

# The New England Journal of Medicine

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VOLUME 346

JUNE 27, 2002

NUMBER 26



## ORAL CONTRACEPTIVES AND THE RISK OF BREAST CANCER

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### ABSTRACT

**Background** It is uncertain whether the use of an oral contraceptive increases the risk of breast cancer later in life, when the incidence of breast cancer is increased. We conducted a population-based, case-control study to determine the risk of breast cancer among former and current users of oral contraceptives.

**Methods** We interviewed women who were 35 to 64 years old. A total of 4575 women with breast cancer and 4682 controls were interviewed. Conditional logistic regression was used to calculate odds ratios as estimates of the relative risk (incidence-density ratios) of breast cancer.

**Results** The relative risk was 1.0 (95 percent confidence interval, 0.8 to 1.3) for women who were currently using oral contraceptives and 0.9 (95 percent confidence interval, 0.8 to 1.0) for those who had previously used them. The relative risk did not increase consistently with longer periods of use or with higher doses of estrogen. The results were similar among white and black women. Use of oral contraceptives by women with a family history of breast cancer was not associated with an increased risk of breast cancer, nor was the initiation of oral-contraceptive use at a young age.

**Conclusions** Among women from 35 to 64 years of age, current or former oral-contraceptive use was not associated with a significantly increased risk of breast cancer. (N Engl J Med 2002;346:2025-32.)

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THE best data available suggest that women who currently use oral contraceptives or who have used them in the previous 10 years have a slightly increased risk of breast cancer, whereas women who have used oral contraceptives less recently do not have an increased risk.<sup>1,2</sup> However, these data were pooled from 54 epidemiologic studies conducted over the past 25 years; new data are need-

ed, now that larger numbers of women who took oral contraceptives early in their reproductive years are reaching the age at which the risk of breast cancer is highest. We conducted the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences (Women's CARE) Study to examine the use of oral contraceptives as a risk factor for breast cancer in women who were 35 to 64 years old and in subgroups of women defined according to race, age, presence or absence of a family history of breast cancer, and other factors.

### METHODS

#### Study Design

The design of the study is described in detail elsewhere.<sup>3</sup> Briefly, we conducted a population-based, case-control study with enrollment at centers in Atlanta, Detroit, Philadelphia, Los Angeles, and Seattle. The Centers for Disease Control and Prevention was the data-coordinating center. Protocols were approved by the institutional review boards at the participating centers. All the women in the study gave written informed consent.

#### Case Subjects

Women who were 35 to 64 years old, resided in the study locations, and had invasive breast cancer initially diagnosed between

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1994 and 1998 were identified in Philadelphia by field-center staff and at other sites through local Surveillance, Epidemiology, and End Results Program cancer registries. Women from this population were selected with the use of selection probabilities that were specific for the study site, nominal self-reported identification as white or black, age, and month of diagnosis. Younger women and black women were oversampled to approximate a uniform distribution across age groups and groups of white and black women. Of 5982 eligible women selected, 4575 (76 percent) were interviewed.

### Controls

We identified controls (women without a diagnosis of invasive or *in situ* breast cancer) in the same geographic locations as the case subjects, using random-digit dialing to contact residential households by telephone. Approximately 82 percent of the households called were screened successfully. Throughout the study, controls were sampled randomly from the group of eligible women identified during telephone screening at rates designed to match the frequency of interviews with controls to the frequency of interviews with case subjects within strata defined according to the study site, race, and age. Of 5956 eligible women selected as controls, 4682 (79 percent) were interviewed.

### Interviews

Study participants were interviewed in person with the use of a standardized questionnaire that incorporated the reference date (for case subjects, the date of the initial, histologically confirmed diagnosis of breast cancer; for controls, the date of telephone screening). We obtained detailed information about the use of oral contraceptives and other hormones. In addition, we asked questions about each woman's reproductive history, health, and family history. Cards listing response categories, photographs of hormonal medications, and a life-events calendar<sup>4</sup> were used to enhance recall.<sup>5</sup> The interviews were conducted between August 1994 and December 1998.

### Classification of Oral Contraceptives

Oral contraceptives were classified as combination contraceptives if they included estrogen and progestin in each cycle (i.e., a monophasic, multiphasic, or sequential formulation) and as progestin-only contraceptives if they contained only progestin throughout the cycle. Oral contraceptives in the United States contain estrogen in the form of either ethinyl estradiol or mestranol.<sup>6</sup> Mestranol has 67 percent of the estrogenic activity of ethinyl estradiol.<sup>7</sup> Formulations containing 50  $\mu\text{g}$  or more of ethinyl estradiol or 75  $\mu\text{g}$  or more of mestranol were classified as providing a high dose of estrogen; other preparations were classified as providing a low estrogen dose. Multiple progestins are used in oral contraceptives, and standard dose equivalencies are unavailable. In some of our analyses, we divided progestins into three groups on the basis of their chemical structure: estranes, gonanes, and others. Gonanes tend to have the most pronounced progestational effects.<sup>8,9</sup>

Among women who knew what kind of oral contraceptive they used, the combination type accounted for 99.5 percent of the months of oral-contraceptive use; the progestin-only type accounted for the other 0.5 percent. In the case of women who did not know what kind of contraceptive they used (accounting for 24.4 percent of total months of use), we classified the contraceptive as the combination type.

