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Impact of teenage oral contraceptive use in a population-based series of early-onset breast cancer cases who have undergone BRCA mutation testing

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Abstract

Oral contraceptive (OC) use in young women has been associated with an increased risk of breast cancer. This matched case-control study aims to elucidate the combined effects of OC use and genetic factors in a population-based series of BRCA1/2 mutation-tested early-onset breast cancers. A first invasive breast cancer was diagnosed in 259 women aged ⩽40 years between 1990 and 1995 in the South Swedish Health Care Region. A total of 245 women were included in this study. Information on family history of cancer, reproductive factors, smoking and OC use was obtained from questionnaires or patient charts. Three age-matched controls per case were chosen from a prospective South Swedish cohort. Ever OC use and current OC use were not associated with breast cancer. Cases were more likely to have used OCs before age 20 years (adjusted odds ratio (OR) 2.10 (95% CI 1.32–3.33)) and before their first child (adjusted OR 1.63 (95% CI 1.02–2.62)). When stratified by age, the effect of early OC use was limited to women diagnosed prior to age 36 years (OR 1.53 (1.17–1.99) per year of OC use prior to age 20 years). The risks were similar for low-dose and high-dose OCs. The probability of being a BRCA1/2 mutation carrier was three times higher among cases who started OC use prior to age 20 years compared with cases who started at age 20 years or older or who had never used OCs. However, the duration of OC use was similar among cases with and without BRCA1/2 mutations. No association was seen with a first-degree family history of breast cancer. Each year of OC use prior to age 20 years conferred a significantly increased risk for early-onset breast cancer, while there was no risk associated with use after age 20 years.

Keywords: Oral contraceptives; BRCA1/2; Early-onset breast cancer; Family history; Population-based case-control study

1. Introduction

Approximately one in eight women in the Western world will develop breast cancer during their lifetime. The median age of diagnosis of female breast cancer in Sweden is 65 years and 3% of these cases occur in women under the age of 40 years (data from the Swedish Cancer register). A positive family history of breast cancer is one of the strongest risk factors for developing the disease. The risk of breast cancer is approximately doubled in women whose mother or sister is affected by the disease [1]. Segregation analyses have predicted the existence of hereditary forms of breast cancer with a

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dominant Mendelian inheritance and a high penetrance [2]. Disease-causing mutations have been identified in several genes, most notably BRCA1 [3] and BRCA2 [4]. BRCA1/2 mutation carriers have approximately 45–65% risk of developing breast cancer up to age 70 years [5] and earlier studies reported up to 80% lifetime risk of developing breast cancer [6,7]. Ford and colleagues [8] reported 12–18% risk of developing breast cancer by age 40 years, although that study was not population-based. Early-onset breast cancer is more likely to be hereditary than late-onset breast cancer. The BRCA mutation prevalence varies considerably between ethnic groups. Between 30% and 35% of Ashkenazi Jewish breast cancer cases under the age of 40 years carry a BRCA1 or a BRCA2 mutation [9,10]. The mutation prevalence in Swedish early-onset breast cancer cases is much lower. Approximately 7% of women diagnosed with breast cancer at age 40 years or younger in Sweden carry a BRCA1 mutation and approximately 2% carry a BRCA2 mutation [11].

Oral contraceptives (OCs) offer convenient birth control. In addition to contraceptive purposes, OCs are prescribed for various conditions ranging from treatment of irregular or painful menstrual periods to treatment of acne. Combined OCs were first introduced for general use in Sweden in 1964. The cumulative lifetime usage among Swedish women is approximately 80–90% (data from the Swedish National Board of Health). Few, if any, other countries in the world, have such long follow-up for women who have been exposed to several years of OC use before age 20 years and before the first full-term pregnancy. Southern Sweden has a long tradition of extensive OC use among very young women, which began after the introduction of OCs in the 1960s. A previous study from the same region reported no significant association between breast cancer risk and total duration of use, but a fivefold increased risk with use before age 20 years [12]. In the general population, an increased risk of breast cancer during and up to 10 years after cessation of OC use in young women has been reported [13], although several studies have reported no apparent association between OC use and the risk of developing breast cancer after the age of 35 years [13–15]. OC use before age 30 years has been associated with breast cancer among women with BRCA1 mutations, but not among those with BRCA2 mutations [16]. Another study reported an increased risk from OC use among women with a family history of breast cancer, especially from the formulas available before 1975 [17].

