (0.02)	1 (0.03)	0
Cervical cancer	1 (0.02)	0	1 (0.07)
Diabetes	1 (0.02)	0	1 (0.07)
Kidney cancer	1 (0.02)	0	1 (0.07)
Lymphoma	1 (0.02)	1 (0.03)	0
Mesothelioma	1 (0.02)	1 (0.03)	0
Myelodysplastic syndrome	1 (0.02)	1 (0.03)	0
Sepsis	1 (0.02)	1 (0.03)	0
Complications of surgery	1 (0.02)	1 (0.03)	0
Suicide	1 (0.02)	0	1 (0.07)
Thyroid cancer	1 (0.02)	0	1 (0.07)
Vulvar cancer	1 (0.02)	0	1 (0.07)
Kidney failure	1 (0.02)	0	1 (0.07)
Other cause	3 (0.07)	3 (0.10)	0
Death cause unknown	18 (0.42)	9 (0.31)	9 (0.64)
Total	228 (5.26)	112 (3.82)	116 (8.29)

Abbreviations: ALS, amyotrophic lateral sclerosis; COPD, chronic obstructive pulmonary disease.

[a] Cardiovascular disease includes myocardial infarction, stroke, and circulatory failure.

were aware of their sequence variation status; however, many women did not receive their genetic test result until after the recommended age for oophorectomy. Among the women with *BRCA1* sequence variations, 48.4% received their test result after age 40 years, and among women with *BRCA2* sequence variations, 47.3% received their test result after age 45 years.

Women with an oophorectomy were also more likely to undergo a risk-reducing mastectomy and to take HRT, but a secondary analysis adjusting for these exposures gave similar results. One cannot rule out the possibility that unmeasured confounders, such as alcohol use and exercise, might contribute to differences in life expectancy.

The women were from 16 different countries and had genetic testing over an extended period of time (1994-2019). It is possible that not all these women were counseled about the risks and benefits of oophorectomy or the safety of HRT postsurgery to alleviate menopausal symptoms. There may be some who were reliant on screening with CA 125 testing and transvaginal ultrasonography; however, screening has not been shown to be effective in terms of reducing mortality.[24,25] Some may have avoided oophorectomy to maintain their fertility; however, among the 2699 women who did not have an oophorectomy by age 45 years, only 268 (9.3%) had a child after age 35 years. Misclassification exposure is unlikely, as self-reported oophorectomy has previously been shown to be highly reproducible and valid.[26] We were missing cause of death for 18 participants (7.9%) who died, and we did not have information on the presence of premalignant lesions in the ovaries of women who underwent preventive surgery.

The prevalence of occult ovarian and fallopian tube cancers identified at the time of oophorectomy varied with age at surgery. Among women with *BRCA1* sequence variations, there were 3 occult cancers diagnosed in 585 women who had an oophorectomy before age 40 years (0.5%) vs 41 occult cancers diagnosed

Table 4. Hazard Ratios (HRs) for Oophorectomy and All-Cause Mortality, by Timing of Oophorectomy and Age at Oophorectomy and by *BRCA* Sequence Variation

Variable	Alive/dead, No.	Basic model, HR (95% CI)[a]	*P* value	Multivariate HR (95% CI)[b]	*P* value
Women with *BRCA1* and *BRCA2* sequence variations					
Oophorectomy					
No	1284/116	1 [Reference]	NA	1 [Reference]	NA
Yes	2820/112	0.32 (0.24-0.42)	<.001	0.36 (0.27-0.49)	<.001
Timing of oophorectomy					
Before baseline	808/43	0.38 (0.21-0.56)	<.001	0.47 (0.31-0.70)	<.001
Within 1 y of baseline	1089/38	0.27 (0.19-0.40)	<.001	0.31 (0.21-0.46)	<.001
>1 y After baseline	923/31	0.33 (0.22-0.49)	<.001	0.36 (0.24-0.54)	<.001
Age at oophorectomy, y					
<40	704/12	0.26 (0.14-0.47)	<.001	0.33 (0.18-0.62)	<.001
40-50	1405/58	0.36 (0.26-0.50)	<.001	0.42 (0.30-0.59)	<.001
>50	743/42	0.29 (0.19-0.43)	<.001	0.30 (0.20-0.45)	<.001
Women with *BRCA1* sequence variation					
Oophorectomy					
No	967/103	1 [Reference]	NA	1 [Reference]	NA
Yes	2104/92	0.28 (0.20-0.38)	<.001	0.32 (0.23-0.44)	<.001
Timing of oophorectomy					
Before baseline	552/36	0.31 (0.20-0.48)	<.001	0.40 (0.25-0.64)	<.001
Within 1 y of baseline	756/29	0.22 (0.14-0.34)	<.001	0.26 (0.17-0.40)	<.001
>1 y After baseline	706/27	0.32 (0.21-0.49)	<.001	0.34 (0.22-0.53)	<.001
Age at oophorectomy, y					
<40	574/11	0.22 (0.11-0.41)	<.001	0.30 (0.16-0.59)	<.001
40-50	982/48	0.32 (0.22-0.45)	<.001	0.38 (0.26-0.55)	<.001
>50	458/33	0.25 (0.16-0.39)	<.001	0.26 (0.16-0.40)	<.001
Women with *BRCA2* sequence variation					
Oophorectomy					
No	316/13	1 [Reference]	NA	1 [Reference]	NA
Yes	806/20	0.43 (0.21-0.90)	.03	0.44 (0.20-0.96)	.04
Timing of oophorectomy					
Before baseline	256/7	0.46 (0.17-1.22)	.12	0.48 (0.17-1.37)	.17
Within 1 y of baseline	333/9	0.47 (0.20-1.14)	.10	0.49 (0.20-1.23)	.13
>1 y After baseline	217/4	0.35 (0.11-1.10)	.07	0.34 (0.11-1.10)	.07
Age at oophorectomy, y					
<40	125/1	0.27 (0.04-2.13)	.22	0.25 (0.03-2.04)	.20
40-50	403/10	0.51 (0.22-1.78)	.11	0.51 (0.21-1.23)	.13
>50	278/9	0.39 (0.15-0.99)	.05	0.41 (0.15-1.10)	.08

