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Research Article

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Oral Contraceptive Use and Survival in Women with Invasive Breast Cancer

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Abstract

Background: Oral contraceptives (OC) are widely used in the United States. Although the relation between OC use and breast cancer incidence has been widely studied, the few studies examining associations between OC use prior to breast cancer diagnosis and survival are inconsistent.

Methods: Women with invasive breast cancer participating in the Women's Contraceptive and Reproductive Experiences (CARE) Study, a population-based case–control study (4565 women ages 35–64 years), and the California Teachers Study (CTS) cohort (3929 women ages 28–91 years) were followed for vital status. A total of 1,064 women died in the CARE Study (median follow-up, 8.6 years) and 523 died in the CTS (median follow-up, 6.1 years). Cox proportional hazards regression provided hazard rate ratio estimates [(relative risk, RR)] with 95% confidence intervals (CIs) for risk of death from any cause and from breast cancer.

Results: No association was observed for any OC use prior to diagnosis and all-cause mortality [CARE Study: RR = 1.01 (95% CI = 0.86–1.19); CTS: RR = 0.84 (95% CI = 0.67–1.05)]. A decreased risk of all-cause mortality was observed in the CTS among women with more than 10 years of OC use (RR = 0.67, 95% CI = 0.47–0.96); however, no trend of decreasing risk with increasing OC duration was observed ($P_{trend} = 0.22$), and no association was observed in the CARE study. No associations were observed for breast cancer-specific mortality.

Conclusions: OC use is not associated with all-cause or breast cancer-specific mortality among women with invasive breast cancer.

Impact: These 2 independent studies demonstrated no overall association between OC use and survival among women with breast cancer. *Cancer Epidemiol Biomarkers Prev; 20(7); 1391–7. ©2011 AACR.*

Introduction

Oral contraceptives (OC) are widely used by women during their reproductive years. Between 2006 and 2008, 82% (43.8 million) U.S. women aged 15 to 44 years used OCs (1). The effect of OCs on breast cancer incidence has been extensively examined and the best data available suggest that OCs have no association with breast cancer risk or slightly increase risk in women who currently use OCs or have used them in the previous few years (2, 3). Among women with breast cancer, whether OC use before diagnosis increases the risk of death is largely unknown. Postmenopausal hormone therapy, particularly estrogen plus progestin, has been suggested to increase the breast cancer mortality (4). Given OCs are also combinations of estrogen and progestin, it is conceivable that OC use might affect disease prognosis after diagnosis.

To examine the association between OC use and survival among breast cancer patients, we employed 2 large epidemiologic studies which used different designs, the Women's Contraceptive and Reproductive Experiences (CARE) Study and the California Teachers Study (CTS).

Materials and Methods

Study population

The Women's CARE Study. A detailed description of the Women's CARE Study, a population-based multicenter breast cancer case–control study, has been published elsewhere (3). Briefly, 1622 (72.2% of eligible) black

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women and 2953 (79.1% of eligible) white women aged 35 to 64 years, diagnosed with histologically confirmed incident invasive breast cancer [International Classification of Diseases for Oncology (ICD-O) codes C50.0–C50.9] were recruited from 5 field sites (Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle) from July 1994 through April 1998. Shortly after breast cancer diagnosis (average: 5.1 months), trained staff administered standardized in-person interviews to collect detailed information on exposures prior to breast cancer diagnosis, including demographic characteristics, medical and reproductive history, OC use, menopausal hormonal therapy (MHT), mammography use, and histories of recreational physical activity, smoking, and alcohol consumption. The Women's CARE Study protocol was approved by the institutional review board of each participating institution.

We abstracted tumor stage at diagnosis, estrogen receptor (ER), and progesterone receptor (PR) status from Surveillance, Epidemiology and End Results (SEER) registry records at the 4 SEER sites (Atlanta, Detroit, Los Angeles and Seattle) and directly from medical records in Philadelphia.

