Oral Contraceptive Use and Breast Cancer: A Prospective Study of Young Women

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ORAL CONTRACEPTIVE USE AND BREAST CANCER: A PROSPECTIVE STUDY OF YOUNG WOMEN

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Abstract

Background—Previous studies convincingly showed an increase in risk of breast cancer associated with current or recent use of oral contraceptives in the 1960's to 1980's. The relation of contemporary oral contraceptive formulations to breast cancer risk is less clear.

Methods—We assessed lifetime oral contraceptive use and the specific formulations used among 116,608 female nurses aged 25 to 42 years at enrollment in 1989, and subsequently updated this information every two years. We related this information to risk of breast cancer up to June 1, 2001.

Results—During 1,246,967 person-years of follow-up, 1,344 cases of invasive breast cancer were diagnosed. Past use of any oral contraceptive was not related to breast cancer risk (multivariate relative risk, 1.12; 95 percent confidence interval 0.95–1.33). Current use of any oral contraceptive was related to a marginally significant higher risk (multivariate relative risk, 1.33; 95 percent confidence interval 1.03–1.73). One specific formulation substantially accounted for the excess risk: the relative risk for current use of triphasic preparations with levonorgestrel as the progestin was 3.05 (95 percent confidence interval, 2.00–4.66, P<0.0001).

Conclusions—Current use of oral contraceptives carries an excess risk of breast cancer. Levonorgestrel used in triphasic preparations may account for much of this elevation in risk.

Impact—Different oral contraceptive formulations may convey different risks of breast cancer; ongoing monitoring of these associations is necessary as oral contraceptive formulations change.

Keywords

breast cancer; oral contraceptives; progestins

Substantial data demonstrate little, if any, association between use of oral contraceptives ten or more years in the past and risk of breast cancer (1–2). However, in earlier reports from the prospective Nurses' Health Study (3) and in a pooled analysis of 53,297 cases and 100,239 controls (4–5) mainly from case-control studies conducted in the 1970's and

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1980's, a modest increase in risk was observed among women who were currently using oral contraceptives, or who had stopped using them in the preceding 10 years. However, few studies have examined the relation of newer formulations of oral contraceptives as used in the 1990's with breast cancer risk. A recent large case-control study (6) reported an odds ratio of 0.9 (95 percent confidence interval 0.8–1.0) for past use of more recent oral contraceptive preparations, and no elevation in risk for current use (odds ratio 1.0, 95 percent confidence interval 0.8 to 1.3). However, the upper bound of the confidence interval for current use included the odds ratio from the pooled analysis (odds ratio = 1.24 for current or recent use). A hospital-based case-control study conducted between 1993 and 2007 observed an increased odds ratio for one or more years of oral contraceptive use of 1.5 (95 percent confidence interval 1.2 to 1.8). although this reflected mainly use more than 5 years prior to diagnosis (7).

To provide accurate estimates of any risks associated with more contemporary oral contraceptive formulations, we analyzed data from the Nurses' Health Study II, a study specifically designed to provide prospective data on the association of these oral contraceptives and breast cancer among mainly premenopausal women.

METHODS

STUDY DESIGN

The Nurses' Health Study II is a prospective study of 116,608 female nurses aged 24 to 43 years at enrollment in 1989. Women who reported cancer at baseline (not including nonmelanoma skin cancer) were excluded. Questionnaires are mailed to participants every two years to obtain information on exposure status and the occurrence of breast cancer and other major illnesses. The response rate among living participants was 90% or greater for each biennial questionnaire.

ASSESSMENT OF ORAL CONTRACEPTIVE USE

On the baseline questionnaire, we asked each woman for a detailed lifetime history of her oral contraceptive use. To assist recall of past oral contraceptive use, we provided a structured calendar on which women first recorded, for each year of age (beginning at ≤13), whether they had had a pregnancy (including completed pregnancies, miscarriages, and abortions). Women were then asked to specify for each year of age whether they had used oral contraceptives for a total of ≥2 months, and if so, whether they had used oral contraceptives for ≥10 months in that year (for women reporting > 2 months but <10 months of use in a year, we assigned 6 months of use; for women reporting > 10 months of use we assigned 12 months). We provided a booklet with photographs, names and the pharmacologic contents of all 227 oral contraceptive preparations marketed in the US up to the time of the study. This list was detailed, and included separate codes for 21 versus 28 day pills with the same pharmacologic formulation and dose, and separate codes for different pharmacologic formulations and doses sold under the same brand name. For each year of age at which an oral contraceptive was used for ≥2 months, we asked women to indicate from the booklet which brand was used (and, if multiple brands were used at that age, the brand used the longest). This information was summarized into a time-dependent variable categorizing each woman as a never, past, or current user of any type of oral contraceptive.

