Previous oral contraceptive use and breast cancer risk according to hormone replacement therapy use among postmenopausal women.

Vanessa Dumeaux, Agnès Fournier, Eiliv Lund, Françoise Clavel-Chapelon

Previous oral contraceptive use and breast cancer risk according to hormone replacement therapy use among postmenopausal women

Vanessa Dumeaux[1,2], Agnès Fournier[2], Eiliv Lund[1] & Françoise Clavel-Chapelon[2,*]

[1]Institute of Community Medicine, University of Tromsø; [2]INSERM ''Nutrition, Hormones, Cancer'', Equipe E3NEPIC, Institut Gustave-Roussy, Villejuif, France

Abstract

Objective: To assess postmenopausal breast cancer risk in relation to particular patterns of oral contraceptive (OC) use according to hormone replacement therapy (HRT) exposure.

Methods: Time-dependent Cox regression models were used to analyse information on postmenopausal women from a large-scale French cohort. Among a total of 68,670 women born between 1925 and 1950, 1405 primary invasive postmenopausal breast cancer cases were identified from 1992 to 2000.

Results: A non-significant decrease in risk of around 10% was associated with ever OC use as compared to never OC use in postmenopausal women. No significant interaction was found between OC and HRT use on postmenopausal breast cancer risk. Breast cancer risk decreased significantly with increasing time since first OC use (test for trend: $p = 0.01$); this was consistent after adjustment for duration of use or for time since last use.

Conclusion: No increase in breast cancer risk was associated with previous OC exposure among postmenopausal women, probably because the induction window had closed. Some women may develop breast cancer soon after exposure to OCs, leading to a deficit of cases of older women. Further investigation is therefore required to identify young women at high risk.

Key words: breast cancer, postmenopausal women, oral contraceptives, patterns of use, hormone replacement therapy.

Introduction

The possibility that oral contraceptives (OCs) might increase the risk of breast cancer has been the subject of intense research. The Collaborative Group on Hormonal Factors in Breast Cancer [1] pooled together data from almost all studies of breast cancer risk in relation to OC use published up to the mid-1990s. It concluded that women who were current or recent users of OCs had a slightly elevated risk of developing breast cancer. However, ten years or more after they stopped using OCs, their risk of developing breast cancer returned to the level at which it would have been if they had never used them.

Since publication of these findings in 1996, reports have reached mixed conclusions on breast cancer risk associated with OC use among different subgroups, notably according to age or menopausal status. A recent population-based case–control study [2] and a prospective cohort study [3], both conducted among young women, reported a trend of increasing risk with increasing total duration of OC use. Two other case–control studies [4, 5] found no association between long-term use of OCs and breast cancer risk in young women, although an increased risk of breast cancer was associated with early age of use. Results for older or postmenopausal women are inconsistent: although a case–control study [6] based on a large population of women 45 years of age or older found no significant association between breast cancer risk and long duration of OC use, a nested case– control study [7] treating postmenopausal women as a separate group concluded that their risk of breast cancer increased with increasing duration of OC use but analyses were not adjusted for HRT use.

* Address correspondence to: F. Clavel-Chapelon, Equipe E3N-EPIC, INSERM ''Nutrition, Hormones, Cancer'', Institut Gustave-Roussy, 94805 – Villejuif, France. Tel.: +33-1-42-11-41-48; Fax: +33-1-42-11-40-00; E-mail: clavel@igr.fr

Women now in their late 50s and early 60s were at the start of their contraceptive life when OCs became readily available in the 1960s. These women, who have had the possibility of using OCs at a young age and for a long duration, are now postmenopausal and are likely to use HRT. Previous studies have shown that recent use of HRT increases breast cancer risk [8–12]. A recent publication from the E3N cohort on HRT use in France [12] showed that estrogen therapy combined with synthetic progestins increased breast cancer risk even after a short duration of use. Recent studies found no strong evidence of interaction between OC and HRT [13–18]. Among them, only one prospective cohort study [17] has investigated the combined effect of OC and HRT on breast cancer risk, however results were limited by the small percentage of women having used both products. Notably, Norman *et al.* [13] did not find any evidence that previous OC use exacerbated the risk associated with HRT use, but rather that breast cancer risk among women with long term use of HRT was lower in OC ever users than in women who had never used OCs, with a significant negative interaction of combined HRT and past OC use. Since lifetime cumulative exposure to estrogens is put forward as a key factor for breast cancer risk [19], HRT use needs to be taken into account as a potential confounder between OC effect and postmenopausal breast cancer risk.

