

# Age at Menarche and Menopause and Breast Cancer Risk in the International BRCA1/2 Carrier Cohort Study

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## Abstract

**Background:** Early menarche and late menopause are important risk factors for breast cancer, but their effects on breast cancer risk in BRCA1 and BRCA2 carriers are unknown.

**Methods:** We assessed breast cancer risk in a large series of 1,187 BRCA1 and 414 BRCA2 carriers from the International BRCA1/2 Carrier Cohort Study. Rate ratios were estimated using a weighted Cox-regression approach.

**Results:** Breast cancer risk was not significantly related to age at menopause [hazard ratio [HR] for menopause below age 35 years, 0.60 [95% confidence interval (95% CI), 0.25-1.44]; 35 to 40 years, 1.15 [0.65-2.04]; 45 to 54 years, 1.02 [0.65-1.60]; ≥55 years, 1.12 [0.12-5.02], as compared with premenopausal women). However, there was some suggestion of a reduction in risk after menopause in BRCA2 carriers. There was some

evidence of a protective effect of oophorectomy (HR, 0.56; 95% CI, 0.29-1.09) and a significant trend of decreasing risk with increasing time since oophorectomy, but no apparent effect of natural menopause. There was no association between age at menarche and breast cancer risk, nor any apparent association with the estimated total duration of breast mitotic activity.

**Conclusions:** These results are consistent with other observations suggesting a protective effect of oophorectomy, similar in relative effect to that in the general population. The absence of an effect of age at natural menopause is, however, not consistent with findings in the general population and may reflect the different natural history of the disease in carriers. (Cancer Epidemiol Biomarkers Prev 2007;16(4):740-6)

## Introduction

Germ line mutations in the BRCA1 and BRCA2 genes confer high lifetime risks of breast and ovarian cancer. In population-based studies, the risk of breast cancer by age 70 has been estimated to be ~65% in BRCA1 mutation carriers and 45% in BRCA2 carriers (1). Many other risk factors for breast cancer

are known, however, and an important unresolved question is the extent to which other risk factors modify the cancer risk in carriers.

In the general population, breast cancer risk is related to several reproductive factors. Specifically, risk increases with early age at menarche and late age at menopause (2). These associations are consistent with the hypothesis that breast cancer risk is related to the total extent of breast mitotic activity, driven by estrogen and progesterone exposure during the luteal phase of the menstrual cycle (3), which will determine the probability of tumorigenic somatic events (4). Thus, early age at menarche increases the period during which the breast is mitotically active, particularly the period before first full-term pregnancy during which breast cells undergo differentiation. The association with age at menopause is explicable in terms of the marked reduction in steroid hormones leading up to the menopause, which also results in a marked decline in the slope of the age-incidence curve for breast cancer at menopause. The age-related association between menopause and breast cancer risk seems to be similar for natural menopause and surgical oophorectomy, strongly suggesting that the association is a direct result of a change in

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hormonal exposure (5). This hypothesis is also supported by the modest association between hormone replacement therapy (HRT) and postmenopausal breast cancer risk.

Combined analyses of case-control studies have shown that the relative effects of age at menarche and menopause are similar in women with a family history of breast cancer and women without such a history, suggesting that these associations are largely independent of genetic susceptibility (6, 7). However, this need not necessarily apply to carriers of BRCA1 or BRCA2 mutations, who only account for a minority of familial breast cancer, and there are reasons for a different association. In particular, the breast cancer incidence in BRCA1 carriers is very different from that in the general population, reaching a maximum by about age 40 with no apparent inflection (1). In contrast, the breast cancer incidence in BRCA2 carriers increases with age; the age-incidence curve showing an inflection as in the general population. Moreover, breast tumors in BRCA1 carriers are of an unusual histologic type, with the majority being high-grade estrogen receptor-negative tumors that express specific basal keratins (8).

To provide accurate estimates of risks to carriers, it is important to determine the effects of these reproductive factors in carriers. Of practical importance is the effect of oophorectomy on breast cancer risk because carriers commonly undergo oophorectomy to prevent ovarian cancer. Recent studies have suggested that oophorectomy is associated with an ~50% reduction in the risk of primary and contralateral breast cancer (9-13) and a reduction of overall and breast cancer-specific mortality by 76% and 90%, respectively (14). No studies have shown a comparable effect for natural menopause.

