ORIGINAL ARTICLE

Oral Contraceptive Use as a Risk Factor for Premenopausal Breast Cancer: A Meta-analysis

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OBJECTIVE: **To perform a meta-analysis of case-control studies that addressed whether prior oral contraceptive (OC) use is associated with premenopausal breast cancer.**

METHODS: **We searched the MEDLINE and PubMed databases and bibliography reviews to identify case-control studies of OCs and premenopausal breast cancer published in or after 1980. Search terms used included *breast neoplasms*, *oral contraceptives*, *contraceptive agents*, and *case-control studies*. Studies reported in all languages were included. Thirty-four studies were identified that met inclusion criteria. Two reviewers extracted data from original research articles or additional data provided by study authors. We used the DerSimonian-Laird method to compute pooled odds ratios (ORs) and confidence intervals (CIs) and the Mantel-Haenszel test to assess association between OC use and cancer.**

RESULTS: **Use of OCs was associated with an increased risk of premenopausal breast cancer in general (OR, 1.19; 95% CI, 1.09-1.29) and across various patterns of OC use. Among studies that provided data on nulliparous and parous women separately, OC use was associated with breast cancer risk in both parous (OR, 1.29; 95% CI, 1.20-1.40) and nulliparous (OR, 1.24; 95% CI, 0.92-1.67) women. Longer duration of use did not substantially alter risk in nulliparous women (OR, 1.29; 95% CI, 0.85-1.96). Among parous women, the association was stronger when OCs were used before first full-term pregnancy (FFTP) (OR, 1.44; 95% CI, 1.28-1.62) than after FFTP (OR, 1.15; 95% CI, 1.06-1.26). The association between OC use and breast cancer risk was greatest for parous women who used OCs 4 or more years before FFTP (OR, 1.52; 95% CI, 1.26-1.82).**

CONCLUSION: **Use of OCs is associated with an increased risk of premenopausal breast cancer, especially with use before FFTP in parous women.**

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CI = confidence interval; FFTP = first full-term pregnancy; OC = oral contraceptive; OR = odds ratio

Breast cancer is the leading cause of cancer in women worldwide and the most common cause of cancer death in US women aged 20 to 59 years.[1] Each year in the United States, approximately 211,000 women develop breast cancer and more than 47,000 (20%) do so before the age of 50 years.[2] Approximately 2 in 15 American women are expected to develop breast cancer in their lifetime, and nearly 40,000 women die of the disease annually.[2] During the past 4 decades, breast cancer rates have risen steadily worldwide and have risen even faster in more developed countries, especially among younger women. For example, from 1973 to 1999 the rate of breast cancer in the United States increased in white women younger than 50 years by 9.8% (ie, 39.8 per 100,000 population to 43.7 per 100,000 population) and by 26.4% in African American women younger than 50 years (ie, 34.8 per 100,000 population to 44.0 per 100,000 population).[3]

Although the medical research community has long recognized breast cancer risk factors such as a positive family history of breast cancer, early menarche, late menopause, nulliparity, and lack of breastfeeding,[4-7] concordance is lacking regarding the carcinogenic potential of female hormones. The Women's Health Initiative Clinical Trial reported that prolonged exposure to exogenous estrogens and progestins in hormone therapy increases a woman's risk of developing breast cancer.[8] In addition, the World Health Organization recently classified both postmenopausal hormone replacement and oral contraceptives (OCs) as group 1 carcinogens.[9]

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The association between OCs and risk of subsequent breast cancer has varied within the medical literature over time. Only 1 of 15 studies performed before 1980 showed a positive association.[10] However, more recent studies have noted an increase in risk among OC users, especially among women who took them before a first full-term pregnancy (FFTP).[10-15] The difference between older and more recent findings may be related to the changing pattern of OC use: women who took OCs from the late 1970s through the 1990s were more likely to use them before FFTP and for longer periods than women who used them in the 1960s and early 1970s.[11] Women who are exposed to carcinogens before FFTP may have a higher risk of developing breast cancer because the glandular tissue of the breast has not yet undergone the further differentiation associated with pregnancy.[16] Differentiation of the mammary gland associated with pregnancy inhibits carcinogenic initiation[16] and may