Our objective was to explore the effect of different patterns of previous OC use on breast cancer risk among postmenopausal women, in a large cohort of women born between 1925 and 1950 with biannually updated measurements of exogenous hormone exposure. For this purpose, we first explored the possibility of an interaction between OC and HRT use. We then investigated the effect of different patterns of OC use among postmenopausal women, taking into account HRT exposure.

Subjects and methods

E3N cohort

The E3N cohort was set up in 1990 to investigate cancer risk factors [20]. At that date, half a million women, aged 40 to 64 years, residing in continental France and insured with the Mutuelle Générale de l'Education Nationale (MGEN), a national health insurance scheme primarily covering teachers, were invited to participate. Twenty percent (98,997 women) agreed to be volunteers, by filling in the first questionnaire and a consent form. From June 1990 onwards, they were asked to complete self-administered questionnaires requesting information on various exposures and medical diagnoses. Follow-up questionnaires were sent out approximately every two years to update the information. A change of address of a participant could be obtained from the insurance company file. Of the women participating to the cohort, 16% did not answer the June 2000 questionnaire (2% had died). Part of the E3N cohort (i.e. women who replied to a dietary questionnaire) is also included in the European Prospective Investigation into Cancer and Nutrition (EPIC) [21].

Exposure to exogenous hormones and menopause

Comprehensive information on use of hormonal treatments (including OCs and HRT) was requested in the 1992 questionnaire, which was returned by 86,164 women. Questions inquired about use of hormonal treatments between menarche and the date of completion of the questionnaire. A booklet containing photographs of the hormonal medications marketed in France was included to facilitate accurate recall. Brand name, age at first use, and duration of use were recorded for 24 possible episodes of use. Information on subsequent use of hormonal treatments up to 2000 was obtained from four follow-up questionnaires, sent out in June 1993, January 1995, April 1997, and June 2000.

Ever use, total duration of use, time since first use, age at first use, and time since last use of OCs were computed from the returned questionnaires. HRT use was defined as any postmenopausal use of exogenous hormones containing orally, transdermally or percutaneously administered estrogens, associated or not with a progestagen. In the E3N cohort, the most widely used types of HRT were transdermal/percutaneous estradiol associated with either micronized progesterone or progesterone derivatives [12].

Information on date of menopause, type of menopause (natural, bilateral oophorectomy, chemotherapy, radiotherapy), date of last menstruation, date of start of menopausal symptoms and date of hysterectomy was updated on receipt of each new questionnaire and was used to determine age at menopause. Postmenopausal women were defined as those whose menstruation had ceased permanently due to natural menopause, bilateral oophorectomy, radiotherapy or chemotherapy or as those who were taking HRT. Women for whom age at menopause could not be determined (e.g. who reported a hysterectomy but gave no information on

oophorectomy or menopausal symptoms, or who indicated they were postmenopausal without any further information) were classified as menopausal at age 46 if menopause was artificial, and at age 50 otherwise. These ages correspond to the median ages for artificial and natural menopause respectively in the cohort.

Case ascertainment, study population and follow-up

Cases were identified by self reports of participants: all questionnaires asked participants whether any cancer had been diagnosed, requesting the addresses of their physicians and permission to contact them to obtain pathology reports. 94.9% of the pathology reports concerning self-reported breast cancers recorded up to the June 2000 questionnaire had been received; of these, 97.8% confirmed the self-reported diagnosis of breast cancer.