### Statistical Analysis

With the study site, race, and age as conditioning variables, we used conditional logistic regression to calculate odds ratios as estimates of the relative risk of breast cancer (incidence-density ratios)<sup>10</sup>; odds ratios are reported with 95 percent confidence intervals. For ease of presentation, we discuss the results as relative risks rather

than odds ratios. A P value of 0.05 or less was considered to indicate statistical significance.

In addition to study site, race, and age as conditioning variables, we included eight factors (Table 1) as an a priori set of confounders in all models; individual factors were omitted when subgrouping made adjustment inappropriate. In selected models, we assessed the following additional factors individually as potential confounders: educational level, income, extent of weekly exercise, number of breast biopsies, duration of breast-feeding, smoking status, amount of alcohol consumed, and the presence or absence of a history of tubal sterilization, mammography, major medical conditions, and contraceptive shots or implants. Specifically, we fitted a conditional logistic model containing the contraceptive-use variables and confounder set, fitted an expanded model with each additional factor, and compared the results obtained from the models. Because none of the additional factors altered the point estimates substantially, we excluded them from all models. For modeling, factors were categorized as shown in Supplementary Appendix 1 (available with the complete text of this article at <http://www.nejm.org>). Tests for linear trend were conducted with models containing the relevant ordinal categorical variable and an indicator variable for contraceptive use (any or none).

To determine whether the use of oral contraceptives influenced the risk of breast cancer differently in subgroups of women, we assessed selected variables as potential effect modifiers, applying likelihood-ratio tests for heterogeneity to models that included relevant interaction terms.<sup>11</sup>

## RESULTS

Sixty-five percent of the women in our study were white, and 35 percent were black. Case subjects and controls had significantly different distributions for multiple characteristics, including the number of term pregnancies and the presence or absence of a family history of breast cancer (Table 1 and Supplementary Appendix 1).

Seventy-seven percent of case subjects and 79 percent of controls had used some type of oral contraceptive. The risk of breast cancer among women who had ever used any type of oral contraceptive, as compared with those who had never used oral contraceptives, was 0.9 (95 percent confidence interval, 0.8 to 1.0). Among women who currently or had previously used only one type, the relative risk of breast cancer was 0.9, 0.6, 0.9, and 0.9 for those who had used monophasic, multiphasic, sequential, and progestin-only formulations, respectively; the relative risks for monophasic and multiphasic formulations were significant (data not shown). Only 32 case subjects and 39 controls had ever used progestin-only formulations. The results of an analysis that excluded data from women who did not know what kind of contraceptive they used were similar to the results of the analysis in which the data were included and attributed to use of combination contraceptives (data not shown). The remainder of our analyses focused on combination preparations.

Examination of multiple aspects of oral-contraceptive use (any, current, or former use; duration of use; age at first use; interval since last use; and estrogen dose) revealed little evidence that oral contraceptives

TABLE 1. CHARACTERISTICS OF THE WOMEN WITH BREAST CANCER AND THE CONTROLS.\*

CHARACTERISTIC	CASE SUBJECTS (N=4575)	CONTROLS (N=4682)	P VALUE†
Age — yr	49.7±8.4	49.5±8.3	0.16
Age at menarche — yr	12.4±1.5	12.4±1.6	0.18
Age at menopause among postmenopausal women — yr	47.0±6.0	45.2±7.1	<0.01
Age at first term pregnancy among parous women — yr‡	23.1±5.3	22.9±5.3	0.02
No. of term pregnancies‡	2.1±1.6	2.3±1.7	<0.01
Body-mass index 5 yr before the reference date§	25.5±5.6	25.8±5.9	0.01
White race — no. (%)	2953 (64.5)	3021 (64.5)	0.98
Menopausal status — no. (%)			0.04
Premenopausal or perimenopausal	2116 (46.3)	2061 (44.0)	
Postmenopausal	1544 (33.7)	1595 (34.1)	
Unable to classify	915 (20.0)	1026 (21.9)	
Family history of breast cancer — no. (%)¶			<0.01
No	3616 (79.0)	4050 (86.5)	
Yes	778 (17.0)	453 (9.7)	
Adopted or unknown	181 (4.0)	179 (3.8)	
Current or previous use of hormone-replacement therapy — no. (%)	1737 (38.0)	1932 (41.3)	<0.01

\*Plus-minus values are means ±SD.

†For continuous variables, P values are based on t-tests for differences between the means; for categorical variables, P values are based on Pearson's chi-square test for association.

‡For the purposes of this study, term pregnancy was defined as a gestation of at least 27 weeks; if a woman was pregnant at the time of the interview, that pregnancy was not counted.