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explain the natural protection that pregnancy has been shown to confer.[17,18]

We undertook a meta-analysis of case-control studies conducted in 1980 or later to clarify the possible association between OC use and breast cancer risk in premenopausal women or women younger than 50 years. For the analyses presented herein, we assumed that most women younger than 50 years were premenopausal. We limited our analyses to studies in which most women developed breast cancer in or after 1980 to allow for an adequate latent period between OC use and breast cancer diagnosis. We further limited analyses to premenopausal women because most postmenopausal women included in studies from the 1980s and 1990s did not have extensive exposure to OCs before FFTP; therefore, the relationships among OC use, pregnancy, and postmenopausal disease are difficult to assess.

METHODS

Literature Search, Data Sources, and Study Selection

We searched the MEDLINE and PubMed databases to identify case-control studies of breast cancer and OC use published in or after 1980. Search terms used included *breast neoplasms*, *oral contraceptives*, *contraceptive agents*, and *case-control studies*. We located additional studies by reviewing the bibliographies of identified studies and previous meta-analyses.[10-15]

Only studies in which cases and controls were younger than 50 years or premenopausal and in which most cases developed breast cancer during or after 1980 were included in our analyses. A total of 60 potentially eligible studies were identified. Twenty-six studies were excluded for various reasons: 8 studies took most of their data before 1980,[19-25] 2 studies (which were identified in the Oxford study[11]) were never published, 1 study examined exclusively noncontraceptive hormone use,[26] 1 study examined women 50 years or older,[27] and 2 studies[28,29] have since been combined into a more recent study and that latter study was included.[30] One study was excluded because most women had used OCs for 6 months or less before FFTP[31]; 11 studies were excluded because we were unable to obtain data specifically on premenopausal women or women younger than 50 years.[32-42] This resulted in 34 eligible studies.[30,43-75] Four studies[66,67,72,75] reported their data by 2 separate age strata. Wingo et al,[72] Shapiro et al,[67] and Rosenberg et al[75] reported their data by age categories of younger than 35 years and 35 to 44 years. Rosenberg et al[66] reported data by age categories of younger than 40 years and 40 to 49 years. That is, for these studies, women were categorized by the age at which their conditions were diagnosed (cases) or they were enrolled in the study (controls). One study used either hospital- or population-based controls, depending on the location; we treated these as 2 independent studies also.[68] Thus, there were a total of 39 potential independent studies for analysis, which are listed in Table 1.[30,43-74] Among these 39 studies, 2 studies[54,74] did not provide any data on ever or never use in all women but provided data for other subgroup analysis categories (ever or never use in parous women, OC use in parous women before and after FFTP); hence, they are included in some of the analyses presented herein.

We attempted to contact the original authors if data on the history of OC use before FFTP were missing. Several authors provided these data.[48,55,61,64,65,71,73,74] We did not analyze the subgroup of women who took OCs before FFTP in studies in which most women used OCs for less than 6 months before FFTP.[31,44] We avoided duplicate entry of the data found in multiple published reports; in these cases, the most recent or comprehensive form of the study was used. Examples include 3 American studies,[4,59,72,75-80] a Swedish study,[57,81] and an Italian study.[28-30]

Data Extraction

All data were independently extracted by 2 people (C.K. and a research assistant) and entered into an Excel spreadsheet (Microsoft Inc, Redmond, Wash). The extraction process included descriptive information on study design and details on exposure and outcome measures. Descriptive information included author, publication year and language, study location, recruitment period, type of design (population or hospital based), participation rates, and type of interview. Exposure measures included ever use of OCs, ever use of OCs by ever parous women, ever use of OCs before and after FFTP by parous women, use of OCs for 4 or more years before FFTP by parous women, and ever use by nulliparous women and use of OCs for 4 or more years by nulliparous women. All extracted data were reviewed by a third person (F.M.), and disagreements were collectively adjudicated.

