

Energy. Co-investigators on the Radium Hill project included Ms. A. Mylvag-
nam, Dr. D. Roder, Dr. P. Crouch, and Professor A. McMichael. The project was
supported by grants from Worksafe Australia, the Anti-cancer Foundation of
South Australia, and the Public Health Research and Development Committee of
the National Health and Medical Research Council. Dr. Pierce was supported by
Public Health Service grants R01CA51007 (National Cancer Institute) and
ES002210 (National Institute of Environmental Health Sciences) from the Na-
tional Institutes of Health, Department of Health and Human Services.

We thank Drs. Colin Muirhead and Roy Shore for their comments and sugges-
tions and Drs. Richard Adamson and Joseph Fraumeni, Jr., of the U.S. National
Cancer Institute, without whose support and encouragement this project could
not have been completed.

Manuscript received November 11, 1994; revised March 20, 1995; accepted
March 30, 1995.

Oral Contraceptives and Breast Cancer Risk Among Younger Women

*Louise A. Brinton, Janet R. Daling, Jonathan M. Liff, Janet B.
Schoenberg, Kathleen E. Malone, Janet L. Stanford, Ralph J.
Coates, Marilie D. Gammon, Louise Hanson, Robert N. Hoover**

Background: Several studies have suggested a link between oral contraceptive use and breast cancer in younger women, but it is possible that chance or bias, including selective screening of contraceptive users, contributed to the putative association. **Purpose:** Given that oral contraceptives were first marketed in the United States in the early 1960s, we conducted a population-based case-control study to examine the relationship between use of oral contraceptives and breast cancer among women in a recently assembled cohort, focusing on women younger than 45 years of age who had the opportunity for exposure throughout their entire reproductive years. **Methods:** Breast cancer patients and healthy control subjects were identified, the latter group by random-digit dialing, in Atlanta, Ga., Seattle/Puget Sound, Wash., and central New Jersey. In Seattle and New Jersey, the study was confined to women 20 through 44 years of age; in Atlanta the age range was extended through 54 years. Patients included women with in situ or invasive breast cancer newly diagnosed during the period of May 1, 1990, through December 31, 1992. In-person interviews were completed by 2203 (86.4%) of 2551 eligible patients and 2009 (78.1%) of 2571 eligible control subjects. Analyses focused on women younger than 45 years of age (1648 patients and 1505 control subjects) to maximize opportunities for extended exposure. Logistic regression analyses were used to obtain maximum likelihood estimates of relative risks (RRs) and their 95% confidence intervals (CIs). **Results:** Among women younger than 45 years, oral contraceptive use for 6 months or longer was associated with an RR for breast cancer of 1.3 (95% CI = 1.1-1.5). Risks were enhanced for breast cancers occurring prior to age 35 years (RR = 1.7; 95% CI = 1.2-2.6), with the RR rising to 2.2 (95% CI = 1.2-4.1) for users of 10 or more years. The RR for breast cancer for those whose oral contraceptive use began early (before age 18 years) and continued long-term (>10 years) was even higher (RR = 3.1; 95% CI = 1.4-6.7). The RRs observed for those who used oral contraceptives within

5 years of cancer diagnosis were higher than for those who had not, with the effect most marked for women younger than age 35 years (RR = 2.0; 95% CI = 1.3-3.1). Oral contraceptive associations were also strongest for cancers diagnosed at advanced stages. Evaluation of screening histories and methods of diagnosis failed to support the speculation that associations could be due to selective screening. Among women 45 years of age and older, no associations of risk with use of oral contraceptives were noted. **Conclusions:** The relationship between oral contraceptives and breast cancer in young women appears to have a biologic basis rather than to be an artifact or the result of bias. [J Natl Cancer Inst 87:827-835, 1995]

Although the relationship of oral contraceptives to breast cancer risk has been the topic of many epidemiologic investigations, the association remains unresolved. While numerous earlier investigations were, for the most part, reassuring, more recent studies have shown elevations in risk in relation to oral contraceptive use in certain subsets of women, the most notable being those diagnosed at young ages (1-17). Within the studies of younger women, an increased risk of breast cancer has been

**Affiliations of authors:* L. A. Brinton, R. N. Hoover, Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Md.

J. R. Daling, K. E. Malone, J. L. Stanford, Fred Hutchinson Cancer Research Center, Seattle, Wash.

J. M. Liff, R. J. Coates, Department of Epidemiology and Biostatistics, Rollins School of Public Health, Emory University, Atlanta, Ga.

J. B. Schoenberg, Special Epidemiology Program, New Jersey State Department of Health, Trenton.

M. D. Gammon, Division of Epidemiology, Columbia University School of Public Health, New York, N.Y.

L. Hanson, Westat, Inc., Rockville, Md.

Correspondence to: Louise A. Brinton, Ph.D., Environmental Epidemiology Branch, National Cancer Institute, Executive Plaza North, Rm. 443, Bethesda, MD 20892.

See "Notes" section following "References."

observed in relation to oral contraceptive use early in life (3,6,8-10,16) or for extended periods of time (2,4,7,10,12-14,16). The relative risks (RRs) in these studies have usually been less than twofold, and some of the more recent studies have found no evidence of increased risk in relation to use (18-23). This difference has led to questions about the extent to which the positive findings were influenced by chance or bias, including selective screening of users (24,25).

Since oral contraceptives were first marketed in the United States in the early 1960s, previous studies have been limited by having insufficient numbers of women with exposure to oral contraceptives early in life or for long durations. We therefore launched a study among a more recent cohort of women, focusing on those younger than 45 years of age, a group with opportunities for exposure over their entire reproductive years.

Methods

This population-based case-control study was conducted in three different geographic areas—the metropolitan areas of Atlanta, Ga. and Seattle/Puget Sound, Wash., and five counties of central New Jersey. The study protocol was approved by institutional review boards in each area and by appropriate U.S. government authorities. In Seattle and New Jersey, the study was confined to women who were 20 through 44 years of age, while in Atlanta the age range was extended through age 54 years to maximize opportunities for evaluating relationships by age and race. All women of these ages who were newly diagnosed with *in situ* or invasive breast cancer during the period May 1, 1990, through December 31, 1992, were identified through rapid-ascertainment systems. All geographic areas were covered by population-based cancer registries, and periodic checks against these registries ensured the completeness of patient ascertainment. Hospital records of eligible patients were abstracted to document details on the clinical and pathologic characteristics of the diagnosed breast cancers.

