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Original Contribution

A Case-Control Study of Oral Contraceptive Use and Incident Breast Cancer

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Oral contraceptive (OC) use has been linked to increased risk of breast cancer, largely on the basis of studies conducted before 1990. In the Case-Control Surveillance Study, a US hospital-based case-control study of medication use and cancer, the authors assessed the relation of OC use to breast cancer risk among 907 case women with incident invasive breast cancer (731 white, 176 black) and 1,711 controls (1,152 white, 559 black) interviewed from 1993 to 2007. They evaluated whether the association differed by ethnicity or tumor hormone receptor status. After control for breast cancer risk factors, the multivariable odds ratio for 1 year or more of OC use, relative to less than 1 year of use, was 1.5 (95% confidence interval: 1.2, 1.8). The estimates were similar within age strata ($<$50 years and $\geq$50 years). The odds ratios were larger for use within the previous 10 years, long-duration use, and black ethnicity, but these differences were not statistically significant. The association of OC use with breast cancer risk did not differ according to the estrogen or progestogen receptor status of the tumor. These results suggest that OC use is associated with an increased risk of breast cancer diagnosed in recent years.

breast neoplasms; case-control studies; contraceptives, oral

Abbreviations: CARE, Contraceptive and Reproductive Experiences; CI, confidence interval; ER, estrogen receptor; OC(s), oral contraceptive(s); PR, progestogen receptor.

Oral contraceptive (OC) use has been associated with an increased incidence of breast cancer. In a 1996 combined analysis of data from 54 studies that included approximately 53,000 breast cancer patients and approximately 100,000 unaffected women, current OC use was associated with a 25% increase in breast cancer risk (1, 2). By approximately 10 years after use had ended, the increased risk had dissipated. Risk increased with increasing duration of use, but the trend was not statistically significant. New OC preparations with lower doses of estrogen and progestin and new types of progestins have been introduced since OCs were first marketed in the early 1960s (3–6). For example, by the mid-1970s, about half of OC prescriptions were for formulations with 50 μg of estrogen or less, and all current preparations contain 50 μg or less; many contain less than 35 μg (5, 6). Women with recently diagnosed breast cancer will have used different preparations from those used by women in the more distant past. Research that has included women studied since the 1996 combined analysis has yielded mixed results (7–13), and it is not clear whether OC use affects breast cancer risk among women diagnosed in recent years. It is also unclear whether an effect differs by ethnic group. Most studies have focused on white women; among the 5 studies that evaluated black women separately (9, 10, 14–16), 3 observed effect estimates that were greater for black women than for white women (14, 17, 18). With regard to the hormone status of the tumor, 3 studies have found stronger associations of OC use with estrogen receptor-negative cancer than with estrogen receptor-positive cancer (13, 19, 20), but others have found no difference (21–26).

We have reported positive associations between OC use and breast cancer risk among white women (27) and black women (14) on the basis of data collected through 1992 in the Case-Control Surveillance Study. In the present analysis, we assessed whether OC use was associated with increased risk of breast cancer among women diagnosed after 1992. We also assessed whether the association differed between

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white women and black women and according to the hormone receptor status of the tumor.

MATERIALS AND METHODS

In the Case-Control Surveillance Study, which focused on the relation of medication use to cancer, patients were interviewed in participating hospitals in Boston, Massachusetts; Philadelphia, Pennsylvania; Baltimore, Maryland; and New York, New York, beginning in 1976. Interviewing ended in 1987 in Boston, in 1993 in New York, and in 1996 in Baltimore, whereas interviews were conducted in Philadelphia throughout the course of the study. The institutional review boards of Boston University and of each participating hospital approved the study, and the participants provided written consent.

Our nurse-interviewers inspected ward logs and admission lists to identify patients with diagnoses of interest whose physicians gave permission for them to be approached. The interviewers administered questionnaires to patients with recently diagnosed cancer and patients admitted for nonmalignant conditions (potential controls) to obtain information on demographic factors, medical and reproductive history, weight, height, and other variables. Only patients living within a 50-mile (80-km) radius of the hospital were included. Information on lifetime history of medication use was obtained by asking about 43 indications that included oral contraception. For each episode of use, the name of the medication, the starting date, and the duration of use were recorded. We obtained pathology reports for patients admitted for cancer and discharge summaries for all patients. The participation rate of patients approached was 90% before 1998 and 82% during and after 1998.