§The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters. The reference date was the date of the diagnosis for women with breast cancer and the date of telephone screening for controls.

¶A family history of breast cancer was defined as breast cancer in the woman's mother, sister, or daughter.

||Data were available for 4574 women with breast cancer and 4681 controls.

increase the risk of breast cancer (Table 2). More than 2500 women had begun using oral contraceptives before the age of 20 years; the relative risk of breast cancer among these women was similar to the relative risk among women who had begun using oral contraceptives at an older age. The results for high-estrogen-dose preparations did not differ markedly from those for low-estrogen-dose preparations.

The results for women who were 35 to 44 years old were similar to the results for women who were 45 to 64 years old (Table 3). There was a nonsignificant relative risk of 1.5 among the older women who were currently using preparations with a low dose of estrogen, as compared with the older women who had never used oral contraceptives (Table 3). Because older women who use oral contraceptives may be screened for breast cancer more frequently than younger women, we analyzed the data after excluding women with stage I tumors; the relative risk was

not decreased (data not shown). The relative risk of breast cancer was not associated with the duration of oral-contraceptive use among older women who had ever used oral contraceptives (Table 3) or those who were currently using them (data not shown). Former use was associated with a small but significant reduction in the relative risk among the older women (Table 3). We also analyzed the data in subgroups defined according to menopausal status; the results for premenopausal and perimenopausal women were similar to the results for women 35 to 44 years old, and the results for postmenopausal women were similar to those for women 45 to 64 years old (data not shown).

Analyses of the interval since the first use of an oral contraceptive, age at last use, duration of use according to the estrogen dose, use in relation to the first term pregnancy, and duration of use before the first term pregnancy also showed no significant increase in the

**TABLE 2. RISK OF BREAST CANCER ACCORDING TO THE USE OF COMBINATION ORAL CONTRACEPTIVES.\***

VARIABLE	CASE SUBJECTS	CONTROLS	ODDS RATIO (95% CI)
	(N=4575)	(N=4682)	
	number		
No use	1032	980	1.0
Any use	3497	3658	0.9 (0.8–1.0)
Current use†	200	172	1.0 (0.8–1.3)
Former use	3289	3481	0.9 (0.8–1.0)‡
Duration of use			
<1 yr	782	822	0.9 (0.8–1.1)
1 to <5 yr	1200	1280	0.9 (0.8–1.0)
5 to <10 yr	848	882	0.9 (0.8–1.0)
10 to <15 yr	426	466	0.8 (0.7–1.0)‡
≥15 yr	234	202	1.0 (0.8–1.3)
Age at first use			
<15 yr	72	79	0.9 (0.6–1.2)
15 to 19 yr	1239	1272	1.0 (0.8–1.1)
20 to 24 yr	1260	1369	0.9 (0.8–1.0)‡
25 to 29 yr	587	592	0.9 (0.8–1.1)
30 to 34 yr	209	239	0.8 (0.6–1.0)‡
35 to 39 yr	84	67	1.2 (0.8–1.6)
≥40 yr	38	35	1.0 (0.6–1.6)
Time since last use			
Current use	200	172	1.0 (0.8–1.3)
7 mo to <5 yr	165	207	0.7 (0.5–0.9)‡
5 to <10 yr	244	239	0.9 (0.8–1.2)
10 to <15 yr	426	418	0.9 (0.8–1.1)
15 to <20 yr	650	717	0.9 (0.7–1.0)
≥20 yr	1803	1899	0.9 (0.8–1.0)
High estrogen dose§			
Any use	1082	1265	0.8 (0.7–0.9)‡
Current use	7	10	0.7 (0.2–1.8)
Former use	1074	1255	0.8 (0.7–0.9)‡
Low estrogen dose¶			
Any use	1460	1560	0.9 (0.8–1.0)
Current use	183	160	1.0 (0.8–1.3)
Former use	1267	1398	0.9 (0.8–1.0)

\*Odds ratios were derived by conditional logistic regression with the study site, race, and age (in five-year categories) as conditioning variables and were adjusted for menopausal status, age at menarche, age at menopause, number of term pregnancies, age at first term pregnancy, body-mass index, presence or absence of a family history of breast cancer, and use or nonuse of hormone-replacement therapy. Unknown oral-contraceptive formulations were classified as combination formulations. Missing values not included in one of the specified categories shown in Supplementary Appendix 1 were excluded. The reference group was the group of women who had never used oral contraceptives. Trend tests for the duration of use, age at first use, and time since last use were not significant at the 0.05 level. CI denotes confidence interval.

†Current use was defined as use of combination oral contraceptives within six months preceding the reference date.

‡The confidence interval does not include 1.0; some confidence limits were rounded to 1.0.

§A high estrogen dose was defined as 50 µg or more of ethinyl estradiol or 75 µg or more of mestranol.