Control subjects in the three geographic areas were ascertained through a series of 13 waves of random-digit dialing (26). To select a sample of women that approximated the anticipated age distribution of patients, information was sought on female residents who were 20-44 years of age (20-54 years in Atlanta). A 90.5% response rate to the telephone screener was obtained from the 16 254 telephone numbers assessed as residential; nonresponse consisted of a 5.4% refusal to the telephone screener, 0.8% for language problems, and 3.3% contact problems. From the screener information, a stratified random sample by 5-year age groups was selected for study inclusion.

Following written informed consent, participants were interviewed in person, using a verbal questionnaire that required, on average, 67 minutes to complete. The interviewer collected detailed information regarding demographic factors, reproductive and menstrual history, contraceptive behavior, use of exogenous hormones, medical and screening history, anthropometry and physical activity, adolescent diet, alcohol consumption, smoking, occupation, family history of cancer, and certain lifestyle factors and opinions about cancer causation. In addition, participants were asked to complete a 100-item dietary questionnaire and to consent to a variety of anthropometric measurements.

To aid recall of use of oral contraceptives, a month-by-month calendar was used to document all contraceptive methods used since menarche. Pregnancies and other life events were first marked on the calendar to serve as a frame of reference for changes in contraceptive use over time. Color photographs and listings of oral contraceptives as marketed (i.e., by year introduced and color of pill) were shown to assist participants in identifying the specific types of oral contraceptives used during each episode of usage.

Completed interviews were obtained from 2203 (86.4%) of the 2551 eligible patients and 2009 (78.1%) of the 2571 eligible control subjects. Reasons for noninterview included refusals (5.4% physician refusal and 6.4% patient versus 18.5% control subject refusal), death (0.4% versus 0.2%), illness (0.6% versus 0.2%), a move outside of the study area (0.6% versus 2.3%), and other miscellaneous reasons (0.2% versus 0.8%). For patients to be comparable with the control subjects who were identified through telephone sampling, the 29 patients who indicated on interview that they did not have a residential telephone were

eliminated, leaving 2174 patients available for analysis. The overall response rate in control subjects was 70.7% (the product of the telephone screener and interview response rates).

Women who could not be interviewed personally were subsequently contacted and asked to participate in a short telephone interview or mailed a questionnaire. The major hypotheses of interest were covered, including questions about use of oral contraceptives. A total of 51 patients and 171 control subjects agreed to participate, with a median interview length of 5 minutes. The addition of the data from nonrespondents provided information for selected analyses for 88.4% of the eligible patients and 84.8% of the eligible control subjects.

Since the women were interviewed at variable times after determination of eligibility for study, all information on risk factors, including oral contraceptive usage, was truncated at the date of diagnosis for patients or the date at completion of the telephone screener interview for control subjects. The relationship of oral contraceptive use to breast cancer risk was assessed through calculation of odds ratios to approximate relative risks (RRs). Logistic regression analyses were used to obtain maximum likelihood estimates of RRs and their 95% confidence intervals (CIs) (27). Analyses involving stage of diagnosis as an outcome used polychotomous logistic regression to compare each patient group simultaneously with the entire group of control subjects (28). The significance of interactions of variables was determined by using multiplicative terms in the regression models.

Results

Since the majority of the participants were younger than 45 years of age, most analyses focused on these women. Major breast cancer risk factors included nulliparity or few full-term births (RR = 2.1 for nulliparous women compared with those with ≥ 4 births), a history of a breast biopsy specimen that proved benign (RR = 1.5), and a family history of breast cancer in a mother or sister (RR = 2.4) (Table 1). Other variables were only weakly related or unrelated to risk.

Among women younger than 45 years of age, the RR for ever versus never use of oral contraceptives was 1.2 (95% CI = 1.0-1.5). This association was not altered by removing from the referent group women who indicated that they had not taken oral contraceptives because of a medical contraindication (e.g., breast problems or circulatory problems). Since oral contraceptive use was so common among the participants younger than 45 years of age (85.0% among patients versus 82.1% among control subjects), we evaluated different referent groups with which oral contraceptive users could be compared. There was no difference in risk between women who had never used any method of contraception, those who had used birth control pills for less than 6 months (as defined by history on the contraceptive calendar), and those who had only used contraceptive methods other than oral contraceptives. We therefore combined these three groups to form the referent group for evaluating effects associated with use of oral contraceptives for 6 months or longer (hereafter referred to as users). This combined group led to a more stable referent, particularly for the young women in whom oral contraceptive use was highly prevalent.

Of the potential breast cancer risk factors shown in Table 1, the only ones that exerted any confounding influence on oral contraceptive associations were race, number of births, and age at first birth; however, the effects were minimal (Table 2). Among women younger than 45 years of age, 76.4% of the patients and 71.4% of the control subjects reported use of oral contraceptives for 6 months or longer, with an adjusted RR of 1.3 (95% CI = 1.1-1.5). In New Jersey and Seattle, the RRs associated with use of oral contraceptives were identical—i.e.,

Table 1. Distribution of risk factors and associated relative risks (RRs) of breast cancer among patients and control subjects younger than 45 years of age

