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ORIGINAL REPORT

Impact of Oophorectomy on Cancer Incidence and Mortality in Women With a *BRCA1* or *BRCA2* Mutation

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
The purposes of this study were to estimate the reduction in risk of ovarian, fallopian tube, or peritoneal cancer in women with a *BRCA1* or *BRCA2* mutation after oophorectomy, by age of oophorectomy; to estimate the impact of prophylactic oophorectomy on all-cause mortality; and to estimate 5-year survival associated with clinically detected ovarian, occult, and peritoneal cancers diagnosed in the cohort.

Patients and Methods
Women with a *BRCA1* or *BRCA2* mutation were identified from an international registry; 5,783 women completed a baseline questionnaire and ≥ one follow-up questionnaires. Women were observed until either diagnosis of ovarian, fallopian tube, or peritoneal cancer, death, or date of most recent follow-up. Hazard ratios (HRs) for cancer incidence and all-cause mortality associated with oophorectomy were evaluated using time-dependent survival analyses.

Results
After an average follow-up period of 5.6 years, 186 women developed either ovarian (n = 132), fallopian (n = 22), or peritoneal (n = 32) cancer, of whom 68 have died. HR for ovarian, fallopian, or peritoneal cancer associated with bilateral oophorectomy was 0.20 (95% CI, 0.13 to 0.30; $P <$ .001). Among women who had no history of cancer at baseline, HR for all-cause mortality to age 70 years associated with an oophorectomy was 0.23 (95% CI, 0.13 to 0.39; $P <$ .001).

Conclusion
Preventive oophorectomy was associated with an 80% reduction in the risk of ovarian, fallopian tube, or peritoneal cancer in *BRCA1* or *BRCA2* carriers and a 77% reduction in all-cause mortality.

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INTRODUCTION

Many women with a mutation in *BRCA1* or *BRCA2* will undergo bilateral salpingo-oophorectomy to reduce their risks of ovarian, fallopian tube, and breast cancer.[1] Risks and benefits of oophorectomy should be weighed, including degree of protection against cancer and consequences of induced surgical menopause on health and quality of life.[2,3] We and others have shown that the risks of ovarian and breast cancers are reduced by preventive oophorectomy,[4-7] but the optimum age for oophorectomy has not been determined, and the impact of oophorectomy on mortality has not been well studied. The optimal age for oophorectomy should reflect age-specific cancer incidence rates and prevalence of occult ovarian cancer at different ages in *BRCA1* and *BRCA2* carriers.

In this extension of our earlier work,[4] we have expanded our cohort of mutation carriers from 1,828 to 5,783 women and extended mean length of follow-up from 3.5 to 5.6 years. We estimate the probability of having an occult cancer by age at oophorectomy, magnitude of risk reduction from prophylactic oophorectomy on cancer incidence, and impact of oophorectomy on all-cause mortality by gene, age group, and history of breast cancer.

PATIENTS AND METHODS

Study Population

Eligible study participants were women carrying a deleterious *BRCA1* or *BRCA2* mutation at one of 43 centers in Canada, the United States, Austria, France, Italy, Norway, or Poland. All participants provided informed

consent. The ethics committees of all participating centers approved the study. Mutation detection was performed using a range of techniques, but all abnormal nucleotide sequences were confirmed by direct DNA sequencing. A woman was eligible for the study when molecular analysis established that she was a mutation carrier. Participants were enrolled onto the study from 1995 to 2011. They completed a baseline questionnaire and at least one follow-up questionnaire a minimum of 2 years thereafter. The questionnaire requested information regarding reproductive history, surgical history (including preventive oophorectomy and mastectomy), and hormone use; it did not distinguish between oophorectomy and salpingo-oophorectomy. Follow-up questionnaires were mailed to each study participant or administered over the telephone by a genetic counselor or research assistant.