This matched case-control study aimed to elucidate the association between OC use and early-onset breast cancer and determine whether this association is modified by a family history of breast cancer or deleterious mutations of the BRCA1 or BRCA2 genes.

2. Patients and methods

Between 1990 and 1995, 259 women aged 40 years or younger were diagnosed with a first invasive breast cancer in the South Swedish Health Care region. These cases have been verified by data from the Swedish Cancer Registry. Fourteen of these women declined to participate, thus leaving 245 women in the study. Information on family history of cancer, reproductive factors, smoking and OC use was obtained from 163 written questionnaires and 76 patient charts (when no questionnaire was available). The mean interval between diagnosis and completion of the questionnaire was 42 months. In six cases, neither questionnaire nor chart was available. No information on ever use was available for an additional 17 cases and these 23 cases and their matched controls are thus excluded from the analyses on OC exposure. The study was approved by the ethics committee at Lund University Hospital.

For several cases, a questionnaire was not available because these women were too ill. Instead of excluding these cases, we chose to carry out a chart review. Information on reproductive factors, such as age at menarche, miscarriages, abortions and ages for full-term pregnancies and OC use is routinely recorded in the charts obtained at the oncology clinic in Lund, where most of the women received their radiation therapy. In most charts, we found information on the start and stop ages as well as the brand names of the different OCs used and the total duration of OC use for women with intermittent use. A comparison between chart and questionnaire for each case was also carried out in order to validate the information provided in the questionnaire, given that the mean interval between diagnosis and completion of the questionnaire was rather long. In general, the information provided by the two sources was internally consistent for each woman.

BRCA1 and BRCA2 mutation analyses of the entire genes were performed as previously described by Loman and colleagues [11].

The controls were chosen among a prospective population-based cohort assessing risk factors for cancer in approximately 30,000 women from the same region, *i.e.*, the South Swedish Health Care Region. The controls completed detailed lifestyle questionnaires between 1990 and 1993. Every eighth woman in the region between the ages of 25 and 65 years was invited to participate in the study and 75% returned a completed questionnaire. The response rate was 75% for all age groups. The questions on OC use and reproductive factors were the same for cases and controls. Three control women were matched on age with each case. Controls were born within 5 years of the case and were at least as old as the case was when her breast cancer was diagnosed. For two of the cases, one or more of the controls were born within 6 years of that case. Controls who had

missing data regarding ever OC use (<0.5%) or who had developed breast cancer were not considered eligible for matching. The three controls for each case were randomly selected from all eligible controls in the cohort using a matching function in the statistical software package STATA 7.0. Matching was carried out without knowledge of the OC status, smoking status, reproductive status or family history of cancer.

In both the questionnaire for the cases and in the questionnaire for the controls, the women were asked to state at what ages and for how long they had used OCs, as well as the brand name for each period of use. For cases and controls who had indicated continuous OC use between certain ages and had given birth during the same period, we subtracted 12 months of use for each full-term pregnancy.

2.1. Statistics

The software SPSS10.0.7 was used for statistical analyses. OC use, smoking status, reproductive factors and the presence of a family history of cancer were compared between cases and controls using conditional logistic regression. For both cases and controls, only OC use and pregnancies that occurred up to the age of breast cancer diagnosis in the matched case were considered. Two cases gave birth after their breast cancer diagnosis and these two pregnancies were not considered in the analyses. The multivariate models were adjusted for the following breast cancer risk factors: age at menarche, ever smoking, a first-degree family history of breast cancer and parity. Spearman rank correlation (rs) was used for evaluation of correlation between OC duration and age at diagnosis in the cases as well as to estimate the cohort effect of OC start ages. Cox regression was used to study survival among cases in relation to OC status, pattern of use and type of OC used (high-dose *versus* low-dose). *Z*-test was used to compare differences in breast cancer risk between OC exposure before age 20 years and at age 20 years or older. Cases with missing values were excluded from analyses containing these variables. All *P*-values were two-tailed. A *P*-value of <0.05 was taken to be significant.