On each subsequent biennial questionnaire, we asked each woman whether she was currently using oral contraceptives and for how many months she had used oral contraceptives in the previous two years (precoded response categories were 1 or less months, 2–4, 5–9, 10–14, 15–19, and 20 or more months). We asked each woman to indicate

the brand and type of oral contraceptive used longest during this time period, and we provided a list of brands currently marketed as a memory aid.

To assess the reliability and accuracy of the baseline questionnaire assessment of oral contraceptive use, we conducted telephone interviews with a random sample of 215 participants an average of 11 months after they completed the baseline questionnaire (8). In brief, women were sent a "life events calendar" to review during the interview. Using a structured protocol, the interviewers sought information about reproductive events, life milestones, and changes of address. Women were then asked to identify all periods of contraceptive use, around the framework of these other life events. From a subset of women, we obtained physician records of the contraceptive prescription corresponding to these intervals. Agreement between the two methods for a history of ever having used oral contraceptives was high (exact agreement 99%). Among ever users, reported durations of lifetime use were equivalent (mean duration 42.7 months by telephone interview and 44.6 months by questionnaire), and the Spearman correlation for duration of use calculated from the two methods was 0.94 ($P<0.001$). For the subset of 158 women who gave us permission to obtain oral contraceptive prescription records, the medical record confirmed the use of an identical or equivalent brand in 75% of intervals of reported use, and many of the disagreements were due to minor differences in dose.

IDENTIFICATION OF BREAST CANCER CASES

On each follow-up questionnaire, we asked participants whether they had been diagnosed with breast cancer in the previous two years. Deaths in the cohort are reported by family members and the postal service or are detected by an annual search of the National Death Index. When a case of breast cancer was identified, we asked the participant (or next of kin for those who had died) for confirmation of the diagnosis and permission to seek relevant hospital records and pathology reports. For cases for whom we obtained a pathology report, the self-reported diagnosis of breast cancer was confirmed in 99 percent of the records. After exclusion of cases rejected on the basis of the pathology reports, cases with missing date of diagnosis and cases of carcinoma-in-situ, 1,388 cases of invasive breast cancer were available for analysis. We included 161 cases whose diagnosis was based on self-report only, because the accuracy of self-report was so high. A further 44 cases were excluded because of missing information on current oral contraceptive use, leaving 1,344 cases in the analysis.

STATISTICAL ANALYSIS

We calculated person-time for each participant from the date of return of the baseline questionnaire to the date of diagnosis of breast cancer, death, or June 1, 2001, whichever came first. Relative risks (RRs) and 95% confidence intervals (CIs) for development of breast cancer were estimated using Cox proportional hazards models with age in months and follow-up cycle as the time scale; all P values are two-sided. Current oral contraceptive use was defined according to the use on the questionnaire at the beginning of each two-year cycle of follow-up. If women did not return a questionnaire for a follow-up cycle, their exposure was set to missing, unless they had a prior tubal ligation, hysterectomy, or were postmenopausal, in which case never and past users were carried forward as such. Covariates obtained from the baseline or subsequent questionnaires were used in multivariate analyses, including body mass index (in kg/m^2, <21, 21–22.9, 23–24.9. 25–29.9, ≥30), family history of breast cancer (mother, sister, maternal grandmother, paternal grandmother as separate indicator variables), menopausal status (premenopausal, postmenopausal), history of benign breast disease (yes/no), age at menarche (<12, 12, 13, ≥14), history of irregular menstrual periods (regular, some irregularity, very irregular), current pregnancy, parity (nulliparous, 1,2,3,4,≥ 5), age at first birth (single years from 16 to

41), duration of breastfeeding (never, <1 month., 1–3, 4–6, 7–11, 12–17, 18–23, 24–35, 36–47, ≥48 months), cigarette smoking (never, past, current), animal fat intake (quintiles), alcohol consumption (g/day 0, 1-<4.9, 5–14.9, ≥15), and history of ovulatory infertility (yes/no). These covariates were chosen based on recognized or potential associations between these factors and risk of breast cancer. We estimated the risk associated with five years' use of each formulation by including a linear term for lifetime duration of use in the multivariate models. We also tested for effect modification of the relation of current oral contraceptive use to breast cancer risk by performing analyses stratified by the above covariates, and by including appropriate interaction terms in the multivariate models. The population attributable risk percent was calculated using a standard formula (9). We calculated incidence rates standardized to the age-distribution of women in the cohort. Statistical analysis was performed using SAS statistical software (SAS Institute Inc, Cary, NC).