Participants were excluded if they had been diagnosed with ovarian, fallopian tube, or peritoneal cancer before the baseline questionnaire. However, those who had a diagnosis of breast cancer were eligible. A total of 8,261 eligible women were identified; 136 were excluded because of missing data; 29 carried both *BRCA1* and *BRCA2* mutations and were excluded; three reported an oophorectomy before age 20 years and were excluded. Of the remaining 8,093 women, we received one or more follow-up questionnaire(s) from 5,783 (71.4%); of these women, 2,561 had a history of breast cancer (46.6%).

This was a purely prospective study; all study participants were established to be mutation carriers before study entry, and only those cancers diagnosed after the study was initiated were considered in the estimation of risk. Incident diagnoses of ovarian, fallopian tube, or peritoneal cancer were ascertained in three ways: one, reported by the woman herself in the follow-up questionnaire; two, reported by a relative who was also a participant in the study; or three, reported by study personnel at the participating center. All new ovarian, fallopian tube, and peritoneal cancers were confirmed with pathology reports and/or review of medical records. Site of origin of cancer (ovarian, fallopian tube, or primary peritoneal) was assigned through review of the pathology report. Cancers were considered clinical or occult. Clinical cancers included those in which patients presented because of symptoms and those diagnosed as a consequence of referral to a gynecologist because of an abnormal screening test. Occult cancers included invasive ovarian and fallopian cancers diagnosed at the time of preventive oophorectomy through examination of pathology specimens. All cases of serous peritoneal cancer diagnosed after prophylactic oophorectomy were considered primary peritoneal cancer cases. In some cases, women were diagnosed with ovarian, fallopian tube, or peritoneal cancer and died before completing a follow-up questionnaire. These diagnoses were reported by the study center or a participating relative and were confirmed through pathology reports or review of medical records. For five women for whom a pathology report was not available, it was not possible to determine whether the primary source was ovarian or fallopian, and the cancers were classified as ovarian. For the women in the cohort who died, date and cause of death were confirmed by review of medical records by the participating center.

Statistical Analysis

Participants were observed from the date of completion of the baseline questionnaire or age 30 years (whichever was later). We estimated the actuarial risk of clinically detected ovarian, fallopian, or peritoneal cancer in women with intact ovaries. Women were observed from study entry until they were diagnosed with ovarian, fallopian, or peritoneal cancer, preventive oophorectomy, death, or last follow-up questionnaire. For this analysis, women with occult ovarian cancer identified at oophorectomy were censored (as unaffected) at the date of oophorectomy. Annual risks were calculated by age group and mutation (*BRCA1 v BRCA2*). Annual and cumulative risks of peritoneal cancer postoophorectomy were estimated. Women were observed from oophorectomy to: one, date of completion of the last follow-up questionnaire; two, development of peritoneal cancer; or three, death. We estimated 10-year survival rates for women diagnosed with clinically detected ovarian, fallopian, or peritoneal cancer (n = 108), occult ovarian, fallopian, or peritoneal cancer (n = 46), and primary peritoneal cancer after oophorectomy (n = 32). Survival rates were estimated from date of diagnosis to death or last follow-up questionnaire using a Kaplan-Meier approach and compared with the log-rank test.

We estimated the extent of risk reduction for ovarian, fallopian, and peritoneal cancers associated with oophorectomy using a Cox proportional hazards approach. Women who underwent an oophorectomy during the follow-up period were transferred from the unexposed group to the exposed group at that time (ie, oophorectomy was time-dependent covariate). Hazard ratio (HR) was adjusted for age at study entry, oral contraceptive use, parity (0, 1, 2, 3, or 4+), mutation (*BRCA1 v BRCA2*), and history of breast cancer at baseline. For this analysis, the 46 women in the cohort who had their ovarian, fallopian, or peritoneal cancer identified at the time of prophylactic oophorectomy were censored as unaffected at the time of oophorectomy.