The participants were followed annually for vital status, date of death and cause of death. Patients from the Atlanta, Detroit, and Seattle study sites were followed through December 31, 2004; follow-up extended through December, 2005 in Philadelphia and through December, 2007 in Los Angeles. The 4 SEER-based field sites used standard SEER follow-up procedures. The Philadelphia field site used state death records to track vital status.

The present analysis excluded 10 women who were lost to follow-up ($n = 2$), or had missing information on duration of OC use ($n = 8$). Thus, this analytical cohort consisted of 4,565 women (1,619 blacks and 2,946 whites) with breast cancer.

The CTS. Detailed information on the CTS has been described elsewhere (5). This cohort study enrolled 133,479 female public school professionals in 1995. Use of human subjects in this study was approved by institutional review boards at each participating institution.

Women were considered eligible for this analysis if they were California residents at baseline and had an incident invasive breast cancer (ICD-O codes C50.0–C50.9) identified through the California Cancer Registry (CCR) from 1995, after joining the cohort, through December 2006.

All participants completed a detailed, self-administered baseline questionnaire that queried information on demographic factors, menstrual and reproductive events, family and personal history of cancer and other diseases, OC and MHT use, and lifestyle factors before cohort entry. We abstracted tumor stage at diagnosis, ER and PR status from CCR records.

All participants were followed through December 31, 2007. Information on dates and causes of death was obtained from the California State mortality files, the Social Security Administration death master files, and the National Death Index. Through December 31, 2006, 4,269 women were diagnosed with first incident invasive breast cancer. Women who were diagnosed between January 1, 2007 and December 31, 2007 were not included in this analysis to ensure that all patients had the opportunity for at least 1 year of follow-up after diagnosis.

We sequentially excluded breast cancer patients who did not report OC use information on the baseline questionnaire ($n = 168$), or were older than 45 years when OCs were first on market in 1961 ($n = 172$).The CTS analytical cohort consisted of 3,929 women.

Statistical analysis

To make the results comparable between studies, we created the similar OC use variables for both studies. Our endpoints were death from any cause and death from breast cancer (ICD codes ICD9–174, ICD10–C50). Multivariable Cox proportional hazards regression models provided estimates of the hazard rate ratio, a measurement of relative risk (RR), and 95% confidence intervals (CIs). Age in days at diagnosis and age in days at death or end of follow-up defined the time scale for analysis. In the analyses of breast cancer-specific mortality, women who died from other causes were censored on their dates of death.

All statistical models were stratified by age in years at diagnosis. Based on prior knowledge and their independent associations with survival in our data, similar potential confounders were included in both analyses. For the Women's CARE study, all models were adjusted for study site (Atlanta, Detroit, Los Angeles, Philadelphia, or Seattle), race (black, white), education (less than high school, high school, some college, college graduate), tumor stage (localized, nonlocalized), ER status (positive, negative, unknown), number of comorbidities before breast cancer diagnosis (0, 1, ≥2), average drinks each week of alcohol since age 15 (nondrinker, <1.0, 1.0–2.0, 2.1–4.5, >4.5, unknown), smoking history (never, former, current), number of mammograms within the 5 years before breast cancer diagnosis (never, 1, 2–3, ≥4, unknown), body mass index (BMI, kg/m^2) 5 years before breast cancer diagnosis (<20, 20–24.9, 25–29.9, ≥30 kg/m^2, unknown) and age at menarche (<12, 12, 13, >13 years). CTS models were adjusted for race (white, other), residential neighborhood-level socioeconomic status (6) (lowest quartile, second, third, highest quartile, unknown), tumor stage (localized, nonlocalized), ER status (positive, negative, unknown), and baseline reports of number of comorbidities before breast cancer diagnosis (0, 1, ≥2), level of alcohol consumption (nondrinker, <15, ≥15 g/d), smoking history (never, former, current smoker), years since last mammogram (never had one, <1 years ago, 1–2 years ago, ≥3 years ago, unknown years ago, missing information), BMI (<20, 20–24.9, 25–29.9, ≥30 kg/m^2, unknown) and age at menarche (<12, 12, >12 years, missing, never had menarche). Comorbidities included hypertension, myocardial infarction, stroke, diabetes, and cancers other than nonmelanoma skin