83,797 of the 86,164 women who returned the baseline questionnaire on use of hormonal treatments (i.e. the 1992 questionnaire) were followed up subsequently. Analysis was restricted to the 74,211 women who were postmenopausal at start of follow-up or who became postmenopausal during the course of the study. Women who had a prevalent cancer other than a basal-cell carcinoma before inclusion (n = 5321) or who were diagnosed as having an *in situ* breast cancer during follow-up (n = 194) were excluded, as well as those who had used injectable OCs (n = 26). This left us a total of 68,670 women available for analysis. Follow-up time for each participant was calculated from the date of return of the 1992 questionnaire for women already postmenopausal at that time and otherwise from the date of menopause, up to the date of cancer diagnosis for cancer cases, the date of the last questionnaire returned for non-respondents and deceased women, or the end of the study period (28th June 2000) for replies received afterwards. During follow-up, 411,323 person-years were accumulated for the 68,670 subjects included in the analysis and 1405 primary invasive breast cancer cases were identified among the subjects. The age of breast cancer cases at the time of diagnosis ranged from 46 to 74 years (mean: 59.2 ± 5.5 years). The mean age at start of follow-up was 53.9 years (SD 5.1) and the mean follow-up time was 6.0 years (SD 2.6).

Statistical analysis

Time-dependent Cox proportional hazards regression analysis [22] was used to investigate the effect of different patterns of OC use and other risk factors on the breast cancer incidence rate. The model with age as the time scale was used [23]. Baseline information was used for age at menarche, age at first birth and parity, and family history of breast cancer in first-degree relatives. Body mass index and history of benign breast disease were derived from the questionnaire returned closest to the date of menopause. Information on alcohol consumption was available only from the questionnaire sent out in 1993. Information on pap smear frequency was used to evaluate gynecological surveillance: each questionnaire asked whether a pap smear exam had been performed during the previous follow-up interval, enabling the proportion of questionnaires reporting a pap smear exam to be calculated. Imputation to the mode was used for adjustment factors with 5% or less of missing values. A separate category corresponding to missing values was created for alcohol consumption as information was missing for more than 5% of women. An additional adjustment was made for time since menopause [10]. HRT use was calculated to one year prior to current age in order to eliminate exposure that was unlikely to be causal [12, 24]. Current use was defined as two years before cessation of use. HRT use and time since menopause were included in the models as time-dependent variables, as well as time since first OC use and time since last OC use.

Relative risks (RRs) are given with 95% confidence intervals (CIs). Tests for trend were calculated by introduction of ordinal variables obtained by assigning consecutive integers to values of the categorized variable. Trends for patterns of OC use were calculated among ever users only. All analyses were performed using the SAS® software, version 8.2.

Results

Characteristics of the 68,670 postmenopausal women included in the analysis are shown in Table 1 according to OC use. At the start of follow-up, OC ever users were younger, had lower BMI, consumed more alcohol, had higher parity, had used HRT less often and more often had a history of benign breast disease than never users. At the end of follow-up, ever use of HRT was more frequent in ever users (73.8%) than in never users (60.7%) of OCs. As expected, OC ever users had more frequently had pap smears.

Table 1. **Characteristics of postmenopausal women ever exposed / never exposed to oral contraceptives – E3N cohort**

Characteristics[a]	Ever OC use n = 28,251	Never OC use n = 40,419
Age (years), Mean (SD)	51.7 (3.8)	55.4 (5.3)
Age at menarche (years), Mean (SD)	12.8 (1.4)	12.8 (1.5)
Age of parous women at first birth (years), Mean (SD)	24.7 (4.0)	24.8 (3.9)
Body Mass Index (kg/m^2), Mean (SD)	22.7 (3.1)	23.1 (3.4)
Alcohol consumption (10 g/day) recorded in 1993 questionnaire, Mean (SD)	1.2 (1.4)	1.0 (1.3)
Parity, Number (%)		
Nulliparous	2617 (9.3)	5677 (14.1)
<3	17,443 (61.7)	22,194 (54.9)
≥ 3	8191 (29.0)	12,548 (31.0)
Family history of breast cancer,[b] Number (%)		
No	25,003 (88.5)	35,615 (88.1)
Yes	3248 (11.5)	4804 (11.9)
HRT use		
Never use	22,021 (77.9)	29,179 (72.2)
Ever use	6230 (22.1)	11,240 (27.8)
HRT use at end of follow-up, Number (%)		
Never use	7407 (26.2)	15,887 (39.3)
Ever use	20,844 (73.8)	24,532 (60.7)
History of benign breast disease,[b] Number (%)		
No	20,149 (71.3)	30,382 (75.2)
Yes	8102 (28.7)	10,037 (24.8)
Pap smear reported in each questionnaire returned, Number (%)		
No	4482 (15.9)	11,639 (28.8)
Yes	23,769 (84.1)	28,780 (71.2)

[a] At start of follow-up unless otherwise indicated.
[b] Values for missing data indistinguishable from ‘‘no’’ responses.