We estimated the impact of prophylactic oophorectomy on all-cause mortality to age 70 years using the Cox proportional hazards regression model with adjustment for age at study entry, mutation (*BRCA1 v BRCA2*), parity (0, 1, 2, 3, or 4+), oral contraceptive use (ever *v* never), and history of breast cancer at study entry. Oophorectomy was treated as a time-dependent covariate. HRs were estimated separately for women with *BRCA1* and *BRCA2* mutations and by age group and for women with and without a history of breast cancer.

RESULTS

In this cohort, 5,783 women with a *BRCA1* or *BRCA2* mutation were observed prospectively for an average of 5.6 years (Table 1); 186 new ovarian, fallopian, and peritoneal cancers were diagnosed, including 108 women diagnosed clinically with intact ovaries (through symptoms or screening), 46 women with an occult cancer at the time of oophorectomy, and 32 women with peritoneal cancer after oophorectomy. Among women with intact ovaries, 98 cancers were diagnosed in *BRCA1* mutation carriers (annual rate, 0.91%), and 10 cancers were diagnosed in *BRCA2* mutation carriers (annual rate, 0.30%). The highest incidence rate for *BRCA1* mutation carriers was observed between the ages of 50 and 59 years (annual risk, 1.7%); for *BRCA2* mutation carriers, it was observed between the ages of 60 and 69 years (annual risk, 0.6%; Table 2).

Of the 46 occult cancers diagnosed at oophorectomy, 27 were classified as ovarian, 18 as primary fallopian tube carcinoma, and one as peritoneal. The earliest cancer discovered at prophylactic oophorectomy was in a *BRCA1* carrier age 34 years; three of the 44 cancers in *BRCA1* carriers were diagnosed at age ≤ 40 years, and 19 were diagnosed between ages 40 and 49 years. Only two *BRCA2* mutation carriers were diagnosed with occult cancer, in both cases after age 60 years (Table 3).

Thirty-two women were diagnosed with primary peritoneal cancer after oophorectomy (mean age at diagnosis, 51.6 years; range, 36 to 69 years); 28 were *BRCA1* mutation carriers, and four were *BRCA2* mutation carriers. On average, 6.1 years had elapsed from preventive surgery to peritoneal cancer diagnosis (range, one to 20 years). Annual risk of peritoneal cancer after oophorectomy was 0.20% for *BRCA1* mutation carriers; it was 0.10% for *BRCA2* mutation carriers.

In women with occult ovarian cancer (ie, only detected at surgery), 5-year survival rate was much better than that in women with clinically detected ovarian cancer (91.6% *v* 54.4%; $P < .01$; Fig 1). In women with peritoneal cancer, 5-year survival rate was 38.4%.

To estimate the extent to which prophylactic oophorectomy reduced risk of ovarian, fallopian tube, or peritoneal cancer, a Cox proportional hazards model was employed. Crude HR associated with oophorectomy was 0.25 (95% CI, 0.17 to 0.38; $P < .001$); adjusted HR was 0.20 (95% CI, 0.13 to 0.30; $P < .001$ [*BRCA1* and *BRCA2* mutation carriers combined]).