The present analyses included patients interviewed from 1993 through 2007 in participating hospitals in Baltimore, New York, and Philadelphia. Eligible cases were 921 white and black women aged 25–69 years with invasive breast cancer diagnosed within the previous year who had had no other cancer besides nonmelanoma skin cancer. We excluded 14 women with missing values for duration or timing of OC use, which left 907 cases. Controls were selected from 2,330 white and black women aged 25–69 years with no history of cancer, other than nonmelanoma skin cancer, who had been admitted for nonmalignant diagnoses that we judged to be unrelated to OC use (musculoskeletal disorders, such as ruptured discs and fractures ($n = 647$); acute infections ($n = 622$); and hernias, kidney stones, gallstones, and skin conditions ($n = 442$)). We did not include patients admitted for nonmalignant illnesses that are possibly caused or prevented by OC use, such as cardiovascular disease or endometriosis (28). Because OC use can cause cardiovascular disease (29), the prevalence of OC use among patients admitted for cardiovascular disease might overestimate OC use in the source population from which the cases were derived. Similarly, because OC use can prevent endometriosis (30), the prevalence of OC use in patients admitted for endometriosis might underestimate OC use in the source population. After exclusion of women with missing values for the duration or timing of OC use, a pool of 2,300 potential controls remained. We frequency-matched up to 4 controls per case on ethnicity (white or black), age, year of interview, and study center. The final case and control groups consisted of 907 cases (731 white, 176 black) and 1,711 controls (1,152 white, 559 black).

The indications that elicited OC use were vaginal discharge, regulation of menstrual periods, menstrual problems, oral contraception, endometriosis, and menopause; contraception was the reason for 96% of reported use. The use of hormonal contraceptives other than OCs—estrogen/progestin patches, progestin injections, vaginal rings, and progestin intrauterine devices—was uncommon. They were reported by only 5 cases and 11 controls in the present study sample, and these forms of contraception were not considered in the analyses. Among the controls, the age-adjusted prevalence of OC use for at least 1 year was 42%, 38%, and 45% in women admitted for musculoskeletal disorders, infections, and other conditions, respectively; the corresponding prevalences were 20%, 18%, and 23% for OC use for 5 or more years and 9%, 8%, and 11% for OC use within the 10 years before interview.

We used unconditional logistic regression analysis to estimate odds ratios for various categories of OC use relative to use for less than 1 year (never use combined with use that lasted less than 1 year), with control for the following potential confounders: age, ethnicity, interview year, study site, body mass index (weight (kg)/height $(m)^2$), breast cancer in a mother or sister, parity, age at first birth, age at menopause, duration of female hormone use, cigarette smoking, alcohol use, and years of education. We tested for trend among OC users across categories of duration of use by including an indicator term coded as the midpoint of each category; the same test was used across categories of time interval since last use. We tested for modification of an OC effect by ethnicity by including an interaction term for ethnicity $\times$ OC use in the logistic regression.

RESULTS

The median age of cases was 50 years, and 84% had been interviewed in Philadelphia. Corresponding figures among the controls were 48 years and 83%.

Table 1 gives odds ratios for categories of duration of OC use and interval since last use, relative to less than 1 year of use. The odds ratios adjusted for the matching factors only—age, interview year, ethnicity, and study site—were closely similar to the multivariable estimates. For OC use of 1 year or more relative to less than 1 year of use, the multivariable estimate was 1.5 (95% confidence interval (CI): 1.2, 1.8). The odds ratio increased as duration of use increased (P for trend $= 0.06$), and the odds ratio estimate for 15 or more years of use was 1.7 (95% CI: 1.0, 2.9). There was no clear trend in the odds ratios across increasing interval since last use (P for trend $= 0.13$); the odds ratio was highest (odds ratio $= 2.7$, 95% CI: 1.7, 4.5) for use that had ended 5–9 years previously, but it was 1.4 both for use that ended less than 5 years previously and use that ended 15 or more years previously.