RESULTS

Baseline characteristics of oral contraceptive users are presented in Table 1. Compared with never and past users, current oral contraceptive users were more likely to be nulliparous, to have no history or a limited duration of breastfeeding, to consume alcohol, and to be non-obese. These variables, along with others, were controlled for in subsequent multivariate analyses.

The association of oral contraceptive use with breast cancer risk is presented in Table 2. After exclusions, we observed 1,344 cases of invasive breast cancer during 1,246,967 person-years of follow-up among 116,413 women. The multivariate relative risk associated with past use was 1.12 (95% percent confidence interval, 0.95–1.33), and among current users the relative risk was significantly elevated (multivariate relative risk, 1.33; 95% confidence interval 1.03–1.73). Among current users, the relative risk was slightly greater with longer duration of use (for 8 or more years use RR = 1.42, 95% confidence interval, 1.05–1.94). Age and other breast cancer risk factors did not appreciably modify the association between current oral contraceptive use and breast cancer. The attributable risk percent associated with current oral contraceptive use was 1.8 percent.

Among current users, we examined the relation between the contraceptive formulations currently used and risk of breast cancer. Due to sparse data, formulations with less than 5,000 person-years of use were collapsed into an "other" category. Compared with never oral contraceptive users the only formulation highly significantly associated with increased risk was triphasic ethinyl estradiol combined with levonorgestrel (multivariate relative risk, 3.05; 95% confidence interval 2.00–4.66) (Table 3). There are two specific brands with this formulation (Tri-Levlen, Triphasil) and both were independently associated with increased risk; the multivariate adjusted RR's for current use were for Tri-Levlen, 2.75 (95 percent confidence interval 1.36–5.59); and for Triphasil, 3.55 (95 percent confidence interval, 2.03–6.21). The multivariate relative risks were 2.79 (95 percent confidence interval 1.69–4.59) for >0-<8 years of use, and 5.21 (95 percent confidence interval 2.13–12.73) for ≥8 or more years of use. When lifetime duration of triphasic formulations combined with levonorgestrel use was considered as a continuous variable the multivariate relative risk associated with five years duration of use was 1.94 (95 percent confidence interval 1.33–2.89). The most commonly used triphasic formulation contains norethindrone as the progestin rather than levonorgestrel, and this was not associated with an increased risk of breast cancer (multivariate relative risk, 0.50; 95 percent confidence interval 0.18–1.35). Non-triphasic formulations using levonorgestrel were not associated with an elevation in risk, but data were sparse. Use of any preparation containing norgestrel was associated with a marginally significant elevation in risk (multivariate relative risk, 1.89; 95 percent confidence interval 1.05–3.41). The attributable risk percent associated with current use of

triphasic ethinyl estradiol combined with levonorgestrel was 1.3 percent. The age-standardized incidence of breast cancer among never users of oral contraceptives in this population was 98/100,000 person-years; among current users of the triphasic ethinyl estradiol combined with levonorgestrel formulation this incidence was 227/100,000 person years. Thus, the excess risk associated with current use of triphasic ethinyl estradiol combined with levonorgestrel formulation among users was 129 cases of invasive breast cancer per 100,000 person-years of use). If users of triphasic ethinyl estradiol combined with levenorgestrel are excluded from current oral contraceptive users, the multivariate relative risk for all other formulations combined was 1.12 (95 percent confidence interval, 0.85–1.49).

Past use of the triphasic ethinyl estradiol combined with levonorgestrel formulation was associated with no apparent elevation in risk for short-term users (multivariate relative risk, 1.24; 95 percent confidence interval, 0.78–1.96 for past users for 1–23 months compared with never users) or among women with ≥ 2 years of past use (multivariate relative risk, 1.19; 95 percent confidence interval, 0.71–2.00). Risk fell with increasing time since cessation of use. With a cutpoint at 4 years (approximately the median time since cessation among cases) the multivariate-adjusted Relative Risks for past use of triphasic ethinyl estradiol combined with levonorgestrel were 1.69 (95 percent confidence interval 1.10–2.60) for ≤ 4 years since cessation, and 0.82 (95 percent confidence interval 0.53–1.27) for ≥ 4 years since cessation, suggesting the increased risk associated with current use is eliminated after 4 years since cessation.

