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ARTICLE

Cancer Risks for *BRCA1* and *BRCA2* Mutation Carriers: Results From Prospective Analysis of EMBRACE

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Background Reliable estimates of cancer risk are critical for guiding management of *BRCA1* and *BRCA2* mutation carriers. The aims of this study were to derive penetrance estimates for breast cancer, ovarian cancer, and contralateral breast cancer in a prospective series of mutation carriers and to assess how these risks are modified by common breast cancer susceptibility alleles.

Methods Prospective cancer risks were estimated using a cohort of 978 *BRCA1* and 909 *BRCA2* carriers from the United Kingdom. Nine hundred eighty-eight women had no breast or ovarian cancer diagnosis at baseline, 1509 women were unaffected by ovarian cancer, and 651 had been diagnosed with unilateral breast cancer. Cumulative risks were obtained using Kaplan–Meier estimates. Associations between cancer risk and covariables of interest were evaluated using Cox regression. All statistical tests were two-sided.

Results The average cumulative risks by age 70 years for *BRCA1* carriers were estimated to be 60% (95% confidence interval [CI] = 44% to 75%) for breast cancer, 59% (95% CI = 43% to 76%) for ovarian cancer, and 83% (95% CI = 69% to 94%) for contralateral breast cancer. For *BRCA2* carriers, the corresponding risks were 55% (95% CI = 41% to 70%) for breast cancer, 16.5% (95% CI = 7.5% to 34%) for ovarian cancer, and 62% (95% CI = 44% to 79.5%) for contralateral breast cancer. *BRCA2* carriers in the highest tertile of risk, defined by the joint genotype distribution of seven single nucleotide polymorphisms associated with breast cancer risk, were at statistically significantly higher risk of developing breast cancer than those in the lowest tertile (hazard ratio = 4.1, 95% CI = 1.2 to 14.5; $P = .02$).

Conclusions Prospective risk estimates confirm that *BRCA1* and *BRCA2* carriers are at high risk of developing breast, ovarian, and contralateral breast cancer. Our results confirm findings from retrospective studies that common breast cancer susceptibility alleles in combination are predictive of breast cancer risk for *BRCA2* carriers.

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Pathogenic mutations in the *BRCA1* and *BRCA2* genes confer high risks of breast, ovarian, and contralateral breast cancer (CBC). However, the precise magnitude of these risks is uncertain. Most penetrance studies to date have been retrospective in design, using either families ascertained on the basis of multiple affected individuals or population-based studies of cancer patients. Estimates in the range of 40% to 87% for *BRCA1* and 18% to 88% for *BRCA2* mutation carriers have been reported for breast cancer, and estimates in the range of 22% to 65% for *BRCA1* and 10% to 35% for *BRCA2* mutation carriers have been reported for ovarian cancer (1–25). Such studies require adjustment for ascertainment to address nonrandom sampling of families and individuals with respect to their disease status. Estimates of CBC risk also vary across studies, with 10-year cumulative risk after unilateral breast cancer ranging from 16% to 35% (26–31). Although some of the observed variation may be explained by different study methods and populations, other factors contribute to variation in risk. Cancer risks in *BRCA1* and *BRCA2* carriers vary by age at diagnosis or site of the cancer in index patient (2,4,32), family history (25,31), type and site of the mutation (2,15,33,34), and lifestyle factors such as parity (35–37). Furthermore, the higher risk in individuals with strong family history is consistent with the existence of genetic modifiers or other familial factors that influence risk (3). Recently, several common alleles have been reported to be associated with breast cancer risk for *BRCA1* and/or *BRCA2* carriers in large retrospective studies (38–45). The effect associated with each of these single nucleotide polymorphisms (SNPs) is small, but in combination these alleles may be useful in stratifying individuals into distinct risk categories (42). Cohort studies, in which

unaffected mutation carriers are followed up prospectively, provide penetrance estimates that are free of ascertainment bias. However such studies to date have generally been limited in size or follow-up time (46–51).

The Epidemiological Study of *BRCA1* and *BRCA2* mutation carriers (EMBRACE) is an ongoing collaborative study established in 1998 that recruits from 28 centers from across the United Kingdom and Ireland. Participants included in these analyses were carriers of pathogenic *BRCA1* or *BRCA2* mutations who were unaffected at date of baseline questionnaire or diagnosed with unilateral breast cancer. We used prospective follow-up data on these individuals to estimate age-specific incidence of breast, ovarian, and contralateral breast cancer and the corresponding cumulative risks. We also examined the effect of bilateral prophylactic oophorectomy on cancer risks. We further constructed genetic profiles, defined by the joint distribution of SNPs previously found to modify cancer risks for mutation carriers in retrospective studies, and assessed their associations with prospective cancer risk.

Methods

Study Participants

EMBRACE recruits mutation carriers referred for genetic testing at clinical genetics centers in the United Kingdom and Ireland (http://ccge.medschl.cam.ac.uk/embrace/). Eligible participants were women, aged at least 18 years at interview, and carriers of a pathogenic *BRCA1* or *BRCA2* mutation. Participants were followed prospectively at 2, 5, and 10 years using questionnaires that included questions on the date of cancer diagnosis, surgical procedures including mastectomy or oophorectomy, and changes in lifestyle factors such as parity. Rates of data completeness by follow-up questionnaire are shown in Supplementary Table 1 (available online). Cancer occurrence was also notified through the Office for National Statistics. The number of individuals included in each analysis is shown in Supplementary Figure 1 (available online). Baseline demographics of the study cohorts are summarized in Table 1. Additional details are available in the Supplementary Methods (available online).