Table 1. Odds Ratio for Invasive Breast Cancer According to Duration of Oral Contraceptive Use and Interval Since Last Use, Case-Control Surveillance Study, 1993–2007

Oral Contraceptive Use	No. of Cases	No. of Controls	OR Adjusted for Matching Factors[a]	95% CI	Multivariable OR[b]	95% CI
Nonuse or <1 year of use	430	1,001	1.0	Referent	1.0	Referent
Duration of use, years						
1–4	209	374	1.3	1.1, 1.7	1.3	1.0, 1.6
5–9	143	201	1.8	1.4, 2.4	1.6	1.2, 2.1
10–14	94	99	2.4	1.7, 3.3	1.9	1.4, 2.7
≥15	31	36	1.9	1.1, 3.2	1.7	1.0, 2.9
P for trend					0.06	
Interval since last use, years						
<5	71	118	1.8	1.3, 2.6	1.4	1.0, 2.1
5–9	46	44	3.0	1.9, 4.9	2.7	1.7, 4.5
10–14	61	86	2.1	1.4, 3.0	1.9	1.3, 2.8
≥15	299	462	1.5	1.2, 1.8	1.4	1.1, 1.7
P for trend					0.13	

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Age, interview year, ethnicity, and geographic area.
[b] Controlled for age, interview year, ethnicity, study site, history of breast cancer in a mother or sister, body mass index, age at menarche, parity, alcohol use, smoking, years of education, age at first birth, age at menopause, and female hormone use.

We reassessed the relations of duration of OC use and interval since last use to breast cancer risk in analyses confined to the study site from which most patients were drawn: Philadelphia. The results were closely similar to those given in Table 1 for the entire study sample. Based on the 763 cases and 1,416 controls from Philadelphia, the multivariable odds ratios for durations of use of 1–4, 5–9, 10–14, and ≥15 years were 1.4 (95% CI: 1.1, 1.7), 1.6 (95% CI: 1.2, 2.2), 2.0 (95% CI: 1.3, 2.9), and 1.7 (95% CI: 1.0, 3.1), respectively. The multivariable odds ratios for intervals since last use of <5, 5–9, 10–15, and ≥15 years were 1.5 (95% CI: 1.0, 2.3), 2.9 (95% CI: 1.7, 4.9), 1.9 (95% CI: 1.2, 2.9), and 1.4 (95% CI: 1.1, 1.8), respectively. Six of the study hospitals in Philadelphia were teaching hospitals, 1 was a community hospital, and 1 was a cancer treatment hospital. Analyses conducted after excluding 273 patients from the latter 2 hospitals were similar to those for the entire Philadelphia sample. All further results given are based on the entire sample from Philadelphia, New York, and Baltimore.

As Table 2 shows, odds ratios for OC use were increased among both women aged less than 50 years and women aged 50 years or more. The multivariable odds ratio for at least 1 year of OC use relative to less than 1 year of use was 1.6 (95% CI: 1.2, 2.0) among women under age 50 years and 1.4 (95% CI: 1.1, 0.8) among women aged 50 years or more.

The multivariable odds ratio for 1 year or more of OC use was 1.8 (95% CI: 1.2, 2.6) among black women and 1.4 (95% CI: 1.1, 1.7) among white women; a test for interaction of OC use with ethnic group yielded a *P* value of 0.23. Table 3 provides data on duration of OC use and interval since last use in relation to breast cancer risk, separately in white and black women. For every category of OC use, the odds ratio was greater among black women than among white women. In both groups, there was a tendency for the odds ratio to increase as the duration of use increased and to decrease as the interval since last use increased, but none of the trends were statistically significant.

We assessed OC use for 1 year or more relative to use for less than 1 year according to estrogen receptor (ER)/progestogen receptor (PR) status in a comparison of 571 cases of breast cancer for whom we had information on ER and PR status with all controls. The multivariable odds ratio for OC use for the entire group of cases was 1.7 (95% CI: 1.4, 2.1). As Table 4 shows, odds ratios for the hormone receptor case groups varied from 1.6 to 1.9. The odds ratio was 1.7 (95% CI: 1.2, 2.3) for ER-negative tumors and 1.7 (95% CI: 1.3, 2.2) for ER-positive tumors.

