Do Oral Contraceptive Agents Affect The Risk Of Breast Cancer? A Meta-Analysis Of The Case-Control Reports

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Abstract: ***Background:*** **We designed a study to assess the association of oral contraceptive use and the development of breast cancer for women in the following groups: (1) ever oral contraceptive users, (2) long-term oral contraceptive users, and (3) oral contraceptive users before a first full-term pregnancy.**

Methods: **A MEDLINE search of studies published in English from 1966 to 1990 was conducted using the following key words: "oral contraceptive and breast carcinoma." Eligible studies included all published case-control reports of nonduplicated data on a population (hospital or community-based). The following data were extracted from each report: country, age of subjects, number of cases and controls, whether it was a hospital or community-based study, and results. Two evaluators using a quality-assessment instrument independently and blindly reviewed the methods and data analysis section from each eligible study. In the category of "ever oral contraceptive users," an estimate of the pooled relative risk with 95 percent confidence intervals (CIs) was calculated. In the categories of "duration of oral contraceptive use" and "duration of oral contraceptive use before a first full-term pregnancy," Spearman's rank correlation coefficient (r_s) was calculated.**

Results: **For the categories of "ever oral contraceptive users" and "long-term oral contraceptive users," no association between the use of oral contraceptives and the development of breast cancer could be detected (pooled relative risk "ever oral contraceptive users" = 1.07, 95 percent CI 0.78 to 1.36, r_s "duration of use" -0.153, $P = 0.189$). For the category of "oral contraceptive use before a first full-term pregnancy," a significant correlation was found ($r_s = +0.497$, $P = 0.011$).**

Many reports failed to demonstrate adequate protection against the biases most relevant to case-control methods (namely, recall bias, interviewer bias, surveillance bias, and nonresponse bias) and therefore received low-quality scores.

Conclusions: **This meta-analysis suggests a possible increased risk for breast cancer in women who use oral contraceptives before a first full-term pregnancy. The data, however, are confounded by studies that are generally of low quality. Further studies addressing the risk for breast cancer in oral contraceptive users need to be designed with methods that limit the biases inherent in case-control studies. (J Am Board Fam Pract 1993; 6:123-135.)**

Approximately 1 of every 9 women will develop breast cancer. In the United States 175,000 new cases of breast cancer were diagnosed and 44,500 women died of the disease in 1991.[1] Epidemiologic studies have elucidated risk factors relevant to this disease. Those risk factors highly associated with breast cancer (relative risk [RR] > 4.0) are age greater than 40 years, country of birth (particularly North American and Northern European), family history of premenopausal breast cancer, and history of cancer in one breast.[2] Other factors associated with an increased risk for breast cancer are upper socioeconomic class, having never been married, urban residence, white race, age greater than 30 years at a first full-term pregnancy, early age at menarche, late age at menopause, postmenopausal obesity, history of fibrocystic breast disease, any first-degree relative with breast cancer, history of primary cancer of the ovary or endometrium, large doses of radiation to the chest, and ethanol consumption.[2-17]

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Despite this knowledge only about one-fourth of breast cancer cases can be accounted for by known risk factors.[18] In an effort to understand the epidemiology of breast cancer, as well as possibly providing recommendations for prevention, researchers have continued to try to identify other risk factors.

An area of research that has received considerable attention since the 1970s has been the investigation of the association of oral contraceptive use and the development of breast cancer. Epidemiologic studies have provided both direct and indirect evidence that exogenous and endogenous hormones play an important oncogenic role in the development of breast cancer.[19-22] Recently a meta-analysis on the effect of estrogen replacement therapy implicated an increased risk of breast cancer for certain subgroups of women.[23] It is not surprising, therefore, that oral contraceptives have been implicated in the cause of breast cancer.

Epidemiologic studies investigating oral contraceptive use and the risk for breast cancer have yielded conflicting conclusions. Many reviews of this literature have been published.[22,24-37] More than 70 case-control and cohort reports have been published that address these issues.[38-109] Most studies detect no increased risk for breast cancer in "ever users" versus "never users" of oral contraceptives, whereas a few report an increased risk. Additionally, many of these studies have investigated oral contraceptive use and risk for breast cancer in subgroups of women who might be more susceptible to possible carcinogenic effects of oral contraceptives.[19-22] Subgroups that have been researched extensively include women who have used oral contraceptives for long durations and who have used oral contraceptives prior to a first full-term pregnancy. The results of these studies have yielded conflicting conclusions. The purpose of this study was to combine the epidemiologic data from published (English language) case-control reports by using the technique of meta-analysis[110,111] to produce a qualitative and quantitative evaluation and summary of the data on the association of oral contraceptive use and the risk for developing breast cancer.

