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Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers

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IMPORTANCE The clinical management of *BRCA1* and *BRCA2* mutation carriers requires accurate, prospective cancer risk estimates.

OBJECTIVES To estimate age-specific risks of breast, ovarian, and contralateral breast cancer for mutation carriers and to evaluate risk modification by family cancer history and mutation location.

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study of 6036 *BRCA1* and 3820 *BRCA2* female carriers (5046 unaffected and 4810 with breast or ovarian cancer or both at baseline) recruited in 1997-2011 through the International *BRCA1/2* Carrier Cohort Study, the Breast Cancer Family Registry and the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer, with ascertainment through family clinics (94%) and population-based studies (6%). The majority were from large national studies in the United Kingdom (EMBRACE), the Netherlands (HEBON), and France (GENEPSO). Follow-up ended December 2013; median follow-up was 5 years.

EXPOSURES *BRCA1/2* mutations, family cancer history, and mutation location.

MAIN OUTCOMES AND MEASURES Annual incidences, standardized incidence ratios, and cumulative risks of breast, ovarian, and contralateral breast cancer.

RESULTS Among 3886 women (median age, 38 years; interquartile range [IQR], 30-46 years) eligible for the breast cancer analysis, 5066 women (median age, 38 years; IQR, 31-47 years) eligible for the ovarian cancer analysis, and 2213 women (median age, 47 years; IQR, 40-55 years) eligible for the contralateral breast cancer analysis, 426 were diagnosed with breast cancer, 109 with ovarian cancer, and 245 with contralateral breast cancer during follow-up. The cumulative breast cancer risk to age 80 years was 72% (95% CI, 65%-79%) for *BRCA1* and 69% (95% CI, 61%-77%) for *BRCA2* carriers. Breast cancer incidences increased rapidly in early adulthood until ages 30 to 40 years for *BRCA1* and until ages 40 to 50 years for *BRCA2* carriers, then remained at a similar, constant incidence (20-30 per 1000 person-years) until age 80 years. The cumulative ovarian cancer risk to age 80 years was 44% (95% CI, 36%-53%) for *BRCA1* and 17% (95% CI, 11%-25%) for *BRCA2* carriers. For contralateral breast cancer, the cumulative risk 20 years after breast cancer diagnosis was 40% (95% CI, 35%-45%) for *BRCA1* and 26% (95% CI, 20%-33%) for *BRCA2* carriers (hazard ratio [HR] for comparing *BRCA2* vs *BRCA1,* 0.62; 95% CI, 0.47-0.82; *P*=.001 for difference). Breast cancer risk increased with increasing number of first- and second-degree relatives diagnosed as having breast cancer for both *BRCA1* (HR for ≥2 vs 0 affected relatives, 1.99; 95% CI, 1.41-2.82; *P*<.001 for trend) and *BRCA2* carriers (HR, 1.91; 95% CI, 1.08-3.37; *P*=.02 for trend). Breast cancer risk was higher if mutations were located outside vs within the regions bounded by positions c.2282-c.4071 in *BRCA1* (HR, 1.46; 95% CI, 1.11-1.93; *P*=.007) and c.2831-c.6401 in *BRCA2* (HR, 1.93; 95% CI, 1.36-2.74; *P*<.001).

CONCLUSIONS AND RELEVANCE These findings provide estimates of cancer risk based on *BRCA1* and *BRCA2* mutation carrier status using prospective data collection and demonstrate the potential importance of family history and mutation location in risk assessment.

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Supplemental content

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The optimal clinical management of women with *BRCA1* and *BRCA2* mutations depends on accurate age-specific cancer risk estimates. These can be used to estimate the absolute risk reduction from preventive strategies and to inform decisions about the age at which to commence cancer screening.[1]

Based on retrospective studies,[2-11] cumulative breast cancer risk estimates to age 70 years range from 40% to 87% for *BRCA1* and from 27% to 84% for *BRCA2* carriers. The corresponding ovarian cancer risks vary from 16% to 68% for *BRCA1* and from 11% to 30% for *BRCA2* carriers. Risk estimates from these studies had wide confidence intervals. Differences in sampling (population-based/high-risk families), population and mutation characteristics, analytic methods, and other genetic and lifestyle/hormonal factors are possible explanations for the variation in risk estimates.[12]

Because *BRCA1* and *BRCA2* mutations are rare in the population, most retrospective penetrance estimates have been derived from family-based studies. Typically, mutation screening has been performed among affected women, selected on the basis of young age at diagnosis or cancer family history. Cancer risks are then estimated using the known or inferred genotypes of the relatives. Estimates from such retrospective, family-based studies are prone to bias if analyses are not correctly adjusted for the ascertainment process or if there are inaccuracies in family history.

Prospective cohort studies, in which mutation carriers are recruited on the basis of their mutation status and followed over time, may avoid these issues. Because the precision of risk estimates depends on the number of prospective incident cancers, a very large sample with long follow-up is required. Prospective penetrance estimates have been based on small samples (<64 breast cancers, 31 ovarian cancers) and are imprecise.[13-15] The purpose of this study was to estimate age-specific risks of breast, ovarian, and contralateral breast cancer using data from a large prospective cohort.

Key Points

Question What are the breast and ovarian cancer risks for *BRCA1* and *BRCA2* mutation carriers and are they related to family history of cancer and mutation position?

Findings From a prospective cohort of 9856 mutation carriers, mainly ascertained through cancer genetic clinics, the cumulative breast cancer risk to age 80 years was 72% for *BRCA1* and 69% for *BRCA2* carriers. The cumulative ovarian cancer risk to age 80 years was 44% for *BRCA1* and 17% for *BRCA2* carriers. Cancer risks differed by cancer family history and mutation position.

Meaning These findings provide cancer risk patterns based on *BRCA* status using prospective data. Family history and mutation position are important additional variables in risk assessment.

Methods

Participants

We used prospective cohort data on carriers of pathogenic *BRCA1* and *BRCA2* mutations recruited through 3 consortia, the International *BRCA1/2* Carrier Cohort Study (IBCCS), the Breast Cancer Family Registry (BCFR), and the Kathleen Cuningham Foundation Consortium for Research Into Familial Breast Cancer (kConFab) (eAppendix in the Supplement). All centers in these consortia obtained written informed consent from study participants and local ethical review committees approved protocols.

Briefly, for the IBCCS, data were available from 7666 female carriers recruited between 1997 and 2011 from 18 European cancer genetics centers and the Quebec province of Canada. The majority were from large national studies in the United Kingdom, the Netherlands, and France. All centers conducted active follow-up through questionnaires. In addition to the active follow-up in all studies, passive follow-up through linkage with cancer, pathology, and death registries was obtained in countries where this is available (cancer/death registries in Denmark, the Netherlands, Sweden, and the United Kingdom; pathology registries to collect information on preventive surgeries in Denmark and the Netherlands), together with medical record validation of self-reported cancer diagnoses and preventive surgeries.

The BCFR is a family cohort that includes data on 1570 mutation carriers recruited from 6 sites in Australia, Canada, and the United States. Families were followed up regularly through annual approaches to probands and 5-year systematic follow-up of families collecting epidemiological and demographic data from all participants.