3. Results

Cases and age-matched controls were similar with respect to number of pregnancies and age at first full-term pregnancy. Cases were on average born 1 calendar year after the controls. Cases had a significantly lower age at menarche ($P = 0.005$), less often had a full-term pregnancy ($P = 0.05$), were less often ever-smokers ($P = 0.01$) and more often had a first-degree family history of breast ($P < 0.001$) or ovarian cancer ($P = 0.03$) (Table 1).

3.1. Questionnaire versus chart-derived information

The cases with information obtained from charts and questionnaires were similar with regard to age at diagnosis, year of birth, age at menarche, ever smoking and parity. However, cases whose information was obtained from their charts reported significantly less OC use than cases who were well enough to fill out a questionnaire.

3.2. Factors associated with OC use

Women who had ever smoked were more likely to have used OCs than women who had never smoked (87% *versus* 77%; $P = 0.0001$), but there was no significant interaction between the two exposures when compared between cases and controls ($P = 0.52$). The difference in OC use between ever smokers and never smokers was especially large for OC use prior to age

Table 1
Characteristics of cases and controls

Characteristics	Number of answers (cases/controls)	Cases ($n = 245$)	Controls ($n = 735$)	Odds ratio (OR)[a] (95% CI)
		Mean (SD) or percent	Mean (SD) or percent	
Age at diagnosis (years)	245/735	36.16 (±3.58)	–	
Year of birth	245/735	1955.98 (±4.19)	1954.62 (±3.25)	1.11 (1.06–1.15)
Age at menarche (years)	184/723	12.68 (±1.26)	12.97 (±1.35)	0.85 (0.75–0.96)
Ever-pregnant (%)	233/731	85%	87%	0.79 (0.53–1.21)
Parous (%)	233/731	80%	85%	0.71 (0.49–1.04)
Parity	232/729	1.84 (±1.24)	1.86 (±1.13)	0.98 (0.86–1.11)
Age at first full-term pregnancy (years)	183/620	24.6 (±4.69)	24.7 (±4.32)	0.99 (0.96–1.03)
Ever-smoking (%)	182/735	57%	67%	0.66 (0.48–0.92)
First-degree relative with breast cancer	238/734	15%	6%	2.94 (1.83–4.71)
First-degree relative with ovarian cancer	237/716	3%	1%	2.74 (1.05–7.20)

CI, confidence interval.

[a] Logistical regression models for continuous variables (year of birth, age at menarche, parity and age at first full-term pregnancy) and χ^2 for dichotomous variables.

20 years (62% *versus* 39%; $P < 0.0001$). Women with an early age at menarche, *i.e.*, prior to age 12 years, also reported more OC use than women with a later age at menarche (91% *versus* 83%; $P = 0.003$). No significant difference in OC prior to age 20 years was seen between women with an early and late age at menarche (60% *versus* 53%; $P = 0.18$).

3.3. OC use among cases and controls

Ever use of OCs did not significantly differ between cases and controls; OR 1.65 (95% CI 0.95–2.87; $P = 0.08$) (Table 2). The exposure to high-dose OCs was also similar among cases and controls (48% *versus* 47%; $P = 0.81$). There was also no significant difference in age at last use (27.9 years *versus* 28.6 years; $P = 0.26$) or percentage of cases and controls who had discontinued use within 1 year of the age at diagnosis of the matched case (27% *versus* 31%; $P = 0.43$). However, cases were more likely to have used OCs before age 20 years (OR 2.10 (95% CI 1.32–3.33; $P = 0.002$)) and before their first child (OR 1.63 (95% CI 1.02–2.62; $P = 0.04$), adjusted for breast cancer risk factors) (Table 2). Because cases and controls were born within up to 5 years of each other, we also performed two subgroup analyses, restricting the data to cases and matched controls who were born within 2 years of each other and for those born during the same calendar year. The adjusted OR for OC use prior to age 20 years was 1.99 (95% CI 1.15–3.46; $P = 0.01$) for cases and matched controls born within 2 years of each other and 1.91 (95% CI 0.58–6.32; $P = 0.29$) for cases and controls born the same calendar year.