Table 1. Characteristics of Study Participants by Oophorectomy Status

Variable	No Oophorectomy (n = 2,270)		Oophorectomy at Baseline (n = 2,123)		Oophorectomy in Follow-Up (n = 1,390)		All (N = 5,783)	
	No.	%	No.	%	No.	%	No.	%
Age at study entry, years								
Mean	42.4		50.5		45.0		46.0	
Range	30-86		30-88		30-82		30-88	
Follow-up, years								
Mean	4.59		5.83		6.80		5.58	
Range	0.001-16.8		0.04-16		0.07-16		0.001-16.8	
Age at oophorectomy, years								
Mean	NA		46.8		47.5		47.1	
Range			20-78		26-83		20-83	
Mutation								
BRCA1	1,824	80.4	1,592	75.0	1,057	76.0	4,473	77.4
BRCA2	446	19.6	531	25.0	333	24.0	1,310	22.6
Breast cancer at baseline								
No	1,334	61.8	905	44.9	697	52.8	2,936	53.4
Yes	825	38.2	1,113	55.2	623	47.2	2,561	46.6
Parity								
Nulliparous	514	23.0	239	11.3	183	13.3	936	16.4
Parous	1,718	77.0	1,875	88.7	1,192	86.7	4,785	83.6
Mean	1.7		2.1		2.0		1.9	
Range	0-10		0-9		0-6		0-10	
Oral contraceptive use								
Ever	1,277	57.3	1,425	68.8	882	65.1	3,585	63.4
Never	950	42.7	647	31.2	474	34.9	2,071	36.6
Hormone replacement therapy								
Ever	159	7.4	676	33.3	140	10.6	975	17.7
Never	1,996	92.6	1,354	66.7	1,179	89.3	4,529	82.3
Tamoxifen								
Ever	279	12.3	467	22.0	215	15.5	961	16.6
Never	1,991	87.7	1,655	78.0	1,175	84.5	4,821	83.4
Incident cancer								
No	2,162	95.2	2,100	98.9	1,335	96.0	5,597	96.8
Yes	108	4.8	23	1.1	55	4.0	186	3.2
Clinically detected	108		0		0		108	
Occult	0		0		46		46	
Peritoneal	0		23		9		32	

NOTE. Participants with missing values not included in calculation of proportions.
Abbreviation: NA, not applicable.

Among all women in the cohort, 507 have died, including 329 as a result of breast cancer, 67 as a result of ovarian, fallopian, or peritoneal cancer, 49 as a result of other cancers, 44 as a result of other causes (not cancer), and 18 as a result of unknown causes. Among the 2,633 women in the cohort who had not been diagnosed with any cancer before completion of the baseline questionnaire, 69 have died, including 22 as a result of breast cancer, 22 as a result of ovarian, fallopian, or peritoneal cancer, four as a result of pancreatic cancer, two as a result of endometrial cancer, five as a result of other cancers, 11 as a result of other causes, and three as a result of unknown causes.

We estimated the impact of oophorectomy on death resulting from any cause until age 70 years. Adjusted HR for all-cause mortality to age 70 years associated with oophorectomy was 0.31 (95% CI, 0.26 to 0.38; $P < .001$). Among women with both ovaries intact at baseline, HR for all-cause mortality to age 70 years associated with oophorectomy was 0.25 (95% CI, 0.18 to 0.35; $P < .001$). HRs by mutation, age at study entry, and history of breast cancer are listed in Table 4. Among women who had been previously treated for breast cancer, HR for all-cause mortality to age 70 years was 0.39 (95% CI, 0.30 to 0.50; $P < .001$) for women who underwent oophorectomy before or within 3 years of breast cancer diagnosis; it was 0.24 (95% CI, 0.17 to 0.32; $P < .001$) for women who underwent oophorectomy $\geq$ 3 years after diagnosis.

DISCUSSION

The striking finding in this study of *BRCA1* or *BRCA2* mutation carriers was the effect of oophorectomy on all-cause mortality. Among women who were unaffected with cancer at study entry, risk of death in the follow-up period fell by 77% after oophorectomy. Impact of oophorectomy on mortality results in large part from reduction in the incidence of ovarian, tubal, and peritoneal cancers—but there is an important component from reducing breast cancer incidence and

Table 2. Annual Risks of Ovarian, Fallopian Tube, and Peritoneal Cancer in *BRCA1* and *BRCA2* Mutation Carriers With Intact Ovaries