The kConFab study included 620 mutation carriers from multiple-case families ascertained through family cancer clinics in Australia and New Zealand since 1997. Participants were systematically followed up using a questionnaire mailed every 3 years.

The end of follow-up was December 2013.

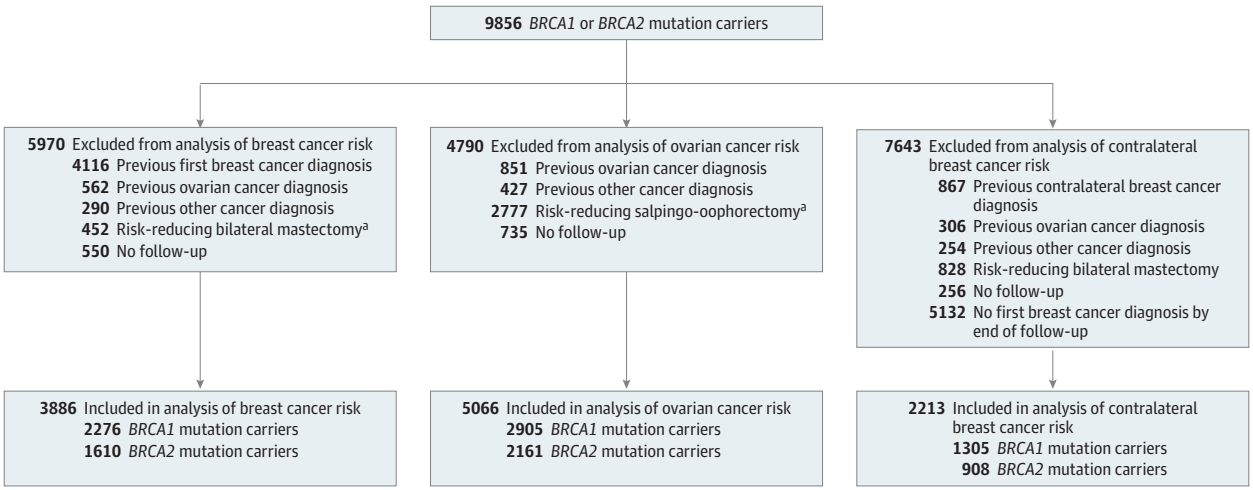
Eligibility and Censoring

For each of the 3 analyses (breast cancer risk, contralateral breast cancer risk, and ovarian cancer risk), we defined a different group eligible at baseline (**Figure 1**). Age at baseline was defined as age at study recruitment or age at the genetic test, whichever was more recent.

Breast Cancer Risk

Women were included in the estimation of first breast cancer risk if at completion of the baseline questionnaire they had not been diagnosed as having any cancer (excluding nonmelanoma skin cancer) nor undergone risk-reducing bilateral mastectomy (with mastectomy: n = 304 *BRCA1;* n = 148 *BRCA2*) (eAppendix in the Supplement). Women were followed up from baseline until the first of the following: age 80 years; death; completion of last follow-up questionnaire or last record linkage (if conducted), whichever happened last; risk-reducing bilateral mastectomy; or diagnosis of any first cancer (excluding nonmelanoma skin cancer). Women diagnosed as having breast cancer (invasive or noninvasive [ductal carcinoma in situ]) during follow-up were considered as affected. Because information on cancers was partly self reported, tumor phenotype-specific

Figure 1. Assembly of Analysis Cohorts



[a] After exclusion of women in the preceding categories.

data were not available other than for invasiveness. Therefore, all types of breast cancer were included in the analysis. Additional analyses were performed in which (1) affected women were considered to be only those diagnosed as having invasive disease and (2) women were censored at the age of risk-reducing salpingo-oophorectomy (eAppendix).

Ovarian Cancer Risk

Women were included in the ovarian cancer analysis if at baseline they had not been diagnosed as having ovarian cancer nor undergone risk-reducing salpingo-oophorectomy (with oophorectomy: n = 1808 *BRCA1*; n = 969 *BRCA2*). Women with a history of breast or nonmelanoma skin cancer were included in the analysis but women with other cancers were not. Women were followed up from baseline until the first of the following: age 80 years; death; completion of last follow-up questionnaire or last record linkage (whichever happened last); risk-reducing salpingo-oophorectomy (or salpingectomy or removal of ovaries for other reasons); or any cancer diagnosis (excluding breast and nonmelanoma skin cancer). Only women diagnosed as having invasive ovarian (or fallopian tube or peritoneal) cancer during follow-up were considered affected.

Contralateral Breast Cancer Risk

Women were included in the contralateral breast cancer analysis if they were diagnosed as having a first breast cancer before the date of their last follow-up questionnaire (or record linkage) and had not been diagnosed as having any other cancer (including contralateral breast cancer) nor undergone risk-reducing bilateral mastectomy before study entry. Only asynchronous contralateral breast cancer was considered, for which there had to be an interval of at least 1 year between first and second breast cancers. Eligible women entered follow-up at their baseline questionnaire date or 1 year after their first breast cancer diagnosis date (whichever was later) and were followed up until the first of the following: age 80 years; death; date at last follow-up; risk-reducing bilateral mastectomy; or any cancer. Women diagnosed as having asynchronous contralateral breast cancer during follow-up were assumed to be affected.

Statistical Analysis

Annual incidences of breast, ovarian, and contralateral breast cancer per 1000 person-years were estimated for 10-year age intervals using standard cohort analysis. Kaplan-Meier analysis was used to estimate cumulative risks. Standardized incidence ratios (SIRs) for breast and ovarian cancer relative to population-specific incidences were also estimated (eAppendix in the Supplement).

We used Cox-regression to compare cancer risks for *BRCA1* mutation carriers with risks for *BRCA2* carriers across all age groups and by attained age. To test for heterogeneity by country, we carried out Cox regression estimating hazard ratios (HRs) for each country (n=6) compared with the baseline (United Kingdom); a χ^2 (n − 1) degree-of-freedom test was carried out on the estimated HRs to test for heterogeneity. The contralateral breast cancer analysis was stratified by age at first breast cancer (<40 years, 40-49 years, or ≥50 years) and Cox regression was used to compare risks between age groups. We evaluated cancer risks by extent of self-reported family history of breast or ovarian cancer separately (eAppendix in the Supplement). Women were classified by the number of cancers in first- or second-degree relatives (0, 1, or ≥2). Separate categories for women with cancers of unknown type among relatives and for those with unknown family history (missing data) were defined, and separate HRs were estimated for these categories. A test for trend was performed using Cox regression by including a continuous variable in the model representing the number of breast or ovarian cancers in female first- or second-degree relatives (taking values of 0, 1, 2, 3, etc).