Methods

Literature Review

A MEDLINE search of studies published in English from 1966 to 1990 was conducted using the following key words: "oral contraceptive and breast carcinoma." Articles were selected that reported data on the association of oral contraceptive use and the risk for breast cancer. The reference list of each retrieved report was scanned for potential additional reports. The authors of all retrieved reports were contacted and asked whether they were aware of any published or unpublished work related to this subject. A manual search of *Index Medicus* was performed as well. Eligible studies included all published case-control reports of nonduplicated data on a population (hospital- or community-based) in which an oral contraceptive was studied for its effect on breast cancer. Noneligible studies included case series, anecdotes, nonexperimental designs, cohort studies, and interim case-control studies with data included in a later report. Sixty-one case-control reports[38-98] were selected using this search strategy. Thirty-eight contained case-control analyses with nonduplicated data and were eligible for inclusion in the meta-analysis. Twenty-three studies were determined ineligible. Of the ineligible studies 15* contained data used in one of the eligible studies and eight† reported data only on subgroups that were not evaluated in this meta-analysis. In several instances only the interim report contained data on a subgroup that was analyzed in this study and therefore remained eligible for inclusion in that subgroup analysis. Table 1 lists all case-control reports and the following data from each report: author, year of publication, years in which cases were diagnosed, age of subjects, country, number of cases and controls, and whether it was a hospital- or community-based study.

Quality Assessment

Two evaluators independently reviewed the methods and data analysis section for each eligible study. Ineligible studies were also independently assessed because the methods section of some of the reports referred to previous reports for more complete details on the methods used. If the interim report received a higher score, this score was given to the eligible study. All identifying information was removed (i.e., journal, authors, study sites, and dates) to keep each

*References 39-41, 44, 50, 54, 61, 62, 69, 71, 93-96.
†References 65, 68, 75, 76, 82, 83, 86, 87, 91.

Table 1. Case-Control Studies on Oral Contraceptives and Breast Cancer.