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Table 1. Distribution of selected characteristics of breast cancer patients according to OC use status in the Women's CARE Study and the CTS

	Women's CARE study ($N = 4,565$) OC use		CTS (age 35–64; $N = 2,222$) OC use		CTS (all; $N = 3,929$) OC use	
	Never ($N = 1,041$)	Ever ($N = 3,524$)	Never ($N = 395$)	Ever ($N = 1,827$)	Never ($N = 1,490$)	Ever ($N = 2,439$)
Age at diagnosis, y						
<35					0.1	0.3
35–39	7.6	17.3	1.3	2.6	0.3	1.9
40–44	8.4	19.0	5.8	3.8	1.5	2.8
45–49	8.7	19.6	10.9	11.2	2.9	8.4
50–54	15.0	19.5	19.5	22.8	5.2	17.1
55–59	22.9	15.0	24.3	32.3	6.4	24.2
60–64	37.6	9.6	38.2	27.4	10.1	20.5
>64					73.4	24.8
Race						
White	62.8	65.0	83.0	88.9	88.4	89.4
Black (CARE)/other (CTS)	37.2	35.0	17.0	11.1	11.6	10.6
Family history of breast cancer (first degree)						
No	77.6	79.4	76.4	80.0	79.7	79.3
Yes	17.4	16.9	19.8	17.2	17.0	17.9
Adopt/unknown	5.0	3.7	3.8	2.8	3.3	2.8
Body mass index (BMI)[a], kg/m^2						
<20	8.3	11.4	9.4	9.7	7.1	8.7
20–24.9	37.6	47.7	44.6	50.5	43.4	49.6
25–29.9	27.8	25.7	30.4	23.8	30.7	24.8
≥30	25.8	14.7	12.9	13.7	13.4	14.0
Unknown	0.6	0.6	2.8	2.4	5.5	2.9
Menopausal status						
Premenopausal	24.3	52.8	38.0	41.3	10.3	31.2
Postmenopausal	68.1	34.3	53.9	41.2	87.5	55.3
Unknown	7.6	12.9	8.1	17.6	2.2	13.5
Stage						
Localized	62.7	59.6	67.1	64.4	70.8	66.7
Nonlocalized	37.3	40.4	32.9	35.6	29.2	33.3
Estrogen status						
Positive	64.7	57.0	73.7	72.5	73.6	72.8
Negative	21.3	30.8	12.9	14.7	11.4	14.2
Unknown	14.0	12.2	13.4	12.8	15.0	13.0
Study site						
Atlanta	19.3	19.3				
Seattle	18.4	24.8				
Detroit	15.3	14.7				
Philadelphia	20.9	13.8				
Los Angeles	26.1	27.5				
Education						
Not a high school graduate	16.3	6.5				
High school graduate	34.9	27.5				
Some college or technical school	26.4	34.2				
College graduate	22.3	31.8				
Socioeconomic status						
Lowest quartile			3.8	3.2	4.5	3.3
Second quartile			13.9	14.7	16.3	14.4
Third quartile			28.6	30.8	30.5	30.5
Highest quartile			52.9	50.4	47.6	50.7
Unknown			0.8	1.0	1.1	1.1

[a]BMI: at 5 years before breast cancer diagnosis for the CARE Study and at cohort entry for the CTS.

Abbreviations: CARE, Contraceptive and Reproductive Experiences; CTS, California Teachers Study; OC, oral contraceptives.

