

## Research Article

## 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 from the 1960s to 1980s. 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 ages 25 to 42 years at enrollment in 1989, and subsequently updated this information every 2 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 (RR), 1.12; 95% confidence interval 0.95-1.33]. Current use of any oral contraceptive was related to a marginally significant higher risk (multivariate RR, 1.33; 95% CI, 1.03-1.73). One specific formulation substantially accounted for the excess risk: the RR for current use of triphasic preparations with levonorgestrel as the progestin was 3.05 (95% CI, 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 might convey different risks of breast cancer; ongoing monitoring of these associations is necessary as oral contraceptive formulations change. *Cancer Epidemiol Biomarkers Prev*; 19(10); 2496-502. ©2010 AACR.

## Introduction

Substantial data show little, if any, association between use of oral contraceptives 10 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 (2, 4), mainly from case-control studies conducted in the 1970s and 1980s, 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 1990s with breast cancer risk. A recent large case-control study (5) reported an odds ratio of 0.9

[95% confidence interval (CI), 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% CI, 0.8-1.3). However, the upper bound of the CI 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% CI, 1.2-1.8). Although this mainly reflected use for more than 5 years prior to diagnosis (6).

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.

## Materials and 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 2 years to

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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  $\leq 13$ ), 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  $\geq 2$  months, and if so, whether they had used oral contraceptives for  $\geq 10$  months in that year (for women reporting  $>2$  mo but  $<10$  mo of use in a year, we assigned 6 mo of use; for women reporting  $>10$  mo of use, we assigned 12 mo). We provided a booklet with photographs, names, and the pharmacologic contents of all 227 oral contraceptive preparations marketed in the United States 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  $\geq 2$  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 2 years (precoded response categories were  $\leq 1$ , 2-4, 5-9, 10-14, 15-19, and  $\geq 20$  mo). 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 (7). 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 agree-

ment 99%). Among ever users, reported durations of lifetime use were equivalent (mean duration 42.7 mo by telephone interview and 44.6 mo 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 2 years. Deaths in the cohort were reported by family members and the postal service or were 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 in which we obtained a pathology report, the self-reported diagnosis of breast cancer was confirmed in 99% of the records. After exclusion of cases rejected on the basis of 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. An additional 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 (RR) and 95% CIs (CI) for the 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 2-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 ( $<21$ , 21-22.9, 23-24.9, 25-29.9, or  $\geq 30$  kg/m<sup>2</sup>), family history of breast cancer (mother, sister, maternal grandmother, or paternal grandmother as separate indicator variables), menopausal status (premenopausal or postmenopausal), history of benign breast disease (yes/no), age at menarche ( $<12$ , 12, 13, or  $\geq 14$ ), history of irregular menstrual periods (regular, some irregularity, or very irregular), current pregnancy, parity

(nulliparous, 1, 2, 3, 4, or  $\geq 5$ ), age at first birth (single years from 16 to 41), duration of breast-feeding (never, <1, 1-3, 4-6, 7-11, 12-17, 18-23, 24-35, 36-47, or  $\geq 48$  mo), cigarette smoking (never, past, current), animal fat intake (quintiles), alcohol consumption (0, 1 to <4.9, 5-14.9, or  $\geq 15$  g/d), 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 5 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 of percentage was calculated using a standard formula (8). We calculated incidence rates standardized to the age-distribution of women in the cohort. Statistical analysis was done using SAS statistical software (SAS Institute, Inc.).

## 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 breast-feeding, to consume alcohol, and to be nonobese. 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 RR associated with past use was 1.12 (95% CI, 0.95-1.33), and among current users, the RR was significantly elevated (multivariate RR, 1.33; 95% CI, 1.03-1.73). Among current users, the RR was slightly greater with longer duration of use (for 8 or more years use RR = 1.42; 95% CI, 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 of percentage associated with current oral contraceptive use was 1.8%.

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 RR, 3.05; 95% CI, 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 RRs for current use were for Tri-Levlen, 2.75 (95% CI, 1.36-5.59); and for Triphasil,

**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 y in 1989)

	Oral contraceptive use		
	Never (%)	Past (%)	Current (%)
Age at menarche (y)			
<12	24	25	22
13	27	27	28
$\geq 14$	19	17	19
Parity			
None	32	19	38
1	12	17	19
2	29	39	31
3	18	19	9
$\geq 4$	9	6	2
Age at first birth (y)			
$\leq 24$	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 <sup>2</sup> )			
<21	21	19	27
21 to <23	19	20	24
23 to <25	16	17	18
25 to <30	21	22	19
$\geq 30$	19	17	11
Alcohol intake			
None	54	44	38
1 to <5 g/d	22	24	29
5 to <15	11	14	19
$\geq 15$ g/d	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
Ovulatory infertility			
Yes	7	7	3
Menstrual cycle irregularity			
Regular	77	73	72
Very irregular	7	7	7
Total breast-feeding duration (mo)			
None	13	16	15
<1	4	5	5
4-6	9	11	13
$\geq 12$	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 = 1,344)	Person-years (1,246,967)	Age-adjusted RR (95% CI)	Multivariate RR* (95% CI)
Never	162	176,581	1.0 (reference)	1.0 (reference)
Past	1,084	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 y <sup>†</sup>	34	55,333	1.17 (0.80-1.70)	1.16 (0.80-1.69)
≥8 y <sup>†</sup>	57	57,899	1.47 (1.08-1.99)	1.42 (1.05-1.94)