Age at first use was compared between cases and controls who had ever used OCs. Cases were significantly younger at first use (18.4 years *versus* 19.5 years; $P = 0.005$). There was a cohort effect among the cases where OC use tended to be initiated earlier and earlier (r_s −0.18; $P = 0.02$) but not among the controls. We therefore restricted our analysis to include only cases and matched controls who were born in 1955 or later. The OR for OC use prior to age 20 years was 2.90 (95% CI 1.22–6.86; $P = 0.016$), adjusted for breast cancer risk factors and OC use at age 20 years or later. Conversely, in the birth cohort restricted to cases and matched controls born in 1954 or earlier, there was no significant effect of OC use prior to age 20 years (OR 1.15 (95% CI 0.55–24; $P = 0.71$), adjusted for breast cancer risk factors and OC use at age 20 years or later).

3.4. Duration of OC use prior to age 20 years and later

We then calculated duration of OC use before age 20 years and duration of use at age 20 years or older for each woman. For all women, each year of OC use prior to age 20 years was associated with a significantly increased risk of having breast cancer (OR 1.17 per year (95% CI 1.03–1.33; $P = 0.01$)), while there was no such association with duration of use at age 20 years or older (OR 1.02 per year (95% CI 0.98–1.07; $P = 0.28$)), adjusted for breast cancer risk factors (Table 3(a)). We then stratified our data by year of birth. Among women and matched controls born after 1955, each year of OC use prior to age 20 years was associated with a significantly increased risk of having breast cancer (OR 1.31 (95% CI 1.07–1.62; $P = 0.01$)), while there was no such

Table 2
Magnitude of breast cancer risk with different patterns of oral contraceptive (OC) use and other known risk factors

Risk factor	Cases/controls	OR	(95% CI)	*P*-value
	$n = 158/462$			
Age at menarche		0.84	(0.73–0.97)	0.02
Ever-smoke (yes)		0.66	(0.45–0.96)	0.03
Parity		0.91	(0.76–1.09)	0.31
First-degree family of breast cancer		2.12	(1.15–3.91)	0.02
Ever-OC use (yes)		1.65	(0.95–2.87)	0.08
	$n = 139/370$			
Age at menarche		0.84	(0.72–0.99)	0.04
Ever-smoke (yes)		0.67	(0.44–1.01)	0.05
Parity		0.84	(0.69–1.03)	0.10
First-degree family of breast cancer		2.34	(1.19–4.60)	0.01
OC use before the first child (yes)		1.63	(1.02–2.62)	0.04
OC use after the first child (yes)		1.03	(0.66–1.61)	0.90
	$n = 141/375$			
Age at menarche		0.82	(0.70–0.97)	0.02
Ever-smoke (yes)		0.57	(0.37–0.89)	0.01
Parity		0.82	(0.67–1.00)	0.05
First-degree family of breast cancer		2.22	(1.14–4.32)	0.02
OC use prior to age 20 years (yes)		2.10	(1.32–3.33)	0.002
OC use age 20 years or older (yes)		1.02	(0.63–1.64)	0.93

All OC use in women who were still nulliparous was classified as use before the first child. The odds ratios (ORs) for age at menarche and parity are given for each year increase in age at menarche (9–18 years) and per child, respectively. Nulliparous women were used as reference.

Table 3
Association of early oral contraceptive (OC) use with breast cancer risk in (a) all women; (b) stratified by birth cohort; and (c) stratified by age at diagnosis of the case

	OR[a]	(95% CI)	*P*-value	*P*-value *Z*-test[b]
(a) All women ($n = 140/372$) (cases/controls)				
Per year of OC use prior to age 20 years	1.17	(1.03–1.33)	0.01	0.06
Per year of OC use age 20 years or older	1.02	(0.98–1.07)	0.28	
(b) (i) Cases and matched controls born in 1955 and later ($n = 88/151$) (cases/controls)				
Per year of OC use prior to age 20 years	1.31	(1.07–1.62)	0.01	0.06
Per year of OC use age 20 years or older	1.05	(0.97–1.14)	0.24	
(ii) Cases and matched controls born in 1954 and earlier ($n = 52/134$) (cases/controls)				
Per year of OC use prior to age 20 years	0.95	(0.74–1.20)	0.65	NS
Per year of OC use age 20 years or older	1.03	(0.97–1.10)	0.34	
(c) (i) Age at diagnosis 35 years or younger ($n = 43/116$) (cases/controls)				
Per year of OC use prior to age 20 years	1.53	(1.17–1.99)	0.002	0.01
Per year of OC use age 20 years or older	1.04	(0.93–1.16)	0.51	
(ii) Age at diagnosis 36 years or older ($n = 97/256$) (cases/controls)				
Per year of OC use prior to age 20 years	1.06	(0.91–1.24)	0.45	NS
Per year of OC use age 20 years or older	1.03	(0.98–1.07)	0.26	

