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

Jenny Chang-Claude,1 Nadine Andrieu,2 Matti Rookus,3 Richard Brohet,3 Antonis C. Antoniou,4 Susan Peock,4 Rosemarie Davidson,5 Louise Izatt,6 Trevor Cole,7 Catherine Nougues,8 Elisabeth Luporsi,9 Laetitia Huiart,10 Nicole Hoogerbrugge,11 Flora E. Van Leeuwen,3 Ana Osorio,12 Jorunn Eyfjord,13 Paolo Radice,14 David E. Goldgar,15 Douglas F. Easton,4 Epidemiological Study of Familial Breast Cancer (EMBRACE), Gene Etude Prospective Sein Ovaire (GENEPSO), Genen Omgeving studie van de werkgroep Hereditair Borstkanker Onderzoek Nederland (GEO-HEBON), the International BRCA1/2 Carrier Cohort Study (IBCCS) collaborators group

1Division of Clinical Epidemiology, German Cancer Research Center, Heidelberg, Germany; 2Institut National de la Sante et de la Recherche Medecale (INSERM), U794, Service de Biostatistiques, Institut Curie, Paris, France; 3The Netherlands Cancer Institute, Department of Epidemiology, Amsterdam, Netherlands; 4Cancer Research UK, Genetic Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom; 5Ferguson-Smith Centre for Clinical Genetics, Glasgow, United Kingdom; 6Department of Clinical Genetics, Guy’s Hospital, London, United Kingdom; 7Clinical Genetics Unit, Birmingham Woman’s Hospital, Birmingham, United Kingdom; 8Centre Rene Huguenin, Saint Cloud, France; 9Centre Alexis Vautrin, Vandoeuvre-les-Nancy, France; 10Institut Paoli-Calmettes, Marseille, France; 11Department of Human Genetics and Medical Oncology, Radboud University Medical Centre, Nijmegen, the Netherlands; 12Department of Human Genetics, Spanish National Cancer Center, Madrid, Spain; 13Molecular and Cell Biology Research Laboratory, Icelandic Cancer Society, Reykjavik, Iceland; 14Department of Experimental Oncology and Laboratories, Istituto Nazionale Tumori, Milan and FIRC Institute of Molecular Oncology Foundation, Milan, Italy; and 15ICRF Lyon, France

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 [0.52-2.05], 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 age at 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.

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 hormone levels at 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

Received 9/29/06; revised 1/15/07; accepted 2/2/07.

Grant support: NIH Award CA81203 and the Europe against Cancer Programme (EU contract nos. SI2.26176 and SPC2002442) (D. Goldgar). D.F. Easton is a Principal Research Fellow of Cancer Research U.K. The EMBRACE and A.C. Antoniou are supported by Cancer Research U.K. The Canadian Institutes of Health Research through the Interdisciplinary Health Research International Team on Breast Cancer Susceptibility (INHERIT BRCAs) research program (D.F. Easton and D. Goldgar). The GENEPSO study is supported by the Fondation de France and the Ligue Nationale contre le Cancer.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note: J. Chang-Claude and N. Andrieu contributed equally to this work.

Requests for reprints: Jenny Chang-Claude, Division of Cancer Epidemiology, German Cancer Research Center, Im Neuenheimer Feld 280 69120 Heidelberg, Germany. Phone: 49-6221-422373; Fax: 49-6221-422373. E-mail: j.chang-claude@dkfz-heidelberg.de or Nadine Andrieu, INSERM U794/Service de Biostatistiques, Institut Curie, 26 one Miller, 75248 Paris Cedex 05, France. Phone: 33-155431363; Fax: 33-155431469. E-mail: nadine.andrieu@curie.net

Copyright © 2007 American Association for Cancer Research.

doi:10.1158/1055-9965.EPI-06-0829

Cancer Epidemiol Biomarkers Prev 2007;16(4):740–6

Cancer Epidemiol Biomarkers Prev

740

April 2007

Downloaded from cebp.aacrjournals.org on October 13, 2017. © 2007 American Association for Cancer Research.
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 at 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 have 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 (EMBRACE)], the Netherlands (GEO-HEBON), and France [Gene Etude Prospective Sein Ovaire (GEPSE)]. 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 censure 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 (≥4 years; HR, 0.49; 95% CI, 0.21-1.66 versus ≤1 year; HR, 0.84; 95% CI, 0.23-3.04; P 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 underwent a postmenopausal oophorectomy before censure.