¶A low estrogen dose was defined as less than 50 µg of ethinyl estradiol or less than 75 µg of mestranol.

risk of breast cancer among women who used oral contraceptives (Supplementary Appendix 2, at <http://www.nejm.org>), and there were no consistent differences in risk between white and black women (Supplementary Appendix 3, at <http://www.nejm.org>).

There were no consistent differences in the risk of breast cancer according to the type of progestin (Table 4). The relative risks tended to be higher among women who were currently using oral contraceptives than among women who no longer used them and were similar among women who had formerly used contraceptives and those who had ever used them (data not shown). In analyses according to the type of progestin, the risks were similar for white and black women (Supplementary Appendix 4, at <http://www.nejm.org>).

The results differed significantly according to the study site. Among the women who had ever used oral contraceptives, the relative risks were as follows: Atlanta, 0.7 (95 percent confidence interval, 0.5 to 0.9); Detroit, 0.7 (95 percent confidence interval, 0.5 to 0.9); Los Angeles, 1.0 (95 percent confidence interval, 0.8 to 1.2); Philadelphia, 1.0 (95 percent confidence interval, 0.8 to 1.3); and Seattle, 1.1 (95 percent confidence interval, 0.8 to 1.4); the results were similar for women who no longer used oral contraceptives (data not shown). The relative risks and confidence intervals for the group of women who were currently using oral contraceptives were based on smaller numbers and varied more widely: Atlanta, 0.8 (95 percent confidence interval, 0.5 to 1.3); Detroit, 0.4 (95 percent confidence interval, 0.2 to 0.8); Los Angeles, 1.4 (95 percent confidence interval, 0.9 to 2.2); Philadelphia, 1.7 (95 percent confidence interval, 0.8 to 3.5); and Seattle, 1.2 (95 percent confidence interval, 0.8 to 2.0).

We performed an analysis to determine whether the association between the use of oral contraceptives and the risk of breast cancer varied according to the presence or absence of a family history of breast cancer, the body-mass index, or menopausal status among women who had ever used oral contraceptives and those who were currently using them (Table 5). The results among these subgroups were generally similar to the results of the overall analysis. The results were also similar when women who had formerly used oral contraceptives were compared with those who had ever used them (data not shown).

## DISCUSSION

In a pooled analysis of 54 studies, the relative risk of breast cancer among women who were currently using oral contraceptives, as compared with those who had never used them, was 1.24 (95 percent confidence interval, 1.15 to 1.33).<sup>1</sup> Our study yield-

TABLE 3. RISK OF BREAST CANCER ACCORDING TO AGE.

VARIABLE	35-44 Yr			45-64 Yr		
	CASE SUBJECTS (N=1447)	CONTROLS (N=1498)	ODDS RATIO (95% CI)*	CASE SUBJECTS (N=3128)	CONTROLS (N=3184)	ODDS RATIO (95% CI)*
	number			number		
No use	165	171	1.0	867	809	1.0
Any use	1264	1305	1.0 (0.8-1.3)	2233	2353	0.9 (0.8-1.0)†
Current use‡	160	146	1.1 (0.8-1.5)	40	26	1.3 (0.8-2.1)
Former use	1102	1157	1.0 (0.8-1.3)	2187	2324	0.9 (0.8-1.0)†
Duration of use						
<1 yr	238	254	1.0 (0.7-1.3)	544	568	0.9 (0.8-1.1)
1 to <5 yr	424	455	1.0 (0.8-1.3)	776	825	0.9 (0.7-1.0)†
5 to <10 yr	317	332	1.0 (0.8-1.4)	531	550	0.9 (0.7-1.0)
10 to <15 yr	174	176	1.0 (0.8-1.4)	252	290	0.8 (0.6-0.9)†
≥15 yr	110	85	1.3 (0.9-1.8)	124	117	0.9 (0.7-1.2)
Age at first use						
<15 yr	55	59	1.0 (0.6-1.5)	17	20	0.8 (0.4-1.5)
15 to 19 yr	779	775	1.1 (0.8-1.4)	460	497	0.9 (0.7-1.1)
20 to 24 yr	313	360	0.9 (0.7-1.2)	947	1009	0.9 (0.7-1.0)
25 to 29 yr	76	73	1.1 (0.8-1.6)	511	519	0.9 (0.7-1.0)
30 to 34 yr	22	24	0.9 (0.5-1.6)	187	215	0.8 (0.6-0.9)†
35 to 39 yr	13	8	1.8 (0.7-4.5)	71	59	1.1 (0.7-1.5)
≥40 yr	5	4	1.4 (0.4-5.5)	33	31	0.9 (0.5-1.5)
Time since last use						
Current use	160	146	1.1 (0.8-1.5)	40	26	1.3 (0.7-2.1)
7 mo to <5 yr	131	150	0.9 (0.6-1.2)	34	57	0.5 (0.3-0.8)†
5 to <10 yr	199	171	1.2 (0.9-1.7)	45	68	0.6 (0.4-0.9)†
10 to <15 yr	242	272	0.9 (0.7-1.3)	184	146	1.1 (0.9-1.4)
15 to <20 yr	292	318	1.0 (0.8-1.3)	358	399	0.8 (0.7-1.0)†
≥20 yr	238	245	1.1 (0.8-1.5)	1565	1654	0.9 (0.8-1.0)†
High estrogen dose§						
Any use	296	387	0.8 (0.6-1.1)	786	878	0.8 (0.7-1.0)†
Current use	5	8	0.7 (0.2-2.1)	2	2	0.7 (0.1-5.2)
Former use	291	379	0.8 (0.6-1.1)	783	876	0.8 (0.7-1.0)†
Low estrogen dose¶						
Any use	836	853	1.0 (0.8-1.3)	624	707	0.9 (0.7-1.0)
Current use	145	137	1.0 (0.7-1.4)	38	23	1.5 (0.9-2.6)
Former use	682	714	1.0 (0.8-1.3)	585	684	0.8 (0.7-1.0)†