Statistical Analysis

Cancer incidence was estimated using standard cohort analysis methods. Cumulative risks were obtained using Kaplan–Meier estimates (52) and represent average cumulative risks over all individuals. The prospective follow-up data were used to evaluate the associations between cancer risk and bilateral prophylactic oophorectomy and between cancer risk and the combined effect of common polymorphisms previously found to be associated with breast cancer risk for *BRCA1* and/or *BRCA2* carriers (38–42,45). Cox proportional hazards regression was used for this purpose. Proportionality was verified with Schoenfeld residuals and by testing for interaction with time in the model. To investigate the association between cancer risk and genetic variants, a risk score was derived under the assumption that the hazard ratios (HRs) for the SNPs combine multiplicatively. All statistical tests were two-sided. SNPs included in the score are described in Supplementary Table 2 (available online). Detailed

Table 1. Characteristics of *BRCA1* and *BRCA2* mutation carriers included in analyses and cancers reported on follow-up*

	Mutation carried		
Cohort	***BRCA1/2***	***BRCA1***	***BRCA2***
Women unaffected with BC or OC	n = 988	n = 501	n = 485
Age at start of follow-up, y			
Mean	41.2	39.6	43
Median (IQR)	39.5 (14.6)	38.2 (14.4)	41.7 (14.0)
Follow-up time, y			
Mean	3.3	3.8	2.9
Median (IQR)	2.6 (3.7)	2.8 (5.0)	2.1 (3.3)
Age at oophorectomy, y	(n = 309)	(n = 162)	(n = 146)
Mean	45.0	44.0	46.2
Median (IQR)	44.0 (10.8)	42.4 (10.6)	44.8 (11.1)
Family size†			
Mean	1.5	1.4	1.7
Range	1–9	1–5	1–9
Age at first birth,‡ y			
Mean	24.9	24.9	24.9
Median (IQR)	25 (8)	25 (8)	24 (8)
Reproductive history,§ No. (%)			
Never pregnant	202 (21%)	105 (21%)	97 (20%)
0 live births	250 (25%)	124 (25%)	126 (26%)
1 live birth	157 (16%)	79 (16%)	78 (16%)
2 live births	351 (36%)	194 (39%)	157 (33%)
≥3 live births	223 (23%)	99 (20%)	122 (25%)
Age at diagnosis of BCs reported on follow-up, y	(n = 64)	(n = 35)	(n = 29)
Mean	44.8	43.8	46.0
Median (IQR)	43.3 (10.7)	42.0 (16.4)	45.0 (7.3)

(Table continues)

Table 1 (Continued).

Cohort	Mutation carried		
	BRCA1/2	***BRCA1***	***BRCA2***
Women without an OC diagnosis	n = 1509	n = 770	n = 736
Age at start of follow-up, y			
Mean	43.7	41.7	45.6
Median (IQR)	41.9 (16.9)	39.8 (14.9)	44.0 (18.6)
Follow-up time, y			
Mean	3.0	3.1	2.8
Median (IQR)	2.0 (3.6)	2.1 (3.8)	1.8 (3.3)
Family size†			
Mean	1.6	1.4	1.8
Range	1–12	1–4	1–12
Age at first birth,‡ y			
Mean	24.8	24.9	24.8
Median (IQR)	24 (7)	25 (7)	24 (7)
Reproductive history,§ No. (%)			
Never pregnant	270 (18%)	152 (20%)	118 (16%)
0 live births	332 (22%)	183 (24%)	149 (20%)
1 live birth	257 (17%)	134 (17%)	123 (17%)
2 live births	557 (37%)	281 (37%)	275 (37%)
≥3 live births	354 (24%)	165 (22%)	187 (26%)
BC diagnoses prior to or on follow-up‖	690 (46%)	365 (47%)	323 (44%)
Unilateral BC	517	265	250
Bilateral BC	173	100	73
Age at diagnosis of OCs reported on follow-up, y	(n = 31)	(n = 24)	(n = 7)
Mean	58.5	58.2	60.0
Median (IQR)	60.9 (13.2)	60.1 (15.6)	62.0 (13.2)
Women with unilateral BC	n = 651	n = 340	n = 309
Age at start of follow-up, y			
Mean	50.2	48.5	52.0
Median (IQR)	49.4 (14.8)	47.5 (14.2)	52.5 (13.3)
Follow-up time, y			
Mean	3.0	3.3	2.8
Median (IQR)	2.0 (3.5)	2.2 (3.9)	1.8 (3.5)
Age at diagnosis of first BCs, y			
Mean	43.4	41.6	45.2
Median (IQR)	42.6 (12.3)	41.0 (11.9)	44.6 (11.7)
Age at oophorectomy, y	(n = 315)	(n = 173)	(n = 141)
Mean	48.5	48.0	48.9
Median (IQR)	47.5 (11.6)	47.2 (11.5)	47.8 (11.8)
Family size†			
Mean	1.15	1.14	1.16
Range	1–4	1–3	1–4
Age at first birth,‡ y			
Mean	24.9	24.2	25
Median (IQR)	24 (7)	24 (6)	24 (7)
Reproductive history,§ No. (%)			
Never pregnant	71 (11%)	47 (14%)	24 (8%)
0 live births	90 (14%)	57 (17%)	33 (11%)
1 live birth	98 (15%)	54 (16%)	44 (14%)
2 live births	281 (43%)	139 (41%)	141 (46%)
≥3 live births	180 (28%)	88 (26%)	91 (30%)
Age at diagnosis of CBCs on follow-up, y	(n = 61)	(n = 42)	(n = 19)
Mean	50.8	50.2	52.1
Median (IQR)	50.3 (14.2)	48.6 (14.4)	54.1 (14.6)