Age Group (years)	*BRCA1*				*BRCA2*			
	No. of Patients	No. of Cancers	Person-Years	Annual Risk (per 100,000 per year)	No. of Patients	No. of Cancers	Person-Years	Annual Risk (per 100,000 per year)
30-34	413	2	865.6	231.1	47	0	90.4	0
35-39	566	6	2,223.1	269.9	92	0	388.7	0
40-49	1,009	43	3,958.6	1,086.2	276	1	1,174.3	85.2
50-59	549	34	2,029.9	1,675.0	207	5	853.2	586.1
60-69	216	9	975.3	922.8	98	3	475.2	631.3
70-74	128	4	659.1	606.9	59	1	363.2	275.3
Total	2,881	98	10,711.6	914.9	779	10	3,344.9	299.0

NOTE. Forty-six cancers diagnosed at prophylactic oophorectomy were excluded from this analysis.

mortality as well. We have previously shown that oophorectomy reduces risk of breast cancer by 48% in women with a *BRCA1* mutation,[6] and once the cancer is diagnosed, it reduces patient case fatality by 70%.[8] Average age at cohort entry was 46.0 years, and women were observed until a mean age of 51.6 years. It is expected that in young women, noncancer causes of death will be rare, and reduction in all-cause mortality associated with oophorectomy may attenuate as the women age and other causes of death emerge. Prolonged follow-up of this cohort will allow us to estimate mortality over the lifespans of the women.

We identified 46 invasive cancers in 1,390 women at the time of prophylactic oophorectomy, representing a prevalence of 4.2% among *BRCA1* mutation carriers and 0.6% among *BRCA2* mutation carriers undergoing surgery. Of the 46 occult cancers, 18 were classified as primary fallopian tube; this observation supports the position that standard of care should include removal of tubes with the ovaries at the time of preventive surgery. Assignment of cancer site was conducted by review of pathology reports and medical records; centralized pathology review was not performed. Distinction between primary cancers of the ovary and fallopian tube is difficult, especially with regard to advanced-stage cancers. However, the current recommendation is for bilateral salpingo-oophorectomy. This study was initiated in 1995, before the recommendation for removal and detailed pathologic evaluation of the fallopian tubes, and therefore, there was no standard procedure across centers regarding salpingectomy. We did not systematically evaluate or record presence of preinvasive fallopian lesions, such as tubal intraepithelial cancers, and 5-year survival of 92% reflects the course of invasive cancers only. Prevalence of occult carcinomas in previous studies of oophorectomy patients varied widely,[9-12] but the numbers of women studied were much smaller. Prevalence was 1.5% for *BRCA1* mutation carriers who underwent oophorectomy at age $<$ 40 years and was 3.8% for women who underwent surgery between age 40 and 49 years. The data presented here support the recommendation for a *BRCA1* mutation carrier to undergo oophorectomy at age 35 years; if a woman with a *BRCA1* mutation chooses to delay salpingo-oophorectomy until age 40 years, we estimate that she will have a 4.0% chance of being diagnosed with ovarian cancer, either clinically before or at the time of salpingo-oophorectomy. If she chooses to wait until age 50 years, the probability rises to 14.2%. Only one case of ovarian cancer was diagnosed at age $<$ 50 years in our cohort of *BRCA2* mutation carriers. Among 245 *BRCA1* mutation carriers who were cancer free at baseline and underwent oophorectomy at age $<$ 40 years, there were three deaths: one resulting from breast cancer, one resulting from occult ovarian cancer, and one resulting from primary peritoneal cancer. Among 567 *BRCA1* mutation carriers who were cancer free at baseline and underwent oophorectomy between ages 40 and 49 years, there were 11 deaths: four resulting from breast cancer, three resulting from primary peritoneal cancer, one resulting from gastric cancer, one resulting from hepatic cancer, one resulting from pancreatic cancer, and one resulting from a noncancer cause.