Author	Year	Diagnoses of Cases	Age (years)	Country	Cases	Controls	C/H†
Alexander, et al.[38]	1987	1978 – 1984	45 – 64	England	186	724	C
Brinton, et al.*[39]	1979	1973 – 1975	≥ 35	USA	543	1422	C
Brinton, et al.*[40]	1982	1973 – 1977	≥ 35	USA	963	858	C
CASH*[41]	1983	1980 – 1981	20 – 54	USA	689	1077	C
CASH[42]	1986	1980 – 1982	20 – 54	USA	4711	4676	C
CASH/Murray, et al.[68]	1989	1980 – 1982	20 – 54	USA	554/777	280/595	C
CASH/Schlesselmann, et al.*[82]	1987	1980 – 1982	20 – 54	USA	72	132	C
CASH/Schlesselman, et al.*[83]	1988	1980 – 1982	20 – 54	USA	4714	4540	C
CASH/Stadel, et al.[85]	1985	1980 – 1982	20 – 54	USA	2088	2065	C
CASH/Stadel, et al.*[86]	1988	1980 – 1982	20 – 54	USA	2945	2646	C
CASH/Stadel, et al.[87]	1989	1980 – 1982	20 – 54	USA	2881	2599	C
Ellery[43]	1986	1980 – 1982	25 – 64	Australia	141	279	C
Fasal & Paffenbarger, et al.*[44]	1975	1970 – 1972	< 50	USA	452	872	H
Harris N, et al.[45]	1982	1977 – 1978	35 – 54	USA	112	469	C
Harris R, et al.[46]	1990	1979 – 1981	< 50	USA	401	519	H
Henderson, et al.[47]	1974	1971 – 1973	< 65	USA	308	308	C
Hennekens, et al.[48]	1984	1960 – 1976	30 – 55	USA	989	9890	H
Janerich, et al.[49]	1983	1974 – 1976	≤ 45	USA	278	520	C
Jick, et al.*[50]	1980	1975 – 1978	≤ 56	USA	102	181	H
Jick, et al.[51]	1989	1975 – 1983	< 43	USA	127	174	H
Kelsey, et al.[52]	1978	1971 – 1973	20 – 44	USA	99	99	H
LeVecchia, et al.*[54]	1986	1982 – 1985	< 60	Italy	776	1282	H
LeVecchia, et al.[56]	1989	1973 – 1988	< 60	Italy	1517	1351	H
Le, et al.[56]	1984	1982 – 1984	≤ 45	France	240	305	H
Le, et al.[57]	1989	1982 – 1985	25 – 45	France	51	95	H
Lee, et al.[58]	1987	1982 – 1984	25 – 58	Costa Rica	171	826	C
Lees, et al.[59]	1978	1971 – 1974	30 – 49	Canada	301	548	H
Lubin, et al.[60]	1982	1976 – 1977	30 – 80	Canada	577	826	C
Lund, et al.*[61]	1989	1984 – 1985	22 – 44	Sweden	317/105	317/210	C
McPherson, et al.*[62]	1983	1980 – 1983	< 45	England	247	247	H
McPherson, et al.[63]	1987	1980 – 1983	≤ 64	England	351/774	351/774	H
Meirik, et al.[64]	1986	1984 – 1985	< 45	Sweden, Norway	722	722	C
Meirik, et al.*[65]	1989	1984 – 1985	< 45	Sweden, Norway	722	722	C
Miller, et al.[66]	1986	1977 – 1983	22 – 44	USA	521	521	H
Miller, et al.[67]	1989	1983 – 1986	25 – 44	USA	424	424	H
Olsson, et al.*[69]	1985	1979 – 1983	< 45	Sweden	225	225	C
Olsson, et al.[70]	1989	1979 – 80/1982 – 85	< 46	Sweden	459	459	C
Paffenbarger, et al.*[71]	1977	1970 – 1972	< 50	USA	872	872	H
Paffenbarger, et al.[72]	1980	1970 – 1977	any age	USA	3391	3391	H
Paul, et al.[73]	1986	1983 – 1985	25 – 54	New Zealand	897	897	C
Paul, et al.[74]	1990	1983 – 1987	25 – 54	New Zealand	1864	1864	C
Pike, et al.[75]	1981	1972 – 1978	< 33	USA	270	270	C
Pike, et al.*[65]	1983	1972 – 1982	< 37	USA	314	314	C
Ravnihar, et al.[77]	1979	1972 – 1974	20 – 49	Yugoslavia	380	380	H
Ravnihar, et al.[78]	1988	1980 – 1983	24 – 54	Yugoslavia	1989	1989	H
Rohan & McMichael[79]	1988	1982 – 1984	20 – 69	Australia	386	386	C
Rosenberg, et al.[80]	1984	1976 – 1981	20 – 59	USA	5026	5026	H
Sartwell, et al.[81]	1977	1969 – 1972	20 – 74	USA	376	376	H
Schidkraut, et al.[84]	1990	1977 – 1978	< 60	USA	1466	1466	C/H
Stanford, et al.[88]	1989	1973 – 1980	≥ 35	USA	2183	2183	C
Talamini, et al.[89]	1990	1979 – 1986	< 62	10 countries	13072	13072	H
UK National[91]	1989	1982 – 1985	< 36	England	755	755	C
UK National[92]	1989	1982 – 1985	< 36	England	755	755	C
Vessey, et al.*[93]	1972	1968 – 1971	16 – 50	England	90	180	H
Vessey, et al.*[94]	1975	1968 – 1974	16 – 50	England	412	322	H
Vessey, et al.*[95]	1979	1968 – 1977	16 – 50	England	707	707	H
Vessey, et al.*[96]	1982	1968 – 1980	16 – 50	England	1176	1176	H
Vessey, et al.*[97]	1983	1968 – 1980	16 – 50	England	1176	1176	H
Yuan, et al.[98]	1988	1984 – 1985	20 – 69	China	534	534	C

*Data not used in analyses.

†C = community-based case-control study, H = hospital-based case-control study, CASH = Cancer and Steroid Hormone Study.

evaluation blind. The criteria for rating the quality of each report are included in Table 2. This quality assessment was formulated from previous work on the quality of case-control studies.[112,113] Additionally, particular attention was given to articles commenting on the potential biases in case-control studies of oral contraceptives and breast cancer.[22,25,114-116] A similar quality assessment instrument for case-control studies has been previously published.[17] The maximum possible score (Q score) was 33. If there was any difference in the scores, a third person reviewed the report. A conference was then held to settle scoring differences.

Table 2. Quality Assessment Scoring Criteria.*

1. Were cases selected from an entire community?
2. Were controls selected from an entire community?
3. Was there adequate control of confounding?
4. Was the data collection technique the same for cases and controls?
5. Was more than one comparison-control group used?
6. Was breast cancer confirmed histologically?
7. Were case subjects blinded to the study hypothesis?
8. Were control subjects blinded to the study hypothesis?
9. Were interviewers blinded to whether subjects were cases or controls?
10. Were contraceptive histories confirmed by an outside source for at least part of the study population?
11. Was information presented on frequency of breast examination (self-examination or physician examination) for cases and controls?