* BC = breast cancer; CBC = contralateral breast cancer; IQR = interquartile range; OC = ovarian cancer.

† Number of members of the same family in the cohort.

‡ Age at first birth for any birth occurring before censoring.

§ Number of women not pregnant any time before censoring, as a percentage of all women responding to the question at baseline or follow-up questionnaire; 0 live births: number of women who have never experienced a live birth or never pregnant before censoring, and as a percentage of all women responding to the question; number of women with 1, 2 or ≥3 live births and as a percentage of all women experiencing any pregnancy, at baseline questionnaire and any available follow-up information.

‖ Number of women diagnosed with breast cancer before or after baseline questionnaire but before diagnosis of ovarian cancer, as percentage of all women included in the cohort.

methods are provided in the Supplementary Methods (available online).

Results

Incidence of Breast, Ovarian, and Contralateral Breast Cancer

Nine hundred eighty-eight women without a previous diagnosis of breast or ovarian cancer were followed from baseline questionnaire to breast cancer or censoring. Age-specific cancer incidences for *BRCA1* and *BRCA2* carriers are shown in Tables 2 and 3. The *BRCA1* breast cancer incidence was estimated to be 8.7 per 1000 in the group aged 20 to 29 years, rising to 36.1 per 1000 for women in the group aged 50 to 59 years. There was one breast cancer diagnosis beyond age 60 years among *BRCA1* carriers. The majority of breast tumors were invasive carcinomas. The average cumulative risk of breast cancer by age 70 years was 60% (95% confidence interval [CI] = 44% to 75%) (Figure 1A). The estimated *BRCA2* incidence peaked in the group aged 40 to 49 years (41.4 per 1000) but was in the range 11.9 to 16.2 per 1000 for other age groups. The average cumulative risk of developing breast cancer for *BRCA2* carriers by age 70 years was 55% (95% CI = 41% to 70%) (Figure 1B).

The analysis of ovarian cancer incidence involved 1509 women without prior diagnosis of ovarian cancer. The *BRCA1* ovarian cancer incidence rose with age to 55.9 per 1000 in the group aged 60 to 69 years. There was only one case of ovarian cancer in *BRCA2* carriers before age 50 years, and the incidence after age 60 years was 11.2 to 15 per 1000. The average cumulative risk of ovarian cancer by age 70 years was 59% (95% CI = 43% to 76%) for *BRCA1* and 16.5% (95% CI = 7.5% to 34%) for *BRCA2* carriers (Figure 1).

Six hundred fifty-one women with a previous unilateral breast cancer diagnosis were included in the analysis of CBC. The CBC incidence rates in *BRCA1* carriers were substantially higher than those for a first breast cancer. For *BRCA2* carriers, incidence rates were lower and the overall incidence rate was similar to that for a first breast cancer. The average cumulative risk of CBC by age 70 years was 83% (95% CI = 69% to 94%) for *BRCA1* and 62% (95% CI = 44% to 79.5%) for *BRCA2* carriers (Figure 1).

Risk-Reducing Salpingo-Oophorectomy and Cancer Risks

To obtain estimates of breast cancer incidences that more closely reflect the natural history of the disease, analyses were performed in which follow-up was stopped at oophorectomy. Estimated incidence and average cumulative risks for breast cancer in previously unaffected women and for CBC were somewhat higher when follow-up was

Table 2. Incidence of breast, ovarian, and contralateral breast cancer in *BRCA1* mutation carriers*

Age, y	No.†	PY	Events	Incidence (per 1000 PY)	95% CI
Breast cancer					
<20	4	2.7	0	0	—
20–29	103	230.7	2	8.7	2.2 to 34.7
30–39	222	652.5	11	16.9	9.3 to 30.4
40–49	214	602.2	12	19.9	11.3 to 35.1
50–59	90	249.1	9	36.1	18.8 to 69.4
60–69	43	134.9	1	7.4	1.0 to 52.6
≥70	11	25.4	0	0	—
Total		1897.5	35	18.4	13.2 to 25.7
Ovarian cancer					
<20	4	2.7	0	0	—
20–29	115	272.0	0	0	—
30–39	324	907.0	1	1.1	0.2 to 7.8
40–49	318	674.2	5	7.4	3.1 to 17.8
50–59	140	294.9	6	20.3	8.1 to 51.0
60–69	80	179.0	10	55.9	30.1 to 103.8
≥70	28	83.7	2	23.9	6.0 to 95.5
Total		2413.7	24	9.9	6.6 to 15.1
Contralateral breast cancer					
<20	—	—	—	—	—
20–29	9	11.0	0	0	—
30–39	69	143.9	6	41.7	18.7 to 92.8
40–49	150	329.8	17	51.9	31.2 to 86.5
50–59	127	382.1	10	26.2	14.1 to 48.6
60–69	71	186.8	7	37.5	17.9 to 78.6
≥70	21	54.5	2	36.7	9.2 to 146.8
Total		1107.9	42	37.9	27.8 to 51.7

* CI = confidence interval; PY = person-years.