DISCUSSION

Over the years since OCs were first marketed in the early 1960s, pharmaceutical manufacturers have lowered the doses of estrogens and progestins (3–6) in the hope of reducing adverse effects. However, use of lower-dose preparations was not associated with lower risk of breast cancer in a combined analysis of 54 studies (1, 2). If anything, the effect estimates were higher for lower-dose OC use, but the differences in estimates according to dose or time period, which correlates with dose, were not statistically significant.

Table 2. Odds Ratio for Invasive Breast Cancer According to Age Group, Duration of Oral Contraceptive Use, and Interval Since Last Use, Case-Control Surveillance Study, 1993–2007

Oral Contraceptive Use	No. of Cases	No. of Controls	Multivariable Odds Ratio[a]	95% Confidence Interval
Age <50 Years				
Nonuse or <1 year of use	154	476	1.0	Referent
Duration of use, years				
1–4	112	245	1.3	1.0, 1.8
5–9	95	127	1.9	1.3, 2.7
10–14	55	67	1.8	1.1, 2.8
≥15	15	24	1.3	0.6, 2.7
P for trend			0.23	
Interval since last use, years				
<5	63	111	1.3	0.8, 1.9
5–9	41	40	2.7	1.5, 4.6
10–14	53	75	2.1	1.3, 3.2
≥15	120	237	1.3	0.9, 1.8
P for trend			0.85	
Age ≥50 Years				
Nonuse or <1 year of use	276	525	1.0	Referent
Duration of use, years				
1–4	97	129	1.3	0.9, 1.8
5–9	48	74	1.3	0.8, 2.0
10–14	39	32	2.0	1.2, 3.5
≥15	16	12	2.4	1.0, 5.5
P for trend			0.09	
Interval since last use, years				
<10	13	11	2.3	0.9, 5.6
10–14	8	11	1.2	0.4, 3.1
≥15	179	225	1.4	1.1, 1.9
P for trend			0.01	

[a] Controlled for age, interview year, ethnicity, study site, history of breast cancer in a mother or sister, body mass index, age at menarche, parity, alcohol use, smoking, years of education, age at first birth, age at menopause, and female hormone use.

Table 3. Odds Ratio for Invasive Breast Cancer According to Ethnicity, Duration of Oral Contraceptive Use, and Interval Since Last Use, Case-Control Surveillance Study, 1993–2007

Oral Contraceptive Use	No. of Cases	No. of Controls	Multivariable Odds Ratio[a]	95% Confidence Interval
Blacks				
Nonuse or <1 year of use	83	347	1.0	Referent
Duration of use, years				
1–4	34	107	1.3	0.8, 2.1
5–9	34	67	2.3	1.3, 3.9
≥10	25	38	2.5	1.3, 4.7
P for trend			0.15	
Years since last use				
1–4	16	19	3.5	1.5, 8.1
5–9	7	7	5.3	1.6, 17.4
10–14	13	31	1.9	0.9, 4.2
≥15	57	155	1.5	1.0, 2.4
P for trend			0.20	
Whites				
Nonuse or <1 year of use	347	654	1.0	Referent
Duration of use, years				
1–4	175	267	1.3	1.0, 1.7
5–9	109	134	1.4	1.0, 1.9
10–14	75	69	1.8	1.2, 2.6
≥15	25	28	1.4	0.8, 2.6
P for trend			0.28	
Years since last use				
1–4	55	99	1.1	0.7, 1.7
5–9	39	37	2.3	1.3, 4.0
10–14	48	55	1.8	1.2, 2.9
≥15	242	307	1.3	1.0, 1.7
P for trend			0.37	

[a] Controlled for age, interview year, study site, history of breast cancer in a mother or sister, body mass index, age at menarche, parity, alcohol use, smoking, years of education, age at first birth, age at menopause, and female hormone use.