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Table 2. RR estimates and 95% CI for the association between OC use and risk of mortality in the Women's CARE Study

	All-cause deaths ($N = 1,064$)		Breast cancer deaths ($N = 828$)	
Baseline variable	**No.**	**RR (95% CI)**	**No.**	**RR (95% CI)**
OC use status				
Never	255	1.00	172	1.00
Ever	809	1.01 (0.86–1.19)	656	1.03 (0.85–1.25)
Former	767	1.01 (0.86–1.19)	616	1.03 (0.85–1.24)
Current	41	0.89 (0.62–1.28)	39	0.95 (0.65–1.40)
OC use duration, y				
<1	187	0.94 (0.77–1.15)	142	0.92 (0.73–1.17)
1–<5	295	1.17 (0.97–1.41)	230	1.15 (0.93–1.43)
5–<10	180	0.97 (0.78–1.19)	154	1.02 (0.80–1.29)
≥10	147	0.93 (0.74–1.16)	130	1.00 (0.78–1.28)
P_{trend}		0.52		0.35
Age at first OC use, y				
<20	324	1.01 (0.82–1.24)	283	1.06 (0.84–1.35)
20–24	264	0.97 (0.80–1.18)	220	1.01 (0.81–1.27)
25–29	136	1.03 (0.83–1.28)	92	0.93 (0.71–1.22)
≥30	84	1.06 (0.82–1.36)	60	1.09 (0.81–1.47)
Years between last OC use and breast cancer diagnosis				
≥25	236	1.11 (0.92–1.34)	175	1.12 (0.90–1.41)
20–24	191	1.01 (0.82–1.23)	145	0.97 (0.77–1.24)
10 to <20	250	0.94 (0.76–1.15)	216	1.00 (0.80–1.27)
<10	131	0.82 (0.64–1.06)	119	0.87 (0.65–1.15)
Years between menarche and first OC use				
<9	408	1.01 (0.83–1.23)	355	1.06 (0.85–1.33)
9 to <15	253	0.95 (0.79–1.15)	198	0.97 (0.77–1.21)
≥15	147	1.08 (0.88–1.33)	102	1.05 (0.82–1.35)
Years of OC use before FFTP				
1st OC use after FFTP	396	1.01 (0.86–1.20)	314	1.05 (0.86–1.29)
No FFTP	125	1.06 (0.84–1.35)	89	0.90 (0.68–1.20)
<3	61	0.89 (0.66–1.21)	51	0.89 (0.63–1.25)
3 to <6	98	1.09 (0.84–1.41)	88	1.15 (0.86–1.52)
≥6	125	0.94 (0.74–1.21)	110	0.96 (0.73–1.27)
Calendar year of first OC use				
<1972	544	1.05 (0.89–1.24)	421	1.07 (0.88–1.31)
≥1973	264	0.87 (0.69–1.09)	234	0.87 (0.67–1.13)

NOTE: Total number of deaths may vary due to missing values in corresponding variables. All models use age (in days) as the time metric and stratify on age (in years) at breast cancer diagnosis. Covariates included in the models are study site, race, ER status, tumor stage, education level, smoking status, alcohol consumption, number of comorbidities, number of mammograms within the 5 years before breast cancer diagnosis, BMI 5 years before cancer diagnosis, and age at menarche.

Abbreviations: CARE, Contraceptive and Reproductive Experiences; FFTP, first full-term pregnancy; OC, oral contraceptives.

cancers for both studies. Additional adjustment for other potential confounders (e.g., MHT) did not influence RR estimates. For direct comparison with the Women's CARE Study, we repeated analyses restricting the CTS patients to the 2,222 women who were 35 to 64 years at diagnosis.

Tests for trend were conducted by fitting ordinal values corresponding to exposure categories and testing whether the slope coefficient differed from zero. Two-sided P values are reported. We did not adjust P values for multiple comparisons. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc).