† Number of women at risk in each age group (ie ,the number of women entering at that age group or a previous one and exiting in that age group or a later one). For each disease, the age-specific incidence was estimated as the ratio of the number of individuals diagnosed with the disease in each age group, divided by the number of years of follow-up in the age group. Among women unaffected by breast cancer (BC) at the baseline questionnaire, four of the BCs arising on follow-up were ductal carcinoma in situ (DCIS). Two fallopian tube and three peritoneal cancers were also diagnosed in *BRCA1* mutation carriers. Among women with breast cancer at baseline questionnaire subsequently diagnosed with contralateral breast cancer (CBC): all first BCs were invasive; three CBCs were DCIS, three were of unknown pathology, and 36 were invasive. Among women with breast cancer at baseline questionnaire but not diagnosed with subsequent CBC, five BCs were DCIS, and five were of unknown pathology. Blank cells denote no data is available or no confidence interval was calculated because there are zero events.

Table 3. Incidence of breast, ovarian, and contralateral breast cancer in *BRCA2* mutation carriers*

Age, y	No.†	PY	Events	Incidence (per 1000 PY)	95% CI
Breast cancer					
<20	2	1.0	0	0	—
20–29	59	110.7	0	0	—
30–39	182	420.2	5	11.9	5.0 to 28.6
40–49	202	434.4	18	41.4	26.1 to 65.8
50–59	112	262.5	4	15.2	5.7 to 40.6
60–69	51	123.3	2	16.2	4.1 to 64.8
≥70	22	49.4	0	0	—
Total		1401.5	29	20.7	14.4 to 29.8
Ovarian cancer					
<20	2	1.0	0	0	—
20–29	63	125.8	0	0	—
30–39	237	580.7	1	1.7	0.2 to 12.2
40–49	232	566.4	0	0	—
50–59	195	413.0	1	2.4	0.3 to 17.2
60–69	117	267.3	4	15.0	5.6 to 39.9
≥70	39	89.3	1	11.2	1.6 to 79.5
Total		2043.6	7	3.4	1.6 to 7.2
Contralateral breast cancer					
<20	—	—	—	—	—
20–29	1	2.0	0	0	—
30–39	38	50.4	3	59.5	19.2 to 184.6
40–49	114	235.2	4	17.0	6.4 to 45.3
50–59	135	297.0	9	30.3	15.8 to 58.2
60–69	87	221.9	3	13.5	4.4 to 41.9
≥70	24	62.7	0	0	—
Total		869.1	19	21.9	13.9 to 34.3

* CI = confidence interval; PY = person-years.

† Number of women at risk in each age group (ie, number entering at that age group or a previous one and exiting in that age group or a later one). For each disease, the age specific incidence was estimated as the ratio of the number of individuals diagnosed with the disease in each age group, divided by the number of years of follow-up in the age group. Among women unaffected by breast cancer (BC) at baseline questionnaire, eight of the BCs arising were DCIS. Two fallopian tube cancers were also diagnosed in *BRCA2* carriers. Among women with BC at baseline questionnaire and subsequently diagnosed with CBC: in 11 cases both first BC and contralateral breast cancer (CBC) were invasive; two CBCs were ductal carcinoma in situ (DCIS) with invasive first BCs; 3 first BCs were DCIS with invasive CBCs and one first BC was of unknown pathology with invasive CBC; In one case, both first BC and CBC were DCIS. Among women with BC at baseline questionnaire but not diagnosed with subsequent CBC, 20 first BCs were DCIS, and two were of unknown pathology. Blank cells denote no data is available or no confidence interval was calculated because there are zero events.

stopped at oophorectomy than for the entire cohort (Supplementary Table 3 and Supplementary Figure 2, available online).

To quantify the effect of bilateral prophylactic oophorectomy on cancer risk, oophorectomy was treated as a time-dependent covariable in a Cox regression model. The point estimates for the hazard ratio were less than one for breast cancer in *BRCA1* (HR = 0.52, 95% CI = 0.24 to 1.13; P = .10) and *BRCA2* (HR = 0.79, 95% CI = 0.35 to 1.80; P = .58) carriers and for CBC risk for *BRCA1* carriers (HR = 0.77, 95% CI = 0.41 to 1.45; P = .42) but did not differ statistically significantly from one (Table 4). A statistically significant reduction in CBC risk after oophorectomy was observed for *BRCA2* carriers (HR = 0.16, 95% CI = 0.04 to 0.66; P = .01) (Table 4). The hazard ratios were virtually identical when analyses were adjusted for parity and age at first birth (data not shown). Oophorectomy carried out at less than 45 years of age was associated with a greater reduction in cancer risks than oophorectomy carried out at ages 45 years or older (Supplementary Table 4, available online).