In all, 264,806 person-years (64.4%) were associated with never use of OCs and 146,517 person-years (35.6%) with ever use of OCs. Nine hundred and fifty-one never users and 454 ever users of OCs developed invasive breast cancer. Compared to never OC use, there was a non-significant 9% decrease in breast cancer risk associated with ever OC use (Table 2; $p = 0.13$). HRT use was associated with a 41% higher risk of developing breast cancer than never HRT use (Table 2; $p<0.0001$). Compared to never use of both OCs and HRT, ever OC use combined with never HRT use was associated with a RR (95% CI) of 0.94 (0.76–1.16). Ever use of both Ocs and HRT was associated with a RR (95% CI) of 1.29 (1.10–1.52), slightly but not significantly lower than for ever use of HRT combined with never use of Ocs (RR = 1.43, 95% CI 1.25–1.64). No significant interaction was seen between OC- and HRT-ever use (test for interaction: $p = 0.73$). This was consistent for current HRT use (RR = 1.20 versus 1.31 for OC ever users and never users, respectively) and for former HRT use (RR= 1.86 versus 2.13 for OC ever users and never users, respectively); the slight decrease in risk associated with OC ever use was still not significant. Finally, the effect of OC ever use was approximately the same according to the HRT regimen used the longest (either estrogens alone, estrogens combined with micronized progesterone, or estrogens combined with synthetic progestins): the risk reduction related to previous OC use was around 10% in each strata and tests for interaction between OCs and each type of HRT were not significant (data not shown).

Table 2. **Relative risks of breast cancer by oral contraceptive (OC) use, hormone replacement therapy (HRT) use and combined use of both among postmenopausal women – E3N cohort**

	Number of cases	Adjusted RR[a]	CI 95%
OC use			
Never use	951	1 (ref)	
Ever use	454	0.91	0.81–1.03
HRT use[b]			
Never use	506	1 (ref)	
Ever use	899	1.41	1.26–1.59
OC use/HRT use[b]			
Never use/Never use	376	1 (ref)	
Ever use/Never use	130	0.94	0.76–1.16
Never use/Ever use	575	1.43	1.25–1.64
Ever use/Ever use	324	1.29	1.10–1.52

[a] Adjusted for age at menarche (≤12, 13–14, ≥15 years), age at first birth and parity (nulliparous, <30 years, ≥30 years and one child, ≥30 years and two or more children), family history of breast cancer, BMI (continuous variable), frequency of pap smear exams (i.e. percentage of questionnaires reporting a pap smear exam), history of benign breast disease, alcohol consumption (≤2.5 g/day, >2.5 g/day, missing), time since menopause (<5 years, [5–10] years, ≥10 years). Further adjusted for OC use (never/ever) or HRT use (never/ever), depending on the variable(s) studied.

[b] Time-dependent variable in Cox models.

At start of follow-up, the median duration of OC use was five years (ranging from 1 month to 33 years) and the median time since first use was approximately 23 years. 51.9% of person-years among OC ever users were associated with first use late in reproductive life (≥ 30 years). Most women had stopped using OCs ten or more years before inclusion (78.2% of person-years among OC ever users). As the variables describing the timing of OC use are highly correlated, there is a possibility of mutual confounding. At start of follow-up, the strongest correlation was between time since first use and age at first use (Pearson: r = -0.82), followed by correlation between time since last use and either total duration (r = -0.60) or time since first use (r = 0.41). To disentangle which factors have an independent effect on breast cancer risk, we analysed the association between each variable and breast cancer risk after mutual adjustment.

Though we did not find any statistical interaction between OCs and HRT, we chose to also present results according to HRT use with a combined referent group of non HRT- and non OC- users. Table 3 presents the RRs of breast cancer by patterns of OC use in all postmenopausal women and according to use of HRT. No significant association was observed between total duration of OC use or time since last use and postmenopausal breast cancer risk. A decreased risk of breast cancer was observed with increasing time since first OC use in all postmenopausal women and in HRT ever users (tests for trend: p = 0.01). Trends were still significant after adjustment for either total duration of OC use or time since last OC use. A decrease in risk in all postmenopausal women and in HRT ever users was observed when women first used OCs 25 or more years ago (Table 3). Risk ratios did not reach significance in HRT never users group, however no significant heterogeneities with HRT ever users were found. In the same manner, we studied age at first use effect on breast cancer risk (data not shown). The results were consistent with those on time since first use (see correlation factor mentioned above): a borderline positive trend of increasing risk was observed with increasing age at first use after adjustment for duration of use among HRT ever users and all postmenopausal women (tests for trend: p = 0.08 and 0.06, respectively).