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

<table>
<thead>
<tr>
<th>Person-years of follow-up</th>
<th>Total cohort (N = 1,601), n (%)</th>
<th>Women with breast cancer (N = 853), n (%)</th>
<th>Unaffected women (N = 748), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis/censure</td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td>BRCA1</td>
<td>1,187 (74.1)</td>
<td>602 (70.6)</td>
<td>414 (11.2)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>414 (25.9)</td>
<td>251 (29.4)</td>
<td>163 (21.8)</td>
</tr>
<tr>
<td>Year of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1940</td>
<td>223 (11.9)</td>
<td>151 (17.7)</td>
<td>72 (9.6)</td>
</tr>
<tr>
<td>1940 to &lt;1950</td>
<td>356 (22.2)</td>
<td>232 (27.2)</td>
<td>124 (16.6)</td>
</tr>
<tr>
<td>1950 to &lt;1960</td>
<td>494 (30.9)</td>
<td>296 (34.7)</td>
<td>198 (26.5)</td>
</tr>
<tr>
<td>≥1960</td>
<td>528 (33.0)</td>
<td>174 (20.4)</td>
<td>354 (47.3)</td>
</tr>
<tr>
<td>Country group*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>358 (22.4)</td>
<td>179 (21.0)</td>
<td>179 (23.9)</td>
</tr>
<tr>
<td>2</td>
<td>171 (10.7)</td>
<td>81 (9.5)</td>
<td>90 (12.0)</td>
</tr>
<tr>
<td>3</td>
<td>539 (33.7)</td>
<td>299 (35.1)</td>
<td>231 (30.9)</td>
</tr>
<tr>
<td>4</td>
<td>542 (33.9)</td>
<td>294 (34.5)</td>
<td>248 (33.2)</td>
</tr>
<tr>
<td>Age at menarche</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤11</td>
<td>275 (17.2)</td>
<td>130 (17.4)</td>
<td>145 (17.0)</td>
</tr>
<tr>
<td>12-14</td>
<td>1,060 (66.2)</td>
<td>506 (67.6)</td>
<td>554 (65.0)</td>
</tr>
<tr>
<td>≥15</td>
<td>243 (15.2)</td>
<td>101 (13.5)</td>
<td>142 (16.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>23 (1.4)</td>
<td>11 (1.5)</td>
<td>12 (1.4)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>1,228 (76.7)</td>
<td>665 (78.0)</td>
<td>563 (75.3)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural</td>
<td>150 (3.5)</td>
<td>78 (9.1)</td>
<td>72 (9.6)</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>55 (9.4)</td>
<td>17 (2.0)</td>
<td>38 (5.1)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>31 (1.9)</td>
<td>15 (1.8)</td>
<td>16 (2.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>137 (8.5)</td>
<td>76 (9.1)</td>
<td>59 (7.9)</td>
</tr>
<tr>
<td>Number of full-term pregnancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>304 (19.0)</td>
<td>145 (17.0)</td>
<td>159 (21.3)</td>
</tr>
<tr>
<td>1</td>
<td>239 (14.9)</td>
<td>137 (16.1)</td>
<td>102 (13.6)</td>
</tr>
<tr>
<td>2</td>
<td>621 (38.8)</td>
<td>329 (38.6)</td>
<td>292 (39.0)</td>
</tr>
<tr>
<td>3</td>
<td>297 (18.6)</td>
<td>161 (18.9)</td>
<td>136 (18.2)</td>
</tr>
<tr>
<td>≥4</td>
<td>138 (8.6)</td>
<td>80 (9.4)</td>
<td>58 (7.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0.1)</td>
<td>1 (0.0)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>HRT use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1,449 (90.5)</td>
<td>790 (92.6)</td>
<td>659 (88.1)</td>
</tr>
<tr>
<td>Ever</td>
<td>152 (9.5)</td>
<td>63 (7.4)</td>
<td>89 (11.9)</td>
</tr>
</tbody>
</table>