In analyses limited to premenopausal women only, the multivariate-adjusted Relative Risk for current use of oral contraceptives was 1.35 (95% confidence interval 1.05–1.75), and for past use was 1.10 (95% confidence interval 0.94–1.30). Among current users with 8 or more years of use the RR was 1.41 (95%CI 1.03–1.93). In analyses restricted to premenopausal women only, the multivariate-adjusted Relative Risk for current use of oral contraceptives formulated with triphasic ethinyl estradiol combined with levonorgestrel was 3.05 (95% confidence interval 2.00–4.67). These results were essentially unchanged from the overall analyses.

We assessed whether tumor characteristics (tumor size, histology, grade, nodal status, estrogen /progesterone receptor status) were different between current users of monophasic oral contraceptives compared with current users of triphasic formulations combined levonorgestrel. No material differences in these characteristics were apparent. Results of analyses including the 350 incident cases of in-situ breast cancer were similar to the main analyses restricted to invasive breast cancer (multivariate RR for any current oral contraceptive use 1.24 (95 percent confidence interval 0.99–1.57), multivariate RR for current use of triphasic ethinyl estradiol combined with levonorgestrel 3.15 (95 percent confidence interval 1.96–5.07).

DISCUSSION

We found that current use of oral contraceptives was associated with breast cancer risk among women using the formulations commonly prescribed in the 1990's. Our findings also suggest that current use of triphasic preparations containing levonorgestrel as the progestin is associated with higher risk than use of other formulations. Although we found no overall increase in risk with past use of oral contraceptives, an increased risk due to long-term past use of triphasic EE/LNG preparations cannot be excluded and requires further evaluation.

The Collaborative Group on Hormonal Factors in Breast Cancer (4–5) has provided the most comprehensive summary of data on the association of oral contraceptives and breast cancer

risk. This analysis pooled primary data from 53,297 cases and 100,239 controls, mainly from case-control studies conducted in the 1970's and 1980's. A modest increase in risk was observed among women who were currently using oral contraceptives, or who had stopped using them in the preceding 10 years (odds ratio = 1.24, 95 percent confidence interval 1.15–1.33). Consistent with prior meta-analyses (10–11), there was no overall increase in risk of breast cancer 10 years or more after stopping use. A recent prospective study also observed an increased risk among current users at young age (12), and a recent large case-control study confirmed the absence of an association with past use a decade or more after use has ceased (6). Despite the massive data on earlier oral contraceptives preparations, the relation of newer oral contraceptives formulations to risk of breast cancer has not been established. Most oral contraceptive use in the Collaborative analysis was of older formulations (only 11% of cases first used oral contraceptives in 1975 or later); the Collaborative Group concluded "there is still insufficient evidence to comment reliably about the effects of specific types of estrogen or of progestogen." (5) A more recent case-control study conducted between 1990 and 1992, reported an elevation in risk associated with recent oral contraceptive use among women younger than 45 years of age(13). A case-control study conducted on Long Island reported an elevation in risk of premenopausal breast cancer associated with ever use of hormonal birth control(14).

Two recent large case-control studies have provided data on specific oral contraceptive formulations and breast cancer risk. In a population-based case-control study with 4,575 cases aged 35–64 years (the Women's Contraceptive and Reproductive Experiences study) (6), there was no apparent difference in risk between users of low and high estrogen dose preparations. The only type of progestin associated with an elevation in risk among current users was ethynodiol diacetate (odds ratio, 3.5; 95 percent confidence interval 1.1–10.7) based on 15 exposed case subjects; past use of this preparation was not associated with an elevation in risk. No increase in risk was observed for preparations containing levonorgestrel (odds ratio for current use, 0.9; 95 percent confidence interval 0.5–1.5). In an earlier population-based case-control study of 1,640 case subjects aged 20–44 years, Althuius et al. (15) observed significant trends in risk associated with recent use of pills with higher estrogen doses. Recent use of levonorgestrel-containing formulations (odds ratio, 1.7; 95 percent confidence interval, 1.0–2.9) and norethindrone-containing formulations (odds ratio, 1.4; 95 percent confidence interval, 1.0–1.8) were marginally significantly associated with increased breast cancer risk. Odds ratios observed for the less commonly used preparations containing ethynodiol diacetate (odds ratio 1.9; 95 percent confidence interval, 0.9–4.2) and norethindrone acetate (odds ratio 1.9; 95 percent confidence interval, 0.9–3.8) were higher, but not statistically significant. In our study, a striking elevation in risk was present for triphasic levonorgestrel-containing preparations, and the two major brands with this formulation had equivalent relative risks. Neither monophasic preparations with levonorgestrel as the progestin, nor triphasic preparations with norethindrone as the progestin were associated with increased risk. This suggests that the dosage schedule associated with triphasic levonorgestrel use may confer risk, but that use of triphasic preparations with other progestins may not convey this risk. Interestingly, in a study of breast cancer survival among younger women, risk of death was increased if the most recent oral contraceptive used prior to diagnosis included levonorgestrel, but no association was seen for other progestin types (16).