*The scoring was done in the following manner: 3 points were given for a "yes" response and 0 points for a "no" response. When the response was "probably yes," 2 points were given, and for "probably no," 1 point was given. The highest possible score was 33.

Analysis

The relative risk for breast cancer and the 95 percent confidence intervals (CIs) were extracted from each eligible study in the following categories if the data were available: (1) ever oral contraceptive use, (2) duration of oral contraceptive use, and (3) duration of oral contraceptive use before a first full-term pregnancy. In several instances[58,59,62,63,74,76] the relative risk for "ever oral contraceptive users" was obtained from articles[34,37] that had calculated relative risk, or it was calculated for this meta-analysis from published data.

In the category of "ever oral contraceptive users," the method described by Woolf[117] was used to estimate the pooled relative risk with 95 percent confidence intervals. The pooled estimate is a weighted average of the log of the relative risk from each study. The weight assigned to each study is proportional to the inverse of the variance in that study.

In the categories of "duration of oral contraceptive use" and "duration of oral contraceptive use before a first full-term pregnancy," the desired method to test for a trend in the relation between duration of oral contraceptive use and breast cancer is a weighted least-squares regression analysis. We found a wide variation in the reporting of time intervals for duration of use, however. Given this difficulty, we chose Spearman's rank correlation coefficient (r_s)[118] that we calculated using the statistical package Systat.[119] In performing these calculations, when a specific time interval was given, the midpoint of the interval was used. When an open-ended upper limit time interval was given (e.g., > n months), we used that time (n) for plotting the relative risk. When a closed-ended lower limit time interval was given (e.g., < n months), we used the midpoint from 0 to "n" for the time interval. For each specific correlation coefficient (r_s) we calculated a P value based on the equation for the large sample approximation of the correlation coefficient.[120]

For both of these statistical analyses (summary pooled relative risk and correlation coefficient), the Q scores of individual studies were taken into account in the following way: a pooled relative risk or a correlation coefficient for each of the categories was calculated for all studies and for all studies with a Q score > 14 (those studies with Q scores > 14 represented the upper tertile of the eligible reports). Additionally, summary graphs of reports with Q scores > 14 were formed by plotting the log of the relative risk with the 95 percent confidence interval for the different categories of oral contraceptive users analyzed. The validity of combining the reports in all categories was analyzed with the statistical test of homogeneity for relative risk estimates.[121] The null hypothesis of homogeneity was rejected at a significance level of 0.10.

Results

Sixty-one case-control reports were retrieved (Table 1). Data reported in 38 of the studies were included in the meta-analysis. The studies, published from 1974 to 1990, were from a wide variety of populations and geographic locations. There were collaborative and inde-

pendent studies. The collaborative studies included the Cancer and Steroid Hormone Study (CASH),[41,42,68,82,83,85-87] the United Kingdom National Case-Control Study Group,[91,92] the WHO Collaborative Study of Neoplasia and Steroid Contraceptives,[90] the Boston Collaborative Drug Surveillance Program,[39,40,88] and the studies published by Miller, et al.[66,67] and Rosenberg, et al.[80] Of the 38 eligible studies 17 were community-based, 21 were hospital-based, and 1 study used both hospital and community controls.[84] Studies included subjects from Australia, Canada, Chile, China, Colombia, Costa Rica, England, France, Germany, Israel, Italy, Kenya, Mexico, New Zealand, Norway, the Philippines, Sweden, Thailand, the United States, and Yugoslavia. The number of subjects studied ranged from 51 to 4714 case subjects and from 95 to 13,072 control subjects. For community-based case-control studies, the quality scores ranged from 6 to 29 (mean score = 16.4), and for the hospital-based control studies, the quality scores ranged from 3 to 17 (mean score = 6.9) (maximum possible score = 33). The specific quality assessment scores (Q scores) are reported in Table 3.

For "ever oral contraceptive users" versus "never oral contraceptive users" for all reports (n = 37), the pooled relative risk and 95 percent confidence intervals were 1.08 (0.55 to 1.61); and for reports with Q scores > 14 (n = 11), the pooled relative risk and 95 percent confidence intervals were 1.07 (0.78 to 1.36). A summary graph of the eligible studies for "ever oral contraceptive use" with Q scores > 14 is presented in Figure 1. The relative risk and 95 percent confidence intervals extracted from each of the eligible studies for "duration of oral contraceptive use" and for "duration of oral contraceptive use before a first full-term pregnancy" (Q scores > 14) are presented in Figures 2 and 3, respectively. Spearman's correlation coefficient for the subgroup "duration of use" was as follows: $r_s = +0.036$ ($P = 0.386$) for all studies (n = 34) and -0.153 ($P = 0.189$) for studies with Q scores < 14 (n = 9). For the subgroup "use before first full-term pregnancy," $r_s = +0.434$ ($P < 0.001$) for all studies (n = 28) and +0.497 ($P = 0.011$) for studies with Q scores > 14 (n = 9). There was statistical homogeneity for all categories analyzed using the methods previously described.