Since postmenopausal breast cancer risk decreased with increasing time since first use, we studied total duration of OC use stratified on time since first use (Table 4). A decreased risk was associated with ten or more years of OC use combined with 30 years or more since first use in all postmenopausal women (RR = 0.63; 95% CI 0.41–0.98) and in HRT ever users (RR = 0.56; 95% CI 0.34 0.94). A significant increase in risk was found among HRT never users who had used OCs for ten or more years and had first used them <25 years ago (RR = 1.60; 95% CI 1.03–2.49). None of the risk estimates presented in Table 4 statistically differed between HRT ever and never users.

Table 3. **Relative risks of breast cancer by patterns of OC use among postmenopausal women – E3N cohort**

	Number of cases and RR[a] [CI 95%]					
	All postmenopausal women		HRT never-users		HRT ever-users	
Duration of OC use, years						
Never use	951	1 (ref)				
<5	217	0.94 [0.81–1.09]	63	0.94 [0.72–1.24]	154	0.94 [0.78–1.12]
5–9	114	0.91 [0.75–1.11]	30	0.87 [0.60–1.27]	84	0.93 [0.74–1.17]
10+	123	0.87 [0.72–1.06]	37	1.00 [0.71–1.41]	86	0.82 [0.66–1.04]
Trend		0.96 [0.86–1.07]		1.01 [0.83–1.24]		0.94 [0.82–1.07]
Trend adjusted for time since last use		0.92 [0.81–1.05]		0.97 [0.78–1.21]		0.90 [0.78–1.04]
Trend adjusted for time since first use		0.98 [0.87–1.09]		1.03 [0.84–1.27]		0.96 [0.84–1.09]
Time since first OC use[b], years						
Never use	951	1 (ref)				
<25	223	1.06 [0.91–1.23]	66	1.02 [0.77–1.33]	157	1.07 [0.90–1.29]
25–29	161	0.83 [0.70–0.99]	46	0.87 [0.64–1.19]	115	0.82 [0.67–1.00]
30+	70	0.77 [0.60–0.98]	18	0.91 [0.57–1.47]	52	0.73 [0.55–0.97]
Trend		0.85 [0.75–0.97]		0.94 [0.73–1.20]		0.82 [0.71–0.96]
Trend adjusted for duration		0.85 [0.75–0.98]		0.94 [0.73–1.20]		0.83 [0.71–0.96]
Trend adjusted for time since last use		0.84 [0.73–0.97]		0.93 [0.72–1.20]		0.82 [0.70–0.96]
Time since last OC use[b], years						
Never use	951	1 (ref)				
<10	90	0.99 [0.79–1.24]	29	0.99 [0.67–1.46]	61	0.99 [0.75–1.29]
10–19	200	0.93 [0.79–1.09]	49	0.84 [0.62–1.14]	151	0.96 [0.80–1.15]
20 +	164	0.87 [0.73–1.03]	52	1.04 [0.77–1.39]	112	0.80 [0.66–0.98]
Trend		0.96 [0.84–1.10]		1.08 [0.85–1.36]		0.92 [0.79–1.07]
Trend adjusted for duration		0.91 [0.78–1.06]		1.02 [0.80–1.31]		0.87 [0.73–1.03]
Trend adjusted for time since first use		1.01 [0.88–1.17]		1.14 [0.89–1.45]		0.97 [0.82–1.14]

a Adjusted for age at menarche (≤12, 13–14, ≥15 years), age at first birth and parity (nulliparous, <30 years; ≥30 years and one child; ≥30 years and two or more children), family history of breast cancer, BMI (continuous variable), frequency of pap smear exams (i.e. percentage of questionnaires reporting a pap smear exam), history of benign breast disease, alcohol consumption (≤2.5 g/day, >2.5 g/day, missing), time since menopause (<5 years, [5–10] years, ≥10 years) HRT use (never/ever).
b Time-dependent variable in Cox models.