Concern regarding progestins in oral contraceptives has been strengthened by findings in postmenopausal women that the addition of progestin to estrogen greatly increases risk of breast cancer (17–19). Breast cell proliferation assessed by thymidine labeling index is higher in the second half of the menstrual cycle, when progesterone levels are highest (20–21). Analyses of proliferation markers in fine needle aspirate biopsies from healthy women confirm a positive correlation of proliferation with serum progesterone levels on the day of

aspiration (22). Among 26 women who underwent fine needle aspirate biopsies before and after 2 months of oral contraceptive use, proliferation was increased during oral contraceptive use (23). In a randomized trial of 42 women who received one cycle of an oral contraceptive containing 30ug ethinyl estradiol and 150ug levonorgestrel, breast tissue proliferative activity in the first week was increased compared with 40 women undergoing a normal menstrual cycle (24). Among 37 women using oral contraceptives containing levonorgestrel, breast epithelial cell proliferation was significantly positively correlated (Spearman r = 0.43) with serum concentrations of levonorgestrel (23). In animal assays of progestin activity, levonorgestrel is substantially more potent than the other commonly used progestins (25); however, the doses used in oral contraceptives are lower in an attempt to make the progestin action equipotent (26). Levonorgestrel is also the most androgenic of the currently used progestins (27); a positive relation between serum androgens and breast cancer risk was observed in a pooled analysis of data from nested case-control studies (28). In addition to the type and dose of progestin, the pattern or temporal component, whether cyclical or continuous, may also influence breast cancer risk.

Our study has several advantages compared with previous investigations of this issue. Its prospective design, with a high follow-up rate, limits the potential for recall bias or selection bias to influence the relative risks observed. In addition, we documented the validity of our assessment in this population of lifetime oral contraceptive use at baseline in 1989 (29). Furthermore, it seems reasonable to expect that contemporary reporting of the current oral contraceptive brand during follow-up will be even more accurate than the report of past brand use at baseline, as assessed in our validation study.

We also had extensive, prospectively collected, information on other breast cancer risk factors that could confound the relation between oral contraceptive use and breast cancer. Current oral contraceptive users had an increased prevalence of several breast cancer risk factors (nulliparity, limited breast feeding, alcohol consumption, and low BMI) that might modestly confound associations with current use. However, control of these and other factors in multivariate models resulted in very little change between the age-adjusted and multivariate point estimates, suggesting little potential for residual confounding by the covariates we measured.

The major limitation of our study is the relatively small number of cases that occurred among women currently using oral contraceptives because breast cancer incidence rates are low at the ages that most women typically use oral contraceptives. The attributable risk associated with current use was less than two percent, emphasizing that current oral contraceptive use is not a major cause of breast cancer. Even larger prospective studies than ours may be needed to determine precisely the relation between different oral contraceptive formulations and health risks and benefits occurring during actual use of these preparations. Because an association specifically with triphasic preparations containing levonorgestrel was not a prior hypothesis, replication of our findings is desirable.

In summary, we confirmed that the modest increase in risk associated with current use of the oral contraceptives also applies to the formulations in contemporary use. In our study, use of triphasic preparations with levonorgestrel as the progestin was associated with particularly high risk, and these formulations accounted for nearly all of the excess risk.