Separate variables were derived for the number of breast cancers and number of ovarian cancers in relatives. We also evaluated differences in breast and ovarian cancer by mutation position (based on base-pair location) using Cox regression. Mutations were grouped into regions based on differences in breast and ovarian cancer risks previously reported in retrospective studies.[16-18] Mutations in *BRCA1* were grouped into 3 regions (5′ to c.2281, c.2282 to c.4071, c.4072 to 3′). For *BRCA2,* mutations were grouped in 3 regions using both the narrow and broad definitions of the ovarian cancer cluster region[16] (OCCR; broad definition: 5′ to c.2830, c.2831 to c.6401, c.6402 to 3′; narrow definition: 5′ to c.3846, c.3847 to c.6275, c.6276 to 3′; see eAppendix). For all analyses, a robust variance approach that clustered observations on family membership was used to adjust standard errors for the fact that the cohort included multiple women from the same family.[19] Analyses were stratified by country (United Kingdom, France, the Netherlands, Australia, United States, or other) and birth cohort (before 1940, 1940-1949, 1950-1959, 1960-1969, 1970-1979, or 1980 or later). Proportionality was evaluated using Schoenfeld residuals, which was met for all analyses. Analyses were carried out in Stata version 13 (Stata Corp). Statistical tests were considered significant based on 2-sided hypothesis tests with $P < .05$.

Results

A total of 9856 participants including 6036 *BRCA1* and 3820 *BRCA2* mutation carriers were available at baseline. The majority of women were ascertained through family clinics (94%), and the remainder (6%) were recruited from studies that used population-based ascertainment. Figure 1 and eTable 1 in the Supplement summarize the baseline cohort study sample (N = 9856) and the assembly of the eligible prospective cohorts for each analysis. **Table 1** summarizes the characteristics of the eligible women included in the prospective analyses. Information on follow-up completeness is summarized in eTable 2 in the Supplement. All studies conducted active follow-up with questionnaires, but the mean interval between questionnaires varied across studies (1.6 to 8.7 years) (eTable 2). In addition, in countries with registry information, active follow-up was complemented with passive follow-up through record linkage. On average, 7% of women in the cohort were lost to follow-up, but this varied among studies (0% to 13%) (eTable 2).

The breast cancer analysis was based on 3886 eligible *BRCA1* and *BRCA2* mutation carriers (median age at study entry, 38 years; interquartile range [IQR], 30-46 years). The ovarian cancer analysis was based on data from 5066 women (median age at study entry, 38 years; IQR, 31-47 years) and the contralateral breast cancer analysis was based on 2213 women (median age at start of follow-up, 47 years; IQR, 40-55 years). During follow-up, among the eligible women, 426 were diagnosed as having breast cancer (483 censored for risk-reducing bilateral mastectomy), 109 were diagnosed as having ovarian cancer (1508 censored for risk-reducing salpingo-oophorectomy), and 245 were diagnosed as having asynchronous contralateral breast cancer. The age-specific cancer incidences, SIRs, and cumulative risks are shown in **Table 2**.

Breast Cancer Risks

For *BRCA1* carriers, the breast cancer incidences per decade of age increased from 21 to 30 years to 31 to 40 years but then remained at 23.5 to 28.3 per 1000 person-years for ages 31 to 70 years ($P = .97$ for trend). The peak incidence occurred in the 41- to 50-year age group (28.3 [95% CI, 23.1-34.7] per 1000 person-years). A similar pattern was seen for *BRCA2* carriers, with peak incidence in the 51- to 60-year age group (30.6 [95% CI, 22.8-41.1] per 1000 person-years) and incidences of 21.9 to 30.6 per 1000 person-years across ages 41 to 80 years ($P = .57$ for trend). The estimated SIRs decreased with increasing age in both *BRCA1* carriers ($P<.001$ for trend) and *BRCA2* carriers ($P<.001$ for trend). The cumulative risk of breast cancer by age 80 years was 72% (95% CI, 65%-79%) for *BRCA1* carriers and 69% (95% CI, 61%-77%) for *BRCA2* carriers (**Figure 2**). While the cumulative risks for *BRCA1* and *BRCA2* carriers to age 80 years were similar, the cumulative risks to age 50 years were higher for *BRCA1* carriers ($P = .03$).

The cumulative risk estimates for breast cancer by age 80 years when censoring at risk-reducing salpingo-oophorectomy were 70% (95% CI, 60%-80%) for *BRCA1* carriers and 75% (95% CI, 67%-83%) for *BRCA2* carriers (eTable 3 and eFigure 1 in the Supplement). From an analysis that excluded known in situ breast cancers, the corresponding risk estimates were 68% (95% CI, 60%-76%) for *BRCA1* carriers and 63% (95% CI, 54%-72%) for *BRCA2* carriers (eTable 4 in the Supplement).

There were no significant differences in the estimated breast cancer incidences by country for either *BRCA1* carriers ($P = .32$ for heterogeneity) or *BRCA2* carriers ($P = .43$ for heterogeneity) (eTable 5 and eFigure 2 in the Supplement). The estimated breast cancer risks were similar when analyses were carried out separately for women identified through family clinics and women who were relatives of mutation carriers identified through populationwide screening of breast cancer cases (eTable 6 in the Supplement).

Ovarian Cancer Risks

There was an increase in ovarian cancer incidence with age up to 61 to 70 years for both *BRCA1* and *BRCA2* carriers. The incidences were higher for *BRCA1* carriers (HR comparing *BRCA1* vs *BRCA2*, 3.6; 95% CI, 2.2-5.9; $P < .001$). The SIRs did not vary with age for either gene (*BRCA1*: overall SIR, 49.6 [95% CI, 40.0-61.5]; $P = .86$ for trend; *BRCA2*: 13.7 [95% CI, 9.1-20.7]; $P = .23$ for trend). The ovarian cancer cumulative risk to age 80 years was 44% (95% CI, 36%-53%) for *BRCA1* carriers and 17% (95% CI, 11%-25%) for *BRCA2* carriers (Table 2 and Figure 2).

Contralateral Breast Cancer Risks

The estimated incidence of contralateral breast cancer for *BRCA1* carriers varied between 23 and 28 per 1000 person-years for the period up to 20 years after the first breast cancer diagnosis (**Table 3**; eTable 7 in the Supplement). The cumulative risk of contralateral breast cancer 20 years after the first

Table 1. Numbers of Mutation Carriers and Incident Cancers Per Study Group Eligible for Each of the Analyses and Other Summary Statistics