\*Odds ratios were derived by conditional logistic regression with the study site, race, and age (in five-year categories) as conditioning variables and were adjusted for menopausal status, age at menarche, age at menopause, number of term pregnancies, age at first term pregnancy, body-mass index, presence or absence of a family history of breast cancer, and use or nonuse of hormone-replacement therapy. Unknown oral-contraceptive formulations were classified as combination formulations. Missing values not included in one of the specified categories shown in Supplementary Appendix 1 were excluded. The reference group was the group of women in the age group who had never used oral contraceptives. Trend tests for duration of use, age at first use, and time since last use were not significant at the 0.05 level; exposure-age interactions were not significant at the 0.05 level except for time since last use. CI denotes confidence interval.

†The confidence interval does not include 1.0; some confidence limits were rounded to 1.0.

‡Current use was defined as use of combination oral contraceptives within six months before the reference date.

§A high estrogen dose was defined as 50 µg or more of ethinyl estradiol or 75 µg or more of mestranol.

¶A low estrogen dose was defined as less than 50 µg of ethinyl estradiol or less than 75 µg of mestranol.

ed a relative risk of 1.0. The pooled analysis, like our study, showed that the risk of breast cancer was not significantly related to the duration of oral-contraceptive use or to the dose of estrogen. In contrast to our study, the pooled analysis showed that the risk was slightly but significantly increased among women who had stopped taking oral contraceptives up to 10 years earlier. Nine percent of the women with

breast cancer in the pooled analysis were less than 35 years old at the time of the diagnosis<sup>1</sup>; our study was restricted to women who were 35 to 64 years old. In both the pooled analysis and our study, 33 percent of women with breast cancer were at least 55 years old at the time of the diagnosis.<sup>1</sup>

A recent study<sup>12</sup> suggested that among women who had a first-degree relative with breast cancer, the risk

**TABLE 4.** RISK OF BREAST CANCER ACCORDING TO THE TYPE OF PROGESTIN.\*

VARIABLE	CASE	CONTROLS	ODDS RATIO (95% CI)
	SUBJECTS (N=4575)	(N=4682)	
	number		
No use	1032	980	1.0
<b>Estrane progestins</b>			
Any use	2439	2598	0.9 (0.8–1.0)
Current use†	113	94	1.1 (0.8–1.5)
Ethinodiol diacetate			
Any use	313	315	1.0 (0.8–1.2)
Current use	15	4	3.5 (1.1–10.7)‡
Norethindrone			
Any use	1993	2143	0.9 (0.8–1.0)‡
Current use	59	51	1.0 (0.7–1.6)
Norethindrone acetate			
Any use	241	244	1.0 (0.8–1.2)
Current use	40	39	1.1 (0.7–1.8)
Norethynodrel			
Any use	163	162	0.9 (0.7–1.2)
Current use	0	0	—
<b>Gonane progestins</b>			
Any use	649	678	1.0 (0.8–1.2)
Current use	85	80	1.0 (0.7–1.5)
Desogestrel, norgestimate, or gestodene§			
Any use	91	97	1.0 (0.7–1.3)
Current use	28	27	0.9 (0.5–1.7)
Levonorgestrel			
Any use	121	114	1.1 (0.8–1.5)
Current use	32	33	0.9 (0.5–1.5)
Norgestrel			
Any use	497	513	1.0 (0.9–1.3)
Current use	28	20	1.4 (0.8–2.5)
<b>Other¶</b>			
Any use	57	76	0.7 (0.5–1.1)
Current use	0	0	—

\*Odds ratios were derived by conditional logistic regression with the study site, race, and age (in five-year categories) as conditioning variables and were adjusted for menopausal status, age at menarche, age at menopause, number of term pregnancies, age at first term pregnancy, body-mass index, presence or absence of a family history of breast cancer, and use or nonuse of hormone-replacement therapy. Unknown oral-contraceptive formulations were classified as combination formulations. Missing values not included in one of the specified categories shown in Supplementary Appendix 1 were excluded. The reference group was the group of women who had never used oral contraceptives. CI denotes confidence interval.