Risk factor	Case patients (n = 1648)	Control subjects (n = 1505)	RR*	95% CI
Race				
White	1302	1184	1.00	
African-American	256	217	1.20	0.9-1.5
Other	90	104	0.81	0.6-1.1
No. of births				
≥4	84	126	1.00	
3	221	240	1.41	1.0-2.0
2	599	506	1.85	1.4-2.5
1	336	298	1.79	1.3-2.5
0	408	335	2.10	1.5-2.9
Age at first birth†				
<20	220	256	1.00	
20-25	373	371	1.12	0.9-1.4
25-29	361	327	1.23	0.9-1.6
≥30	285	216	1.42	1.1-1.9
No. of months breast fed‡				
None	509	445	1.00	
<12	446	422	0.96	0.8-1.2
12-23	159	168	0.85	0.6-1.1
≥24	119	128	0.92	0.7-1.3
No. of miscarriages§				
0	1047	968	1.00	
1	265	231	1.06	0.9-1.3
≥2	92	90	0.95	0.7-1.3
No. of induced abortions§				
None	1006	937	1.00	
1	276	247	0.98	0.8-1.2
≥2	122	105	1.02	0.8-1.4
Age at menarche, y				
≥14	294	306	1.00	
13	443	446	1.01	0.8-1.2
12	512	402	1.28	1.0-1.6
<12	397	350	1.17	0.9-1.4
Previous breast biopsy				
No	1486	1411	1.00	
Yes	162	94	1.52	1.1-2.0
Body mass index 				
<23	633	479	1.00	
23-26	477	447	0.80	0.7-0.9
≥27	484	474	0.76	0.6-0.9
Mother or sister with breast cancer				
No	1411	1405	1.00	
Yes	237	100	2.35	1.8-3.0
Cigarette smoker¶				
No	914	818	1.00	
Yes	734	685	0.96	0.8-1.1
Alcohol consumer#				
Abstainer	204	207	1.00	
Infrequent drinker	355	363	0.99	0.8-1.3
More frequent drinker	1089	933	1.16	0.9-1.4
Years of education				
High school or less	432	403	1.00	
Technical school	112	119	0.84	0.6-1.1
Some college	438	413	0.92	0.8-1.1
College graduate	410	367	0.94	0.8-1.2
Postgraduate work	256	203	0.99	0.8-1.3

*Standard logistic model included study site (Atlanta, New Jersey, or Seattle), age (as a continuous variable), race (white, African-American, or other), number of births (0, 1, 2, 3, or ≥4), and age at first birth (<25 or ≥25). Model for number of births, however, included only the first three variables. All other variables were entered individually to the standard model. Unknowns were included in the analyses but are not shown in table.

†Restricted to women with at least one birth.

‡Restricted to women with at least one live birth.

§Restricted to ever-pregnant women.

||Body mass index = [measured weight (kg)/measured height (m)²]. Not shown are 54 patients and 105 control subjects with missing data on weight or height.

¶Smokers defined as women who had smoked 100 cigarettes or more in their lives and who smoked on a regular basis for 6 months or longer.

#Drinkers defined as women who had drunk more than 12 drinks of alcoholic beverages in their lives. More frequent drinkers additionally had drunk at least once a month for 6 months or longer.

Table 2. Relative risks (RRs) of breast cancer by use of oral contraceptives according to varying ages of study subjects

Age, y	Patients		Control subjects		Adjusted		
	No.	% users*	No.	% users*	RR†	RR‡	95% CI
All <45	1648	76.4	1505	71.4	1.30	1.27	1.1-1.5
<35	268	76.9	291	66.3	1.64	1.74	1.2-2.6
35-39	488	77.7	474	70.9	1.44	1.36	1.0-1.8
40-44	892	75.6	740	73.6	1.13	1.12	0.9-1.4
45-49§	276	73.6	264	69.7	1.23	1.23	0.8-1.8
50-54§	250	55.2	240	59.2	0.85	0.94	0.6-1.4

*Users of oral contraceptives for 6 months or longer.

†Adjusted for age. Further adjusted for study site in women younger than 45 years of age.

‡Adjusted further for race, number of births, and age at first birth.

§All participants were from the Atlanta study site. For comparison, the adjusted RRs associated with use of oral contraceptives among younger Atlanta participants were 1.77 (95% CI = 0.8-4.0), 1.06 (95% CI = 0.6-2.0), and 1.31 (95% CI = 0.8-2.0), respectively, for the three age groups (<35, 35-39, and 40-44 years).

RR = 1.1 (95% CI = 0.8-1.5), whereas in Atlanta the RR was slightly higher (1.4; 95% CI = 0.9-1.9). Since these differences between areas were not statistically significant, further analyses concentrated on the grouped data, after controlling for study site, age, race, number of births, and age at first birth.

The RR associated with use of oral contraceptives was significantly elevated among women younger than 35 years of age (RR = 1.7; 95% CI = 1.2-2.6) (Table 2). The risk was less marked among women aged 35-39 years (RR = 1.4; 95% CI = 1.0-1.8), while among women aged 40-44 years, no significant elevation associated with oral contraceptive use was noted (RR = 1.1; 95% CI = 0.9-1.4). This interactive effect of pill use with age approached statistical significance ($P = .06$, two-sided test).

For women younger than 35 years of age, risk increased with years of use, with the RR significantly elevated for those with

10 or more years of use (Table 3). Elevated risks were associated with extended use in all three study sites (RRs for ≥ 10 years among participants of all races of 2.8 in Atlanta, 3.1 in New Jersey, and 1.5 in Seattle). Further, the effects were apparent in both white and nonwhite women. Risk also increased with years since first use; the risk rose to a significant twofold excess (95% CI = 1.2-3.4) for women with 15 or more years since first use (data not shown). In contrast, risk declined with years since last use; those reporting use within the last 5 years had an RR of 2.0 (95% CI = 1.3-3.1). Elevated risks for use within the preceding 5 years prevailed in all three study sites (RRs of 2.6 in Atlanta, 2.5 in New Jersey, and 1.5 in Seattle), but further elevations in risk were not associated with more recent usage (<2 years). Women who began using oral contraceptives prior to 18 years of age were at elevated risk (RR =

Table 3. Relative risks (RRs) and 95% CIs of breast cancer by oral contraceptive use patterns according to varying ages of patients: women younger than 45 years of age*