Analysis and Study	All Carriers	*BRCA1*	*BRCA2*
Breast Cancer Analysis[a]			
Eligible, No.[b]			
IBCCS	2691	1624	1067
BCFR	582	327	255
kConFab	613	325	288
All	3886	2276	1610
Incident breast cancers, No.			
IBCCS	250	164	86
BCFR	83	50	33
kConFab	93	55	38
All	426	269	157
Invasive breast cancers	366	240	126
Ductal carcinoma in situ	60	29	31
Age at start of follow-up, median (IQR), y	38 (30-46)	37 (29-45)	39 (31-48)
Follow-up time, median (IQR), y[c]	5 (2-7)	5 (2-8)	4 (2-7)
Age at cancer diagnosis, median (IQR), y	45 (38-53)	44 (37-51)	48 (42-56)
Ovarian Cancer Analysis[d]			
Eligible, No.[b]			
IBCCS	3493	2059	1434
BCFR	1022	558	464
kConFab	551	288	263
All	5066	2905	2161
Incident ovarian cancers, No.			
IBCCS	67	51	16
BCFR	26	23	3
kConFab	16	11	5
All	109	85	24
Age at start of follow-up, median (IQR), y	38 (31-47)	37 (30-45)	40 (33-50)
Follow-up time, median (IQR), y[c]	4 (2-7)	4 (2-7)	4 (2-7)
Age at cancer diagnosis, median (IQR), y	54.5 (46-63)	54 (43.5-62.5)	59.5 (53.3-64.7)
Contralateral Breast Cancer Analysis[e]			
Eligible, No.[b]			
IBCCS	1576	949	627
BCFR	562	310	252
kConFab	75	46	29
All	2213	1305	908
Incident contralateral cancers, No.			
IBCCS	152	110	42
BCFR	87	58	29
kConFab	6	5	1
All	245	173	72
Age at start of follow-up, median (IQR), y	47 (40-55)	46 (38-53)	49 (42-57)
Follow-up time, median (IQR), y[c]	4 (2-7)	5 (2-7)	4 (2-7)
Age at cancer diagnosis, median (IQR), y	51 (42-57.5)	48 (41-57)	51 (44-59)

Abbreviations: BCFR, Breast Cancer Family Registry; IBCCS, International *BRCA1/2* Carrier Cohort Study; IQR, interquartile range; kConFab, Kathleen Cuningham Foundation Consortium for Research Into Familial Breast Cancer.

[a] Women free of all cancers and who did not have risk-reducing bilateral mastectomy at baseline.

[b] Eligibility for each analysis is described in the "eligibility and censoring" methods section.

[c] After taking into account the censoring process.

[d] Women free of ovarian or other (nonbreast) cancer and who did not have risk-reducing salpingo-oophorectomy at baseline.

[e] Women diagnosed as having unilateral breast cancer and who were free of other cancers and who did not have risk-reducing bilateral mastectomy at start of follow-up.

breast cancer diagnosis was 40% (95% CI, 35%-45%). The HR for contralateral breast cancer declined with increasing age at the first breast cancer diagnosis (for women with first breast cancer at age 40-50 years, HR, 0.81 [95% CI, 0.58-1.12], and for women with first breast cancer at age >50 years, 0.71 [95% CI, 0.45-1.11], relative to women with first breast cancer at age <40 years).

For *BRCA2* carriers, the estimated contralateral breast cancer incidence varied between 13 and 18 per 1000 person-years during the years after the first breast cancer diagnosis. The cumulative risk of contralateral breast cancer at 20 years after the first breast cancer diagnosis was 26% (95% CI, 20%-33%) and was lower than for *BRCA1* carriers (HR comparing *BRCA2* vs *BRCA1* carriers, 0.62; 95% CI, 0.47-0.82; P = .001).

Table 2. Breast and Ovarian Cancer Incidence Rates Per 1000 Person-Years, Kaplan-Meier Estimates of the Cumulative Risks, and Standardized Incidence Rates by 10-Year Age Groups

Age, During Follow-up, y[a]	No. of Women Contributing in Age Category[a]	No. of Person-Years	No. of Events	Incidence per 1000 Person-Years (95% CI)	Cumulative Risk, % (95% CI)[b]	Standardized Incidence Rate (95% CI)[c]
Breast Cancer						
BRCA1 mutation carriers						
≤20	53	74.0	0	0		
21-30	605	2222.5	13	5.9 (3.4-10.1)	4 (2-7)	73.7 (42.9-126.8)
31-40	1048	3831.6	90	23.5 (19.1-28.9)	24 (21-29)	46.2 (37.3-57.1)
41-50	870	3317.8	94	28.3 (23.1-34.7)	43 (39-48)	17.2 (14.0-21.2)
51-60	479	1905.9	49	25.7 (19.4-34.0)	56 (51-61)	9.7 (7.2-12.9)
61-70	201	761.3	19	25.0 (15.9-39.1)	66 (61-72)	7.0 (4.5-11.0)
71-80	55	243.0	4	16.5 (6.2-43.9)	72 (65-79)	4.8 (1.8-12.8)
Total	2276[d]	12356.1	269	21.8 (19.3-24.5)		16.6 (14.7-18.7)
BRCA2 mutation carriers						
≤20	30	44.0	0	0		
21-30	329	1046.0	5	4.8 (2.0-11.5)	4 (2-9)	60.8 (25.5-144.9)
31-40	625	2136.1	23	10.8 (7.2-16.2)	13 (9-19)	20.3 (13.5-30.5)
41-50	669	2365.0	65	27.5 (21.6-35.1)	35 (29-41)	16.4 (12.9-20.9)
51-60	384	1437.2	44	30.6 (22.8-41.1)	53 (46-59)	11.4 (8.4-15.5)
61-70	174	610.2	14	22.9 (13.6-38.7)	61 (55-68)	6.4 (3.8-10.7)
71-80	68	274.6	6	21.9 (9.8-48.6)	69 (61-77)	6.6 (3.0-14.7)
Total	1610[d]	7913.1	157	19.8 (17.0-23.2)		12.9 (11.1-15.1)
Ovarian Cancer						
BRCA1 mutation carriers						
≤20	53	74.0	0	0		
21-30	667	2493.0	0	0		
31-40	1464	5506.6	10	1.8 (1.0-3.4)	2 (1-3)	41.4 (22.27-76.8)
41-50	1061	3558.2	25	7.0 (4.7-10.4)	8 (6-12)	56.7 (38.05-84.5)
51-60	501	1744.7	24	13.8 (9.2-20.5)	20 (16-26)	53.3 (35.78-79.5)
61-70	230	817.3	24	29.4 (19.7-43.8)	41 (33-50)	69.1 (45.17-105.7)
71-80	88	351.0	2	5.7 (1.4-22.8)	44 (36-53)	11.8 (2.94-47.0)
Total	2905[d]	14544.8	85	5.8 (4.7-7.2)		49.6 (40.0-61.5)
BRCA2 mutation carriers						
≤20	30	44.0	0	0		
21-30	353	1134.0	0	0		
31-40	831	2953.0	1	0.3 (0.1-2.4)	0 (0-2)	7.3 (1.03-51.9)
41-50	862	2961.0	0	0	0 (0-2)[e]	
51-60	534	1836.5	12	6.5 (3.7-11.5)	7 (4-11)	24.5 (13.91-43.1)
61-70	267	974.0	10	10.3 (5.5-19.1)	15 (10-23)	21.5 (11.20-41.3)
71-80	108	435.0	1	2.3 (0.3-16.3)	17 (11-25)	4.4 (0.62-31.0)
Total	2161[d]	10337.5	24	2.3 (1.6-3.5)		13.7 (9.1-20.7)

[a] Each woman could contribute to more than 1 age category.

[b] Kaplan-Meier estimate.