\*Multivariate models control for age (in months), follow-up cycle, body mass index (in kg/m<sup>2</sup>), family history of breast cancer (mother, sister, maternal grandmother, or 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.

<sup>†</sup>Seven cases who were current users and 4,888 person-years among current users were missing duration of use.

3.55 (95% CI, 2.03-6.21). The multivariate RRs were 2.79 (95% CI, 1.69-4.59) for >0 to <8 years of use, and 5.21 (95% CI, 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 RR associated with 5 months' duration of use was 1.94 (95% CI, 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 RR, 0.50; 95% CI, 0.18-1.35). Nontriphasic formulations us-

ing 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 RR, 1.89; 95% CI, 1.05-3.41). The attributable risk of percentage associated with current use of triphasic ethinyl estradiol combined with levonorgestrel was 1.3%. 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

**Table 3.** Type of progestin formulation among current oral contraceptive users and RR of breast cancer compared with never oral contraceptive users (Nurses' Health Study II)

	Person-years	Cases	Age-adjusted RR (95% CI)	Multivariate* RR (95% CI)	P
Never OC use	176,581	162	1.00 (reference)	1.00 (reference)	
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
Ethinodiol 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 <sup>†</sup>	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<sup>2</sup>), family history of breast cancer (mother, sister, maternal grandmother, or 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.

<sup>†</sup>"Other" includes: norethynodrel, desogestrel, monophasic norgestimate, triphasic norgestimate, medroxyprogesterone, chlormadinone, dimethisterone, and unknown brands for current users.

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 levonorgestrel are excluded from current oral contraceptive users, the multivariate RR for all other formulations combined was 1.12 (95% CI, 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 RR, 1.24; 95% CI, 0.78-1.96 for past users for 1-23 mo compared with never users) or among women with  $\geq 2$  years of past use (multivariate RR, 1.19; 95% CI, 0.71-2.00). Risk decreased with increasing time since cessation of use. With a cutpoint at 4 years (approximately the median time since cessation among cases) the multivariate-adjusted RRs for past use of triphasic ethinyl estradiol combined with levonorgestrel were 1.69 (95% CI, 1.10-2.60) for  $\leq 4$  years since cessation, and 0.82 (95% CI, 0.53-1.27) for  $\geq 4$  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 RR for current use of oral contraceptives was 1.35 (95% CI, 1.05-1.75), and for past use was 1.10 (95% CI, 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 RR for current use of oral contraceptives formulated with triphasic ethinyl estradiol combined with levonorgestrel was 3.05 (95% CI, 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 with 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% CI, 0.99-1.57), multivariate RR for current use of triphasic ethinyl estradiol combined with levonorgestrel was 3.15 (95% CI, 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 1990s. 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 (2, 4) 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 1970s and 1980s. 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% CI, 1.15-1.33). Consistent with prior meta-analyses (9, 10), 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 (11), and a recent large case-control study confirmed the absence of an association with past use a decade or more after use had ceased (5). Despite the massive data on earlier oral contraceptive preparations, the relation of newer oral contraceptive formulations with 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 that "there is still insufficient evidence to comment reliably about the effects of specific types of estrogen or of progestogen" (4). 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 (12). A case-control study conducted in Long Island reported an elevation in risk of premenopausal breast cancer associated with ever use of hormonal birth control (13).

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 ages 35 to 64 years (the Women's Contraceptive and Reproductive Experiences study; ref. 5), 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% CI, 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% CI, 0.5-1.5). In an earlier population-based case-control study of 1,640 case subjects aged 20 to 44 years, Althuis et al. (14) 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% CI, 1.0-2.9) and norethindrone-containing formulations (odds ratio, 1.4; 95% CI, 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%

CI, 0.9-4.2) and norethindrone acetate (odds ratio, 1.9; 95% CI, 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 RRs. 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 might confer risk, but that use of triphasic preparations with other progestins might 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 (15).