Statistical Analyses

This meta-analysis used the DerSimonian-Laird random-effects model[82] to compute the pooled odds ratios (ORs), 95% confidence intervals (CIs), and *P* values for the null hypothesis of no association between OC use and cancer. Individual ORs and their variances were computed from each study's published crude number of cases and controls. Homogeneity of the ORs was assessed in the standard manner, using the Q statistic (see, for example, DerSimonian and Laird[82]).

For analyses that involved the subgroup of parous women who used OCs before FFTP, most studies defined never users as women who never used OCs. However, one study[58] defined never users as women who did not use OCs

TABLE 1. **Studies of Oral Contraceptive Use and Breast Cancer Risk in Premenopausal Women or Women Younger Than 50 Years, 1980-2004**

Reference	Recruitment period	Design*	No. of cases†	Participation rate among eligible cases (%)	Source of controls	No. of controls	Participation rate among eligible controls (%)	Method of data collection
Brinton et al,[43] 1995	1990-1992	P	1648 <45 y	86.40	Random digit dialing	1505	78.1	In-person interview
Chie et al,[44] 1998	1993-1994	H	97 premen	99	Hospital patients	237	Unknown	In-person interview
UK National,[45] 1989	1982-1985	P	755 <36 y	Unknown	Clinic patients	755	Unknown	Home interview
Clavel et al,[46] 1991	1983-1987	H	358 premen	99	Hospital patients	379	98	In-person interview
Ewertz,[47] 1992	1983-1984	P	203 <40 y	90	General population	212	80	Questionnaire
Gomes et al,[48] 1995	1978-1987	H	96 <45 y	Unknown	Clinic patients	183	Unknown	Medical record review
Le et al,[49] 1985	1982-1984	H	240 <45 y	Unknown	General population	305	Unknown	In-person interview
Lee et al,[50] 1987	1982-1984	H	100 <50 y	Unknown	Hospital patients	200	Unknown	In-person interview
Lee et al,[51] 1992	1986-1988	H	77 <50 y	66.80	Random population	498	92.80	In-person interview
Marchbanks et al,[52] 2002	1994-1998	P	2229 <50 y	76.50	Random digit dialing	2355	78.60	In-person interview
Marcus et al,[53] 1999	1993-1996	P	273 <50 y	77	Random digit dialing	200	68	In-person interview
Marubini et al,[54] 1988	1982-1985	H	106 premen	Unknown	Hospital patients	116	Unknown	In-person interview
McCredie et al,[55] 1998	1992-1995	P	467 <40 y	72.50	Random digit dialing	408	64.40	In-person interview
McPherson et al,[56] 1987	1980-1984	H	351 <45 y	Unknown	Hospital patients	351	Unknown	In-person interview
Meirik et al,[57] 1986	1984-1985	P	422 <45 y	89.20	Random digit dialing	527	87.30	In-person interview
Moorman et al,[58] 2001	1993-1996	P	858 <50 y	Unknown	Random population	789	Unknown	In-person interview
Newcomb et al,[59] 1996	1988-1991	P	1050 <45 y	80.70	Random population	1921	84.20	Telephone interview
WHO study,[60] 1990	1982-1984	H	301 <35 y	90	Hospital patients	4335	90	In-person interview
Olsson et al,[61] 1989	1979-1985	P	174 premen	100	Random population	459	92	In-person interview
Palmer et al,[62] 1995	1977-1992	H	219 <45 y	Unknown	Hospital patients	582	Unknown	In-person interview
Paul et al,[63] 1990	1983-1985	P	191 <45 y	88	Random population	570	84	Telephone interview
Primic-Zakelj et al,[64] 1995	1988-1990	P	501 premen	94.40	Random population	470	82.50	In-person interview
Rookus et al,[65] 1994	1986-1989	P	671 <45 y	60	Random population	671	72	In-person interview
Rosenberg et al,[66] 1992	1982-1986	P	79 <40 y	75.80	Random population	159	65	In-person interview
Rosenberg et al,[66] 1992	1982-1986	P	177 (40-49 y)	75.80	Random population	356	65	In-person interview
Rosenberg et al,[75] 1996	1977-1992	H	323 (25-34 y)	95	Hospital patients	895	Unknown	In-person interview
Rosenberg et al,[75] 1996	1977-1992	H	1104 (35-44 y)	95	Hospital patients	1572	Unknown	In-person interview
Shapiro et al,[67] 2000	1994-1997	H	70 <35 y	98.80	Hospital patients	394	99.90	In-person interview
Shapiro et al,[67] 2000	1994-1997	H	189 (35-44 y)	98.80	Hospital patients	667	99.90	In-person interview
Tavani et al,[30] 1999	1983-1994	H	579 <40 y	Unknown	Hospital patients	668	Unknown	In-person interview
Tessaro et al,[68] 2001	1995-1998	P	48 <45 y	Unknown	Hospital patients	152	Unknown	In-person interview
Tessaro et al,[68] 2001	1995-1998	H	52 <45 y	Unknown	Hospital patients	175	Unknown	In-person interview
Traina et al,[69] 1996	1992-1994	H	300 <46 y	Unknown	Hospital patients	300	Unknown	In-person interview
Ursin et al,[70] 1999	1983-1988	P	742 <40 y	76.70	General population	742	Unknown	In-person interview
Weinstein et al,[71] 1991	1984-1986	P	325 <50 y	75	Random population	325	Unknown	Telephone interview
White et al,[73] 1994	1983-1990	P	747 (21-45 y)	83.20	Random digit dialing	961	78	In-person interview
Wingo et al,[72] 1993	1980-1982	P	524 (20-34 y)	80.40	Random digit dialing	704	83.40	In-person interview
Wingo et al,[72] 1993	1980-1982	P	1565 (35-44 y)	80.40	Random digit dialing	1361	83.40	In-person interview
Yuan et al,[74] 1988	1984-1985	P	195 <50 y	94	Random population	218	89	In-person interview