[c] Standardized incidence rates for breast cancer and ovarian cancer relative to population-specific incidences. Age- and calendar period–specific population disease incidences were obtained from Cancer in Five Continents (http://ci5.iarc.fr/Default.aspx) and NORDCAN (http://www-dep.iarc.fr/NORDCAN/english/frame.asp).

[d] Total number of women contributing to the overall analysis.

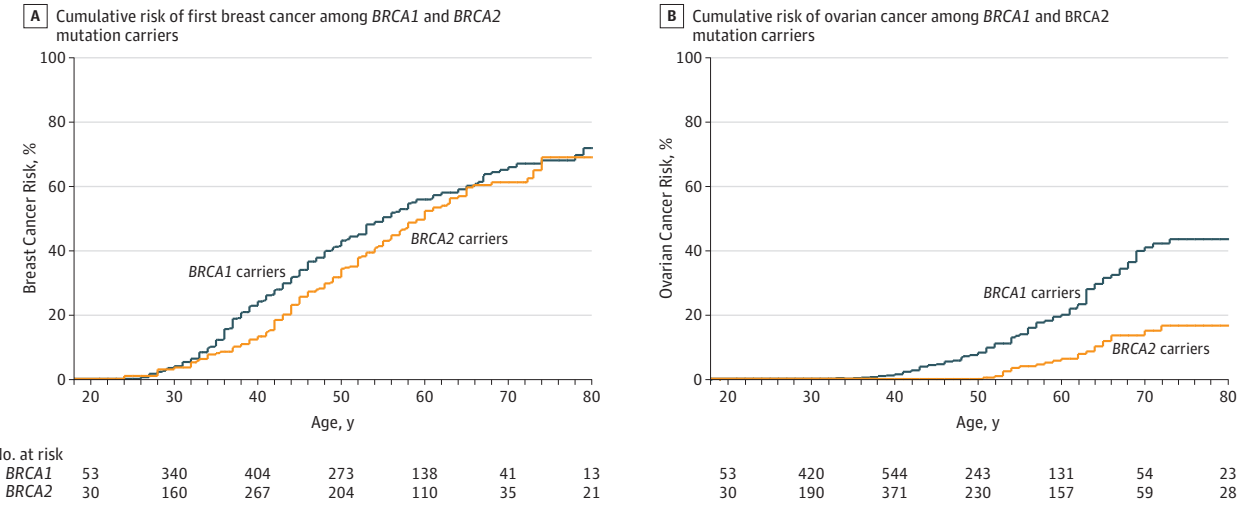
[e] Remains equal to the estimate in the previous age group because there are no events.

The HR for contralateral breast cancer when first breast cancer diagnosis was between ages 40 and 50 years was 0.73 (95% CI, 0.41-1.26), and when the first breast cancer diagnosis was at age greater than 50 years, the HR was 0.76 (95% CI, 0.43-1.36) compared with a first breast cancer before age 40 years.

When women were censored at the age of risk-reducing salpingo-oophorectomy, the contralateral breast cancer risks at 20 years after the first breast cancer were 38% (95% CI, 31%-45%) for *BRCA1* carriers and 34% (95% CI, 25%-45%) for *BRCA2* carriers (eTable 8 in the Supplement).

To investigate potential survival bias, the analysis was repeated after excluding women whose first breast cancer diagnosis occurred more than 5 years prior to study recruitment. The estimated cumulative risk of contralateral breast

Figure 2. Estimated Cumulative Risks of Breast and Ovarian Cancer in Mutation Carriers



Kaplan-Meier estimates of cumulative risks of breast and ovarian cancers. In the breast cancer analysis, women were censored at risk-reducing bilateral mastectomy. In the ovarian cancer analysis, women were censored for risk-reducing salpingo-oophorectomy. Number at risk indicates the number of women who remained at risk at the end of the 10-year age category (eg, in panel A, there were 138 women with *BRCA1* mutations still at risk of breast cancer at the end of the age 50-60 years period). The earliest follow-up started at age 18 years.

cancer at 20 years after the first breast cancer diagnosis was 41% (95% CI, 32%-53%) for *BRCA1* and 21% (95% CI, 15%-50%) for *BRCA2* carriers.

Breast and Ovarian Cancer Risks by Family History

The estimated cumulative breast and ovarian cancer risks by family history are shown in **Table 4** and eFigure 3 in the Supplement. Breast cancer risk estimates for both *BRCA1* and *BRCA2* carriers increased with the number of first- and second-degree relatives diagnosed as having breast cancer ($P<.001$ for trend for *BRCA1*; $P=.02$ for *BRCA2*) (Table 4). For women with 2 or more first- or second-degree relatives diagnosed as having breast cancer compared with those with no family history of breast cancer, the HR for breast cancer was 1.99 (95% CI, 1.41-2.82) for *BRCA1* carriers (cumulative risk estimates to age 70 years: 73% [95% CI, 65%-80%] vs 53% [95% CI, 39%-69%]) and the HR for breast cancer was 1.91 (95% CI, 1.08-3.37) for *BRCA2* carriers (cumulative risks to age 70 years: 65% [95% CI, 56%-74%] vs 39% [95% CI, 25%-56%]) (Table 4).

There was no significant difference in ovarian cancer risk for *BRCA1* carriers with family history of ovarian cancer compared with those without (HR, 1.37; 95% CI, 0.89-2.11) (Table 4; eFigure 3 in the Supplement). A similar pattern was observed for *BRCA2* carriers, but the number of events for women with ovarian cancer family history was small (n = 5). Results were similar when family history of cancer was restricted to first-degree relatives (eTable 9 in the Supplement) or when analyses were stratified by the presence of family history of breast or ovarian cancer (eTables 10-13 in the Supplement). For *BRCA1* mutation carriers, the risk of breast cancer was lower for women with a family history of ovarian cancer compared with those with no family history of ovarian cancer (HR, 0.71 [95% CI, 0.51-0.99] in women with a family history of breast cancer; HR, 0.38 [95% CI, 0.21-0.70] in those without) (eTable 12).

Breast and Ovarian Cancer Risks by Mutation Position

BRCA1 mutations located outside the region bounded by positions c.2282 to c.4071 were associated with a significantly higher breast cancer risk compared with mutations within the region (HR, 1.46; 95% CI, 1.11-1.93; $P = .007$) (**Table 5**; eFigure 4 in the Supplement), but there was no significant difference in ovarian cancer risk. There was no significant difference in the breast or ovarian cancer risks for either the *BRCA1* c.68_69delAG or c.5266dupC mutations compared with *BRCA1* mutations in the same region (Table 5). *BRCA2* mutations outside the OCCR were associated with a significantly higher breast cancer risk compared with mutations within the OCCR (based on the narrow OCCR definition: HR, 1.70 [95% CI, 1.18-2.46]; $P = .005$; based on the broad OCCR definition: HR, 1.93 [95% CI, 1.36-2.74]; $P < .001$) (Table 5), but there was no significant difference in ovarian cancer risk. There was no significant difference in breast cancer risk for *BRCA2* c.5946delT mutation carriers compared with other OCCR *BRCA2* mutations (HR, 0.73; 95% CI, 0.35-1.54; $P = .41$). The associations by mutation position remained significant after adjusting for family history of breast cancer and after excluding carriers of the *BRCA2* c.5946delT mutation from the OCCR (eTable 14 in the Supplement).