The effect of age of menopause has not been previously studied, and the effect of age at menarche has only been previously studied by one article (15). Therefore, we have analyzed data from a large cohort of women collected as part of the International BRCA1/2 Carrier Cohort Study (IBCCS; ref. 16) to evaluate the effects of ages at menarche and menopause on breast cancer risk in BRCA1 and BRCA2 carriers.

## Subjects and Methods

**Study Group.** IBCCS was initiated in 1997 to estimate prospectively the risks of breast, ovarian, and other cancers in BRCA1 and BRCA2 (BRCA1/2) carriers and to assess lifestyle and genetic factors that may modify the cancer risks. A specific aim of this project is to study the role of reproductive factors as modifiers of BRCA1/2 carrier cancer risks. Details of the design and rationale of the study have been described elsewhere (14). Subjects eligible for the IBCCS must be a carrier of a mutation in either BRCA1 or BRCA2. In addition, they must be more than 18 years of age, mentally capable, and must have been counseled as to their mutation status.

The present retrospective analyses were based on a sample consisting of 1,601 women with proven BRCA1 (1,187; 74.1%) or BRCA2 (414, 25.9%) mutations that were recruited into the IBCCS study during the period 1997 to 2002. These women were all European, with the exception of 88 subjects from Quebec, Canada. About two thirds (1,064/1,601) of the subjects were participants in large ongoing national studies of BRCA1/2 carriers in the United Kingdom and Eire [Epidemiological Study of Familial Breast Cancer (EM-BRACE)], the Netherlands (GEO-HEBON), and France [Gene Etude Prospective Sein Ovaire (GENEPSO)]. A standardized questionnaire was administered either by mail, in person interview at the time of genetic counseling, or through telephone interview, depending on the study center. The questionnaire requested detailed information on ages at menarche and menopause, the reasons for menopause, detailed pregnancy history, and oral contraceptive and HRT use. The research protocol was approved by the relevant ethics committees, and all participants provided written informed consent.

**Statistical Methods.** The data presented here were analyzed using a modified Cox proportional hazards model. Standard Cox regression may lead to biased estimates of the hazard ratio (HR) because the women in this study were taken from high-risk families qualified for genetic testing. The disease status may therefore have affected the likelihood of ascertainment leading to an oversampling of affected women. To correct for this potential bias, the Cox regression analyses were done using the weighted regression approach described by Antoniou et al. (17), where individuals are weighted such that the observed breast cancer incidence rates in the study sample are consistent with established breast cancer risk estimates for BRCA1 and BRCA2 carriers (1). Subjects were followed from birth and censored at the date of diagnosis, for women who were affected by any cancer, or the date at which they underwent prophylactic bilateral mastectomy or the date of interview, for unaffected women. Because parity and menopausal status changed over time until censoring, they were all analyzed as time-dependent covariates. Women with an unknown age at menopause were classified as unknown status. Women who had undergone hysterectomy without oophorectomy were considered to be of unknown menopausal status from the date of hysterectomy. To avoid biases due to changes in menopausal status related to breast cancer diagnosis or treatment, menopausal status was analyzed according to its value 2 years before age at diagnosis or censure. Similarly, because some cancers are diagnosed during or shortly after pregnancy and their diagnosis may be facilitated by the pregnancy, pregnancies were only included if they occurred 1 year before age of censure. We also evaluated the association between breast cancer risk and the estimated total duration of ovulatory cycles. Because breast mitotic activity varies with the menstrual cycle, the total duration of ovulatory cycles has been suggested as a measure of total mitotic activity and, hence, an alternative risk factor for breast cancer. Duration of ovulatory cycles was estimated as the time between menarche and either menopause (for postmenopausal women) or censure (for premenopausal women), subtracting 6 months per full-term pregnancy. The last 6 months of a pregnancy result in a dramatic decrease in mitotic activity and in the differentiation of breast tissue, which is supposed to counteract carcinogenesis, whereas the first 3 months are associated with marked proliferation of breast tissue. The time periods of oral contraceptive use were included because breast cell mitotic activity has been found in the later weeks of the oral contraceptive cycle leading to similar activity over an oral contraceptive cycle and a normal cycle (4). We refer to this measure as "duration of breast mitotic activity." This measure was also analyzed as a time-dependent covariate.