Associations With Common Breast Cancer Susceptibility Alleles

The combined effects of common breast cancer susceptibility alleles on breast cancer risk for *BRCA1* and *BRCA2* mutation carriers were assessed by constructing a risk score based on the joint distribution of these variants, under the assumption that the hazard ratios combine multiplicatively. Individuals were not followed up after oophorectomy in these analyses. Figure 2 shows the cumulative breast cancer risk in unaffected *BRCA2* carriers stratified by tertiles of the risk score. *BRCA2* carriers at the highest tertile of the score distribution were at statistically significantly higher risk than women at the lowest tertile (HR = 4.1, 95% CI = 1.2 to 14.5; P = .02). The risk by age 70 years for *BRCA2* carriers in the highest tertile was 72%, compared with 20% for those in the lowest tertile. We also tested for trend in risk across the risk score as a continuous variable; the effect was in the same direction, although the association was not statistically significant (HR = 2.9, 95% CI = 0.74 to 11.4; P = .13). Analyses were also repeated with the entire cohort, adjusting for oophorectomy (test for trend across tertiles P = 0.07). The hazard ratios for the SNPs by tertile were consistent with those derived from the retrospective analysis in CIMBA (HR = approximately 1.9) (42). A risk score based on four genetic variants associated with *BRCA1* risk was also constructed. There was no evidence of an association, although the estimated risk was higher for women in the highest tertile of risk score (HR = 2.74 for highest vs lowest tertile; P = .41). There was