Discussion

This study estimated age-specific risks of breast, ovarian, and contralateral breast cancer for *BRCA1* and *BRCA2* mutation

Table 3. Contralateral Breast Cancer Incidence Rates Per 1000 Person-Years and Kaplan-Meier Estimates of the Cumulative Risks of Contralateral Breast Cancer by Time Since First Breast Cancer, Overall and Stratified by Age at First Breast Cancer

Years Since First Breast Cancer Diagnosis	No. of Women Contributing in Category	No. of Person-Years	No. of Events	Incidence Rate per 1000 Person-Years (95% CI)	Cumulative Risk, % (95% CI)
BRCA1					
≤5	827	2107	60	28.5 (22.1-36.7)	13 (10-16)
>5-10	618	2071	53	25.6 (19.6-33.5)	23 (20-27)
>10-15	435	1438	33	22.9 (16.3-32.3)	32 (28-36)
>15-20	236	675	17	25.2 (15.7-40.5)	40 (35-45)
>20-45	132	661	10	15.1 (8.1-28.1)	53 (44-62)
First breast cancer diagnosis at age <40 y					
≤5	370	920	31	33.7 (23.7-47.9)	15 (11-21)
>5-10	278	945	28	29.6 (20.5-42.9)	27 (21-33)
>10-15	217	739	20	27.1 (17.5-41.9)	36 (30-43)
>15-20	129	378	8	21.2 (10.6-42.3)	43 (36-50)
>20-45	70	343	6	17.5 (7.9-38.9)	60 (46-74)
First breast cancer diagnosis at age ≥40-50 y					
≤5	283	725	15	20.7 (12.5-34.3)	10 (6-16)
>5-10	225	718	19	26.5 (16.9-41.5)	21 (15-28)
>10-15	152	480	11	22.9 (12.7-41.4)	30 (23-38)
>15-20	74	222	6	27.0 (12.1-60.2)	39 (30-49)
>20-39	52	280	4	14.3 (5.4-38.1	49 (37-62)
First breast cancer diagnosis at age ≥50 y					
≤5	174	462	14	30.3 (17.9-51.2)	14 (8-22)
>5-10	115	408	6	14.7 (6.6-32.7)	20 (14-30)
>10-15	66	219	2	9.1 (2.3-36.5)	24 (16-35)
>15-20	33	75	3	40.0 (12.9-124.0)	38 (24-57)
>20-27	10	38	0	0.0	38 (24-57)
BRCA2					
≤5	565	1468	27	18.4 (12.6-26.8)	8 (6-12)
>5-10	476	1543	26	16.9 (11.5-24.8)	16 (12-21)
>10-15	285	880	11	12.5 (6.9-22.6)	21 (17-26)
>15-20	138	355	5	14.1 (5.9-33.8)	26 (20-33)
>20-43	68	290	3	10.3 (3.3-32.1)	65 (25-98)
First breast cancer diagnosis at age <40 y					
≤5	180	485	11	22.7 (12.6-41.0)	9 (5-17)
>5-10	163	542	9	16.6 (8.6-31.9)	17 (11-25)
>10-15	104	314	5	15.9 (6.6-38.2)	23 (16-32)
>15-20	58	149	4	26.9 (10.1-71.5)	31 (22-43)
>20-43	29	127	2	15.8 (3.9-63.0)	68 (29-98)
First breast cancer diagnosis at age ≥40-50 y					
≤5	206	550	7	12.7 (6.1-26.7)	6 (3-14)
>5-10	181	554	9	16.3 (8.5-31.2)	14 (8-22)
>10-15	107	322	5	15.5 (6.5-37.3)	20 (13-29)
>15-20	52	143	1	7.0 (1.0-49.6)	23 (15-35)
>20-37	29	123	1	8.1 (1.2-57.7)	28 (17-44)
First breast cancer diagnosis at age ≥50 y					
≤5	179	433	9	20.8 (10.8-40.0)	9 (5-17)
>5-10	132	447	8	17.9 (9.0-35.8)	17 (11-27)
>10-15	74	244	1	4.1 (0.6-29.1)	20 (13-30)
>15-20	28	63	0	0.0	20 (1330)
>20-30	10	40	0	0.0	20 (1330)

Table 4. Hazard Ratio Estimates for Breast and Ovarian Cancer Associated With Family History of Breast or Ovarian Cancer in First- and Second-Degree Relatives and Corresponding Cumulative Risk Estimates

Family History Category	No. of Women	No. of Person-Years	No. of Events	Hazard Ratio (95% CI)	*P* Value	Cumulative Risk by Age, % (95% CI)			
						40 y	50 y	60 y	70 y
Breast cancer risk for *BRCA1* mutation carriers									
No breast cancers	600	3283	54	1 [Reference]		16 (10-23)	35 (27-44)	43 (34-53)	53 (39-69)
1 breast cancer	719	4176	91	1.51 (1.08-2.11)	.02	27 (21-35)	47 (40-55)	56 (48-64)	68 (59-77)
≥2 breast cancers	737	3864	108	1.99 (1.41-2.82)	<.001	31 (23-40)	50 (42-58)	67 (60-75)	73 (65-80)
Family history unknown	205	906	13	1.06 (0.54-2.08)	.86				
Cancer type unknown in family	15	128	3	2.57 (1.16-5.71)	.02				
≥1 breast cancers	1456	8040	199	1.67 (1.23-2.26)	.001	28 (23-34)	48 (43-54)	62 (57-68)	71 (66-80)
Per affected relative with breast cancer				1.15 (1.07-1.24)	<.001				
Breast cancer risk for *BRCA2* mutation carriers									
No breast cancers	302	1499	17	1 [Reference]		5 (1-18)	26 (16-40)	39 (25-56)	39 (25-56)
1 breast cancer	495	2675	49	1.53 (0.86-2.70)	.15	14 (8-24)	30 (21-41)	55 (44-67)	62 (51-74)
≥2 breast cancers	634	3112	78	1.91 (1.08-3.37)	.02	14 (8-24)	40 (32-50)	57 (48-66)	65 (56-74)
Family history unknown	166	575	13	1.82 (0.80-4.14)	.15				
Cancer type unknown in family	13	53	0						
≥1 breast cancers	1129	5787	127	1.69 (0.99-2.88)	.05	14 (9-21)	36 (30-43)	56 (49-63)	64 (57-71)
Per affected relative with breast cancer				1.15 (1.02-1.30)	.02				
Ovarian cancer risk for *BRCA1* mutation carriers									
No ovarian cancers	1706	8774	46	1 [Reference]		2 (1-4)	7 (4-11)	15 (10-21)	41 (30-53)
1 ovarian cancer	689	3286	21	1.24 (0.75-2.03)	.40	1 (0-6)	11 (6-20)	27 (16-43)	45 (30-64)
≥2 Ovarian cancers	228	1117	12	1.77 (0.90-3.46)	.10	5 (1-18)	15 (7-31)	40 (23-62)	45 (27-67)
Family history unknown	230	1000	4	1.08 (0.36-3.23)	.90				
Cancer type unknown in family	52	368	2	1.21 (0.29-5.07)	.79				
≥1 ovarian cancers	917	4403	33	1.37 (0.89-2.11)	.16	2 (1-6)	12 (8-20)	31 (22-43)	44 (32-58)
Per affected relative with ovarian cancer				1.20 (0.94-1.55)	.15				
Ovarian cancer risk for *BRCA2* mutation carriers									
No ovarian cancers	1558	7845	18	1 [Reference]		0	0	6 (3-12)	16 (10-25)
1 ovarian cancer[a]	331	1463	4	1.26 (0.43-3.69)	.67				
≥2 Ovarian cancers	55	215	1						
Family history unknown	169	558	1	0.83 (0.10-6.70)	.87				
Cancer type unknown in family	48	257	0						
≥1 ovarian cancers	386	1678	5	1.09 (0.37-3.25)	.87	1 (0-10)	1 (1-10)	8 (2-26)	15 (5-39)
Per affected relative with ovarian cancer				0.94 (0.39-2.26)	.90				