Results

The Women's CARE Study

The mean age at breast cancer diagnosis was 49.7 years. During a median follow-up of 8.6 years, 1,064 women

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Table 3. RR estimates and 95% CI for the association between OC use and mortality in the CTS

	All-cause deaths ($N = 523$)		Breast cancer deaths ($N = 261$)	
Baseline variable	**No.**	**RR (95% CI)**	**No.**	**RR (95% CI)**
OC use status				
Never	287	1.00	106	1.00
Ever[a]	236	0.84 (0.67–1.05)	155	0.89 (0.64–1.23)
OC use duration, y				
<1	34	0.77 (0.52–1.14)	19	0.83 (0.49–1.43)
1 to <5	80	0.85 (0.63–1.16)	54	0.88 (0.59–1.33)
5 to <10	67	0.99 (0.72–1.36)	44	0.97 (0.63–1.50)
≥10	45	0.67 (0.47–0.96)	32	0.75 (0.48–1.18)
P_{trend}		0.22		0.72
Age at first OC use, y				
<20	26	0.76 (0.46–1.26)	23	0.87 (0.49–1.55)
20–24	78	0.66 (0.46–0.95)	58	0.65 (0.42–1.02)
25–29	51	0.87 (0.61–1.24)	35	0.99 (0.63–1.57)
≥30	74	0.90 (0.68–1.18)	33	0.94 (0.61–1.45)
Years between last OC use and breast cancer diagnosis				
≥25	141	0.84 (0.65–1.07)	83	0.85 (0.59–1.21)
20–24	38	0.84 (0.57–1.24)	30	0.98 (0.60–1.58)
10 to <20	37	1.00 (0.66–1.53)	27	0.99 (0.58–1.67)
<10	8	0.47 (0.18–1.22)	7	0.44 (0.15–1.31)
Years between menarche and first OC use				
<9	49	0.71 (0.47–1.08)	41	0.82 (0.50–1.34)
9 to <15	82	0.76 (0.55–1.06)	60	0.79 (0.52–1.21)
≥15	97	0.90 (0.69–1.16)	47	0.94 (0.64–1.37)
Years of OC use before FFTP				
First OC after FFTP	89	0.79 (0.61–1.03)	49	0.90 (0.62–1.32)
No FFTP	59	1.09 (0.77–1.53)	33	0.82 (0.51–1.32)
<3	10	0.62 (0.31–1.26)	5	0.52 (0.20–1.34)
3 to <6	29	0.84 (0.53–1.32)	25	0.97 (0.57–1.65)
≥6	44	0.82 (0.54–1.24)	38	0.84 (0.51–1.38)
Calendar year of first OC use				
<1972	207	0.85 (0.68–1.08)	133	0.90 (0.65–1.26)
≥1973	22	0.57 (0.30–1.06)	16	0.45 (0.20–1.03)

NOTE: Total number of deaths may vary due to missing values in corresponding variables. All models use age (in days) as the time metric and stratify by age (in years) at breast cancer diagnosis. Covariates included in the models are race, ER status, tumor stage, socioeconomic status, smoking status, alcohol consumption, number of comorbidities, years since last mammogram, BMI at cohort entry and age at menarche.

[a]Two deaths occurred among current OC users.

Abbreviations: CTS, California Teachers Study; FFTP, first full-term pregnancy; OC, oral contraceptives.

died, 828 from breast cancer. Overall, 3,524 (77.2%) women had used OC. Women who were younger, more educated, thinner, or premenopausal were more likely to have used OCs (Table 1).

All-cause mortality was not associated with having used OCs (RR = 1.01, 95% CI = 0.86–1.19) (Table 2). OC use duration also was not associated with all-cause mortality ($P_{trend} = 0.52$). Similarly, no association was observed between all-cause mortality and age at first OC use, years between last OC use and breast cancer diagnosis, years between menarche and first OC use, years of OC use before first full-term pregnancy (FFTP) or the calendar year of first OC use. Similar null associations were observed for breast cancer-specific mortality (Table 2).