Abbreviation: NA, not applicable.

[a] Basic model adjusted for age at baseline and country of residence.

[b] Multivariable model adjusted for age at baseline and country of residence, smoking, oral contraceptives, bilateral mastectomy, hormone replacement therapy, and parity. Oophorectomy included bilateral surgery only (with or without salpingectomy) and was included as a time-dependent exposure.

in 1521 women who had an oophorectomy after age 40 years (2.7%). Among the women with *BRCA2* sequence variations, there were no occult cancers diagnosed in the 333 women who had an oophorectomy before age 45 years, compared to 2 occult cancers diagnosed in the 493 women who had an oophorectomy after age 45 years (0.4%). The HRs for all-cause mortality did not vary substantially by age at oophorectomy. The benefit of oophorectomy was present for women older than 50 years as well as for premenopausal women. This suggests that factors associated with oophorectomy other than estrogen and progesterone may affect mortality, but to date, these factors remain unknown and will be the subject of future studies. In an earlier study, we showed that those women who took estrogen-only hormonal therapy postoophorectomy did not experience any increase in the rate of breast cancer.[27] In the current study, we saw a modest but significant effect on the incidence of breast cancer associated with oophorectomy in women with *BRCA1* sequence variations (HR, 0.79; 95% CI, 0.63-0.99; *P* = .04). This result contrasts with that of our recent nested case-control study of oophorectomy and breast cancer incidence in women with *BRCA1* sequence variations (odds ratio, 1.21; 95% CI, 0.87-1.70; *P* = .26),[13] but the present study includes more incident cases (n = 448) than in the earlier study (n = 330). This will be addressed in future studies.

Limitations

This study has limitations. Causes of death were reported by the study center or the next of kin and were not all confirmed by medical records or death certificates. This was an observational study, and the choice of oophorectomy was not randomized but was determined by patient choice. We did not have in-

Table 5. Annual Mortality Rates of Women With *BRCA1* and *BRCA2* Sequence Variations (All-Cause) by Oophorectomy Status

	No oophorectomy (*BRCA1*, n = 1071; *BRCA2*, n = 329)			Oophorectomy (*BRCA1*, n = 2106; *BRCA2*, n = 826)			
Age group, y	Person-years	Deaths, No.	Annual rate, %[b]	Person-years	Deaths, No.	Annual rate, %[b]	*P* value[a]
BRCA1							
35-44.9	6370.3	25	0.39	3768.5	7	0.19	.07
45-54.9	2248.8	40	1.78	6694.3	34	0.51	<.001
55-64.9	791.0	28	3.54	4045.1	35	0.87	<.001
65-74.9	276.0	10	3.62	1249.0	16	1.28	.07
All	9686.2	103	1.06	15 756.9	92	0.58	NA
BRCA2							
35-44.9	1669.4	3	0.18	887.7	0	0.00	.56
45-54.9	906.2	1	0.11	2253.6	7	0.31	.45
55-64.9	441.5	6	1.36	1746.3	8	0.46	.05
65-74.9	203.7	3	1.47	723.9	5	0.69	.38
All	3220.8	13	0.40	5610.6	20	0.36	NA

Abbreviation: NA, not applicable.

[a] Fisher 2-sided test.

[b] Annual rate = ratio of the number of events (deaths) and the number of person-years of risk accumulated in each age interval expressed as percentage.

formation on the presence of precancerous lesions of the fallopian tube. The mean duration of follow-up was approximately 9 years; ideally, all participants would be followed up until age 75 years. This will be the topic of a future study.

Conclusions

To our knowledge, this cohort study represents the largest prospective cohort of oophorectomy and all-cause mortality in women without a cancer diagnosis with a *BRCA* sequence variation. The data on relative cancer rates, the estimated HRs, and the prevalence of occult cancers by age at oophorectomy support the current National Comprehensive Cancer Network guidelines for oophorectomy between ages 35 and 40 years for women with *BRCA1* sequence variations and before age 45 years for women with *BRCA2* sequence variations. We hope that the findings in this study will reassure women with a positive genetic test result who face high risks of breast and ovarian cancer.

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