	<35 y			35-39 y			40-44 y			<45 y		
	No.	RR	95% CI	No.	RR	95% CI	No.	RR	95% CI	No.	RR	95% CI
No use or use for <6 months	62	1.00		109	1.00		218	1.00		389	1.00	
No. of years used												
6 mo to <5	96	1.55	0.9-2.4	189	1.32	0.9-1.8	364	1.19	0.9-1.5	649	1.27	1.1-1.5
5-9	67	1.82	1.1-3.0	120	1.57	1.1-2.3	189	1.00	0.7-1.3	376	1.27	1.0-1.6
≥ 10	43	2.25	1.2-4.1	70	1.20	0.8-1.9	121	1.14	0.8-1.6	234	1.29	1.0-1.6
No. of years since first use												
<15	137	1.63	1.1-2.5	64	1.61	1.0-2.6	23	1.43	0.7-2.9	224	1.43	1.1-1.9
15-19	67	2.02	1.2-3.4	219	1.26	0.9-1.8	148	1.17	0.8-1.6	434	1.29	1.1-1.6
≥ 20	2	3.01	0.3-34.9	96	1.47	0.9-2.2	503	1.09	0.8-1.4	601	1.19	0.9-1.5
No. of years since last use												
<5	135	2.03	1.3-3.1	106	1.46	0.9-2.2	57	1.25	0.8-2.0	298	1.47	1.2-1.8
5-9	40	1.48	0.8-2.6	72	1.33	0.9-2.0	91	1.16	0.8-1.7	203	1.29	1.0-1.7
≥ 10	31	1.20	0.6-2.2	201	1.33	0.9-1.9	526	1.10	0.9-1.4	758	1.20	1.0-1.4
Age at first use, y												
<18	72	2.20	1.3-3.7	87	1.27	0.8-1.9	75	0.99	0.7-1.4	234	1.31	1.0-1.7
18-21	87	1.41	0.9-2.2	227	1.46	1.0-2.0	374	1.11	0.9-1.4	688	1.25	1.0-1.5
≥ 22	47	2.02	1.2-3.5	65	1.21	0.8-1.9	225	1.19	0.9-1.6	337	1.30	1.0-1.6

*Adjusted for study site, age, race, number of births, and age at first birth.

2.2; 95% CI = 1.3-3.7), but there was no dose-response relationship with age at first use. In addition, there was no further increase in risk for earlier ages at first use (e.g., <16 years).

Among the women 35 years of age and older, there were no striking trends with years of use or years since first use. In addition, risk did not vary substantially by ages at first use. In both the age groups 35-39 years and 40-44 years, recent users (within the last 5 years) were at highest risk.

Among the women younger than 45 years of age, years since first use, years since last use, and age at first use were examined by years of use (Table 4). Recent users (<5 years since last use) had excess risks across most duration of use categories. A cross-tabulation of years of use with either years since first use or ages at first use revealed no distinctive patterns.

Further analyses regarding effects of use by combined parameters of usage focused on the three age-at-diagnosis groups (<35 years, 35-39 years, and 40-44 years). Since both recent and long-term users were previously identified as having some excess risk, particular attention focused on their combined effects. In the individual age groups, recentness of use did not clearly emerge as a more important determinant of risk than duration of use, even in women younger than 35 years of age. Other combined parameters of usage were also not especially informative. However, among the women younger than 35 years of age, particularly high risks were noted for long-term pill users (≥ 10 years) who had either initiated pill use prior to 18 years of age (RR = 3.1; 95% CI = 1.4-6.7) or who had 15 or more years since first pill use (RR = 3.2; 95% CI = 1.4-7.0).

Among women younger than 45 years of age, we further evaluated risk in relation to early use of oral contraceptives (Table 5). No specific patterns of risk were observed in relation to either number of years of use prior to 25 years of age, or, in parous women, to number of years of use prior to a full-term birth. Examination of these same parameters of early use among women younger than 35 years of age revealed somewhat higher risks for extended use prior to a first birth, but this finding appeared largely to reflect longer periods of total use among these women.

Information on stage of breast cancers at diagnosis (Surveillance, Epidemiology, and End Results [SEER] Program)¹ was

available for 98.1% of the patients younger than 45 years of age. A total of 14.0% were diagnosed as in situ cancers, 48.7% at local stages, and 37.3% at regional or distant stages. Among these women, the RRs associated with ever use of oral contraceptives were 0.9, 1.3, and 1.4, respectively, for the cancers diagnosed at in situ, local, and regional or distant stages (Table 6). Risks associated with 10 or more years of use were 0.9 for in situ tumors, 1.2 for local disease, and 1.5 for regional/distant cancers. A similar pattern of increasing risk with stage of disease was seen for recent oral contraceptive use. The stage distribution of patients diagnosed before they were 35 years of age was similar to cancers of patients diagnosed before they were 45 years of age. Among women who had cancers when younger than 35 years of age, the RRs associated with 10 or more years of use rose from 0.7 (95% CI = 0.1-3.8) to 2.3 (95% CI = 1.1-4.8) to 2.9 (95% CI = 1.4-6.2) for in situ, local, and regional/distant disease, respectively. Among these younger women, use within the last 5 years was associated with RRs of 1.4 (95% CI = 0.6-3.7) for in situ cancer, 2.2 (95% CI = 1.3-3.9) for local disease, and 2.1 (95% CI = 1.2-3.8) for regional/distant disease.

Among African-Americans, who accounted for 15.0% of the women younger than age 45 years and 70.9% of the nonwhites, the RR associated with use of oral contraceptives was 1.3 (95% CI = 0.9-2.0), while the RRs associated with less than 5, 5-9, and 10 or more years were 1.0, 1.6, and 1.8, respectively. Comparable risks among the whites were 1.2 (95% CI = 1.0-1.5) for ever use and 1.3, 1.2, and 1.2 for the three categories of duration of use, respectively. Recent usage (within the last 5 years) was associated with an RR of 1.6 among African-Americans and 1.4 among whites. Among women younger than 35 years of age, the RRs associated with 5 or more years of use of oral contraceptives were 2.1 (95% CI = 0.6-7.3) among African-Americans (based on only 29 exposed patients) and 2.1 (95% CI = 1.2-3.5) among whites (75 exposed patients). Among these younger women, recent use was somewhat more strongly related to risk in whites (RR = 2.4; 95% CI = 1.4-4.0) compared with African-Americans (RR = 1.4; 95% CI = 0.4-4.5).