There were a total of 65,675 individual person-years of observation, each corresponding to a single year of observation. All analyses were stratified by the women's year of birth (<1940, 1940-1949, 1950-1959, 1960+), four country groupings (group 1: Austria, Belgium, Germany, Holland, Hungary; group 2: Iceland, Denmark, Sweden; group 3: France, Spain, Italy, Quebec; group 4: United Kingdom/Eire), and adjusted for the number of full-term pregnancies and HRT use (ever/never). To account for potential familial correlations in risk factors and disease status, confidence intervals for all parameter estimates were computed using robust variance estimators, clustering on family membership (18). Eighteen women (16 affected, 2 unaffected) with missing values on age at first pregnancy were excluded from the analysis.

All statistical analyses were done using the STATA version 7 statistical package (Stata Corporation, College Station, TX).

## Results

A total of 879 women had been affected with breast cancer at the time of their interview, although only 853 of these were

considered as affected in this analysis because 26 cases had breast cancer following a previous cancer (usually ovarian cancer). The remaining 748 women were censored at age at diagnosis with ovarian cancer (122 subjects); age at diagnosis of another cancer (20 subjects); the age at which they underwent prophylactic bilateral mastectomy (31 subjects); or age at interview (579 subjects). The average age at censor for the 748 subjects without breast cancer was similar to the age at diagnosis of the cases, although the age at interview was substantially older for the breast cancer cases, reflecting the pattern of genetic testing among participants. Characteristics of the entire cohort and distribution of age at menarche and menopause are presented in Table 1.

The estimated risks associated with the age at menarche, the time between menarche and first full-term pregnancy, and the total period of breast mitotic activity from the weighted Cox regression are summarized in Table 2. There was no evidence of an effect of any of these covariates on the risk of breast cancer. Analyses were also done for BRCA1 and BRCA2 mutation carriers separately and by menopausal status, but no associations were found.

There was no evidence of a difference in risk by menopausal status [HR, 0.97; 95% confidence interval (95% CI), 0.68-1.39], nor any evidence for a trend in risk with age at menopause (Table 3). There was some evidence for a reduced risk in postmenopausal BRCA2 carriers (HR, 0.51; 95% CI, 0.21-1.22), but the estimated HR does not differ significantly from that in BRCA1 carriers (HR, 1.01; 95% CI, 0.68-1.49). The data suggested a reduced risk associated with oophorectomy (HR, 0.56;

95% CI, 0.29-1.09), but an increased risk associated with "other" types of menopause (such as medication or X-ray treatment). There was a suggestion of a stronger protective effect of oophorectomy below age 35 (HR, 0.07; 95% CI, 0.01-0.57). This effect was, however, based on only 1 case among 13 carriers (12 BRCA1 and 1 BRCA2). The observed increased risk for oophorectomy at ages 35 to 44 years in BRCA2 carriers was based on 4 cases among 13 oophorectomized women whereby all 4 cases and 3 unaffected carriers underwent oophorectomy between 35 and 44 and, therefore, most likely due to chance. The protective effect of an oophorectomy also seemed to increase as time since oophorectomy increased ( $\geq 4$  years; HR, 0.49; 95% CI, 0.21-1.16 versus  $\leq 1$  year; HR, 0.84; 95% CI, 0.23-3.04;  $P_{\text{trend}} = 0.042$  with time since oophorectomy as continuous variable). The effect of a postmenopausal oophorectomy on breast cancer risk could not be assessed in these data because only three carriers and no case have undergone a postmenopausal oophorectomy before censor.