*P = population based; H = hospital based; WHO = World Health Organization.

†Number of cases below a cutoff age within a certain age range (shown in parentheses) or premen (premenopausal).

before FFTP (but may have used OCs after). Two studies[43,75] defined never users as less than 6 or 12 months of use, respectively. Analyses were conducted including and excluding these 3 studies, with no differences in results.

RESULTS

Of the 34 studies identified for inclusion in this study, 14 were hospital based, 19 were population based, and 1 was a combination of hospital and population controls. The studies were from several countries: Australia (1),[55] Brazil (2),[48,68] Canada (1),[66] China (1),[74] Costa Rica (1),[50] Denmark (1),[47] England (2),[45,56] France (2),[46,49] Italy (3),[30,54,69] New Zealand (1),[63] Singapore (1),[51] Slovenia (1),[64] South Africa (1),[67] Sweden (2),[57,61] Taiwan (1),[44] the Netherlands (1),[65] and the United States (11).[42,43,52,53,58,59,62,71-73,75] One study analyzed multinational data.[60]

Overall, OC use was associated with an increase in breast cancer risk (Figure 1), with a calculated pooled OR of 1.19 (95% CI, 1.09-1.29). Of the 39 studies indicated in Table 1, 2 studies[54,74] did not include data on ever or never use of OCs and thus were not included in the analysis of Figure 1. Of the remaining 37 studies, 29 had ORs greater than 1, and 8 had ORs less than 1. Nine studies reported