Attempts were also made to determine whether the associations between oral contraceptive use and breast cancer were

Table 4. Relative risks (RRs) and 95% CIs* of breast cancer by combined measures of oral contraceptive use patterns: women younger than 45 years of age

	Used 6 mo to <5 y		Used 5-9 y		Used ≥ 10 y	
	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)
No. of years since first use						
<15	136	1.44 (1.1-1.9)	66	1.55 (1.0-2.3)	22	1.27 (0.7-2.4)
15-19	221	1.14 (0.9-1.4)	120	1.45 (1.1-2.0)	93	1.58 (1.1-2.2)
≥ 20	292	1.29 (1.0-1.6)	190	1.10 (0.8-1.4)	119	1.11 (0.8-1.5)
No. of years since last use						
<5	80	1.66 (1.1-2.4)	87	1.49 (1.0-2.1)	131	1.37 (1.0-1.8)
5-9	66	1.28 (0.9-1.9)	71	1.49 (1.0-2.2)	66	1.13 (0.8-1.7)
≥ 10	503	1.21 (0.9-1.5)	218	1.14 (0.9-1.5)	37	1.34 (0.8-2.3)
Age at first use, y						
<18	79	1.04 (0.7-1.5)	80	1.55 (1.1-2.2)	75	1.47 (1.0-2.2)
18-21	342	1.32 (1.1-1.6)	224	1.21 (0.9-1.5)	122	1.12 (0.8-1.5)
≥ 22	228	1.29 (1.0-1.6)	72	1.21 (0.8-1.8)	37	1.68 (0.9-3.0)

*Adjusted for study site, age, race, number of births, and age at first birth. All risks relative to women with no use or use of oral contraceptives for less than 6 months (389 patients and 431 control subjects).

Table 5. Relative risks (RRs) of breast cancer by use of oral contraceptives at young ages: women younger than 45 years of age

Use	Patients	Control subjects	RR*	95% CI
None or <6 mo prior to age 25 y	389	431	1.00	
Prior to age 25 y				
6 mo to <2 y	359	296	1.34	1.1-1.6
2-3 y	358	341	1.13	0.9-1.4
4-5 y	278	239	1.24	0.9-1.6
≥6 y	164	128	1.43	1.1-1.9
Only after age 25 y				
6 mo to <2 y	36	26	1.46	0.9-2.5
2-3 y	42	21	2.11	1.2-3.6
4-5 y	11	9	1.19	0.5-2.9
≥6 y	11	14	0.72	0.3-1.6
None or <6 mo prior to first live birth†	274	322	1.00	
Prior to a first birth†				
6 mo to <2 y	243	201	1.40	1.1-1.8
2-3 y	186	177	1.21	0.9-1.6
4-5 y	141	92	1.67	1.2-2.3
≥6 y	155	132	1.27	0.9-1.7
Only after a first birth†				
6 mo to <2 y	82	69	1.52	1.0-2.2
2-3 y	45	50	1.10	0.7-1.7
4-5 y	38	35	1.31	0.8-2.2
≥6 y	75	92	0.94	0.7-1.4

*Adjusted for study site, age, race, number of births, and age at first birth.

†Analysis is restricted to parous women.

Table 6. Relative risks (RRs)* and 95% CIs of breast cancer by use of oral contraceptives according to stage of breast cancer at diagnosis: women younger than 45 years of age

	Stage at diagnosis†					
	In situ		Local		Regional/distant	
	No. of patients	RR (95% CI)	No. of patients	RR (95% CI)	No. of patients	RR (95% CI)
Ever use						
None or <6 mo	65	1.00	182	1.00	135	1.00
≥6 mo	162	0.92 (0.7-1.3)	605	1.33 (1.1-1.6)	468	1.37 (1.1-1.7)
Length of use						
6 mo to <5 y	81	0.90 (0.6-1.3)	311	1.32 (1.1-1.7)	247	1.37 (1.1-1.8)
5-9 y	51	0.99 (0.7-1.5)	189	1.40 (1.1-1.8)	129	1.25 (0.9-1.7)
≥10 y	30	0.88 (0.5-1.4)	105	1.24 (0.9-1.7)	92	1.53 (1.1-2.1)
No. of years since last use						
<5	30	0.92 (0.6-1.5)	138	1.43 (1.1-1.9)	121	1.76 (1.3-2.4)
5-9	26	0.90 (0.6-1.5)	93	1.28 (0.9-1.8)	81	1.50 (1.1-2.1)
≥10	106	0.92 (0.6-1.3)	374	1.30 (1.0-1.6)	266	1.20 (0.9-1.5)

*Adjusted for study site, age, race, number of births, and age at first birth.

†Excludes 31 patients with unknown stages at diagnosis (seven nonusers of oral contraceptives and 24 users).

modified by other breast cancer risk factors. Among women younger than 45 years of age, there was no evidence of any effect modification. However, among the women younger than 35 years, extended use of oral contraceptives appeared to exert stronger effects in those with a mother or a sister with breast cancer, although the interaction was not statistically significant. Among women with an affected relative, use of oral contraceptives for 5 or more years was associated with an RR of 3.1 (95% CI = 0.7-13.6) compared with an RR of 1.9 (95% CI = 1.2-3.1) among those without such a family history. This and other interactions will be explored more fully in future analyses.