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Table 1

Age-adjusted proportion of person-years for breast cancer risk factors according to oral contraceptive use, among women followed-up in the Nurses' Health Study II population (n= 116,413 women aged 24–43 years in 1989)

	Oral Contraceptive Use		
	Never (%)	Past (%)	Current (%)
Age at Menarche (yrs):			
<12	24	25	22
13	27	27	28
≥14	19	17	19
Parity:			
None	32	19	38
1	12	17	19
2	29	39	31
3	18	19	9
≥4	9	6	2
Age at first birth (yrs):			
≤24	39	42	38
>30	11	9	12
Family history of breast cancer:			
Yes	7	6	5
Benign breast disease:			
Yes, biopsy confirmed	12	13	8
BMI (kg/m^2):			
<21	21	19	27
21-<23	19	20	24
23-<25	16	17	18
25-<30	21	22	19
≥30	19	17	11
Alcohol intake:			
None	54	44	38
1-<5 g/day	22	24	29
5-<15	11	14	19
≥15 g/day	2	4	4
Animal fat intake (quintiles):			
Quintile 1 (lowest)	17	15	15
Quintile 3	15	15	14
Quintile 5 (highest)	14	15	13
Smoking:			
Never	77	62	71
Past	16	25	20
Current	7	13	9

	Oral Contraceptive Use		
Ovulatory infertility:			
Yes	7	7	3
Menstrual cycle irregularity			
Regular	77	73	72
Very irregular	7	7	7
Total breast feeding duration (months):			
none	13	16	15
<1	4	5	5
4–6	9	11	13
≥12	52	41	36

Table 2

Oral contraceptive use and breast cancer risk in never, past and current oral contraceptive users, Nurses' Health Study II.

	Cases (n=1344)	Person-years (1,246,967)	Age-adjusted RR 95 percent CI	Multivariate RR** 95 percent CI
Never	162	176,581	1.0(ref)	1.0(ref)
Past	1084	952,266	1.10(0.94–1.30)	1.12(0.95–1.33)
Current	98	118,120	1.36(1.06–1.76)	1.33(1.03–1.73)
> 0–8 years*	34	55,333	1.17(0.80–1.70)	1.16(0.80–1.69)
≥8 years*	57	57,899	1.47(1.08–1.99)	1.42(1.05–1.94)

*Seven cases who were current users and 4,888 person-years among current users were missing duration of use.

**Multivariate models control for: age (in months), follow-up cycle, body mass index (in kg/m^2), family history of breast cancer (mother, sister, maternal grandmother, paternal grandmother), menopausal status, history of benign breast disease, age at menarche, history of irregular menstrual periods, current pregnancy, parity, age at first birth, duration of breastfeeding, cigarette smoking, animal fat intake, alcohol consumption and history of ovulatory infertility.

Table 3

Type of progestin formulation among current oral contraceptive users and relative risk of breast cancer compared with never oral contraceptive users, Nurses' Health Study II.

	Person-years	Cases	Age-adjusted RR RR 95% CI	Multivariate* RR RR 95% CI	P
Never OC use	176,581	162	1.00 (ref)	1.00 (ref)	
Current use					
Progestin type					
Norethindrone	27,561	12	0.82 (0.46–1.48)	0.81 (0.45–1.45)	0.47
Triphasic	17,248	4	0.50 (0.19–1.37)	0.50 (0.18–1.35)	0.17
Norethindrone					
Norethindrone acetate	10,744	15	1.39 (0.82–2.37)	1.34 (0.79–2.28)	0.28
Ethynodiol diacetate	5,607	4	1.35 (0.50–3.65)	1.22 (0.45–3.32)	0.70
Triphasic	16,688	26	3.05 (2.00–4.64)	3.05 (2.00–4.66)	<0.0001
Levonorgestrel					
Levonorgestrel	6,662	4	0.87 (0.32–2.35)	0.86 (0.32–2.34)	0.77
Norgestrel	12,025	12	1.85 (1.02–3.33)	1.89 (1.05–3.41)	0.04
Other **	21,584	21	1.31 (0.83–2.07)	1.27 (0.80–2.01)	0.32

* Multivariate model controls for: age (in months), follow-up cycle, body mass index (in kg/m^2), family history of breast cancer (mother, sister, maternal grandmother, paternal grandmother), menopausal status, history of benign breast disease, age at menarche, history of irregular menstrual periods, current pregnancy, parity, age at first birth, duration of breast feeding, cigarette smoking, animal fat intake, alcohol consumption and history of ovulatory infertility.

** "other" includes: norethynodrel, desogestrel, monophasic norgestimate, triphasic norgestimate, medroxyprogesterone, chlormadinone, dimethisterone and unknown brands for current users.