Reference	Cases/controls: OC users	Cases/controls: OC nonusers	OR (95% CI)	*P* value
All			1.19 (1.09-1.29)	9.5×10^{-5}
Wingo,[72] 1993*	117/976	328/298	1.04 (0.87-1.24)	.70
Wingo,[72] 1993†	432/556	57/104	1.42 (1-2)	.058
White,[73] 1994	689/879	58/82	1.11 (0.78-1.57)	.63
Weinstein,[71] 1991	175/145	151/178	1.42 (1.04-1.94)	.031
Ursin,[70] 1999	618/626	124/116	0.92 (0.7-1.22)	.62
Traina,[69] 1996	103/138	197/162	0.61 (0.44-0.85)	.0047
Tessaro,[68] 2001‡	40/139	8/13	0.47 (0.18-1.21)	.19
Tessaro,[68] 2001§	44/146	8/29	1.09 (0.47-2.56)	.99
Tavani,[30] 1999	221/227	358/441	1.2 (0.95-1.51)	.14
Shapiro,[67] 2000*	91/274	98/393	1.33 (0.96-1.84)	.099
Shapiro,[67] 2000†	36/140	34/254	1.92 (1.15-3.21)	.017
Rosenberg,[66] 1992*	98/225	79/131	0.72 (0.5-1.04)	.099
Rosenberg,[66] 1992†	66/118	13/41	1.76 (0.88-3.53)	.15
Rosenberg,[75] 1996*	455/606	617/940	1.14 (0.98-1.34)	.10
Rosenberg,[75] 1996†	184/421	134/462	1.51 (1.16-1.95)	.0023
Rookus,[65] 1994	613/605	58/66	1.15 (0.8-1.67)	.51
Primic-Zakelj,[64] 1995	250/249	251/221	0.88 (0.69-1.14)	.37
Paul,[63] 1990	345/1081	43/130	0.96 (0.67-1.39)	.92
Palmer,[62] 1995	119/222	65/275	2.27 (1.6-3.22)	5.4×10^{-6}
Olsson,[61] 1989	143/329	31/130	1.82 (1.18-2.82)	.0092
WHO study,[60] 1990	160/1613	141/2722	1.91 (1.51-2.42)	5.2×10^{-8}
Newcomb,[59] 1996	862/1555	188/366	1.08 (0.89-1.31)	.47
Moorman,[58] 2001	428/328	75/79	1.37 (0.97-1.94)	.087
Meirik,[57] 1986	326/371	96/156	1.43 (1.06-1.92)	.021
McPherson,[56] 1987	240/229	111/122	1.15 (0.84-1.58)	.42
McCredie,[55] 1998	418/366	46/42	1.04 (0.67-1.62)	.94
Marcus,[53] 1999	428/328	76/79	1.36 (0.96-1.92)	.10
Marchbanks,[52] 2002	1264/1305	165/171	1.0 (0.8-1.26)	.98
Lee,[50] 1987	50/302	47/302	1.06 (0.69-1.63)	.86
Lee,[51] 1992	41/80	68/127	0.96 (0.59-1.54)	.95
Le,[49] 1985	161/217	79/88	0.83 (0.57-1.19)	.35
Gomes,[48] 1995	35/60	64/169	1.54 (0.93-2.56)	.12
Ewertz,[47] 1992	165/167	38/45	1.17 (0.72-1.9)	.61
Clavel,[46] 1991	204/204	154/175	1.14 (0.85-1.52)	.43
UK National,[45] 1989	688/675	67/80	1.22 (0.86-1.71)	.30
Chie,[44] 1998	13/26	84/211	1.26 (0.62-2.56)	.66
Brinton,[43] 1995	1259/1074	389/431	1.3 (1.11-1.52)	.0015