Table 3. Quality Scores for Eigible Case-Control Studies on Oral Contraceptives and Breast Cancer.

Author	Year	Q Score*
Community-based case-control studies		
Alexander, et al.[38]	1987	16
CASH[42]	1986	19
CASH/Stadel, et al.[85]	1985	19
Harris N, et al.[45]	1982	15
Henderson, et al.[47]	1974	6
Janerich, et al.[49]	1983	15
Lee, et al.[58]	1987	17
Lubin, et al.[60]	1982	14
Meirik, et al.[64]	1986	15
Olsson, et al.[70]	1989	13
Paul, et al.[74]	1990	29
Pike, et al.[75]	1981	14
Rohan & McMichael[79]	1988	15
Stanford, et al.[88]	1989	7
UK National, et al.[91]	1989	18
Yuan, et al.[98]	1988	17
Hospital-based case-control studies		
Ellery, et al.[43]	1986	5
Harris R, et al.[46]	1990	6
Hennekens, et al.[48]	1984	7
Jick, et al.[51]	1989	14
Kelsey, et al.[52]	1978	7
Kelsey, et al.[53]	1981	7
LaVecchia, et al.[55]	1989	3
Le, et al.[56]	1984	9
Le, et al.[57]	1989	9
Lees, et al.[59]	1978	17
McPherson, et al.[63]	1987	7
Miller, et al.[67]	1986	5
Miller, et al.[67]	1989	5
Paffenbarger, et al.[72]	1980	4
Ravnihar, et al.[77]	1979	7
Ravnihar, et al.[78]	1988	7
Rosenberg, et al.[80]	1984	6
Sartwell, et al.[81]	1977	6
Talamini, et al.[89]	1985	5
Thomas & Noonan[90]	1990	8
Vessey, et al.[97]	1983	7
Community- and hospital-based case-control studies		
Schildkraut[84]	1990	14

*Q score = quality score.

Discussion

Do the existing data support the conclusion that oral contraceptive use is associated with an increased risk for breast cancer? A meta-analysis of all published case-control studies was performed to try to answer this important and controversial question.

The summary analysis of the data suggests no increased risk for breast cancer in women who have ever used oral contraceptives or who have

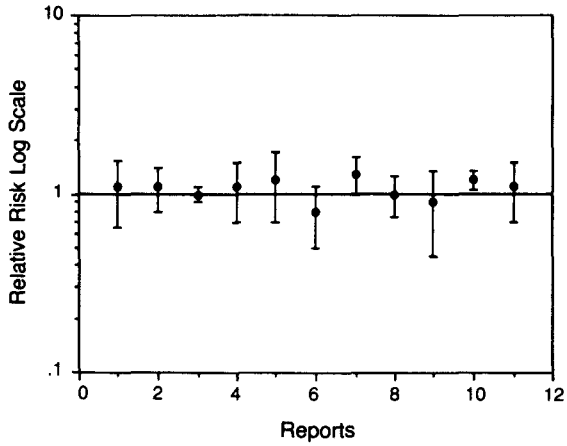

Figure 1. Relative risks (with 95 percent confidence intervals) of breast cancer in women who have ever used oral contraceptives; a summary of the eligible case-control studies with quality scores > 14.

used them for long durations (up to 14 years). The data do suggest, however, an association between oral contraceptive use before a first full-term pregnancy and an increased risk for breast cancer. This result is worrisome, but there is some uncertainty about its significance, as many of the studies were of low quality and did not control for biases inherent in case-control studies. Many reports failed to demonstrate adequate protection against the problems of most concern to case-control methods and therefore received low Q scores. This finding was particularly evident for the hospital-based case-control reports. Nineteen of 21 reports from hospital-based studies received Q scores of < 10. Only 2 of 17 community-based studies received scores of > 20.