The CTS

The mean age at breast cancer diagnosis was 63.0 years (age range: 28–91 years). During a median follow-up of 6.1 years, 523 women died, 261 from breast cancer. Overall, 2,439 (62.1%) women had used OCs, 545 for more than 10 years. Younger women and premenopausal women were more likely to have used OCs (Table 1).

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OC use was not statistically significantly associated with all-cause mortality (RR = 0.84, 95% CI = 0.67–1.05) (Table 3). Women who used OCs for at least 10 years had a statistically significant decreased risk of all-cause mortality (RR = 0.67, 95% CI = 0.47–0.96), but not breast cancer-specific mortality (RR = 0.75, 95% CI = 0.48–1.18). No duration–response effect was observed. No statistically significant association was observed for other OC use variables.

Among 2,222 CTS women who were diagnosed with breast cancer between age 35 and 64 years, the mean age at diagnosis was 55.2 years. During a median follow-up of 6.6 years, 211 deaths occurred; 153 were attributed to breast cancer. In this subset of breast cancer patients, OC use for at least 10 years was not associated with a statistically significant decreased risk of all-cause mortality (P_{trend} = 0.51; RR = 0.72, 95% CI = 0.45–1.13). The risk estimates for other variables were similar to those presented for all CTS patients (data not shown).

Discussion

Using women diagnosed with invasive breast cancer from 2 studies, a population-based case–control study and a cohort study, we found no association between OC use and all-cause or breast cancer-specific mortality.

These overall null results are consistent to those from most previous studies (7–16). Several studies found better survival among OC users (17–20), including a history of any OC use (19), short-term use (17), or longer time since last use (18, 20). However, none of these studies observed a clear dose–response effect for duration of use, age at first use or years between last use and breast cancer diagnosis. Studies that have reported poorer survival for OC users had limited sample sizes suggesting that these study results should be interpreted with caution (21–24).

Among CTS breast cancer patients who used OCs for at least 10 years, we observed a statistically significant decreased risk of death from any cause but not specifically from breast cancer. With longer follow-up, this result could achieve statistical significance. However, if OCs reduce mortality from causes other than breast cancer, we should see lower overall mortality associated with OC use among members of the CTS cohort with no cancer diagnosis. We investigated this by assessing all-cause mortality (4,943 deaths) in relation to OC use, and observed no association with mortality (data not shown). Thus, the statistically significant decrease in all-cause mortality among CTS breast cancer patients may be due to chance, especially given that no dose–response effect was observed.

A major strength of our primary analyses is the use of 2 large, well-designed studies which used different design approaches and enrolled women with different demographic characteristics. Second, the detailed information on OC use collected in both studies enabled us to create variables with the same cut-points. Finally, both studies collected detailed information on a large number of potential risk factors for breast cancer incidence and mortality, enabling us to consider many potential confounders in multivariable models although these factors were not measured exactly the same in both studies.

A limitation of our study is that we did not abstract medical treatment records; however, by controlling for age, stage of disease and receptor status, we have provided some control for treatment differences. Another limitation is that the CTS collected OC use information up to enrollment in the cohort (ranging from <1 year to 11 years before breast cancer diagnosis) and did not incorporate OC use after recruitment into our exposure variables. Given the older age-at-diagnosis distribution of CTS breast cancer patients, this is unlikely to have affected the results. Finally, as we did not adjust for multiple testing, some results (e.g., the CTS finding of decreased all-cause mortality risk for 10 or more years OC use) may be false positives.

In summary, we show no association between OC use and survival among women with invasive breast cancer or at most a slightly decreased risk of all-cause mortality for women who used OCs for a long time.

Disclosure of Potential Conflicts of Interest

The ideas and opinions expressed herein are those of the authors, and endorsement by the state of California, Department of Public Health, the National Cancer Institute, the Centers for Disease Control and Prevention, or their contractors and subcontractors is not intended nor should be inferred. They do not necessarily represent the official position of the Centers for Disease Control and Prevention. No potential conflicts of interest were disclosed.

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