The reference categories were no OC use prior to age 20 years and no OC use age 20 years or older.
NS, not significant.
[a] Adjusted for age at menarche (continuous), parity (continuous with nulliparous as the reference), first-degree family history of breast cancer (yes) and having ever smoked (yes).
[b] A *Z*-test was performed to determine whether the magnitude of breast cancer risk from OC use prior to age 20 years *versus* OC use at age 20 years or older was significantly different from each other.

association with duration of use at age 20 years or older (OR 1.05 per year (95% CI 0.97–1.14; $P = 0.24$)), adjusted for breast cancer risk factors. Among cases and matched controls born in 1954 or earlier, there was no significant effect from duration of OC use at any age (Table 3(b)). The results remained essentially the same when we excluded the cases where the information was based on the chart and when we excluded women with less than 1 year of OC use.

3.5. Duration of OC use prior to the first child and later

We then calculated duration of OC use before the first child and later use for each woman and adjusted for breast cancer risk factors. Among all women there was an increased likelihood of being a case with increasing duration of OC use before the first child (OR per year of use 1.05 (95% CI 1.00–1.11; $P = 0.05$)), but not with later use.

3.6. High-dose versus low-dose OCs

We excluded all cases and controls who had been exposed to high-dose OCs or an unknown brand before 1975. Of all the women who had used high-dose OCs, 39% were classified as high-dose users because they had used an unknown OC prior to 1975. Each year of low-dose OC use prior to age 20 years conferred an OR of 1.80 (95% CI 1.24–2.61; $P = 0.002$), adjusting for breast cancer risk factors and duration of later OC use. No significant effect was seen from OC use at age 20 years or more.

3.7. Timing of OC use in relation to age at diagnosis

The association of early OC use with breast cancer risk varied according to age at diagnosis. No significant effect was seen from OC use prior to age 20 years or later use among the group where the case was diagnosed between the ages of 36 and 40 years. Cases aged 35 years or younger had significantly more often been exposed to long durations of OC use prior to age 20 years than controls (OR per year of OC use prior to age 20 years 1.53 (95% CI 1.17–1.99; $P = 0.002$)), adjusted for breast cancer risk factors and later OC use (Table 3(c)). The association between early-onset breast cancer and OC use was significantly different depending on the age when the OCs were used ($P = 0.01$). All cases who were diagnosed at age 35 years or younger were born in 1955 or later.

3.8. Family history and OC use

A family history in and of itself did not predict duration of OC use either before age 20 years ($P = 0.98$) or at age 20 years or older ($P = 0.42$). A case-case analysis comparing OC use prior to age 20 years showed that cases with a first-degree family history used OCs non-significantly shorter than other cases adjusting for breast cancer risk factors. However, cases with a first-degree

family history of breast cancer had an earlier age at menarche than other cases (12.2 years *versus* 12.8 years; $P = 0.05$). The results remained essentially the same when we excluded the cases where the information was based on the chart and when we excluded women with less than 1 year of OC use.

3.9. BRCA1/2 mutation status and OC use

Of the 245 cases, 231 had agreed to undergo BRCA1 and BRCA2 mutation testing. No BRCA1/2 mutation was detected among 212 women, with a mean age of diagnosis of 36.3 (±3.4) years. A BRCA1 mutation was found among 14 women, with a mean age of diagnosis of 34.3 (±4.5) years. A BRCA2 mutation was found in five women with a mean age of 31.0 (±4.8) years. A first-degree family history of breast cancer was found in 12.5% of the non-carriers, in 28.6% of the BRCA1 mutation carriers and in 60.0% of the BRCA2 mutation carriers. Because the controls had not undergone BRCA1/2 mutation testing, we chose to perform a case–case analysis to examine the prevalence of OC use in relation to BRCA1/2 mutation carrier status. Among the cases who had undergone mutation testing, all BRCA1/2 mutation carriers had used OCs at some point, compared with 84% of the non-carriers ($P = 0.08$). OC use prior to age 20 years was also non-significantly more common among BRCA1/2 mutation carriers compared with cases without a BRCA1/2 mutation (81% *versus* 58%; $P = 0.06$). The probability of being a BRCA1/2 mutation carrier was three times higher among cases who started OC use prior to age 20 years compared with cases who started at age 20 years or older or never used OCs (12% *versus* 4%; $P = 0.06$). However, there was no significant difference either in total duration of OC use (OR 0.95 (0.83–1.10)), or in duration of OC use prior to age 20 years (OR 0.78 (95% CI 0.48–1.28)), or at age 20 years or older (OR 0.98 (0.83–1.15)) between cases with and without BRCA1/2 mutations, after adjusting for breast cancer risk factors. There was also no significant difference in OC use prior to the first full-term pregnancy (88% *versus* 74%; $P = 0.23$) between BRCA1/2 mutation carriers and non-carriers.