One of the most serious problems in case-control studies is that the procedures used to select case subjects and control subjects might produce groups that are not truly comparable.[113,116] One way of dealing with factors that can confuse the comparison between case subjects and control subjects is to match these groups adequately. Matching controls for factors that are known to be related to the outcome could potentially confound the results.[113] In many of the studies included in this analysis, there was inadequate matching between case and control subjects to account for known risk factors for breast cancer. In many of the reports subjects were matched only according to age. Chilvers and Deacon[25] noted many of the studies that matched for age often did so in 5-year intervals and that this broad range of matching might be inadequate. Many studies did adjust for risk factors in their analyses; however, the risks that were accounted for varied among the studies.

Another concern is that using different types of control groups could produce inconsistent results. Lund, et al.[61] investigated the validity of different control groups used in a Norwegian and Swedish case-control study of oral contraceptive use in young women. In the study the three different series of control groups yielded the same adjusted point estimate of relative risk, although the 95 percent confidence intervals were wide. They suggested this finding indicates that case-control studies of oral contraceptive use and breast cancer are not biased by use of different types of control series. On the other hand, they stated that most case-control studies based on community or neighborhood control subjects face the problem of selection bias resulting from nonresponse. Although this study is reassuring, one way to deal with the problem of appropriate control groups is to use more than one comparison group and thus produce several estimates of the relative risk, as in the study by Schildkraut, et al.[84] Use of hospital-based versus community-based control groups also presents problems. Clear differences exist between these two groups of control subjects. Many investigators believe that biases are likely with any

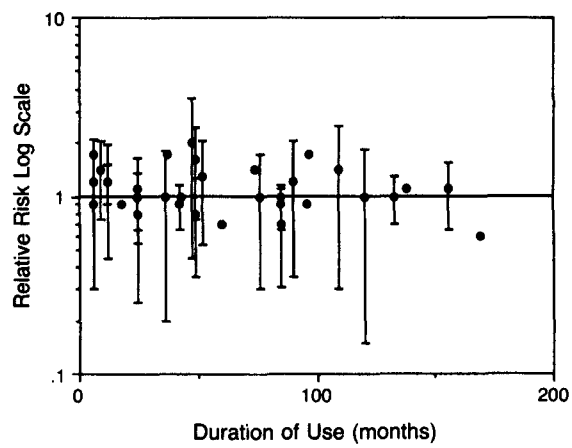

Figure 2. Relative risks (with 95 percent confidence intervals) of breast cancer in women by total duration of use; a summary of the data from eligible case-control studies with quality scores > 14.

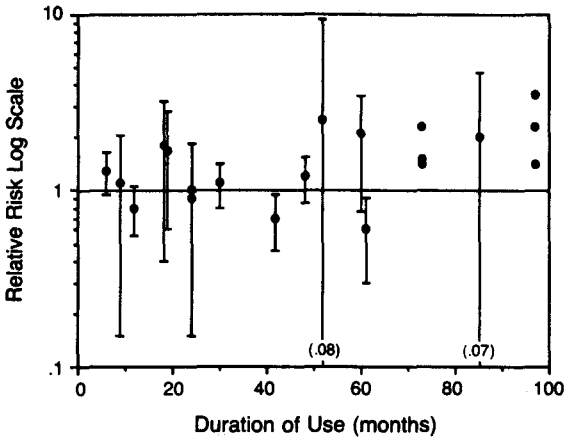

Figure 3. Relative risks (with 95 percent confidence intervals) of breast cancer in women by total duration of use before a first full-term pregnancy; a summary of the data from eligible case-control studies with quality scores > 14.

hospital-based control subject and that these subjects might not be representative of the general population.[25,113] Certainly, the quality of the hospital-based studies was substantially lower than the quality of community-based studies in this analysis.

There was insufficient attention to other biases inherent in case-control studies of oral contraceptives and breast cancer. These biases included interviewer bias, recall bias, surveillance bias, and nonresponse bias.[25,116] Failure to blind the interviewers to whether participants were case or control subjects, failure to ensure that case and control subjects were not aware of the study hypothesis, failure to confirm the contraceptive histories given by subjects from an outside source, failure to provide information on the frequency of breast examination (self-examination or physician examination) for case and control subjects, and failure to provide information on patterns of oral contraceptive use among nonresponders could result in erroneous study outcomes.

Coulter, et al.[114] have suggested that accuracy of recall about past oral contraceptive use can be high; however, the possibility of misinformation does exist. Suggestions for avoiding the possibility of misinformation caused by a recall bias include using photographs of oral contraceptives and a calendar to document life events that can improve accuracy of recall,[114] keeping both the subject and interviewer blinded to the study hypothesis, using a structured questionnaire and trained interviewers, and comparing at least some of the histories with a documented medical record.[117] The possibility that women taking oral contraceptives might have their breasts examined more frequently through self-examination or by a health care worker could produce a surveillance bias in two ways. More frequent surveillance among oral contraceptive users could lead to earlier diagnosis and hence to an apparent excess of cases in the younger age groups who have taken oral contraceptives. Second, there could be preferential inclusion of oral contraceptive users with breast lumps that, although histologically malignant, are in fact biologically benign. Because these lesions might never have been detected without frequent surveillance, a question about the frequency of breast examination should be included in each questionnaire or interview.