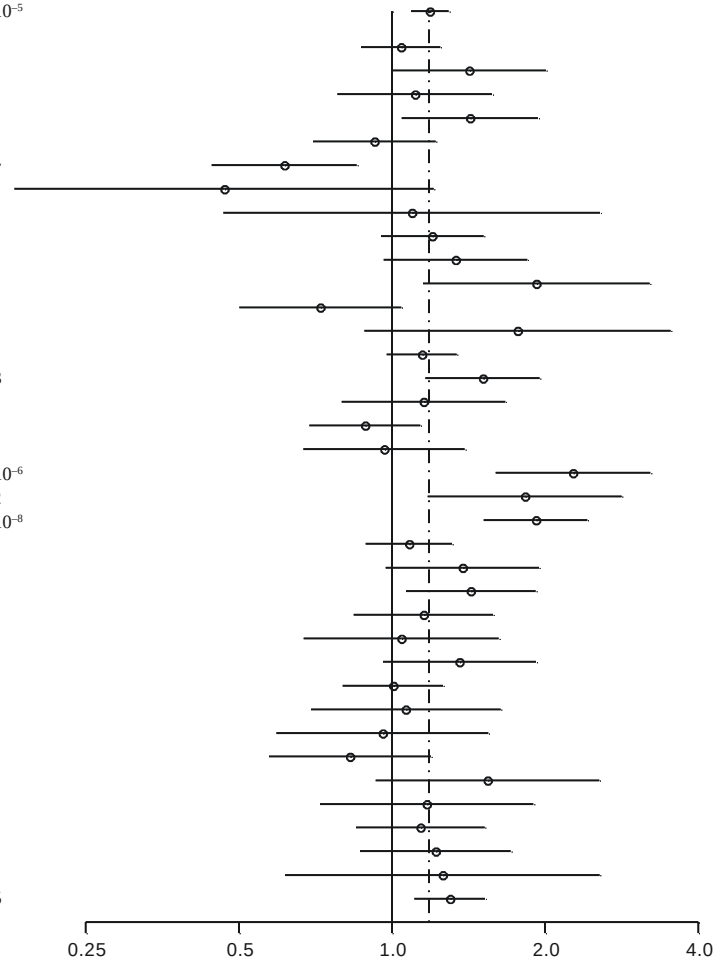
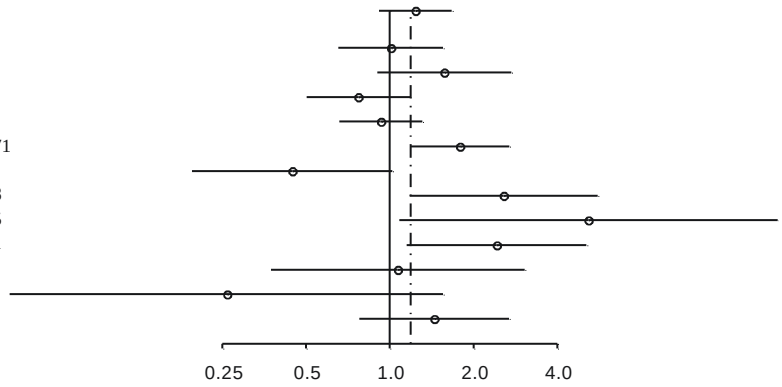


FIGURE 1. Summary estimates of risk of breast cancer in premenopausal women and women younger than 50 years associated with ever use of oral contraceptives (OCs). Among the 39 eligible studies listed in Table 1, 37 provided data on ever or never use of OCs. Includes case-control studies of both parous and nulliparous premenopausal women (or those <50 years) who used OCs at any time vs women with no use. For each study, most patients developed breast cancer after 1980. *Subset of women 35 (Rosenberg,[75] Wingo[72]) or 40 (Rosenberg[66]) years and older. †Subset of women younger than 35 (Rosenberg[75], Wingo[72]) or 40 (Rosenberg[66]) years. ‡Neighborhood controls. §Hospital controls. CI = confidence interval; OR = odds ratio; WHO = World Health Organization. Only first author mentioned because of space constraints.

P<.05 (ranging from 5×10^{-8} to 0.031) for the null hypothesis of no association between OC use and cancer; of these 9 studies, only 1 had an OR less than 1. For the pooled analysis, the *P* value for no association between OC use and cancer was 9.5×10^{-5}. We note that the *P* value for homogeneity among the studies was 2.0×10^{-6}; thus, there is clear evidence for differences among the studies. Heterogeneity is clearly present, but the source can neither be traced nor inferred from the individual reports. It is likely that it derives from both variability in the genetic pool of individual study populations and various cultural and environmental factors.