3.10. Predictors of age of breast cancer onset among cases

We constructed a multivariate linear regression model to elucidate which factors predicted age of breast cancer onset among the cases. The final model included parity, ever smoking, BRCA1/2 mutation status, duration of OC use prior to age 20 years and duration of OC use at age 20 years or older. The strongest predictor of an early age of breast cancer onset was duration of OC use prior to age 20 years. Each year of OC use prior to age 20 years was associated with a 9 month earlier diagnosis ($P = 7 \times 10^{-6}$). Conversely, each year of OC use at age 20 years or older was associated with a 1.5 month delay in diagnosis ($P = 0.03$). Each full-term pregnancy was associated with a delay of 10 months ($P = 0.0002$). Ever smoking was associated with a delay of 23.5 months ($P = 0.0004$). BRCA1/2 mutation carriers were diagnosed approximately 2.5 years earlier than non-carriers ($P = 0.02$). Age at menarche, a family history of breast cancer and total duration of OC use were not associated with age of breast cancer onset (all Ps > 0.86).

4. Discussion

The main findings of this study were that OC use prior to age 20 years and OC use before the first child were associated with an increased risk of early-onset breast cancer. Each year of OC use prior to age 20 years conferred a significantly increased risk for early-onset breast cancer, while there was no risk associated with use after age 20 years. This is in line with other studies [18–21]. To our knowledge, this is the first report of the impact of OC use in a larger population-based series of early-onset breast cancer where BRCA1 and 2 mutation testing has been performed. In the general population, an increased risk of breast cancer during and up to 10 years after cessation of OC use in young women has been reported [13]. We did not find any difference between cases and controls in age at last use or use within 1 year of the age at diagnosis of the matched case. Our finding of an increased likelihood of being a case after a long duration of OC use prior to age 20 years remained highly significant after adjustment for age at menarche, parity, a first-degree family history of breast cancer and smoking-status.

Most breast cancers are thought to originate in the terminal end ducts or intralobular terminal ducts [22]. These structures are most numerous in nulliparous women and diminish with the differentiation occurring during pregnancy and lactation [23]. We have previously reported the breast epithelial proliferation rate to be significantly higher among women who had used OCs before the first full-term pregnancy compared with late or never users [24]. Animal experiments show that the susceptibility of the mammary gland to cancer is related to the proliferation rate of breast epithelial cells, and is inversely related to the degree of differentiation [25]. A recent case-control study of breast cancer in twins suggested that the breast tissue in women with a certain genotype might show an unusual sensitivity to pubertal hormones and an absence of linkage to hormonal milestones later in life [26]. Pike and colleagues [27] hypothesised that combination oral contraceptives may stimulate mitotic activity in the breast and that this may, in young women, counteract the natural protection

caused by frequent anovulatory cycles. Behind this hypothesis lies the assumption that, during the luteal phase of each menstrual cycle, women are more sensitive to external risk factors because of increased mitotic activity. The female breast is also most sensitive to ionising radiation at young ages [28], and this may apply also to other mutagenic agents.