There was no trend in risk with age at natural menopause or with time since the natural menopause in the whole cohort. There was some suggestion of a protective effect of natural menopause in BRCA2 carriers, but this was not statistically significant (HR, 0.60; 95% CI, 0.21-1.73) and did not show a clear trend with age at menopause or time since menopause. Among BRCA1 carriers, the estimated risk was  $>5$  years after natural menopause than before, although not significantly so.

Because HRT may increase the risk of breast cancer, we reanalyzed the data excluding women who used HRT. The

**Table 1. Characteristics of the cohort study of BRCA1/2 mutation carriers**

	Total cohort (N = 1,601), n (%)	Women with breast cancer (N = 853), n (%)	Unaffected women (N = 748), n (%)
Person-years of follow-up	65,675		
Age at interview, mean (SD)	46.7 (12.0)	50.1 (10.7)	42.9 (12.3)
Age at diagnosis/censor			
Mean (SE)	41.5 (10.1)	41.6 (9.0)	41.4 (11.2)
Mutation			
BRCA1	1,187 (74.1)	602 (70.6)	585 (78.2)
BRCA2	414 (25.9)	251 (29.4)	163 (21.8)
Year of birth			
<1940	223 (11.9)	151 (17.7)	72 (9.6)
1940 to <1950	356 (22.2)	232 (27.2)	124 (16.6)
1950 to <1960	494 (30.9)	296 (34.7)	198 (26.5)
$\geq 1960$	528 (33.0)	174 (20.4)	354 (47.3)
Country group*			
1	358 (22.4)	179 (21.0)	179 (23.9)
2	171 (10.7)	81 (9.5)	90 (12.0)
3	539 (33.7)	299 (35.1)	231 (30.9)
4	542 (33.9)	294 (34.5)	248 (33.2)
Age at menarche			
$\leq 11$	275 (17.2)	130 (17.4)	145 (17.0)
12-14	1,060 (66.2)	506 (67.6)	554 (65.0)
$\geq 15$	243 (15.2)	101 (13.5)	142 (16.6)
Unknown	23 (1.4)	11 (1.5)	12 (1.4)
Menopausal status			
Premenopausal	1,228 (76.7)	665 (78.0)	563 (75.3)
Postmenopausal			
Natural	150 (3.5)	78 (9.1)	72 (9.6)
Oophorectomy	55 (9.4)	17 (2.0)	38 (5.1)
Other reasons	31 (1.9)	15 (1.8)	16 (2.1)
Unknown	137 (8.5)	78 (9.1)	59 (7.9)
Number of full-term pregnancies			
0	304 (19.0)	145 (17.0)	159 (21.3)
1	239 (14.9)	137 (16.1)	102 (13.6)
2	621 (38.8)	329 (38.6)	292 (39.0)
3	297 (18.6)	161 (18.9)	136 (18.2)
$\geq 4$	138 (8.6)	80 (9.4)	58 (7.8)
Unknown	2 (0.1)	1 (0.0)	1 (0.1)
HRT use			
Never	1,449 (90.5)	790 (92.6)	659 (88.1)
Ever	152 (9.5)	63 (7.4)	89 (11.9)

\*Group 1: Austria, Belgium, Germany, Holland, Hungary; group 2: Iceland, Denmark, Sweden; group 3: France, Spain, Italy, Quebec; group 4: United Kingdom/Eire.

estimated protective effect of oophorectomy was slightly greater, although still not statistically significant, in women who did not use HRT compared with premenopausal women (HR, 0.53; 95% CI, 0.21-1.32). There remained no effect of early natural menopause in BRCA1 carriers (HR, 1.55; 95% CI, 0.55-4.38 for menopause <45). The point estimate for the effect of early natural menopause in BRCA2 carriers was slightly lower but still not statistically significant (HR, 0.58; 95% CI, 0.14-2.44).

## Discussion

In this study, we have attempted to estimate the effects of age at menopause, both natural and surgical, and age at menarche, on breast cancer risk. There are a number of important limitations to this analysis. Most breast cancer cases identified as carriers are relatively young, so that despite the substantial study size, the number of postmenopausal women is quite small. A second difficulty is that of choosing an adequate control group, given the highly selected nature of the cohort. We have used a weighted cohort approach to adjust for the oversampling of cases in the study and have shown theoretically that this should remove most of the bias.