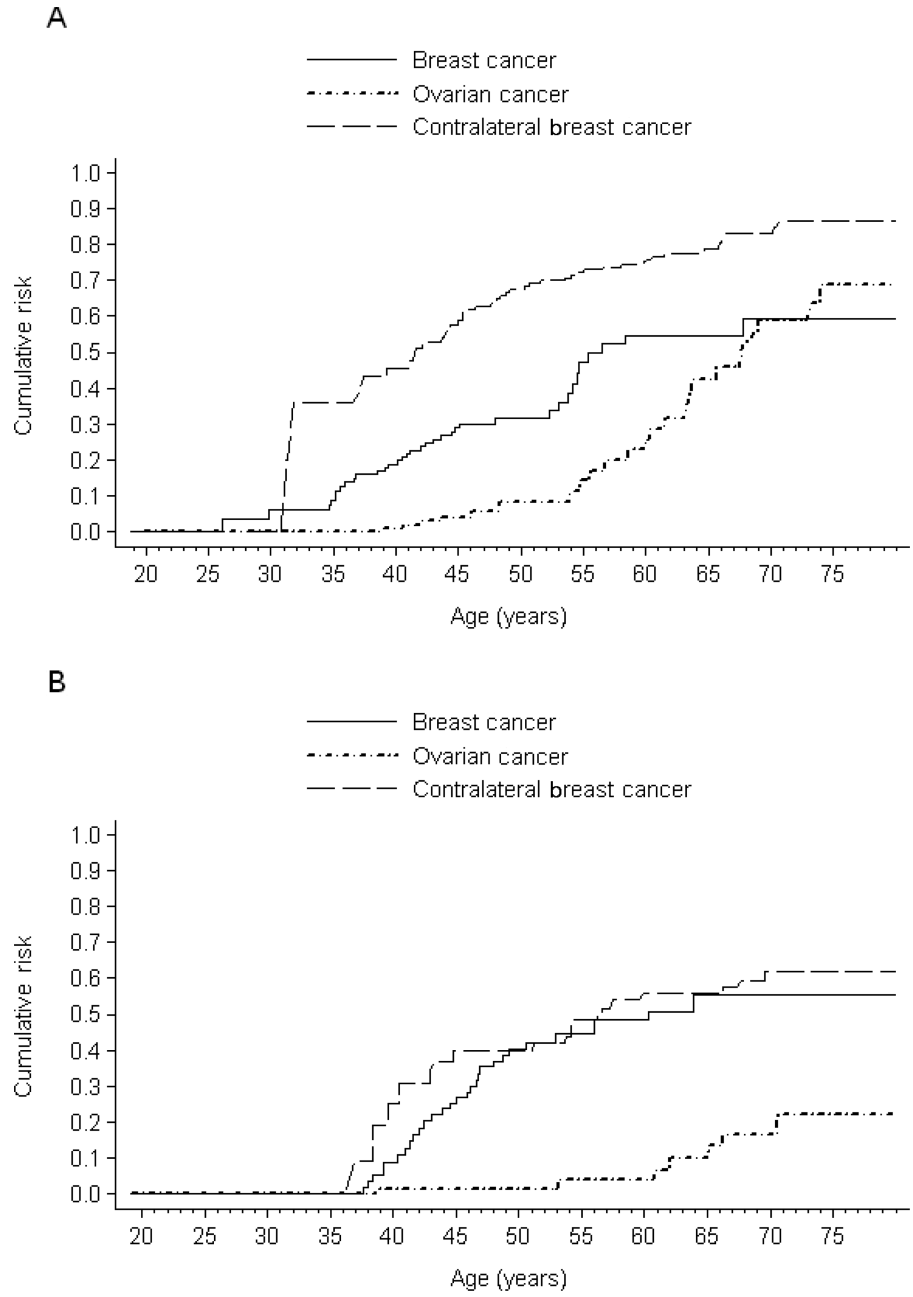


Figure 1. Average cumulative risk of breast, ovarian, and contralateral breast cancer for *BRCA1* and *BRCA2* mutation carriers. The average cumulative risk (1 – Kaplan Meier estimate) of breast cancer for mutation carriers without a previous diagnosis of breast or ovarian cancer at baseline questionnaire; ovarian cancer for women without a previous diagnosis of ovarian cancer at baseline questionnaire; and contralateral breast cancer for women with a previous diagnosis of unilateral breast cancer at baseline questionnaire for *BRCA1* (**A**) and *BRCA2* (**B**) mutation carriers. In addition, breast cancer was diagnosed in one *BRCA1* carrier after ovarian cancer, and contralateral breast cancer was diagnosed in one *BRCA2* carrier after ovarian cancer. These individuals were censored at ovarian cancer. Contralateral breast cancer and ovarian cancer were diagnosed simultaneously in one *BRCA2* carrier. Among 130 women who underwent bilateral mastectomy, one breast cancer was diagnosed after the procedure. Among 417 women who underwent oophorectomy during the follow-up, one ovarian cancer developed after oophorectomy in a *BRCA2* carrier.

no evidence for an association between risk scores and CBC risk for either *BRCA1* or *BRCA2* carriers (data not shown).

Discussion

The EMBRACE cohort is one of the largest prospective studies reporting cancer risks in proven *BRCA1* and *BRCA2* mutation carriers. Follow-up rates were high (>75% were followed up by questionnaire, and all participants were flagged for notification of death or cancer through the Office for National Statistics). We included individuals diagnosed with breast cancer in ovarian cancer analyses because a diagnosis of breast cancer was not associated with risk of ovarian cancer in Cox regression ($P = .30$ for *BRCA1*, and $P = .60$ for *BRCA2* carriers). Survival from breast cancer could, however, potentially affect incidence of ovarian cancer. The study population is enriched for families that meet high or moderate

Table 4. Hazard ratio (HR) estimates for developing breast or contralateral breast cancer after bilateral prophylactic oophorectomy*

			With‡ Oophorectomy		Without Oophorectomy		HR		
Mutation	**No.†**	**PY**	**No.**	**BC§**	**No.**	**BC**	**BC¶**	**95% CI**	***P***
All carriers	988	3301	309	18	679	46	0.62	0.35 to 1.09	.10
BRCA1	501	1898	162	9	339	26	0.52	0.24 to 1.13	.10
BRCA2	485	1401	146	9	339	20	0.79	0.35 to 1.80	.58
			No.	**CBC‖**	**No.**	**CBC**	**CBC#**		
All carriers	651	1983	315	23	336	38	0.59	0.35 to 0.99	.05
BRCA1	340	1108	173	21	167	21	0.77	0.41 to 1.45	.42
BRCA2	309	870	141	2	168	17	0.16	0.04 to 0.66	.01

* Cox proportional hazards regression was used to evaluate the association between bilateral prophylactic oophorectomy and breast or contralateral breast cancer risk. Oophorectomy was treated as a time-dependent covariable. All statistical tests were two-sided. CI = confidence interval; PY = person-years.

† Number of individuals.

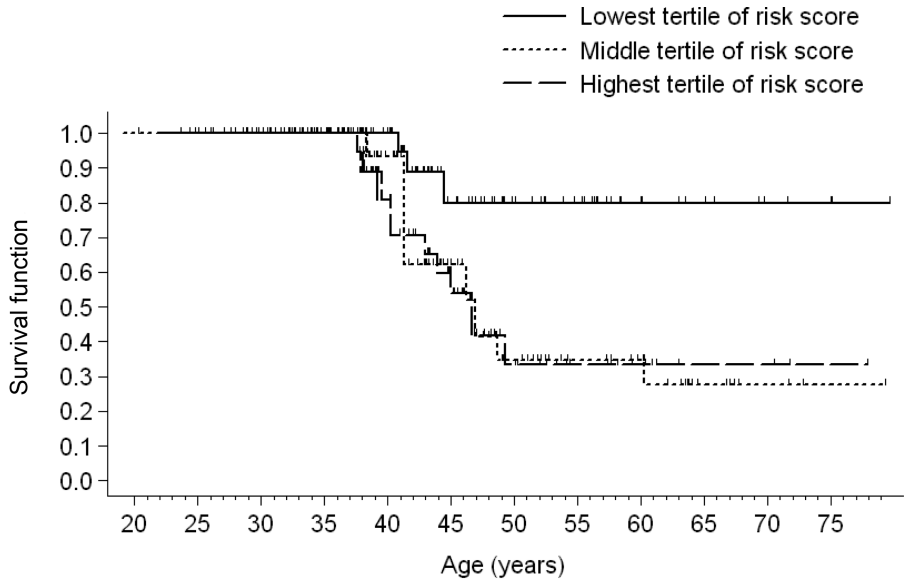
‡ Oophorectomy taking place at any time before the questionnaire or after the questionnaire date but before the end of follow-up time.