[a] Numbers too small to obtain estimates.

carriers using data from a prospective cohort. Because the study mainly included unaffected women identified by mutation screening based on cancer family history, early age at onset of a family member, or both, the overall estimates are relevant to mutation carriers identified through clinical testing. However, the wide range of family histories represented allowed an examination of the relationship between family history and cancer risk. The results indicate that family history is a strong risk factor for mutation carriers and that cancer risks vary by mutation location, suggesting that individualized counseling should incorporate both family history profiles and mutation location.

The cumulative risk of developing breast cancer by age 80 years was 72% for *BRCA1* mutation carriers and 69% for *BRCA2* mutation carriers, respectively. For ovarian cancer, the cumulative risks by age 80 years were 44% for *BRCA1* carriers and 17% for *BRCA2* carriers. Breast cancer incidence for carriers increased rapidly with age in early adulthood then plateaued to remain relatively constant throughout the remaining lifetime. The age at which this plateau was reached was 31 to 40 years for *BRCA1* carriers and 5 to 10 years later for *BRCA2* carriers. The incidence during the plateau was similar for both groups of mutation carriers. This is consistent with the model for genetic risk of breast cancer based on twin data,[20] in which

Table 5. Hazard Ratio Estimates for Breast and Ovarian Cancer Associated With Mutation Location and Corresponding Cumulative Risk Estimates

Mutation Location Category	No. of Women	No. of Person-Years	No. of Events	Hazard Ratio (95% CI)	*P* Value	Cumulative Risk by Age, % (95% CI)			
						40 y	50 y	60 y	70 y
Breast cancer risk for *BRCA1* mutation carriers									
5′ to c.2281	926	5014.1	116	1.43 (1.05-1.94)	.02	26 (20-33)	46 (39-53)	60 (53-67)	68 (60-77)
c.2282 to c.4071	671	3631.2	62	1 [Reference]		15 (9-22)	34 (27-43)	48 (39-58)	56 (46-67)
c.4072 to 3′	672	3684.8	91	1.51 (1.10-2.08)	.01	31 (24-39)	48 (41-57)	58 (50-67)	71 (62-80)
Missing[a]	7	26.0	0						
5′ to c.2281 and c.4072 to 3′	1598	8698.9	207	1.46 (1.11-1.93)	.007	28 (23-33)	47 (42-52)	59 (54-65)	70 (64-76)
Ashkenazi Jewish mutations									
Non-Ashkenazi mutations in 5′ to c.2281 and c.4072 to 3′	1226	6506.0	150	1 [Reference]		27 (21-33)	46 (40-52)	57 (51-64)	69 (62-77)
c.68_69delAG	185	1163.0	33	1.37 (0.91-2.07)	.14	24 (14-39)	44 (32-60)	73 (57-87)	84 (68-94)
c.5266dupC	187	1029.9	24	1.22 (0.76-1.94)	.41	39 (26-56)	52 (38-68)	60 (45-75)	60 (45-75)
Ovarian cancer risk for *BRCA1* mutation carriers									
5′ to c.2281	1176	5900.6	33	0.71 (0.42-1.20)	.20	2 (1-5)	7 (4-13)	19 (13-28)	36 (25-50)
c.2282 to c.4071	802	3859.2	30	1 [Reference]		1 (0-5)	13 (8-22)	27 (18-39)	51 (36-67)
3′ to c.4072	921	4769.0	22	0.66 (0.39-1.13)	.13	2 (0-5)	6 (3-12)	16 (9-28)	39 (26-56)
Missing[a]	6	16.0	0						
5′ to c.2281 and c.4072 to 3′	2097	10669.6	55	0.69 (0.43-1.10)	.12	2 (1-4)	7 (4-10)	18 (13-24)	37 (28-48)
Ashkenazi Jewish mutations									
Non-Ashkenazi mutations in 5′ to c.2281 and c.4072 to 3′	1552	7714.6	40	1 [Reference]		2 (1-4)	7 (4-11)	17 (11-25)	40 (29-54)
c.68_69+delAG	281	1614.0	11	1.03 (0.50-2.14)	.93	3 (1-12)	8 (3-22)	26 (14-45)	35 (20-56)
c.5266dupC	264	1341.0	4	0.57 (0.22-1.48)	.25		3 (0-17)	10 (2-40)	34 (13-73)
Breast cancer risk for *BRCA2* mutation carriers									
Narrow definition of the ovarian cancer cluster region									
5′ to c.3846	492	2341.3	47	1.63 (1.07-2.49)	.02	14 (8-25)	41 (31-53)	52 (41-64)	69 (55-81)
c.3847 to c.6275	538	2994.3	45	1 [Reference]		6 (3-15)	18 (12-28)	42 (32-53)	51 (39-63)
c.6276 to 3′	571	2601.5	63	1.77 (1.16-2.70)	.008	20 (12-32)	44 (34-54)	61 (51-71)	67 (57-76)
Missing[a]	9	26.0	2						
5′ to c.3846 and 3′ to c.6276	1063	4942.8	110	1.70 (1.18-2.46)	.005	17 (11-24)	42 (35-50)	57 (50-65)	66 (58-74)
Wide definition of the ovarian cancer cluster region									
5′ to c.2830	406	1941.3	42	1.95 (1.28-2.99)	.002	16 (9-29)	45 (34-57)	55 (43-68)	69 (56-82)
c.2831 to c.6401	634	3414.3	50	1 [Reference]		5 (2-12)	18 (12-27)	40 (31-51)	51 (40-63)
3′ to c.6402	561	2531.5	63	1.91 (1.28-2.85)	.001	20 (12-32)	44 (35-55)	62 (52-72)	68 (58-77)
Missing[a]	9	26.0	2						
5′ to c.2830 and c.6402 to 3′	967	4472.8	105	1.93 (1.36-2.74)	<.001	18 (12-26)	44 (37-52)	59 (52-67)	68 (60-75)
Ashkenazi Jewish mutations									
Non-Ashkenazi mutations in c.2831 to c.6401	543	2828.3	43	1 [Reference]		6 (3-15)	22 (14-31)	42 (32-53)	53 (41-67)
c.5946delT	91	586.0	7	0.73 (0.35-1.54)	.41			32 (14-62)	41 (20-70)