In our analyses, we found no overall association with either age at menarche or age at menopause. The former is not necessarily surprising. Although an association with age at menarche has been consistently found for breast cancer diagnosed at all ages in the general population, it is quite weak. For example, Hsieh et al. (19) estimated a 10% reduction in risk for each 2-year delay in menarche, so that one might expect an odds ratio of ~0.8 between the earliest and latest categories of menarche in our analysis. Some studies have found a weaker effect in early-onset cases below 35 years of age (20). A recent study by Kotsopoulos et al. (15) found a strong inverse relationship between age at menarche and breast cancer risk in BRCA1 carriers, with an odds ratio of 0.46 for women aged 14 to 15 years at menarche compared with those aged <12 years, but no effect in BRCA2 carriers. Although consistent with a weak protective effect of early age at menarche, our results seem to exclude such a large effect. The differences may be partially explained by their use of a matched case-control design, whereby 20% of the eligible subjects were excluded due to missing information on age at menarche.

The lack of an effect of age at menopause is more notable. In population studies, there is a marked and consistent association between late age at menopause and breast cancer risk. A recent overview estimated this effect to be equivalent to a 2.8% increase in risk for every year of delay in menopause, with no apparent difference between natural menopause and bilateral oophorectomy (5). For women with menopause below age 40, the risk was ~50% that of women with menopause over age 50. These results are not directly comparable, however, because the majority of women in our study were diagnosed below age 50, and few published data on the effect of early menopause in this group are available. A possible factor is that the effect of menopause increases with time since menopause. Because the majority of women in our study were diagnosed below age 50, half of them were within only 5 years of menopause, and about three quarters were within 10 years. Extrapolating from the overview (5), one would predict a reduction in risk 5 years after menopause of ~13%. However, even this moderate effect is not apparent from our data; our estimates are not precise enough to exclude this effect definitively. There is no previous study on the effect of age at menopause in BRCA1 and BRCA2 carriers with which to compare.

Our results raise a more intriguing possibility of a genuine difference in the natural history of breast cancer in carriers with respect to reproductive factors. It is notable that the age incidence of breast cancer in BRCA1 carriers follows a different pattern from that in the general population (1). The incidence seems to increase sharply to a maximum at around age 40 and remains roughly constant thereafter. Thus, there is no evidence of the decline in slope in the age-incidence curve at approximately age 50 that is seen in the general population. The observation that age of menopause has no apparent effect on risk would therefore be consistent with this. The same considerations do not apply to BRCA2, for which the pattern of age-specific relative risks is similar to that in the general population. It is interesting to note that there is some evidence for a reduction in risk with menopause in BRCA2 carriers, but the numbers are too small to examine the pattern with age in detail.

Although we found no evidence of an association with age at menopause overall, we found some evidence for a protective effect of oophorectomy and a significant effect of time since oophorectomy. The estimated HR (0.56) was similar to that reported in retrospective studies in BRCA1 and BRCA2 carriers by Rebbeck et al. (ref. 10; HR, 0.47; 95% CI, 0.29-0.77)