§ Breast cancers occurring in women without breast or ovarian cancer at time of the baseline questionnaire.

‖ Contralateral breast cancers occurring in women diagnosed with unilateral breast cancer at time of the baseline questionnaire.

¶ Hazard ratio for developing breast cancer, stratified by birth cohort.

Hazard ratio for developing contralateral breast cancer, stratified by birth cohort.



Number of women at risk

Tertile of risk score	<30 years	30–39 years	40–49 years	≥50 years
Lowest	10	46	47	35
Middle	11	40	38	39
Highest	20	44	45	29

Figure 2. Kaplan–Meier curve for breast cancer risk in unaffected *BRCA2* carriers stratified by tertiles of the risk score. **Tick marks** indicate censoring events (apart from failure). The **table** below the figure indicates the number of women at risk in each age group and tertile of risk score. All statistical tests were two-sided.

risk screening criteria presenting to genetic clinics; therefore the estimates will be most relevant to similar families. Because of this selection bias, the risk estimates are likely to be higher than would be obtained in a population-based study, albeit such a study would be infeasible because of the low prevalence of mutations in the general population.

The average cumulative risks of breast cancer by age 70 years were estimated for *BRCA1* and *BRCA2* carriers. Risks in *BRCA1* carriers were similar to those derived from retrospective models based on complex segregation analysis but slightly higher in *BRCA2* carriers. The latter observation is consistent with the aggregation of genetic modifiers in families because carriers in EMBRACE

were identified through clinical genetic testing of individuals with stronger family history (2,3). The average cumulative risks of ovarian cancer by age 70 years for *BRCA1* and *BRCA2* carriers were also somewhat higher than estimated through segregation analysis (3), particularly for *BRCA1* carriers. Because model-based estimates of ovarian cancer penetrance were derived from population-based studies and apply to women with weaker family history than those recruited in EMBRACE, these results are again consistent with the influence of genetic modifiers or other factors that cluster in families and modify cancer risks for mutation carriers.

The analyses for breast cancer were censored at ovarian cancer. As an alternative, we also performed competing risk analyses for breast and ovarian cancer in which the cumulative probabilities of each cancer were estimated simultaneously (Supplementary Table 5, available online). These estimates were somewhat lower. For example, cumulative incidence of breast cancer by age 70 years was 55% (95% CI = 34% to 72%) for *BRCA1* and 52% (95% CI = 34% to 67%) for *BRCA2* carriers.

A few prospective studies have reported cancer incidence in unaffected mutation carriers (47–49,51). Kramer et al. reported breast cancer risk by age 70 years of 76% among 98 *BRCA1* carriers from multiple-case families (47). Moller et al. published a larger study, but breast and ovarian cancer incidences were not reported separately (49). Recently Metcalf et al. published risks of breast and ovarian cancer similar to ours, in a large series of mutation carriers (25). This study also confirmed the influence of family history on disease risks (25).

We also estimated the average cumulative risks of CBC for *BRCA1* and *BRCA2* carriers, respectively. These results cannot be directly compared with previous studies. However, in a retrospective analysis in our dataset, 10-year risks of CBC after a first breast cancer were 33.5% for *BRCA1* carriers and 19.5% for *BRCA2* carriers (Supplementary Table 6, available online). Metcalf et al. reported a combined 10-year actuarial risk of 29.5% (95% CI = 20.6% to 38.3%) using pedigrees segregating *BRCA1* and *BRCA2* mutations that were "retrospectively" ascertained (29). In a subsequent cohort study, these investigators reported risks of 24% for *BRCA1* and 19% for *BRCA2* carriers (31). Pierce et al. reported a 10-year risk of 26.0% (95% CI = 22.0% to 30.0%) among 71 *BRCA1/2* carriers (30). Graeser et al. reported a lower risk (16.6%, 95% CI = 13.3% to 19.9%) (27). This study differed from ours in several respects: index patients were excluded from analyses; only 17% of relatives were proven mutation carriers; and ascertainment of cancer occurrence was incomplete (27). Malone et al. reported lower CBC risk in a nested case–control study (53), which may reflect use of a population-based design (53). An increased CBC risk has been associated with decreasing age at diagnosis of the first cancer (31,53) and with family history of breast cancer (31). Our results confirm high risks of CBC for both *BRCA1* and *BRCA2* mutation carriers. For *BRCA1* carriers, the risks were higher than the corresponding risks for the first cancer. This higher risk presumably reflects risk modification by other genetic factors or other risk factors enriched in women with breast cancer.

Cancer rates may have been slightly underestimated if there were underreporting of prophylactic surgeries. Assuming similar rates of prophylactic surgery among women who did not respond to follow-up questionnaires as those responding, breast cancer incidence may have been underestimated by approximately 7%, CBC by approximately 10%, and ovarian cancer by approximately 20%. This would correspond to a cumulative breast cancer risk by age 70 years in *BRCA1* carriers, for example, of approximately 63% rather than 60% and an ovarian cancer risk of approximately 67% rather than 60%. There was a suggestion of a cohort effect in cancer risks in our study. Both breast and CBC incidence appeared to be increased in birth cohorts after 1950 compared with those before 1950 (data not shown), as has been observed previously (2,3). On the other hand, the incidence of ovarian cancer appeared to be reduced in later cohorts. This could be the result of oral contraceptive (54) use which became widespread in the United Kingdom in the 1970s. The number of individuals enrolled from earlier birth cohorts was, however, insufficient to definitively establish these effects.