†Current use was defined as use of combination oral contraceptives containing the specified progestin within six months before the reference date.

‡The confidence interval does not include 1.0; some confidence limits were rounded to 1.0.

§These are sometimes referred to as “new” or “third-generation” progestins.<sup>6</sup> A total of 128 women were former or current users of desogestrel, 65 were former or current users of norgestimate, and 1 was a former user of gestodene; 6 women in this group used more than one type of progestin.

¶A total of 79 women were former or current users of chlormadinone acetate, 28 were former or current users of medroxyprogesterone acetate, and 26 were former or current users of dimethisterone; no woman in this group used more than one type of progestin.

of breast cancer among those who had used oral contraceptives before 1976 (when preparations were likely to contain high doses of estrogen and progestin) was three times as high as the risk among women who had never used oral contraceptives. In our study, oral-contraceptive use was not associated with an increased relative risk of breast cancer among women with such a family history. In this group of women, the relative risk associated with the use of high-estrogen-dose preparations for less than 1 year, 1 to less than 5 years, 5 to less than 10 years, 10 to less than 15 years, and 15 or more years was 1.0, 1.2, 1.2, 0.5, and 0.8, respectively, and for low-estrogen-dose preparations, the relative risk was 0.9, 0.8, 0.7, 0.5, and 0.5, respectively; none of the relative risks were significantly increased.

Young women with *BRCA1* or *BRCA2* mutations who have used oral contraceptives may have an increased risk of breast cancer<sup>13</sup>; the same may be true for young women with a family history of breast cancer.<sup>14</sup> In our study, the relative risk of breast cancer among women who were 35 to 44 years old, had a family history of breast cancer, and had ever used oral contraceptives was higher than that among older women with such a history, but this difference was not significant.

The incidence of breast cancer in the United States is higher among white women, but the rate of death from breast cancer is higher among black women.<sup>15–17</sup> Access to care may account in part for this discrepancy.<sup>18</sup> In addition, the biology of breast cancer in white women and black women may differ; black women may be at higher risk for breast cancer that is negative for estrogen and progesterone receptors<sup>19,20</sup> and for more histologically aggressive disease.<sup>21</sup> Because of these possible differences and the possibility that white women and black women use oral contraceptives differently,<sup>22</sup> we evaluated these two groups separately. We did not find consistent evidence that the effect of oral contraceptives on the risk of breast cancer differs between white women and black women.

In 1990, the labeling of U.S. oral contraceptives was revised; specifically, the reference to an increased risk of death from cardiovascular causes among healthy women 40 years of age or older who do not smoke was deleted.<sup>23</sup> This revision may have led to increased use of oral contraceptives among older women for contraceptive or noncontraceptive reasons. In our study, the oldest current users of combination and progestin-only oral contraceptives were 54 and 62 years old, respectively, and among women who were 45 to 64 years, the risk of breast cancer was not significantly higher among the women who were currently using oral contraceptives containing a low dose of estrogen than among those who had never used oral contraceptives. However, our finding in this older

TABLE 5. RISK OF BREAST CANCER AMONG SUBGROUPS OF WOMEN.\*

VARIABLE	ANY USE			CURRENT USE†		
	NO. OF CASE SUBJECTS	NO. OF CONTROLS	ODDS RATIO (95% CI)*	NO. OF CASE SUBJECTS	NO. OF CONTROLS	ODDS RATIO (95% CI)
Family history‡						
All women						
No	2778	3173	0.9 (0.8–1.0)	174	156	1.1 (0.8–1.4)
Yes	595	349	0.8 (0.6–1.1)	24	13	0.7 (0.3–1.6)
Women 35–44 yr						
No	1038	1179	1.0 (0.8–1.3)	141	134	1.1 (0.8–1.5)
Yes	189	93	1.4 (0.7–2.9)	17	10	0.9 (0.3–2.5)
Women 45–64 yr						
No	1740	1994	0.9 (0.8–1.0)	33	22	1.4 (0.8–2.4)
Yes	406	256	0.8 (0.5–1.1)	7	3	0.9 (0.2–4.0)
Body-mass index						
All women						
<21.5	930	928	0.9 (0.7–1.1)	86	83	0.8 (0.6–1.3)
21.5 to <28.5	1889	1902	1.0 (0.8–1.1)	95	68	1.3 (0.9–1.9)
≥28.5	678	828	0.8 (0.6–1.0)§	19	21	0.8 (0.4–1.7)
Women 35–44 yr						
<21.5	446	443	0.8 (0.5–1.2)	68	71	0.8 (0.4–1.3)
21.5 to <28.5	640	623	1.4 (1.0–1.9)	78	57	1.7 (1.0–2.7)§
≥28.5	178	239	0.9 (0.6–1.6)	14	18	1.0 (0.4–2.4)
Women 45–64 yr						
<21.5	484	485	0.9 (0.6–1.2)	18	12	1.4 (0.6–3.2)
21.5 to <28.5	1249	1279	0.9 (0.8–1.1)	17	11	1.4 (0.6–3.1)
≥28.5	500	589	0.7 (0.6–0.9)§	5	3	1.0 (0.2–4.6)
Menopausal women						
All women						
Premenopausal or perimenopausal	1843	1779	1.1 (0.9–1.3)	190	166	1.2 (0.9–1.6)
Postmenopausal	974	1078	0.8 (0.7–1.0)§	4	2	1.6 (0.3–9.9)
Women 35–44 yr						
Premenopausal or perimenopausal	1131	1124	1.0 (0.8–1.3)	154	143	1.1 (0.8–1.5)
Postmenopausal	35	63	0.6 (0.1–3.4)	4	1	2.1 (0.1–38.1)
Women 45–64 yr						
Premenopausal or perimenopausal	712	655	1.2 (0.9–1.6)	36	23	1.6 (0.9–3.0)
Postmenopausal	939	1015	0.8 (0.7–1.0)§	0	1	—