Table 3. Occult Ovarian, Fallopian Tube, and Peritoneal Cancers Found at Preventive Surgery

Age at Oophorectomy (years)	*BRCA1*			*BRCA2*		
	No. of Cancers	No. of Patients	Prevalence of Cancer (%)	No. of Cancers	No. of Patients	Prevalence of Cancer (%)
30-34	1	42	2.38	0	9	0
35-39	2	160	1.25	0	31	0
40-44	10	261	3.83	0	55	0
45-49	9	241	3.73	0	85	0
50-54	12	172	6.98	0	57	0
55-59	5	98	5.10	0	45	0
60-64	5	42	11.9	1	30	3.33
65-69	0	24	0	1	11	9.09
$\geq$ 70	0	17	0	0	10	0
Total	44	1,057	4.16	2	333	0.60

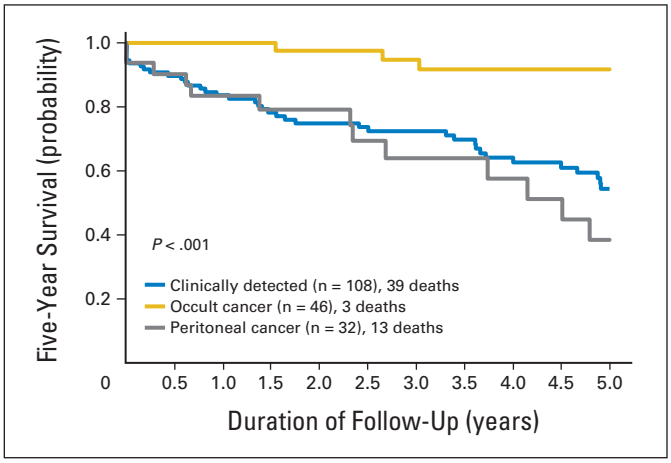

Fig 1. Five-year survival after cancer in *BRCA1* or *BRCA2* mutation carriers by type of cancer.

There were 108 clinically detected ovarian cancers, but it was not possible to distinguish those that were symptomatic and those that were detected because of screening. Nevertheless, all women in the cohort were aware of their mutation status, and for most, ovarian screening had been recommended. In women with clinically detected ovarian cancer, 10-year survival rate was 35%, similar to that in mutation carriers diagnosed with ovarian cancer in a separate cohort who did not know their mutation status at time of diagnosis.[13] Survival of women with occult ovarian cancer was much better. Together, these observations suggest that the benefit of awareness of mutation status regarding ovarian cancer mortality is attributable to oophorectomy, through prevention and earlier detection.

We estimate the risk of peritoneal cancer in the 20 years after oophorectomy to be 3.9% for *BRCA1* mutation carriers and 1.9% for *BRCA2* mutation carriers, based on 32 incident cases of peritoneal cancer after oophorectomy. It is possible that some of these were actually metastases of subclinical disease present at time of surgery; if so, these might have been prevented if oophorectomy had been performed earlier. There were two cases of peritoneal cancer diagnosed among 646 women who underwent oophorectomy at age < 40 years (0.3%) versus 12 cases among 1,632 women who underwent oophorectomy between ages 40 and 50 years (0.7%).

In a large historical cohort study similar to ours, Domchek et al[5] observed 2,482 *BRCA1* and *BRCA2* mutation carriers for a mean of 5.0 years. They estimated that risk reduction in all-cause mortality was significant for *BRCA1* mutation carriers (HR, 0.38; 95% CI, 0.24 to 0.62) but not for *BRCA2* mutation carriers (HR, 0.52; 95% CI, 0.22 to 1.23). We confirm here the impact of oophorectomy on mortality in our study of 5,783 carriers, and we report that the effect of oophorectomy on all-cause mortality is equally strong for *BRCA1* (HR, 0.30; 95% CI, 0.24 to 0.38) and *BRCA2* mutation carriers (HR, 0.33; 95% CI, 0.22 to 0.50). The observation that oophorectomy has a profound protective effect on all-cause mortality has several important implications. Age distribution of ovarian cancers should not be the sole criterion for determining the optimum age for surgery, because some of the benefit of oophorectomy may derive through means other than preventing ovarian cancer (particularly for breast cancer risk). After early oophorectomy, women have reported an increase in vasomotor symptoms, loss of libido, and a modest diminution of overall quality of life.[2,3] It is difficult to compare formally the decline in quality of life with an increase in life expectancy, and it is unlikely that any study can resolve this. Women without a history of breast cancer may be administered hormone replacement therapy for the relief of the acute symptoms of menopause without increasing their risk of breast cancer.[14,15] It is important that we ascertain the long-term effects of salpingo-oophorectomy and design effective treatments and preventive strategies for these.