Inadequate matching and failure to account for the aforementioned biases clearly could have had an impact on many of the studies and the conclusions that were drawn. With 60 to 80 million current oral contraceptive users worldwide,[122] drawing erroneous conclusions from low-quality data could have widespread effects. On the other hand, it would be premature to discount the findings at this time. It is important, therefore, to understand the implications of the results of this meta-analysis.

First, it makes biologic sense that women who are exposed to oral contraceptives before a first full-term pregnancy could be more susceptible to the possible carcinogenic effects of oral contraceptives than women who have used them at later times in their reproductive lives. Dewaard and Trichopoulos[123] have stated that a young age at first full-term pregnancy provides a lifelong degree of protection against breast cancer, and the period of life before the first birth is critical for the risk of breast cancer later in life. The susceptibility of a tissue to a carcinogenic agent correlates with the rate of proliferation of that tissue and inversely correlates with its degree of differentiation.[23,124] Before the first full-term pregnancy the ductal epithelium of the breast is relatively undifferentiated and proliferates at rates higher than differentiated breast tissue, with maximal proliferation

between 12 and 18 years of age.[21,23] Pregnancy is accompanied initially by cell proliferation, but nearer to term it is followed by marked differentiation of mammary epithelial cells, making the cells less susceptible to carcinogens.[21] Combined oral contraceptives contain levels of ovarian hormones similar to those occurring naturally in the luteal phase of a menstrual cycle, when there is a higher mitotic rate of breast epithelium than in the follicular phase. A woman using combined oral contraceptives will undergo more breast epithelial mitoses in a cycle than a woman having natural ovulatory cycles and hence could increase breast cancer risk.[20]

Second, most studies investigating oral contraceptive use before a first full-term pregnancy detected an increase risk for breast cancer in premenopausal women. The main reason for this finding is that this subgroup of oral contraceptive users is only now reaching perimenopausal and postmenopausal ages. The overall incidence of breast cancer in premenopausal women is significantly lower than in perimenopausal and postmenopausal women.[25,125,126] In the United States only 13 percent of breast cancers occur before the menopause, with an incidence of approximately 1 in 500[126] compared with a lifetime incidence of approximately 1 in 9.[1] If early oral contraceptive use increased the risk for breast cancer in these older age groups, it would be of major public health importance.[25]

Third, the oral contraceptive users in many of the studies could have been exposed to the higher dose oral contraceptives of the 1960s and early 1970s. Since then the formulations and dosages have changed.[127] The association of oral contraceptive use before a first full-term pregnancy and an increased risk for breast cancer detected in some of the studies could reflect use of the higher dose oral contraceptives in the 1960s and 1970s.[122] The findings of this study, i.e., an increased risk for breast cancer in women who used oral contraceptives before they experienced a first full-term pregnancy, might only reflect the use of high-dose oral contraceptives and not the use of current low-dose oral contraceptives. Only future studies with women who have used only new formulations and lower doses will be able to answer this question.

Fourth, the issue of latency time from oral contraceptive use to development of breast cancer must be considered. It takes approximately 30 cell divisions before a malignant breast tumor can be diagnosed, and thus there is a latent period of 10 to 30 years.[22,23] An increased risk for breast cancer might be detected only among women who used oral contraceptives for an extended amount of time a long time ago. If studies used recent oral contraceptive users, then an increased risk for breast cancer might not be apparent. Future studies are needed in which surveillance of the risk of breast cancer continues for the entire lifetime of oral contraceptive users.

Specific problems with our study relate to the stated weaknesses of meta-analysis and are as follows: combining potentially heterogeneous studies, the effects of publication bias, problems with pooling results, difficulty in extracting data not adequately presented in a report, and obtaining all the available reports.[108] Although we have performed this meta-analysis using specific criteria recommended by L'abbe, et al.[111] to minimize biases inherent in a meta-analysis, problems do exist with this study.