**Table 2. Risk of breast cancer (HR) associated with age at menarche and duration of ovarian activity**

	Whole cohort			BRCA1 carriers	BRCA2 carriers
	Pyr <sup>s</sup> *	BC <sup>†</sup>	HR <sup>‡</sup> (95% CI)	HR <sup>‡</sup> (95% CI)	HR <sup>‡</sup> (95% CI)
Age at menarche					
≤11 y	10,940	145	1	1	1
12-14 y	42,727	554	0.89 (0.68-1.15)	0.80 (0.61-1.05)	1.09 (0.62-1.92)
≥15 y	10,252	142	0.96 (0.68-1.36)	0.86 (0.60-1.25)	1.22 (0.61-2.43)
Unknown	903	12	1.22 (0.53-2.82)	0.95 (0.39-2.29)	1.00 (0.05-21.7)
Duration of breast mitotic activity before first full-term pregnancy <sup>§</sup>					
<10 y	43,646	253	1 <sup>  </sup>	1	1
10-20 y	17,300	450	0.94 (0.74-1.20)	0.89 (0.70-1.14)	1.26 (0.71-2.23)
≥20 y	2,043	118	0.82 (0.54-1.24)	0.72 (0.46-1.14)	1.68 (0.65-4.38)
Unknown	1,833	32	0.71 (0.32-1.61)	0.54 (0.22-1.33)	0.66 (0.07-6.60)
Lifetime duration of breast mitotic activity menstrual cycles <sup>§</sup>					
<20 y	49,463	72	1 <sup>  </sup>	1	1
20-30 y	8,111	348	0.92 (0.63-1.34)	1.07 (0.71-1.60)	0.51 (0.15-1.69)
≥30 y	3,196	221	1.00 (0.63-1.61)	1.16 (0.71-1.92)	0.42 (0.11-1.65)
Unknown	4,052	112	0.99 (0.62-1.58)	1.11 (0.68-1.81)	0.48 (0.11-2.04)

\*Number of person-years of observation in the specified cohort.

†Number of breast cancer cases occurring in the specified cohort.

‡Estimated hazard ratio, stratified by birth cohort and country group and adjusted for number of children and oophorectomy.

§Defined as in Statistical Methods.

||Estimated hazard ratio, stratified by birth cohort and country group and adjusted for number of children, oophorectomy and HRT use.

**Table 3. Risk of breast cancer (HR) associated with type and age of menopause**

	Whole cohort			BRCA1 carriers	BRCA2 carriers
	Pyr*s	BC <sup>†</sup>	HR <sup>‡</sup> (95% CI)	HR <sup>‡</sup> (95% CI)	HR <sup>‡</sup> (95% CI)
Menopausal status					
Premenopause	57,459	665	1	1	1
Postmenopause	1,857	110	0.97 (0.68-1.39)	1.01 (0.68-1.49)	0.51 (0.21-1.22)
Unknown	6,359	78	0.87 (0.61-1.22)	0.85 (0.59-1.24)	0.75 (0.30-1.88)
Type of menopause					
Oophorectomy	420	17	0.56 (0.29-1.09)	0.50 (0.24-1.04)	0.40 (0.07-2.44)
Natural	1,200	78	1.03 (0.67-1.59)	1.17 (0.73-1.90)	0.60 (0.21-1.73)
Other type	237	15	1.71 (1.04-2.81)	1.84 (1.20-2.82)	0.24 (0.03-2.11)
Age at menopause					
Premenopause	57,459	665	1	1	1
<35	274	8	0.60 (0.25-1.44)	0.50 (0.21-1.21)	~0 (—)
35-44	525	36	1.02 (0.65-2.04)	1.41 (0.72-2.79)	0.79 (0.28-2.21)
45-54	1,000	62	1.15 (0.65-1.60)	1.08 (0.66-1.77)	0.39 (0.12-1.26)
≥55	58	4	1.12 (0.25-5.02)	2.47 (0.54-11.2)	~0 (—)
Unknown	6,359	78	0.88 (0.63-1.25)	0.87 (0.60-1.27)	0.73 (0.29-1.84)
Type of menopause and age at oophorectomy					
Premenopause	57,459	665	1	1	1
Oophorectomy					
<35	140	1	0.07 (0.01-0.57)	0.05 (0.01-0.49)	~0 (—)
35-44	140	11	1.17 (0.43-3.22)	0.90 (0.27-3.01)	4.19 (1.53-11.5)
≥45	140	5	0.57 (0.24-1.38)	0.80 (0.36-1.76)	~0 (—)
Postmenopausal, natural	1,200	78	1.03 (0.67-1.59)	1.19 (0.74-1.93)	0.51 (0.18-1.49)
Postmenopausal, other type	237	15	1.71 (1.04-2.81)	1.84 (1.21-2.81)	0.25 (0.03-2.24)
Unknown	6,359	78	0.87 (0.62-1.23)	0.86 (0.60-1.25)	0.67 (0.27-1.68)
Time since oophorectomy					
Premenopause	57,459	665	1	1	1
≤1 y	55	3	0.84 (0.23-3.04)	0.98 (0.26-3.73)	~0
2-3 y	79	3	0.61 (0.21-1.74)	0.68 (0.25-1.88)	~0
≥4 y	289	11	0.49 (0.21-1.16)	0.37 (0.14-1.00)	0.77 (0.08-7.07)
Type of menopause and age at natural menopause					
Premenopause	57,459	665	1	1	1
Postmenopausal, natural					
<45	332	20	0.94 (0.44-2.04)	1.49 (0.56-3.97)	0.64 (0.19-2.18)
45-54	810	54	1.09 (0.66-1.78)	1.03 (0.60-1.79)	0.61 (0.16-2.29)
≥55	58	4	1.04 (0.23-4.79)	2.24 (0.46-10.9)	~0 (—)
Postmenopausal, oophorectomy	420	17	0.57 (0.29-1.09)	0.50 (0.24-1.04)	0.39 (0.06-2.38)
Postmenopausal, other type	237	15	1.71 (1.04-2.81)	1.83 (1.19-2.81)	0.24 (0.03-2.11)
Unknown	6,359	78	0.87 (0.62-1.23)	0.85 (0.59-1.24)	0.75 (0.30-1.88)
Time since natural menopause					
Premenopause	57,459	665	1	1	1
<5 y	594	36	0.98 (0.60-1.60)	1.05 (0.60-1.85)	0.66 (0.20-2.11)
5-9 y	275	17	1.02 (0.50-2.11)	1.45 (0.60-3.49)	0.54 (0.15-1.90)
>9 y	331	25	1.26 (0.60-2.65)	1.51 (0.55-4.09)	0.54 (0.12-2.52)