Because of concerns that any excess risks for oral contraceptive users might be linked with more intensive screening, we examined the effect of several surveillance methods used at least 1 year prior to diagnosis or interview. Study participants younger than 45 years of age who reported performing breast self-examinations (79.1% of control subjects) were at somewhat reduced risk (RR = 0.9; 95% CI = 0.7-1.0), but those who had a mammogram (48.7% of control subjects) were at somewhat elevated risk (RR = 1.2; 95% CI = 1.0-1.4). Although women who regularly practiced breast self-examination were more likely to have used oral contraceptives (73.5%) than those who did

not examine themselves (63.2%), the differences in oral contraceptive history according to mammography history were less marked (73.7% versus 69.3%, respectively, for those with and without a prior mammogram). There was no substantial confounding of the oral contraceptive risks by either breast self-examination or mammography history, for either the women younger than 45 years of age or those younger than 35 years of age. Further, there was no evidence that oral contraceptive effects were stronger in women with more intensive screening histories. For instance, among the women younger than 45 years of age, the RRs associated with 10 or more years of use were 1.5 and 1.1, respectively, for those without and with a previous mammogram, and 1.5 and 1.2, respectively, for those without and with previous breast self-examinations. Effects of recent use varied little by screening history (1.5 and 1.4, respectively, for women without and with a previous mammogram and 1.7 and 1.4, respectively, for women without and with previous breast self-examinations).

We also assessed the possibility of detection bias by examining methods by which breast cancers were detected. For the patients younger than 45 years of age, detection methods included breast self-examination (33.8% of patients), accidental self-discovery by either the patient or her partner (32.5%), routine mammography (19.1%), routine physical examination (8.1%), and miscellaneous ways (5.4%). There was no evidence that tumors were more often detected by medical methods in oral contraceptive users compared with nonusers, with the respective percentages in users and nonusers being 7.9% and 8.7%, respectively, for routine physical examination, and 18.4% and 21.3%, respectively, for routine mammography. Methods of detection for patients diagnosed prior to 35 years of age also did not vary by oral contraceptive history. Further assessment of effects of different patterns of use of oral contraceptives according to methods of diagnosis also did not support the theory of detection bias. For instance, among women whose cancers were diagnosed accidentally, the RR associated with ever use of oral contraceptives was 1.3 among women younger than age 45 years and 2.0 among those younger than age 35 years. There was little variation among this subset compared with the total patient series with respect to long-term (RR for ≥ 10 years: 1.5 for women < 45 years and 2.7 for those < 35 years) or recent use (RR for < 5 years: 1.7 for women < 45 years and 2.5 for those < 35 years).

Selection bias was evaluated by assessing oral contraceptive use among the nonrespondents to the personal interview who agreed to participate in the short telephone interview. Although the nonrespondent control subjects were slightly more likely than patients to report ever use of oral contraceptives (74.5% and 69.0%, respectively), this differential did not explain the previously observed excesses associated with use. Among the 16 women younger than 35 years of age who completed the nonrespondent questionnaire, the rate of use of oral contraceptives was higher among patients (75.0%) than among control subjects (50%).

Among women 45 years of age and older, all of whom were from Atlanta, the adjusted RRs associated with ever use of oral contraceptives were 1.2 for women aged 45-49 years and 0.9 for women aged 50-54 (see Table 2). There were no specific trends

with any of the measures of oral contraceptive use (data not shown). For instance, the RRs for varying categories of duration of use were 1.0 (95% CI = 0.7-1.3) for less than 5 years, 1.0 (95% CI = 0.7-1.5) for 5-9 years, and 1.1 (95% CI = 0.7-1.6) for 10 or more years. Similarly, no specific trends were observed with years since first use or age at first use of oral contraceptives. These relationships were not altered by adjustment for screening histories, and associations did not vary substantially by methods of detection of the tumors. Only two patients reported use of oral contraceptives within the last 5 years, preventing assessment of effects associated with recent use.

Discussion

In this study, which was designed to evaluate the relationship of various parameters of usage to early-onset breast cancers, we found that oral contraceptives were associated with a modest increase in risk of breast cancers occurring among women younger than 45 years of age (RR = 1.3). Further increases in risk in this age group were not seen with extended use of oral contraceptives, leading to caution in interpretation of the findings. However, oral contraceptives were more strongly linked to cancers diagnosed prior to age 35 years. In this group, more than twofold excess risks were observed for recent users as well as those with 10 or more years of use. These findings are consistent with a number of other recent studies that have shown that oral contraceptives are associated with increased risk among very young women, although in several of these studies the magnitude of risk was somewhat lower than that observed in our study. Groups at risk from oral contraceptive use in the case-control studies have included women aged 32 years or younger (8), younger than ages 35-37 years (1,7,9,10,12,15-17), younger than age 40 years (11), younger than age 45 years (2-5), ages 20-49 years (14), premenopausal women (6), and those with premenopausal, bilateral disease (13). However, within these studies the patterns of use that have been related to excess risk have been somewhat inconsistent, leading to some doubt about the reality of the association. In addition, among older women, a few investigations have shown decreases in risk with either increasing intervals since first or last use of oral contraceptives (11,15). These patterns have been interpreted as support for the belief that oral contraceptives merely advance the presentation of disease rather than acting as true causal factors (15).

Our data failed to show a decreased risk associated with oral contraceptive use among older women. In addition, our results failed to support the theory that associations were due to either detection or screening biases. Alternative explanations for the increased risk associated with oral contraceptive use among younger women must therefore be sought, including effects of timing of use and of the influence of additional breast cancer risk factors.

Several studies have suggested that the critical exposure among younger women might be use of oral contraceptives at young ages, including young ages at first use (6), use prior to age 25 years (9), use before age 20 years (10), use before a first full-term pregnancy (3,8,29), or use within 5 years of menarche (16). In our study, among all women younger than 45 years of age, neither duration of use nor use at an early age were par-