We also investigated the effect of oophorectomy on cancer risks. There is considerable evidence that prophylactic oophorectomy reduces cancer risks in mutation carriers (31,46,47,55–64). One meta-analysis reported 50% reduction in breast cancer risk associated with oophorectomy (64). However, as the authors of this meta-analysis pointed out, studies varied widely with respect to methodology and inclusion criteria (64). For example, some studies examined only unaffected women, whereas others included women with previous breast cancer. Fewer studies have reported gene-specific effects. In this study, we stratified analyses by genotype and by first breast cancer or CBC. We observed a trend toward reduction in breast cancer risk for both *BRCA1* and *BRCA2* carriers; in *BRCA1* carriers, breast cancer risk was halved. Although not statistically significant, the effect size is consistent with previous estimates (55,59,62,64). As has been observed previously, oophorectomy carried out at younger ages had greater impact on breast cancer risk (59). There was a suggestion that oophorectomy reduces risk of CBC for *BRCA1* carriers but has a larger and statistically significant effect on risk for *BRCA2* carriers. Kauff et al. reported a similar risk reduction in *BRCA2* carriers (55). In their study, women with and without a history of previous breast cancer were included in analyses and hazard ratios were adjusted for differences in history of breast cancer between the oophorectomy and surveillance groups (55).

In a collaborative study, Domchek et al. reported a reduction in breast cancer risk associated with oophorectomy in unaffected *BRCA1* carriers (HR = 0.63, 95% CI = 0.41 to 0.96) and for *BRCA2* carriers (HR = 0.36, 95% CI = 0.16 to 0.82) but did not observe any effect on CBC risk (58). There is some overlap between centers included in the PROSE collaboration reported by Domchek et al. (58) and EMBRACE. After excluding potential overlapping centers, however, our results were essentially unchanged. Although the estimated relative risks in the two studies are consistent, it is important to note that the analytical approaches were different. Domchek et al. considered only ooophorectomy occurring after ascenrtainment and used women not having oophorectomy as a historical control group, whereas we considered oophorectomy both before and after recruitment and analyzed oophorectomy as a time-dependent covariable.

This study also had some limitations. Whether our results reflect true differences in the effect of oophorectomy in *BRCA1* and *BRCA2* carriers, differences in the timing of oophorectomy and follow-up

in different subgroups, or random variation due to small numbers remains to be tested in larger cohorts. The results may have also been confounded if, for example, women with family history of ovarian cancer were more likely to undergo oophorectomy and a family history was associated with breast cancer risk or if factors such as parity, oral contraceptive, or hormone receptor therapy use, which may be related to both oophorectomy uptake and cancer risk (65–67), were inadequately adjusted for (55). In addition therapies associated with the first breast cancer may be responsible for risk reduction, rather than oophorectomy per se. A potential shortcoming of this study is lack of data on tamoxifen, other therapies, and surgical procedures carried out for unilateral breast cancer (60,64,68–70). In addition, there may have been some underreporting of prophylactic oophorectomy in women without cancer, resulting in underestimation of the effect of oophorectomy on cancer risks.

We further investigated the role of common breast cancer susceptibility alleles and their associations with breast cancer risk in this cohort. A number of genetic modifiers of *BRCA1* and *BRCA2* have been identified (38–45). The relative effect of each individual locus is small (per-allele HR < 1.3). However, because the absolute risk of breast cancer conferred by mutations in *BRCA1* and *BRCA2* is already high, the effects of genetic modifiers on the absolute risk of disease are much greater than in the general population (40,71). In this study, we constructed a risk score based on the joint distribution of the associated loci and tested the effect on breast cancer risk of tertiles of the risk score in our cohort of unaffected mutation carriers. The variants were assumed to act multiplicatively on risk (40,42). For the risk score based on the combination of seven *BRCA2*-associated variants, the third of *BRCA2* carriers with the highest risk score are at more than threefold increased risk of breast cancer compared with the third of carriers at lowest risk. The association between the risk score and breast cancer risk in *BRCA1* carriers was in the expected direction but was not statistically significant. However, only four risk alleles were tested for *BRCA1*. To our knowledge, this is the first study to evaluate the effects of SNPs on cancer risk in carriers (72) prospectively. These results confirm findings based on retrospective analysis from the CIMBA consortium and suggest that genetic profiles may be useful for improving risk prediction in mutation carriers, but the confidence intervals surrounding the estimates are wide, and larger studies are needed to provide more accurate prospective estimates.

The results from our prospective study provide absolute estimates of cancer risk in carriers and of the modifying effects of genetic polymorphisms and oophorectomy. Clearly, larger prospective studies with longer follow-up are required to provide definitive estimates—collaborations such as the International *BRCA1/2* Carrier Cohort Study (IBCCS) will provide a mechanism to generate such estimates. Incorporating these factors into risk prediction models should improve the accuracy of these models and guide clinical management of *BRCA1* and *BRCA2* carriers.

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