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 (16-18). Breast cell proliferation assessed by thymidine labeling index is higher in the second half of the menstrual cycle, when progesterone levels are highest (19, 20). 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 (21). 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 (22). In a randomized trial of 42 women who received one cycle of an oral contraceptive containing 30 µg of ethinyl estradiol and 150 µg of levonorgestrel, breast tissue proliferative activity in the 1st week was increased compared with 40 women undergoing a normal menstrual cycle (23). 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 (22). In animal assays of progestin activity, levonorgestrel is substantially more potent than the other commonly used progestins (24); however, the doses used in oral contraceptives are lower in an attempt to make the progestin action equipotent (25). Levonorgestrel is also the most androgenic of the currently used progestins (26); a positive relation between serum androgens and breast cancer risk was observed in a pooled analysis of data from nested case-control studies (27). 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 RRs observed. In addition, we documented the validity of our assessment in this population of lifetime oral contraceptive use at baseline in 1989 (7). 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 <2%, emphasizing that current oral contraceptive use is not a major cause of breast cancer. Even larger prospective studies than ours might be needed to precisely determine 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.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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## References

- Davidson NE, Helzlsouer KJ. Good news about oral contraceptives. *N Engl J Med* 2002;346:2078–9.
- Collaborative Group on Hormonal Factors in Breast Cancer. 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* 1996;347:1713–27.
- Romieu I, Willett WC, Colditz GA, et al. Prospective study of oral contraceptive use and risk of breast cancer in women. *J Natl Cancer Inst* 1989;81:1313–21.
- Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: further results. *Contraception* 1996;54:1–106S.
- Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. *N Engl J Med* 2002;346:2025–32.
- Rosenberg L, Zhang Y, Coogan PF, Strom BL, Palmer JR. A case-control study of oral contraceptive use and incident breast cancer. *Am J Epidemiol* 2009;169:473–9.
- Hunter DJ, Manson JE, Colditz GA, et al. Reproducibility of oral contraceptive histories and validity of hormone composition reported in a cohort of US women. *Contraception* 1997;56:373–8.
- Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd edition. Philadelphia: Lippincott-Raven Publishers; 1998.
- Romieu I, Berlin JA, Colditz GA. Oral contraceptives and breast cancer: review and meta-analysis. *Cancer* 1990;66:2253–63.
- Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. *Epidemiology* 1993;4:218–28.
- Kumle M, Weiderpass E, Braaten T, Persson I, Adami HO, Lund E. Use of oral contraceptives and breast cancer risk: the Norwegian-Swedish Women's Lifestyle and Health Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2002;11:1375–81.
- Althuis MD, Brogan DD, Coates RJ, et al. Breast cancers among very young premenopausal women (United States). *Cancer Causes Control* 2003;14:151–60.
- Shantakumar S, Terry MB, Paykin A, et al. Age and menopausal effects of hormonal birth control and hormone replacement therapy in relation to breast cancer risk. *Am J Epidemiol* 2007;165:1187–98.
- Althuis MD, Brogan DR, Coates RJ, et al. Hormonal content and potency of oral contraceptives and breast cancer risk among young women. *Br J Cancer* 2003;88:50–7.
- Trivers KF, Gammon MD, Abrahamson PE, et al. Oral contraceptives and survival in breast cancer patients aged 20 to 54 years. *Cancer Epidemiol Biomarkers Prev* 2007;16:1822–7.
- Pike MC, Ross RK. Progestins and menopause: epidemiological studies of risks of endometrial and breast cancer. *Steroids* 2000;65:659–64.
- Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000;283:485–91.
- Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol* 2000;152:950–64.
- Anderson TJ, Battersby S, King RJ, McPherson K, Going JJ. Oral contraceptive use influences resting breast proliferation. *Hum Pathol* 1989;20:1139–44.
- Spicer DV, Pike MC. Sex steroids and breast cancer prevention. *J Natl Cancer Inst Monogr* 1994:139–47.
- Soderqvist G, Isaksson E, von Schoultz B, Carlstrom K, Tani E, Skoog L. Proliferation of breast epithelial cells in healthy women during the menstrual cycle. *Am J Obstet Gynecol* 1997;176:123–8.
- Isaksson E, von Schoultz E, Odland V, et al. Effects of oral contraceptives on breast epithelial proliferation. *Breast Cancer Res Treat* 2001;65:163–9.
- Garcia y Narvaiza D, Navarrete MA, Falzoni R, Maier CM, Nazario AC. Effect of combined oral contraceptives on breast epithelial proliferation in young women. *Breast J* 2008;14:450–5.
- Dorflinger LJ. Relative potency of progestins used in oral contraceptives. *Contraception* 1985;31:557–70.
- Collins DC. Sex hormone receptor binding, progestin selectivity, and the new oral contraceptives. *Am J Obstet Gynecol* 1994;170:1508–13.
- Phillips A, Hahn DW, Klimek S, McGuire JL. A comparison of the potencies and activities of progestogens used in contraceptives. *Contraception* 1987;36:181–92.
- Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst* 2002;94:606–16.

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