\*Number of person-years of observation in the specified cohort.

† Number of breast cancer cases occurring in the specified cohort.

‡ Estimated hazard ratio, stratified by birth cohort and country group and adjusted for number of children and HRT use.

and, more recently, by Eisen et al. [ref. 13; odds ratio (OR), 0.46; 95% CI, 0.32-0.65]. A similar effect has also been observed in the cohort study of BRCA1 carriers (HR, 0.38; 95% CI, 0.15-0.97; ref. 21). The apparent difference between surgical and natural menopause is surprising. Although surgical menopause might have a more pronounced effect on risk, given the more abrupt change in hormones, this is not apparent in epidemiologic studies in the general population (5). However, the observed risk reductions associated with oophorectomy show some unusual features. The risk reduction in the Rebbeck et al. (9) study is essentially independent of age, with a marked reduction even among cases diagnosed over age 50, although they found some suggestion of a stronger protective effect below age 35. Eisen et al. (13) also found a slightly stronger effect for oophorectomy done below age 40 (OR, 0.33), but still, a clear protective effect at older ages (for example, OR, 0.43 for ages 41-50 years). Eisen et al. (13) also found no effect of time since oophorectomy, with a protective effect within 15 years of oophorectomy. The cohort study of Kramer (21) should be less subject to some of the recall and selection biases inherent in the retrospective studies and, hence, provides the clearest evidence for an effect of oophorectomy. Unfortunately, the data presented do not permit an evaluation by age at oophorectomy. Our study showed a clear effect of time since oophorectomy,

but no apparent effect of age at oophorectomy, although the estimates are too imprecise to draw firm conclusions. The apparent risk reduction associated with oophorectomy at older ages seen in the three retrospective studies differs from the effects seen in the general population. It might suggest either that the effect of oophorectomy, particularly at older ages, is subject to some other bias and is being overestimated, or possibly that some other mechanism operates in carriers to reduce breast cancer risk following oophorectomy.

In conclusion, we found no evidence of an association between breast cancer risk and ages at menarche or menopause in BRCA1 and BRCA2 carriers, but some evidence to support a protective effect of early oophorectomy on breast cancer risk, including a significant trend of decreasing risk with increasing time since oophorectomy. Further large studies, preferably including population-based and/or prospective studies, will be required to provide more definitive risk estimates.

## Appendix A

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