OC users in recent studies will have taken lower doses of estrogen and progestin than women included in early studies. In the present analyses of women diagnosed with breast cancer after 1992, we found a positive association of OC use with increased breast cancer risk, and it was present among both younger and older women. Results from other reports based on women studied after the early 1990s have been inconsistent. In a follow-up study of Norwegian women, the relative risk estimate was 1.6 (95% CI: 1.2, 2.1) for women who were current or recent OC users at baseline (7). In a follow-up study in the Netherlands, long-duration OC use was associated with increased breast cancer risk among women aged 55 years or older but not younger women (12). In a Long Island case-control study of breast cancer, recent OC use and long-duration OC use were associated with increased breast cancer risk among premenopausal women but not among postmenopausal women (11). In the population-based Carolina Breast Cancer Study, results were close to the null for white women, but OC use within the previous 5 years was associated with increased risk among black women (9). In a population-based breast cancer study conducted in Los Angeles, California, results for OC use were

Table 4. Odds Ratio for Invasive Breast Cancer According to Hormone Receptor Status of the Tumor, Case-Control Surveillance Study, 1993–2007

Disease Status and Hormone Receptor Status	No. of Participants		Multivariable Odds Ratio[a]	95% Confidence Interval
	≥1 Year of OC Use	Nonuse or <1 Year of OC Use		
Controls	710	1,001	1.0	Referent
All cases[b]	328	243	1.7	1.4, 2.1
ER+	209	160	1.7	1.3, 2.2
ER−	119	82	1.7	1.2, 2.3
PR+	179	136	1.7	1.2, 2.2
PR−	147	103	1.7	1.3, 2.3
ER+, PR+	167	127	1.6	1.2, 2.2
ER+, PR−	40	30	1.9	1.1, 3.2
ER−, PR+	12	8	1.9	0.7, 5.2
ER−, PR−	107	73	1.7	1.2, 2.4

Abbreviations: ER+, estrogen receptor-positive; ER−, estrogen-receptor-negative; OC, oral contraceptive; PR+, progestogen receptor-positive; PR−, progestogen receptor-negative.

[a] Controlled for age, interview year, ethnicity, study site, history of breast cancer in a mother or sister, body mass index, age at menarche, parity, alcohol use, smoking, years of education, age at first birth, age at menopause, and female hormone use.

[b] Cases with available information on ER or PR receptor status.

null (13). Results from the largest population-based case-control study, the Women's Contraceptive and Reproductive Experiences (CARE) Study, which included 4,575 cases and 4,682 controls, were largely null (10).

Numbers were sufficient in the CARE Study to informatively assess associations of duration of OC use and interval since last use with breast cancer risk according to menopausal status, age, and ethnic group (white or black), and there were no associations with increased breast cancer risk. Similarly, there were no differences according to dose of estrogen or type of progestin in the OC formulation. The only significant differences were by study site. Subjects were drawn from Atlanta, Georgia (19%), Detroit, Michigan (16%), Los Angeles, California (27%), Philadelphia, Pennsylvania (16%), and Seattle, Washington (22%). Odds ratios for ever use of OCs were 0.7, 0.7, 1.0, 1.0, and 1.1, respectively, and 95% confidence intervals for the first 2 estimates excluded 1.0 (10). For current OC use (within the 6 months before the index date), the estimates were 0.8, 0.4, 1.4, 1.7, and 1.2, respectively, and the 95% confidence interval for Detroit excluded 1.0. The authors were not able to explain the discrepancies according to study site and noted that relative risks for a variety of other factors, such as hormone replacement therapy, were consistent across sites.

If an effect of OC use on breast cancer risk is relatively small, one would expect variability of results among studies and within studies, and if recent OC use is more strongly related to risk than more distant use, an association might be weaker or absent among older women or postmenopausal women because of the scarcity of recent users. However, small effects would not be an explanation for the generally null results of the CARE Study, which had excellent power to detect small increases in risk associated with recent and long-duration OC use.