Table 4. **Relative risks of breast cancer by total duration and time since first use of oral contraceptives among postmenopausal women – E3N cohort**

Time since first use (year)b/	All postmenopausal women		HRT never users		HRT ever users	
Duration of use (year)	Cases	RR[a] [CI 95%]	Cases	RR[a] [CI 95%]	Cases	RR[a] [CI 95%]
Never use	951	1 (ref)				
<25						
[0–4]	116	1.03 [0.84–1.25]	31	0.90 [0.62–1.30]	85	1.09 [0.86–1.37]
[4–9]	56	1.03 [0.79–1.36]	13	0.78 [0.45–1.36]	43	1.15 [0.84–1.56]
10+	51	1.16 [0.87–1.55]	22	1.60 [1.03–2.49]	29	0.96 [0.66–1.39]
[25–30]						
[0–4]	68	0.85 [0.66–1.09]	23	1.01 [0.66–1.54]	45	0.79 [0.58–1.07]
[4–9]	42	0.84 [0.61–1.15]	14	1.05 [0.61–1.79]	28	0.76 [0.52–1.12]
10+	51	0.80 [0.60–1.07]	9	0.55 [0.28–1.06]	42	0.89 [0.65–1.22]
≥30				1.00 [0.51–1.93]		
[0–4]	33	0.88 [0.62–1.24]	9	0.72 [0.23–2.26]	24	0.84 [0.56–1.26]
[4–9]	16	0.80 [0.48–1.31]	3	0.92 [0.41–2.06]	13	0.81 [0.47–1.41]
10+	21	0.63 [0.41–0.98]	6		15	0.56 [0.34–0.94]

[a] Adjusted for age at menarche (≤12, 13–14, ≥15 years), age at first birth and parity (nulliparous, <30 years; ≥30 years and one child; ≥30 years and two or more children), family history of breast cancer, BMI (continuous variable), frequency of pap smear exams (i.e. percentage of questionnaires reporting a pap smear exam), history of benign breast disease, alcohol consumption (≤2.5 g/day, >2.5 g/day, missing), time since menopause (<5 years, [5–10] years, ≥10 years) HRT use (never/ever).
[b] Time–dependent variable in Cox models.

Discussion

Overall, no increase in breast cancer risk was associated with past OC use in postmenopausal women, whatever their exposure to HRT. Conversely, there was a nonsignificant decrease in breast cancer risk associated with past OC use. No significant interaction was found between OC and HRT use on postmenopausal breast cancer risk. A significant decrease in breast cancer risk was observed with increasing time since first OC use after adjustment for either total duration of OC use or time since last OC use.

The slight decrease in postmenopausal breast cancer risk associated with past OC use and the decrease in risk with increasing time since first use support the hypothesis that some women develop breast cancer soon after exposure to OCs. In studies of postmenopausal breast cancer, only OC users who have not developed breast cancer before menopause are kept in the analyses, i.e. the women most likely to develop breast cancer after OC exposure are excluded. The decrease in risk of around 10% associated with OC use according to the multiplicative model (RR = 1 versus 0.91; RR = 1 versus 0.94; RR = 1.43 versus 1.29 in all postmenopausal women, HRT never users and HRT ever users respectively) would thus reflect an excess of cases of younger women and hence a deficit of cases of older women. Supporting this hypothesis, the decrease in risk with increasing time since first use implies that the maximum induction period after OC exposure has passed in the cohort [25]. Wingo *et al.* [26] and more recently Althuis *et al.* [2, 27] found that the risk of breast cancer among premenopausal women associated with recent use of Ocs decreased with increasing age. In agreement with our results, recent studies of older or postmenopausal women [6, 17] found no increase in breast cancer risk with OC use. One recent nested case–control study of women aged over 55 years [7] found an increased risk of breast cancer with past OC use, but the increase in risk might be due to HRT use which was not taken into account. Furthermore, since older women are more likely to have stopped using OCs more than ten years ago [16], results on long time since last use should be in line with results for older women. The collaborative reanalysis of 54 epidemiological studies [1] including a large proportion of older women (64.7% of women were 45 or more years old), i.e. women for whom the maximum induction period might have passed, observed a decreased risk of breast cancer when OC use had stopped ten or more years ago. The two recent cohort studies [3, 28] that did not find a decreased risk of breast cancer associated with long time since last OC use were conducted on younger women (<45 years old). Finally, one study [2] found a decreased risk with increasing time since last OC use among women aged 20–44 years, but the analysis was neither stratified by nor adjusted for total duration of use, a variable strongly correlated to recency of use especially among young women [16].