ticularly predictive of risk. A fairly consistent finding across all age groups was some increase in risk with recent use, similar to results from one recent cohort study (30). This pattern of risk suggests that oral contraceptives might promote the growth of existing tumors. However, it is unclear why risks were particularly enhanced among the women younger than 35 years of age, where risk appeared affected not only by recentness but also by duration of use. Thus, among these younger women, risk increased to more than a twofold excess for users of 10 or more years, and was particularly elevated among long-term users who had initiated use prior to age 18 years. Our results thus confirm and expand on several other investigations that have shown remarkably similar relationships of young-onset breast cancer with long durations of use of oral contraceptives (7,10,12,16). Whether the greater risk associated with oral contraceptives in younger women is due to use patterns or to distinct disease characteristics (e.g., hormone receptor status or proliferative activity) remains to be determined. Studies have also suggested a differential effect of other risk factors among younger women (31), which was confirmed in this study. For instance, effects of limited numbers of births were attenuated among the women younger than 35 years of age and those of obesity and family history of breast cancer were enhanced. Although the effects of oral contraceptives in younger women were stronger in women with a family history of breast cancer, consistent with several other studies (5,16,32), this interaction did not explain the high risks in women younger than 35 years of age. Future analyses will focus on whether use of certain pills might be involved or whether the effects are explained by unique tumor characteristics. It is doubtful, however, that the relationship will be explained by use of higher dose preparations, since the majority of these younger women would have initiated pill use during an era when both estrogen and progestin doses would have been reduced. Of further interest is our finding that oral contraceptive associations were stronger for more advanced tumors, consistent with observations from several other studies (1,30,33) and with evidence that oral contraceptives can induce cell proliferation (33). However, the relationships with stage are difficult to reconcile, with recent declines in breast cancer mortality rates among white women in the United States (34) as well as with studies showing that oral contraceptive users tend to have tumors that are smaller and less often late-stage than nonusers (10,12,17,24,35).

Because African-American women younger than 40 years of age have higher incidence rates of breast cancer than white women (a trend that is reversed at older ages) (31), we examined relationships of oral contraceptive use by race. Several studies have shown that effects of oral contraceptive use are somewhat higher among African-Americans (36) or nonwhites (5) than among whites. The present study showed that among women younger than 45 years of age, oral contraceptive associations were slightly higher for African-Americans than for whites, although the risk estimates were not significantly different. However, among women younger than 35 years of age, the risks associated with 5 or more years of use were identical for African-Americans and whites. Because of limited numbers, it was not possible to examine in detail various exposure

measures in African-Americans, necessitating additional studies with larger numbers of nonwhite women.

In attempting to assess the reality of an excess risk associated with oral contraceptive use among younger women, this study was able to evaluate a number of alternative explanations. As previously discussed, surveillance bias did not appear to explain our findings. In addition, it is unlikely that confounding explained our associations, since the study collected extensive information on a variety of possible risk factors and none of the factors exerted any substantial confounding influence on the oral contraceptive relationships. This analysis included adjustment for various recently hypothesized risk factors, including history of induced abortions, breast feeding practices, interval since the last pregnancy, and alcohol consumption. The possibility of recall bias was assessed through eliminating women who indicated that they thought that breast cancer was caused by oral contraceptive use. However, since this analysis resulted in elimination of a substantial number of study participants, particularly patients with long durations of use (37), an alternative approach to evaluating this bias was to examine interview-participation rates according to oral contraceptive histories. Thus, it was reassuring that there was no evidence of selective participation based on the short interview completed by nonrespondents. However, further consideration of the adequacy of patient responses will involve a comparison of respondent information on oral contraceptive use with that recorded in medical records of selected women. If similar to previous such analyses, this analysis should provide good concordance between the two sources of information (38-40).

Although several previous studies have suggested that long-term oral contraceptive use increases risk for early-onset breast cancer, it has been unclear to what extent findings could be explained by extraneous factors, including various sources of bias. Our results indicate that chance or bias are unlikely explanations for the observed excesses of early-onset breast cancers among long-term or recent users of oral contraceptives. Fortunately, however, since the absolute risk of developing breast cancer in women younger than 35 years of age is relatively low, the usage patterns at the levels observed in our study would result in only about 0.1 additional cases per year for every 10 000 women in the general population. Nonetheless, it is critical that studies determine why young women might be especially susceptible to effects of oral contraceptives. These studies should include an assessment of tumor characteristics as well as effects of usage of specific preparations. Further, it will be important to monitor whether these excess risks persist as this cohort of women ages.

References

- (1) Kay CR, Hannaford PC: Breast cancer and the pill—a further report from the Royal College of General Practitioners' oral contraception study. *Br J Cancer* 58:675-680, 1988
- (2) Lund E, Meirik O, Adami HO, et al: Oral contraceptive use and premenopausal breast cancer in Sweden and Norway: possible effects of different pattern of use. *Int J Epidemiol* 18:527-532, 1989
- (3) McPherson K, Vessey MP, Neil A, et al: Early oral contraceptive use and breast cancer: results of another case-control study. *Br J Cancer* 56:653-660, 1987
- (4) Meirik O, Lund E, Adami HO, et al: Oral contraceptive use and breast cancer in young women. A joint national case-control study in Sweden and Norway. *Lancet* 2:650-654, 1986