Management of healthy women with a *BRCA1* or *BRCA2* mutation is a multidisciplinary effort, and options include chemoprevention, screening, oophorectomy, preventive mastectomy, and breast reconstruction. We have previously shown that preventive salpingo-oophorectomy is acceptable by the majority of women with a *BRCA1* or *BRCA2* mutation,[16] that oophorectomy rates among healthy mutation carriers are high worldwide,[17] and that patients report a high degree of satisfaction after surgery.[3] In our study, we show that among unaffected women with a *BRCA1* or *BRCA2* mutation, all-cause mortality to age 70 years is reduced by 77% with oophorectomy. Among women with a history of breast cancer, the reduction in mortality is similar. This implies that genetic testing is likely to be beneficial in countries where patients who

Table 4. Association Between Oophorectomy and All-Cause Mortality by Age Group, Mutation Status, and History of Breast Cancer

		BRCA1			*BRCA2*			All Patients		
Variable	No. of Patients	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age group at study entry, years										
≤ 40	2,104	0.27	0.15 to 0.48	< .001	0.44	0.17 to 1.09	.08	0.30	0.19 to 0.49	< .001
41-50	1,906	0.23	0.16 to 0.33	< .001	0.29	0.14 to 0.59	< .001	0.24	0.17 to 0.33	< .001
51-60	1,189	0.28	0.19 to 0.43	< .001	0.19	0.08 to 0.43	< .001	0.27	0.18 to 0.38	< .001
≥ 61	584	0.43	0.25 to 0.71	.001	0.89	0.33 to 2.43	.84	0.49	0.31 to 0.76	.002
Total	5,783	0.30	0.24 to 0.38	< .001	0.33	0.22 to 0.50	< .001	0.31	0.26 to 0.38	< .001
Previous breast cancer										
Yes	2,561	0.31	0.24 to 0.39	< .001	0.34	0.22 to 0.52	< .001	0.32	0.26 to 0.39	< .001
No	2,633	0.21	0.12 to 0.37	< .001	0.67	0.08 to 5.35	.70	0.23	0.13 to 0.39	< .001

NOTE. Adjusted by age at study entry, oral contraceptive use (duration), parity (0, 1, 2, 3, or 4+), mutation (*BRCA1* or *BRCA2*), and history of breast cancer at baseline.
Abbreviation: HR, hazard ratio.

test positive for a mutation have access to salpingo-oophorectomy, even if limited resources are available for other aspects of care, such as magnetic resonance imaging, tamoxifen treatment, or breast reconstruction.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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GLOSSARY TERMS

***BRCA1*:** A tumor suppressor gene known to play a role in repairing DNA breaks. Mutations in this gene are associated with increased risk of developing breast or ovarian cancer.

***BRCA2*:** A tumor suppressor gene whose protein product is involved in repairing chromosomal damage. Although structurally different from *BRCA1*, *BRCA2* has cellular functions similar to *BRCA1*. *BRCA2* binds to RAD51 to fix DNA breaks caused by irradiation and other environmental agents. Also known as the breast cancer 2 early-onset gene.

Cox proportional hazards regression model: A statistical model for regression analysis of censored survival data, examining the relationship of censored survival distribution to one or more covariates. This model produces a baseline survival curve and covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

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Appendix

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