Our results among HRT never users were not statistically different than among HRT users; no significant association between any pattern of OC use and breast cancer risk was observed in postmenopausal women who never used HRT probably due to lack of statistical power. Previous studies [4, 5, 29–32] found an association of early OC use and breast cancer risk among young women. In our study, it was impossible to determine whether there was a greater susceptibility of breast tissue to hormonal exposure at young ages [33]. Due to the long time between OC exposure and inclusion in the study, susceptible women would in fact have already developed breast cancer and consequently were not included in our study population. Stratified on time since last use, significant risk ratios were observed in some strata, but they could be due to chance because of multiple testing following stratification. Finally, there is some potential for misclassification of OC exposure as most of the women included in the analysis had stopped OC use more than ten years before baseline. However, given the prospective design of the study, any misclassification would be non-differential.

Our study has several strengths. Updated information on exogenous hormone exposure and menopausal status was used (see Statistical analysis section), both to reduce misclassification bias and to allow the most accurate evaluation of the interaction between OC and HRT use. In a sensitivity analysis, the models were stratified on birth cohort to assess breast cancer risk associated with patterns of OC use regardless of the evolution of OC formulations [2, 28] and results were approximately the same. Finally, there may be a questionable ‘‘surveillance bias,’’ due to greater contact with doctors and earlier diagnosis of breast cancer among users of OCs or HRT. However, the potential for such a bias was limited by controlling for ‘‘frequency of pap smear exams performed.’’

In conclusion, no effect of OC use on breast cancer risk was observed among postmenopausal women, probably because the induction window had closed. Our results support the hypothesis that some women develop breast cancer soon after exposure to OCs, leading to a deficit of cases in older women. However, further

investigation is required to identify young women at high risk, necessitating new prospective cohort studies of younger women.

Acknowledgements
The authors are indebted to all participants for providing the data and to practitioners for providing pathology reports. They are grateful to V. Avenel, R. Chaït, M. Fangon, Y. Follain, L. Hoang and M. Niravong for managing the data and to G. Evans for his assistance with the English. They thank the French League against Cancer, the European Community, the 3M Company, the Mutuelle Générale de l'Education Nationale, the Institut Gustave-Roussy and the Institut National de la Santé et de la Recherche Médicale for supporting the E3N study financially.