\*Odds ratios were derived by conditional logistic regression with the study site, race, and age (in five-year categories) as conditioning variables and were adjusted for menopausal status, age at menarche, age at menopause, number of term pregnancies, age at first term pregnancy, body-mass index, presence or absence of a family history of breast cancer, and use or nonuse of hormone-replacement therapy (except that analyses according to a family history of breast cancer omitted adjustment for this variable, analyses according to body-mass index omitted adjustment for this variable, analyses according to menopausal status omitted adjustment for this variable, and analyses restricted to premenopausal or perimenopausal women omitted adjustment for age at menopause). Unknown oral contraceptive formulations were classified as combination formulations. Missing values not included in one of the specified categories shown in Supplementary Appendix 1 were excluded. Two-way exposure–age interactions for each category of family history, body-mass index, and menopausal status were not significant. Two-way interactions between exposure and family history, body-mass index, and menopausal status for all women and within each age group were not significant, except for any use of oral contraceptives according to menopausal status among all women. CI denotes confidence interval.

†Current use was defined as use of combination oral contraceptives within six months before the reference date.

‡A family history of breast cancer was defined as breast cancer in the woman's mother, sister, or daughter.

§The confidence interval does not include 1.0; some confidence limits were rounded to 1.0.

group may not be definitive, and further investigation of this question is warranted.

It has been reported that the relation between the presence or absence of a history of oral-contraceptive use and the risk of breast cancer varies according to age, with older women having a slightly lower risk.<sup>24</sup> Similarly, we found that women 45 to 64 years old who had ever used oral contraceptives had a small but

significant reduction in the relative risk of breast cancer.

We cannot explain why our results varied according to the study site. Chance, biology, or bias could account for these findings. The study site did not influence estimates of relative risk for a variety of other factors, including use of hormone-replacement therapy.

The population-based design of our study mini-

mized the potential for a biased selection of cases and controls. We interviewed 76 percent of eligible women with cancer and 79 percent of eligible controls. Because the controls were selected by random-digit dialing and 82 percent of households were screened, the actual response rate among the controls was 65 percent. To the degree that women who participated in our study differed from those who did not, our results may be biased. We have no reason to believe, however, that the participation of case subjects and controls was influenced differently by their histories of hormone use.

We did not validate information on the use of oral contraceptives. However, we used memory aids that increase recall.<sup>5,25</sup> Other limitations include representation of only white and black women, the absence of information on diet and environmental exposures (e.g., radiation and toxic chemicals), and small subgroups. We have no information on women under the age of 35 years. In the pooled analysis,<sup>2</sup> the relative risk of breast cancer was highest among women under the age of 35 years who were current or recent users (with recent use defined as use within the previous 5 years) and who had started using oral contraceptives before the age of 20. When we examined the data for our youngest subgroup of women, those who were 35 to 39 years old, the relative risk of breast cancer did indeed tend to be higher than that in older subgroups. However, we found little evidence that the initiation of oral-contraceptive use at a young age was associated with a substantially increased risk of breast cancer, even among current users. In the group of current users who had started using oral contraceptives before the age of 20 years, the relative risk was 1.0, 1.0, and 1.1 among women who were 35 to 39, 40 to 44, and 45 to 64 years old, respectively.

In conclusion, current or former use of oral contraceptives among women 35 to 64 years old did not significantly increase the risk of breast cancer. Our data provide strong evidence that former oral-contraceptive use does not increase this risk later in life, when the incidence of breast cancer is higher.

Supported by the National Institute of Child Health and Human Development, with additional support from the National Cancer Institute, through contracts with Emory University (N01-HD-3-3168), the Fred Hutchinson Cancer Research Center (N01-HD-2-3166), the Karmanos Cancer Institute at Wayne State University (N01-HD-3-3174), the University of Pennsylvania (N01-HD-3-3176), and the University of Southern California (N01-HD-3-3175) and through an intraagency agreement with the Centers for Disease Control and Prevention (Y01-HD-7022). The Centers for Disease Control and Prevention contributed additional staff and computer support. The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute provided assistance for study sites in Atlanta (N01-PC-67006), Detroit (N01-CN-65064), Los Angeles (N01-PC-67010), and Seattle (N01-CN-0532).