- (5) Miller DR, Rosenberg L, Kaufman DW, et al: Breast cancer before age 45 and oral contraceptive use: new findings [see comment citation in Medline]. *Am J Epidemiol* 129:269-280, 1989
- (6) Olsson H, Moller TR, Ranstam J: Early oral contraceptive use and breast cancer risk among premenopausal women: final report from a study in southern Sweden. *J Natl Cancer Inst* 81:1000-1004, 1989
- (7) Paul C, Skegg DC, Spears GF: Oral contraceptives and risk of breast cancer. *Int J Cancer* 46:366-373, 1990
- (8) Pike MC, Henderson BE, Casagrande JT, et al: Oral contraceptive use and early abortion as risk factors for breast cancer in young women. *Br J Cancer* 43:72-76, 1981
- (9) Pike MC, Henderson BE, Krailo MD, et al: Breast cancer in young women and use of oral contraceptives: possible modifying effect of formulation and age at use. *Lancet* 2:926-930, 1983
- (10) Rookus MA, van Leeuwen FE: Oral contraceptives and risk of breast cancer in women aged 20-54 years. The Netherlands Oral Contraceptives and Breast Cancer Study Group [see comment citation in Medline]. *Lancet* 344:844-851, 1994
- (11) Rosenberg L, Palmer JR, Clarke EA, et al: A case-control study of the risk of breast cancer in relation to oral contraceptive use. *Am J Epidemiol* 136:1437-1444, 1992
- (12) Oral contraceptive use and breast cancer risk in young women. UK National Case-Control Study Group [see comment citations in Medline]. *Lancet* 6:973-982, 1989
- (13) Ursin G, Aragaki CC, Paganini-Hill A, et al: Oral contraceptives and premenopausal bilateral breast cancer: a case-control study. *Epidemiology* 3:414-419, 1992
- (14) Weinstein AL, Mahoney MC, Nasca PC, et al: Breast cancer risk and oral contraceptive use: results from a large case-control study [see comment citation in Medline]. *Epidemiology* 2:353-358, 1991
- (15) Wingo PA, Lee NC, Ory HW, et al: Age-specific differences in the relationship between oral contraceptive use and breast cancer. *Cancer* 71:1506-1517, 1993
- (16) White E, Malone KE, Weiss NS, et al: Breast cancer among young U.S. women in relation to oral contraceptive use. *J Natl Cancer Inst* 86:505-514, 1994
- (17) Breast cancer and combined oral contraceptives: results from a multinational study. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives [see comment citation in Medline]. *Br J Cancer* 61:110-119, 1990
- (18) Clavel F, Andrieu N, Gairard B, et al: Oral contraceptives and breast cancer: a French case-control study. *Int J Epidemiol* 20:32-38, 1991
- (19) Ewertz M: Oral contraceptives and breast cancer risk in Denmark. *Eur J Cancer* 28A:1176-1181, 1992
- (20) Harris RE, Zang EA, Wynder EL: Oral contraceptives and breast cancer risk: a case-control study. *Int J Epidemiol* 19:240-246, 1990
- (21) Schildkraut JM, Hulka BS, Wilkinson WE: Oral contraceptives and breast cancer: a case-control study with hospital and community controls [see comment citation in Medline]. *Obstet Gynecol* 76:395-402, 1990
- (22) Stanford JL, Brinton LA, Hoover RN: Oral contraceptives and breast cancer: results from an expanded case-control study. *Br J Cancer* 60:375-381, 1989
- (23) Vessey MP, McPherson K, Villard-Mackintosh L, et al: Oral contraceptives and breast cancer: latest findings in a large cohort study. *Br J Cancer* 59:613-617, 1989
- (24) Schlesselman JJ, Stadel BV, Korper M, et al: Breast cancer detection in relation to oral contraception. *J Clin Epidemiol* 45:449-459, 1992
- (25) Skegg DC: Potential for bias in case-control studies of oral contraceptives and breast cancer [see comment citation in Medline]. *Am J Epidemiol* 127:205-212, 1988
- (26) Waksberg J: Sampling methods for random digit dialing. *J Am Stat Assoc* 73:40-46, 1978
- (27) Breslow NE, Day NE: Statistical methods in cancer research. Volume 1 - The analysis of case-control studies. IARC Sci Publ 32:5-338, 1980
- (28) Dubin N, Pasternack BS: Risk assessment for case-control subgroups by polychotomous logistic regression. *Am J Epidemiol* 123:1101-1117, 1986
- (29) Rohan TE, McMichael AJ: Oral contraceptive agents and breast cancer: a population-based case-control study. *Med J Aust* 149:520-526, 1988
- (30) 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* 81:1313-1321, 1989
- (31) Velentgas P, Daling JR: Risk factors for breast cancer in younger women. *Monogr Natl Cancer Inst* 16:15-22, 1994
- (32) Oral contraceptive use and breast cancer risk in young women: subgroup analyses. UK National Case-Control Study Group. *Lancet* 335:1507-1509, 1990
- (33) Olsson H, Ranstam J, Baldetorp B, et al: Proliferation and DNA ploidy in malignant breast tumors in relation to early contraceptive use and early abortions. *Cancer* 67:1285-1290, 1991
- (34) Smigel K: Breast cancer death rates decline for white women [news]. *J Natl Cancer Inst* 87:173, 1995
- (35) Vessey M, Baron J, Doll R, et al: Oral contraceptives and breast cancer: final report of an epidemiological study. *Br J Cancer* 47:455-462, 1983
- (36) Mayberry RM, Stoddard-Wright C: Breast cancer risk factors among black women and white women: similarities and differences. *Am J Epidemiol* 136:1445-1456, 1992
- (37) Brinton LA, Malone KE, Stanford KE, et al: Re: Should we consider a subject's knowledge of the etiologic hypothesis in the analysis of case-control studies? [letter; see comment citation in Medline] *Am J Epidemiol* 140:1054-1056, 1994
- (38) Coulter A, Vessey M, McPherson K: The ability of women to recall their oral contraceptive histories. *Contraception* 33:127-137, 1986
- (39) Rosenberg MJ, Layde PM, Ory HW, et al: Agreement between women's histories of oral contraceptive use and physician records. *Int J Epidemiol* 12:84-87, 1983
- (40) Stolley PD, Tonascia JA, Sartwell PE, et al: Agreement rates between oral contraceptive users and prescribers in relation to drug use histories. *Am J Epidemiol* 107:226-235, 1978

Notes

¹*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

We gratefully acknowledge invaluable input on the study design from Drs. Donna Brogan, Tim Byers, Virginia Ernster, Jennifer Kelsey, Nancy Potoschman, Bruce Stadel, Christine Swanson, and Dimitrios Trichopoulos. Successful management of the project was due to the efforts of Florence Wilson and Betsy Bridgman in Atlanta, Tom English in New Jersey, and Diane Setterholm in Seattle, who worked with an extremely competent group of interviewers. The integrity of data was further assured by the following individuals at Westat, Inc.: Elizabeth Lovoy, Eric Mehl, Linea Efner, and Diana Seybolt. Finally, we thank the many women who graciously agreed to participate in this study.

Manuscript received October 12, 1994; revised March 31, 1995; accepted March 31, 1995.

Get regular mammograms starting at age 50.



A message from the National Cancer Institute's Cancer Information Service and National Black Leadership Initiative on Cancer. Call 1-800-4-CANCER for more information.