We are concerned with the many dissimilarities among the 39 eligible studies included in this meta-analysis. For example, subjects from 20 different countries were studied. Olsson[22] has suggested that some of the inconsistencies in epidemiologic studies in oral contraceptive use could be explained by different contraceptive habits in different geographic areas. There were many methodologic differences in the reports, which contributed to differing conclusions. Subject groups varied from study to study. For example, in evaluating the risk for breast cancer with oral contraceptive use before a first full-term pregnancy, some investigators included only parous women, others included only nulliparous women, and others combined the two groups. The age ranges of subjects also were inconsistent. As mentioned previously, duration of oral contraceptive use is reported in different intervals for each study, which made it difficult to combine the data. Other issues contributing to cross-study differences included different criteria for selection of case and control subjects, different time intervals between disease diagnosis and survey, and different survey methods.

Cohort studies are often used to correct for the deficiencies of case-control methods. Of the studies retrieved, we were unable to combine re-

sults for these studies, as there was inadequate information from these data. As noted by Olsson,[22] most of the cohort studies included few women with an extensive oral contraceptive use at a young age, and the findings of these studies were of little assistance in assessing breast cancer risk with oral contraceptive use before a first full-term pregnancy. Of the published reports only the Royal College of General Practitioners' study[101] has suggested an increased risk for current oral contraceptive users aged 15 to 34 years. The largest of the cohort studies, the Nurses' Health Study,[104] was a cohort of 121,700 female registered nurses 30 to 55 years of age in the United States who were given mailed questionnaires requesting information about medical conditions and lifestyle practices. After 10 years no association could be found between oral contraceptive use and the risk of breast cancer.

Finally, we did not combine data that addressed the issue of latency because the data were heterogenous, and we believed it still would be too soon to evaluate adequate latent intervals of 10 to 30 years for the development of breast cancer for long-term oral contraceptive use. This topic certainly deserves further study. Of note was another meta-analysis on this subject by Romieu, et al.[35] This study did not include 12 of the most recently published studies. The authors observed no increase in the risk of breast cancer for women who had ever used oral contraceptives even after a long duration of use. Using a different statistical test to combine the data, however, they found a statistically significant positive trend ($P = 0.001$) in the risk of premenopausal breast cancer for women exposed to oral contraceptives for longer durations, especially in women who used oral contraceptives for at least 4 years before their first full-term pregnancy (relative risk 1.72; 95 percent CI 1.36 to 2.19). It remains unclear whether this relation will hold true as the population ages. They analyzed studies that reported on the possible latent effect of oral contraceptive use and also combined data from five cohort studies. They combined 11 studies that reported data on time since first oral contraceptive use of 12 years or more and found no increase risk for breast cancer (relative risk 1.08; 95 percent CI 0.95 to 1.22). The pooled relative risk of five cohort studies did not suggest an increased risk for breast cancer in oral contraceptive users (relative risk 1.06; 95 percent CI 0.92 to 1.22). What distinguishes our work from that of Romieu, et al.[35] was the use of a quality-assessment instrument. Although there was no difference in the quantitative conclusions of the reports, the addition of the Q score added to the understanding of the difficulties encountered in drawing substantive conclusions from reading the literature in this field. Specifically, many of the published reports failed to control for biases inherent in case-control methods.

Summary

A systematic qualitative and quantitative review of all published case-control reports investigating oral contraceptive use and breast cancer was performed using the technique of meta-analysis. This study detected no association between oral contraceptive use and an increased risk for breast cancer for the categories of "ever oral contraceptive users" and "long-term oral contraceptive users." For the category of "oral contraceptive users before a first full-term pregnancy," however, a significant correlation was found.

For the reasons previously discussed, in particular the low quality of many of the studies, we are hesitant to accept the results of this analysis and would not recommend any change in prescription practices at this time. Importantly, the study that received the highest score[74] showed no increased risk of breast cancer for women who had used oral contraceptives before their first pregnancy or even for prolonged periods of use (13 years). Additionally, many authors have commented on the lack of consistency and the contradictory results of the different studies.[24,25,36,116,126] Mishell, et al.[126] stated that one of the hallmarks of a solid statistical conclusion is consistency between reports. Schlesselman, et al.[36] have said that the inconsistency in findings prevents one from concluding that the suggested increased risks are in fact a consequence of oral contraceptive use. It is clear from our analysis that future research in this field requires substantial reevaluation of issues of study design and methods that had an impact on previous reports.

Finally, it is important to consider other benefits and risks of oral contraceptive use. Benefits include reduction of ovarian cancer, endometrial cancer, benign breast disease, functional ovarian cysts, pelvic inflammatory disease, dysmenorrhea, and anemia. These benefits must be weighed

against the possible risks of oral contraceptive use, which include thromboembolic disease, hypertension, cerebral vascular accident, and hepatic tumors.[122,128,129] Only future well-designed studies will determine whether breast cancer will be added to the potential risks of oral contraceptive use.

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