*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 75% 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

<table>
<thead>
<tr>
<th>Age at menarche</th>
<th>Whole cohort</th>
<th>BRCA1 carriers</th>
<th>BRCA2 carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pys*</td>
<td>BC †</td>
<td>HR ‡ (95% CI)</td>
</tr>
<tr>
<td>≤11 y</td>
<td>10,940</td>
<td>145</td>
<td>1 (Referent)</td>
</tr>
<tr>
<td>12-14 y</td>
<td>42,727</td>
<td>554</td>
<td>0.89 (0.68-1.15)</td>
</tr>
<tr>
<td>≥15 y</td>
<td>10,252</td>
<td>142</td>
<td>0.96 (0.98-1.36)</td>
</tr>
<tr>
<td>Unknown</td>
<td>903</td>
<td>1.22 (0.53-2.82)</td>
<td>0.95 (0.39-2.29)</td>
</tr>
<tr>
<td>Duration of breast mitotic activity before first full-term pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10 y</td>
<td>43,464</td>
<td>253</td>
<td>1 (Referent)</td>
</tr>
<tr>
<td>10-20 y</td>
<td>17,300</td>
<td>450</td>
<td>0.94 (0.74-1.20)</td>
</tr>
<tr>
<td>≥20 y</td>
<td>2,043</td>
<td>118</td>
<td>0.82 (0.54-1.24)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1,833</td>
<td>0.71 (0.32-1.61)</td>
<td>0.54 (0.22-2.13)</td>
</tr>
<tr>
<td>Lifetime duration of breast mitotic activity menstrual cycles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 y</td>
<td>49,463</td>
<td>72</td>
<td>1 (Referent)</td>
</tr>
<tr>
<td>20-30 y</td>
<td>8,111</td>
<td>348</td>
<td>0.92 (0.63-1.34)</td>
</tr>
<tr>
<td>≥30 y</td>
<td>3,196</td>
<td>221</td>
<td>1.00 (0.63-1.61)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4,052</td>
<td>0.99 (0.62-1.58)</td>
<td>1.11 (0.68-1.81)</td>
</tr>
</tbody>
</table>

*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.

Cancer Epidemiology, Biomarkers & Prevention 2007;16(4). April 2007
Downloaded from cebp.aacrjournals.org on October 13, 2017. © 2007 American Association for Cancer Research.
Our study showed a clear effect of time since oophorectomy, presented do not permit an evaluation by age at oophorectomy. Unfortunately, the data from retrospective studies and, hence, provides the clearest evidence for an effect 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, 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 ages seen in the three retrospective studies differs from the apparent risk reduction associated with oophorectomy at older ages seen in the general population. It might suggest either that the effect of oophorectomy, particularly at older ages, is subject to other bias and is being overestimated, or that some other mechanism operates in carriers to reduce breast cancer risk following oophorectomy.

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. It might suggest either that the effect of oophorectomy, particularly at older ages, is subject to 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.