The odds ratios for the association of OC use with breast cancer risk in the present study were larger for black women than for white women, and breast cancer risk in black women decreased with increasing interval since last use and increased with increasing duration of use. However, the number of cases among black women was small, and none of these findings were statistically significant. In the population-based Cancer and Steroid Hormone Study, conducted from 1980 to 1982, there was a suggestion of increasing breast cancer risk with increasing duration of OC use among black women but not among white women (16); recency of use was not assessed. In the Women's Interview Study of Health, a population-based case-control study conducted from 1990 to 1992, breast cancer risk increased with increasing duration of use among black women but not among white women (15). Again, recency of use was not assessed. In the Carolina Breast Cancer Study, there was a significant trend of increasing risk with decreasing interval since last use among black women but not among white women (9). There was also a suggestion of a tendency for breast cancer risk to increase as duration of use increased among black women. Thus, our present findings are consistent with results from several other studies and with findings from our earlier data (14, 27). However, contrary to this evidence, no increases in risk were observed among black or white OC users in the CARE Study, which was based on large numbers of black and white cases (1,622 and 2,953, respectively) (10).

We found no evidence that the association of breast cancer risk with OC use differed according to the ER or PR status of the tumor, in agreement with several previous studies (21–25). However, stronger associations with ER-negative tumors than with ER-positive tumors were found among women under age 35 years in the Women's Interview Study of Health (19), in a case-control study conducted in Australia (20), and in a case-case study conducted in Los Angeles (13). The prevalence of ER-negative tumors is greater in black women than in white women (31), so a stronger association of OC use with ER-negative tumors than with ER-positive tumors would be particularly important for black women. In the present study, numbers were too small to assess OC use in relation to tumor ER/PR status among black women specifically, and to our knowledge no other studies have published informative data on this question.

Selection bias is a particular concern in the present study. The overall participation rate of targeted subjects in the Case-Control Surveillance Study was high, but we could not assess the participation rate specifically among patients with the diagnoses included in the present analyses, because we did not record the diagnoses of people who refused participation. Selective referral of cases and controls (contingent on OC use) to the participating hospitals, which were a mix of teaching/research, cancer, and community hospitals, could have been a source of bias. To reduce the possibility of referral bias, we included in the study only women who lived within a 50-mile radius of the hospital. While we

believe that this restriction is likely to have reduced referral bias, we are unable to demonstrate that this was the case. As a further guard against selection bias, we confined the control series to women with diagnoses unrelated to OC use. The prevalence of use was uniform across the various diagnostic categories, suggesting that the selection of controls was appropriate (28).

All case-control studies based on interview are subject to reporting bias. Our inquiries about contraception were made in the context of questions about 43 indications for medication use in a study of many cancers, which masked the present hypothesis from participants and interviewers. On the other hand, because the goal of the Case-Control Surveillance Study was to assess a wide range of medications, not just OCs, the interviewers were not able to spend the amount of time that would have been necessary to elicit the most detailed information possible about OC use, nor did they use pictures or packets of OC pills marketed over the years to aid recall. Validation studies indicate that women are able to recall the duration of OC use accurately, with correlation coefficients exceeding 0.8 in some studies, but that recall of the formulation used is appreciably less accurate (32). In the present study, women did not report the name of the preparation for 46% of their episodes of OC use, and they could not remember the exact dose of the components for an additional 11%. Thus, the inability to assess specific types of OC preparations is a limitation of the present study. However, younger women would probably have used lower-dose OCs than older women (3–6), and we found similar and significantly increased odds ratios for OC use among women aged less than 50 years and women aged 50 years or more.

If OC users were more likely to undergo mammography and have their tumors detected, this could have contributed to positive associations with OC use. We lacked data on mammography use, but we did limit the analyses to invasive tumors. Major risk factors for breast cancer were controlled in the analysis.

Previous research based on data from the Case-Control Surveillance Study has found inverse associations of OC use with risk of endometrial cancer (33) and ovarian cancer (34, 35) and a positive association with liver cancer (36), in agreement with the literature (37, 38). Results on breast cancer risk factors based on the data from the Case-Control Surveillance Study (39–43) are similar to findings from other studies (44–48). Agreement between these findings supports the validity of the methods and data in the Case-Control Surveillance Study, but complete reassurance about the present results will require confirmation by other studies.

In summary, the present findings suggest that OC use is associated with an increased risk of breast cancer diagnosed in recent years. The data are compatible with a stronger association in black women than in white women and with a contribution of duration of use to risk, especially among black women, but the observed differences in risk by ethnic group or duration were not statistically significant. There were no differences according to hormone receptor status of the tumor. Given the widespread use of OCs, continued evaluation of their possible health effects may be warranted.

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