(continued)

Table 5. Hazard Ratio Estimates for Breast and Ovarian Cancer Associated With Mutation Location and Corresponding Cumulative Risk Estimates (continued)

Mutation Location Category	No. of Women	No. of Person-Years	No. of Events	Hazard Ratio (95% CI)	*P* Value	Cumulative Risk by Age, % (95% CI)			
						40 y	50 y	60 y	70 y
Ovarian cancer risk for *BRCA2* mutation carriers									
Narrow definition of the ovarian cancer cluster region									
5′ to c.3846	655	3002.5	6	0.83 (0.27-2.52)	.75			5 (1-19)	18 (8-36)
c.3847 to c.6275	733	3793.0	11	1 [Reference]		1 (0-5)	1 (0-5)	9 (4-18)	14 (8-26)
3′ to c.6276	761	3508.0	7	0.67 (0.22-2.00)	.47			6 (2-15)	17 (7-38)
Missing[a]	12	34.0	0						
5′ to c.3846 and c.6276 to 3′	1416	6510.5	13	0.75 (0.29-1.93)	.55			5 (2-11)	17 (10-29)
Wide definition of the ovarian cancer cluster region									
5′ to c.2830	539	2459.5	6	1.07 (0.36-3.17)	.91			6 (2-23)	21 (10-41)
c.2831 to c.6401	867	4426.0	11	1 [Reference]		1 (0-5)	1 (0-5)	8 (4-16)	13 (7-23)
c.6402 to 3′	743	3418.0	7	0.78 (0.27-2.30)	.65			6 (2-16)	17 (7-38)
Missing[a]	12	34.0	0						
5′ to c.2830 and c.6402 to 3′	1282	5877.5	13	0.91 (0.36-2.28)	.84			6 (3-12)	18 (10-32)
Ashkenazi Jewish mutations									
Non-Ashkenazi mutations in c.2831 to c.6401	744	3796.0	11	1 [Reference]		1 (0-6)	1 (0-6)	9 (4-19)	16 (8-28)
c.5946delT	123	630.0	0						

[a] Numbers too small to obtain estimates.

the age-specific incidence for genetically susceptible women increases to a high constant level by a predetermined age that varies among families.

The estimated breast and ovarian cancer risks were consistent with findings from retrospective family-based studies.[2,3,6,10] The breast cancer SIRs decreased with increasing age for both *BRCA1* and *BRCA2* carriers, but the estimates were higher than those previously reported for younger age groups.[2,21] From this prospective study, the estimated cumulative risks of ovarian cancer were low up to age 40 years for *BRCA1* mutation carriers and up to age 50 years for *BRCA2* mutation carriers.

This study was limited in the extent to which differences by birth cohort could be assessed because birth cohort was strongly associated with age. For age intervals with sufficient observations, there was no evidence of risk differences by birth cohort (eFigure 5 in the Supplement).

In line with retrospective studies of contralateral breast cancer risks,[22,23] the present prospective analysis of *BRCA1* and *BRCA2* carriers combined demonstrated a higher risk when the first breast cancer was diagnosed before age 40 years vs after age 50 years ($P = .03$).

The contralateral breast cancer analysis also included women diagnosed as having breast cancer prior to study recruitment. The median interval between first breast cancer diagnosis and study recruitment was 4 years, and this did not vary by age at first breast cancer diagnosis or by gene. The inclusion of survivors could potentially bias the estimation of contralateral breast cancer risks if such risks were related to the outcome of the first cancer; however, there is no strong evidence of such a relationship in the general population. Furthermore, the results were similar after excluding women whose first breast cancer diagnosis occurred more than 5 years prior to study recruitment, suggesting that any bias is likely to be small. Contralateral breast cancer risks have been shown to be reduced by adjuvant treatment of the first cancer.[24,25] *BRCA2* carriers are more likely to develop estrogen receptor–positive cancers, so their lower contralateral breast cancer risk estimates may in part be due to greater use of endocrine therapy. Hormone and chemotherapeutic treatments were not considered, so the present estimates represent risks averaged over different treatments.

There was increasing breast cancer risk for both *BRCA1* and *BRCA2* carriers with increasing number of relatives who had been diagnosed with breast cancer. Similar patterns were observed for the risk of ovarian cancer but the number of events for women with family history of ovarian cancer was small. The overall breast cancer risk estimates were somewhat higher than those estimated by kin cohort analyses, in which the risks are derived from cohorts of relatives of carriers identified among unselected cases.[3,21] The present cohort of mutation carriers was primarily identified through clinical genetics centers and included women who, on average, are likely to have stronger family history of cancer compared with mutation carriers identified through population-based sampling of cases. Therefore, a likely explanation for the higher estimated risks in the present study is that cancer risks for mutation carriers are modified by genetic and nongenetic risk factors which aggregate in families, in line with evidence that other genetic factors modify cancer risks for mutation carriers.[18,26-29]

These results confirm that family history should be taken into account in determining cancer risks for carriers, as modeled explicitly in BOADICEA.[3]

This prospective analysis validates retrospective analyses demonstrating that cancer risk varies by mutation location within the *BRCA1* or *BRCA2* gene.[16-18] Consistent with those findings, mutations that lie in exon 11 of either gene were associated with a lower breast cancer risk and possibly higher ovarian cancer risk. The number of women in this prospective cohort was too small to estimate risks for additional, recently identified breast or ovarian cancer cluster regions.[18]

This study has several limitations. Data on tumor phenotypes of cancers were not available. Therefore, the results represent average estimates over all phenotypes of breast and ovarian cancer. Although there was variation in the cancer risks for mutation carriers by cancer family history, the study sample was not identified through population screening of unaffected women. Therefore, the overall estimates may not be directly applicable to such women. The present results suggest that cancer risks for women with no family history are likely to be lower than those estimated here. The cancer risk estimates may be subject to some selection bias if the decision to participate in the study or opt for testing was related to factors that are associated with disease risk. It was not possible to contrast the unaffected study participants to all other unaffected family members who had negative test results or who did not opt for a genetic test or for study participation, as those data could not be collected. However, the analysis by family history addresses possible selection bias with respect to family history of cancer and the family history–specific estimates are expected to be unbiased. The number of events in some of the subgroups considered was small and therefore the estimates have wide confidence intervals. Family size was not taken into consideration because data on unaffected family members were not collected systematically. In addition, risk estimates are limited by the lack of information about the use of hormone therapies to prevent either first primary or contralateral breast cancers.

Conclusions

These findings provide information on cancer risk for *BRCA1* and *BRCA2* mutation carriers using prospective data and demonstrate the potential importance of family history and mutation location in risk assessment.

ARTICLE INFORMATION

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