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

<table>
<thead>
<tr>
<th>Menopausal status</th>
<th>Whole cohort</th>
<th>BRCA1 carriers</th>
<th>BRCA2 carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pyrs*</td>
<td>BC</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Menopause status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>57,459</td>
<td>665</td>
<td>0.97 (0.68-1.39)</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>1,857</td>
<td>110</td>
<td>1.07 (0.69-1.62)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6,359</td>
<td>78</td>
<td>1.07 (0.69-1.59)</td>
</tr>
<tr>
<td>Type of menopause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oophorectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>57,459</td>
<td>665</td>
<td>0.56 (0.29-1.09)</td>
</tr>
<tr>
<td>Postmenopause, natural</td>
<td>1,200</td>
<td>78</td>
<td>1.03 (0.67-1.59)</td>
</tr>
<tr>
<td>Natural</td>
<td>237</td>
<td>15</td>
<td>1.71 (1.04-2.81)</td>
</tr>
<tr>
<td>Other type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>57,459</td>
<td>665</td>
<td>0.60 (0.25-1.44)</td>
</tr>
<tr>
<td>Postmenopause, natural</td>
<td>1,200</td>
<td>78</td>
<td>1.03 (0.67-1.59)</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>57,459</td>
<td>665</td>
<td>0.75 (0.47-1.21)</td>
</tr>
<tr>
<td>Postmenopause, natural</td>
<td>1,200</td>
<td>78</td>
<td>1.03 (0.67-1.59)</td>
</tr>
<tr>
<td>Natural</td>
<td>237</td>
<td>15</td>
<td>1.71 (1.04-2.81)</td>
</tr>
<tr>
<td>Type of menopause and age at oophorectomy</td>
<td>Premenopause</td>
<td>57,459</td>
<td>665</td>
</tr>
<tr>
<td>Type of menopause and age at natural menopause</td>
<td>Premenopause</td>
<td>57,459</td>
<td>665</td>
</tr>
</tbody>
</table>

*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.


IBCCS Collaborating Group:
Vienna, Austria: Teresa Wagner, Verena Korn
Odense, Denmark: Anne-Marie Gerdes

Downloaded from cebp.aacrjournals.org on October 13, 2017. © 2007 American Association for Cancer Research.
Budapest, Hungary: Edith Olah
Reykjavik, Iceland: Jorunn Eyfod
Milan, Italy: Paolo Radice, Sironanoush Manoukian, Marco A. Pierotti
Madrid, Spain: Javier Benitez, Ana Osorio
Madrid Spain: Trinidad Caldes, Miguel de la Hoya
Szczecin, Poland: Jan Lubinski
Stockholm, Sweden: Brita Arver
Lund, Sweden: H. Olsson, Niklas Loman
Quebec, Canada: Jacques Simard
Brussels, Belgium: Catherine Sibille

GEO-HEBON Collaborating Centers:
Department of Clinical Genetics, Leiden University Medical Center: Christi van Asperen
Department of Clinical Genetics, Erasmus Medical Center, Rotterdam: Hanne Meijers-Heijboer
Department of Clinical Genetics, Erasmus Medical Center, Utrecht, Utrecht: Margreet Ausems
Department of Clinical Genetics and Human Genetics, VU University Medical Center, Amsterdam: Fred Menko
Department of Clinical Genetics, Maastricht University Medical Center, Maastricht: Encarna Gomez-Garcia

EMBRACE Collaborating Centers:
Coordinating Centre, Cambridge: Susan Peock, Margaret Cook, Cassandra Engel
North of Scotland Regional Genetics Service, Aberdeen: Neva Haite, Helen Gregory
Northern Ireland Regional Genetics Service, Belfast: Patrick Morrison
West Midlands Regional Clinical Genetics Service, Birmingham: Trevor Cole, Carole McKeown
South West Regional Genetics Service, Bristol: Alan Donaldson
East Anglian Regional Genetics Service, Cambridge: Joan Paterson
Medical Genetics Services for Wales, Cardiff: Jonathan Gray
St. James’s Hospital, Dublin, and National Centre for Medical Genetics, Dublin: Peter Daly, David Barton
South East of Scotland Regional Genetics Service, Edinburgh: Mary Porteus, Michael Steel
Peninsula Clinical Genetics Service, Exeter: Carole Brewer, Julia Rankin
West of Scotland Regional Genetics Service, Glasgow: Rosemarie Davidson, Victoria Murday
South East Thames Regional Genetics Service, Guys Hospital London: Louise Izatt, Gabriella Pichert
North West Thames Regional Genetics Service, Harrow: Huw Dorkins
Leicestershire Clinical Genetics Service, Leicester: Richard Trembath
Yorkshire Regional Genetics Service, Leeds: Tim Bishop, Carol Chu
Merseyside & Cheshire Clinical Genetics Service, Liverpool: Ian Ellis