One study by Narod and colleagues [16] including 1311 case-control pairs with BRCA1 and BRCA2 mutations reported an association between OC use before age 30 years and breast cancer among women with BRCA1 mutations, but not among those with BRCA2 mutations. In addition, a very small population-based study of 50 breast cancer cases of Ashkenazi Jewish decent, of whom only 14 were BRCA mutation carriers, suggested that OCs conferred a higher risk among carriers than among non-carriers [29]. Heimdal and colleagues [30] reported that the hazard ratio for breast cancer with ever OC use was doubled among BRCA1 mutation carriers in a series of 1423 women with hereditary/familial breast cancer, but that there was no interaction between BRCA1 mutations and OC use. Among our cases, we found that ever use of OCs prior to age 20 years was three times more common among BRCA1/2 mutation carriers than non-carriers, but the numbers were small. However, there was no relationship between duration of OC use prior to age 20 years or later and carrier status when confounding factors were taken into account. In the present study, BRCA1/2 mutation carriers were more likely than other breast cancer cases to have tried OCs for a short period of time during their teenage years and then quickly discontinued their use. Due to the high incidence of early-onset breast cancer among BRCA1 or BRCA2 carriers [8] it is possible that the majority of women with early-onset breast cancers and BRCA1 or BRCA2 mutations would have developed their cancers even without exposure to OCs. An alternative explanation would be that BRCA1 and BRCA2 carriers are especially sensitive to the combination of exogenous oestrogens and progestagens in the OCs and that even a short exposure to OCs is sufficient to initiate a new tumour or promote a pre-existing breast cancer. The two genes act through different pathways [31]. However, the expression of the BRCA1 gene is regulated by oestrogen and progesterone in combination [32], and BRCA2 expression occurs simultaneously with BRCA1 expression [33]. In the mammary gland, BRCA1 expression is induced during puberty and pregnancy, is believed to counteract proliferation and promote differentiation [34], and the increase in BRCA1/2 expression, which is necessary for genomic integrity, is likely to be impaired in women with both BRCA1 and BRCA2 mutations, during the administration of oestrogen- plus progestagen-containing OCs. In the present study, both teenage OC use and being a BRCA1/2 mutation carrier were independently associated with earlier age of breast cancer onset.

In contrast to our finding of an association between BRCA1/2 mutations, teenage OC use and breast cancer risk, there was no association with a positive family history in the present study. This is in line with the findings by the Collaborative Group on Hormonal Factors in Breast Cancer [13].

The present study is a case-control study and is therefore susceptible to recall bias, as are all case-control studies. However, it is unlikely that recall bias would explain our findings of no significant difference in ever use or in use after age 20 years between cases and controls, but a highly significant difference in use prior to age 20 years. Since recall bias may be especially present in short-term users [13], we also re-ran our analyses after exclusion of women with less than 1 year of OC use, and the results remained essentially the same. The controls were born on average 1 year prior to the cases. We therefore performed subgroup analyses including only cases and controls who were matched within 2 years of birth of each other and during the same calendar year. Similarly, we restricted the analyses of ever use to those women who had completed information on early OC use and use prior to the first full-term pregnancy. These analyses yielded similar risk estimates for early OC use as the whole material. We chose to only match controls that had answered the question on ever OC use, because they would have been excluded from all the analyses pertaining to OC use had this information been missing.

In Sweden, it is common for the doctor to ask detailed questions about OC use and to record this information in the chart. We therefore retrieved all the patients' charts to compare the information between charts and available questionnaires. The comparison between the chart and the questionnaire for each case was also carried out to validate the information provided in the questionnaire given that the mean interval between diagnosis and completion of the questionnaire was rather long. In general, the information provided by the two sources was internally consistent for each woman. After comparing the information we decided to use the information on OC use provided in the charts for cases who had not filled out a questionnaire because this would minimise the bias that would arise from excluding the cases who had been too ill to complete the questionnaire.

Early OC use, especially OC use prior to age 20 years, had its greatest impact among the youngest cases. One must remember that most women who use OCs prior to age 20 years do not develop breast cancer. It is therefore likely that these young breast cancer cases represent a group of women whose breast epithelium is especially vulnerable to the exogenous hormones when used at an early age. As of today, no predictive test exists to identify these women. More research is urgently needed to determine whether sensitive women could be easily iden-

tified by genotyping of polymorphic variants in key genes. The importance of such research is underscored by our observation that women are starting OC use at younger and younger ages.

The main finding of this study was that each year of OC use prior to age 20 years conferred a significantly increased risk for early-onset breast cancer, while there was no risk associated with use after age 20 years. Low-dose OCs conferred the same risk as high-dose OCs.

Conflict of interest statement

None declared.

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