References

1. Collaborative Group on Hormonal Factors in Breast Cancer (1996) Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet 347: 1713–1727.
2. Althuis MD, Brogan DR, Coates RJ, et al. (2003) Hormonal content and potency of oral contraceptives and breast cancer risk among young women. Br J Cancer 88: 50–57.
3. Kumle M, Weiderpass E, Braaten T, Persson I, Adami HO, Lund E (2002) Use of oral contraceptives and breast cancer risk: the Norwegian-Swedish Women's Lifestyle and Health Cohort Study. Cancer Epidemiol Biomarkers Prev 11: 1375–1381.
4. Ursin G, Ross RK, Sullivan-Halley J, Hanish R, Henderson B, Bernstein L (1998) Use of oral contraceptives and risk of breast cancer in young women. Breast Cancer Res Treat 50: 175–184.
5. Chie WC, Li CY, Huang CS, Chang KJ, Yen ML, Lin RS (1998) Oral contraceptives and breast cancer in Taiwan, a country of low incidence of breast cancer and low use of oral contraceptives. Int J Cancer 77: 219–223.
6. Marchbanks PA, Mc Donald JA, Wilson HG, et al. (2002) Oral contraceptives and risk of breast cancer. N Engl J Med 346: 2025–2032.
7. Van Hoften C, Burger H, Peeters PHM, Grobbe DE, Van Noord PAH, Leufkens HGM (2000) Long term oral contraceptive use increases breast cancer risk in women over 55 years of age: the DOM cohort. Int J Cancer 87: 591–594.
8. Million Women Study Collaborators (2003) Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 362: 419–427.
9. Writing Group for the Women's Health Initiative Investigators (2002) Risk and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial. JAMA 288: 321–333.
10. Collaborative Group on Hormonal Factors in Breast Cancer (1997) Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 Previous oral contraceptive use and breast cancer risk 543 women with breast cancer and 108,411 women without breast cancer. Lancet 350: 1047–1059.
11. Bakken K, Alsaker E, Eggen AE, Lund E (2004) Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer study. Int J Cancer 112: 130–134.
12. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F (2004) Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int J Cancer (in press).
13. Norman SA, Berlin JA, Weber AL, et al. (2003) Combined effect of oral contraceptive use and hormone replacement therapy on breast cancer risk in postmenopausal women. Cancer Causes Control 14: 933–943.
14. Ursin G, Tseng CC, Paganini-Hill A, et al. (2002) Does menopausal hormone replacement therapy interact with known factors to increase risk of breast cancer? J Clin Oncol 20: 699–706.
15. Brinton LA, Brogan DR, Coates RJ, Swanson CA, Potischman N, Stanford JL (1998) Breast cancer risk among women under 55 years of age by joint effects of usage of oral contraceptives and hormone replacement therapy. Menopause 5: 145–151.
16. Collaborative Group on Hormonal Factors in Breast Cancer (1996) Breast cancer and hormonal contraceptives: Further results. Contraception 54(Suppl.3): 1S–106S.
17. Schuurman AG, van den Brandt A, Goldbohm RA (1995) Exogenous hormone use and the risk of postmenopausal breast cancer: results from the Netherlands Cohort Study. Cancer Causes Control 6: 416–424.
18. Stanford JL, Weiss NS, Voigt LF, Daling JR, Hable LA, Rossing MA (1995) Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. JAMA 274: 137–142.
19. Clemons M, Goss P (2001) Estrogen and the risk of breast cancer. N Engl J Med 344: 276–285.
20. Clavel-Chapelon F, van Liere MJ, Guibout C, et al. (1997) E3N, a French cohort study on cancer risk factors. Eur J Cancer Prev 6: 473–478.

21. Riboli E (1992) Nutrition and cancer: background and rationale of the European Prospective Investigation into Cancer and Nutrition (EPIC). Ann Oncol 3: 783–791.
22. Altman DG, De Stavola BL (1994) Practical problems in fitting a proportional hazards model to data with updated measurements of the covariates. Stat Med 13: 301–341.
23. Thiébaut CMA, Bénichou J (2004) Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Stat Med 23: 3803–3820.
24. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R (2000) Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA 283: 485–491.
25. Greenland S (1998) Applications of stratified analysis methods. In: Rothman KJ, Greenland S, eds. Modern Epidemiology. 2nd edn. Philadelphia: Lippincott-Raven, pp. 297–300.
26. Wingo PA, Lee NC, Ory HW, Beral V, Peterson HB, Rhodes P (1993) Age-specific differences in the relationship between oral contraceptive use and breast cancer. Cancer 71(suppl): 1506–1517.
27. Althuis MD, Brogan DD, Coates RJ, et al. (2003) Breast cancers among very young premenopausal women (United States). Cancer Causes Control 14: 151–160.
28. Dumeaux V, Alsaker E, Lund E (2003) Breast cancer and specific types of oral contraceptives: a large Norwegian cohort study. Int J cancer 105: 844–850.
29. White E, Malone KE, Weiss NS, Daling JR (1994) Breast cancer among young US women in relation to oral contraceptive use. J Natl Cancer Inst 86: 505–514.
30. McPherson K, Vessey MP, Neil A, Doll R, Jones L, Roberts M (1987) Early oral contraceptive use and breast cancer: results of another case–control study. Br J Cancer 56: 653–660.
31. Rookus MA, Van Leeuwen FE (1994) Oral contraceptives and risk of breast cancer in women aged 20–54 years. Lancet 344: 844–851.
32. Brinton LA, Daling JR, Liff JM, Schoenberg JB (1995) Oral contraceptives and breast cancer risk among younger women. J Natl Cancer Inst 87: 827–835.
33. Whittemore AS (1977) The age distribution of human cancer for carcinogenic exposures of varying intensity. Am J Epidemiol 106: 418–432.