Department of Cancer Genetics, Royal Marsden Hospital London: Ros Eeles
North Trent Clinical Genetics Service, Sheffield: Jackie Cook, Oliver Quarrell
South West Thames Regional Genetics Service, London: Shirley Hodgson
Wessex Clinical Genetics Service, Southampton: Diana Eccles, Anneke Lucassen

GENEPSO Collaborating Centers:
Coordinating Center, Centre René Huguenin, Saint Cloud: Catherine Nogués, Emmanuelle Fourme, Rosette Lidereau, Denise Stevens
Institut Curie, Paris: Dominique Stoppa-Lyonnet, Marion Gaultier-Villain
Institut Gustave Roussy, Villejuif: Agnès Champret
Centre René Huguenin, Saint Cloud: Catherine Nogués
Centre Paul Strauss, Strasbourg: Jean-Pierre Fricker
Centre Léon Bérard, Lyon: Christine Lasset, Valérie Bonadonna
Centre François Baclesse, Caen: Pascaline Berthet
Centre Alexis Vautrin, Vandoever-les-Nancy: Elisabeth Luporsi
Institut Paoli-Calmettes, Marseille: Hagay Sobol, François Eisinger, Laetitia Huiart
Institut Claudius Regaud, Toulouse: Laurence Gladieff, Rosine Guimbaud
Centres Paul Papin, René Gauducheau and Catherine de Sienne, Angers, Nantes: Alain Lorholtry
Centre Antoine Lacassagne, Nice: Marc Fréauy
Hôpital D’Enfants CHU, Dijon: Laurence Faivre
Institut Bergonié, Bordeaux: Michel Longy
Institut Jean Godinot, Reims: Tan Dat Nguyen
CH Georges Renon, Niort: Paul Gest
Centre Oscar Lambret, Lille: Philippe Vennin, Claude Adenis
Hôpital Charles Nicolle, Centre Henri Becquerel, Rouen: Annie Chevrier, Annick Rossi
Centre Jean Perrin, Clermont-Ferrand: Yves-Jean Bignon
Hôpital Civil, Strasbourg: Jean-Marc Limacher
Centre Eugène Marquis, Rennes: Catherine Dugast
Polyclinique Courlany, Reims: Liliane Demange
Hôpital de la Timone, Marseille: Hélène Zattara-Cannoni
Clinique Sainte Catherine, Avignon: Hélène Dreyfus
CHU Aix Arnaud Villeneuve, Montpellier: Mehrdad Noruzinia
CHR Dupuytren, Limoges: Laurence Venat-Bouvet

Acknowledgments
The authors gratefully acknowledge the technical assistance of Helene Renard, Colette Bonnardel, and Othman Yaqoubi at IARC, Marie-Lise Manche-Thiévenot and Claude Picard (Centre René Huguenin, Saint-Cloud, France) for the GENEPSO study and Cristina Bellati at the Istituto Nazionale Tumori.

References


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

Jenny Chang-Claude, Nadine Andrieu, Matti Rookus, et al.


Updated version
Access the most recent version of this article at:
http://cebp.aacrjournals.org/content/16/4/740

Cited articles
This article cites 21 articles, 4 of which you can access for free at:
http://cebp.aacrjournals.org/content/16/4/740.full#ref-list-1

Citing articles
This article has been cited by 9 HighWire-hosted articles. Access the articles at:
http://cebp.aacrjournals.org/content/16/4/740.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.