*We are indebted to the women who participated in this study for their generosity and to all past and present members of the Women's CARE Study team for their diverse contributions.*

## APPENDIX

In addition to the authors, the Women's CARE Study included the following investigators: J.M. Liff, D.M. Deapen, E.W. Flagg, M.F. Press, and R.J. Coates. Members of the Scientific Advisory Committee included B.S. Hulka, C. Hunter, D. Lezotte, and J. Schlesselman.

## REFERENCES

1. 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.
2. *Idem*. Breast cancer and hormonal contraceptives: further results. *Contraception* 1996;54:Suppl:1S-106S.
3. Marchbanks PA, McDonald JA, Wilson HG, et al. The NICHD Women's Contraceptive and Reproductive Experiences Study: methods and operational results. *Ann Epidemiol* 2002;12:213-21.
4. Wingo PA, Ory HW, Layde PM, Lee NC. The evaluation of the data collection process for a multicenter, population-based, case-control design. *Am J Epidemiol* 1988;128:206-17.
5. West SL, Strom BL. Validity of pharmacoepidemiology drug and diagnosis data. In: Strom BL, ed. *Pharmacoepidemiology*. 3rd ed. Sussex, England: John Wiley, 2000:661-705.
6. Hatcher RA, Guillebaud J. The pill: combined oral contraceptives. In: Hatcher RA, Trussell J, Stewart F, et al., eds. *Contraceptive technology*. 17th rev. ed. New York: Ardent Media, 1998:405-66.
7. Dickey RP. *Managing contraceptive pill patients*. 4th ed. Durant, Okla.: Creative Infomatics, 1984.
8. *Idem*. *Managing contraceptive pill patients*. 10th ed. Dallas: EMIS Medical, 2000.
9. Department of Drugs, Division of Drugs and Technology. *Drug evaluations*. 6th ed. Chicago: American Medical Association, 1986.
10. Greenland S, Thomas DC. On the need for the rare disease assumption in case-control studies. *Am J Epidemiol* 1982;116:547-53. [Erratum, *Am J Epidemiol* 1990;131:1102.]
11. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic research: principles and quantitative methods*. Belmont, Calif.: Lifetime Learning, 1982.
12. Grabrick DM, Hartmann LC, Cerhan JR, et al. Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer. *JAMA* 2000;284:1791-8.
13. Ursin G, Henderson BE, Haile RW, et al. Does oral contraceptive use increase the risk of breast cancer in women with BRCA1/BRCA2 mutations more than in other women? *Cancer Res* 1997;57:3678-81.
14. Ursin G, Li C, Pike MC. Should women with a family history of breast cancer avoid use of oral contraceptives? *Epidemiology* 2000;11:615-6.
15. Wingo PA, Ries LAG, Rosenberg HM, Miller DS, Edwards BK. Cancer incidence and mortality, 1973-1995: a report card for the U.S. *Cancer* 1998;82:1197-207.
16. Dignam JJ. Differences in breast cancer prognosis among African-American and Caucasian women. *CA Cancer J Clin* 2000;50:50-64.
17. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. *CA Cancer J Clin* 2000;50:7-33.
18. Eley JW, Hill HA, Chen VW, et al. Racial differences in survival from breast cancer: results of the National Cancer Institute Black/White Cancer Survival Study. *JAMA* 1994;272:947-54.
19. Elledge RM, Clark GM, Chamness GC, Osborne CK. Tumor biologic factors and breast cancer prognosis among white, Hispanic, and black women in the United States. *J Natl Cancer Inst* 1994;86:705-12.
20. Beverly LN, Flanders WD, Go RCP, Soong S-J. A comparison of estrogen and progesterone receptors in black and white breast cancer patients. *Am J Public Health* 1987;77:351-3.
21. Chen VW, Correa P, Kurman RJ, et al. Histological characteristics of breast carcinoma in blacks and whites. *Cancer Epidemiol Biomarkers Prev* 1994;3:127-35.
22. Piccinino LJ, Mosher WD. Trends in contraceptive use in the United States: 1982-1995. *Fam Plann Perspect* 1998;30:4-10, 46.
23. Wallach M, Grimes DA, eds. *Modern oral contraception*. Totowa, N.J.: Emron, 2000.
24. Wingo PA, Lee NC, Ory HW, Beral V, Peterson HB, Rhodes P. Age-specific differences in the relationship between oral contraceptive use and breast cancer. *Obstet Gynecol* 1991;78:161-70.
25. Coulter A, Vessey M, McPherson K, Crossley B. The ability of women to recall their oral contraceptive histories. *Contraception* 1986;33:127-37.

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