As shown in Figure 2, the ORs for nulliparous women who ever used OCs (OR, 1.24; 95% CI, 0.92-1.67) was similar to that of nulliparous women who used OCs for 4 years or more (OR, 1.29; 95% CI, 0.85-1.96). Among parous women (Figures 3 and 4), the association between OC use and breast cancer risk for ever use was 1.29 (95% CI, 1.20-1.40). The risk for breast cancer with OC use before FFTP (OR, 1.44; 95% CI, 1.28-1.62; 99% CI, 1.24-

Reference	Cases/controls: OC users	Cases/controls: OC nonusers	OR (95% CI)	*P* value
All			1.24 (0.92-1.67)	.17
Wingo,[72] 1993*	147/96	79/52	1.01 (0.65-1.56)	.94
Wingo,[72] 1993†	107/161	22/52	1.57 (0.9-2.74)	.14
Ursin,[70] 1999	216/227	58/47	0.77 (0.5-1.18)	.28
Rosenberg,[75] 1996*	99/122	153/175	0.93 (0.66-1.31)	.73
Rosenberg,[75] 1996†	74/173	51/213	1.79 (1.19-2.69)	.0071
Paul,[63] 1990	26/127	11/24	0.45 (0.2-1.02)	.09
Palmer,[62] 1995	20/23	21/62	2.57 (1.18-5.58)	.028
Olsson,[61] 1989	18/33	2/19	5.18 (1.08-24.81)	.055
Meirik,[57] 1986	44/40	15/33	2.42 (1.15-5.1)	.031
McPherson,[56] 1987	26/27	9/10	1.07 (0.38-3.06)	.89
Ewertz,[47] 1992	10/11	7/2	0.26 (0.04-1.56)	.27
UK National,[45] 1989	138/113	22/26	1.44 (0.78-2.68)	.32



Reference	Cases/controls: OC users	Cases/controls: OC nonusers	OR (95% CI)	*P* value
All			1.29 (0.85-1.96)	.24
Ursin,[70] 1999	117/131	58/47	0.72 (0.46-1.14)	.21
Rosenberg,[75] 1996*	47/62	153/175	0.87 (0.56-1.34)	.60
Rosenberg,[75] 1996†	35/77	51/213	1.9 (1.15-3.14)	.017
Paul,[63] 1990	16/77	11/24	0.45 (0.18-1.11)	.13
Palmer,[62] 1995	12/11	21/62	3.22 (1.24-8.38)	.028
Meirik,[57] 1986	23/22	15/33	2.3 (0.99-5.36)	.084
McPherson,[56] 1987	15/11	9/10	1.52 (0.46-4.98)	.70
UK National,[45] 1989	105/71	22/26	1.75 (0.92-3.32)	.12

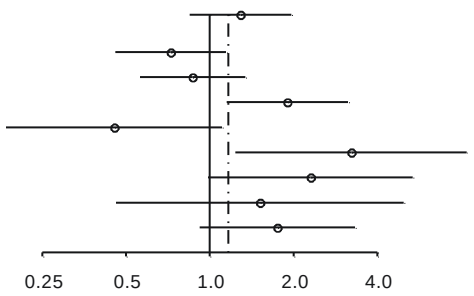


FIGURE 2. Summary estimates of risk of breast cancer in nulliparous premenopausal women and women younger than 50 years associated with ever use of oral contraceptives (OCs). *Subset of women 35 years and older. †Subset of women younger than 35 years. CI = confidence interval; OR = odds ratio. Only first author mentioned because of space constraints.
Top, Among the 39 eligible studies listed in Table 1, 12 provided data on ever and never use of OCs in nulliparous women. Includes case-control studies of nulliparous premenopausal women (or those <50 years) who used OCs at any time vs nulliparous women with no use. For each study, most patients developed breast cancer after 1980.
Bottom, Among the 39 eligible studies listed in Table 1, 8 provided data on ever use of OCs for 4 or more years in nulliparous women. Includes case-control studies of nulliparous premenopausal women (or those <50 years) who used OCs for 4 or more years vs nulliparous women with no use. For each study, most patients developed breast cancer after 1980.

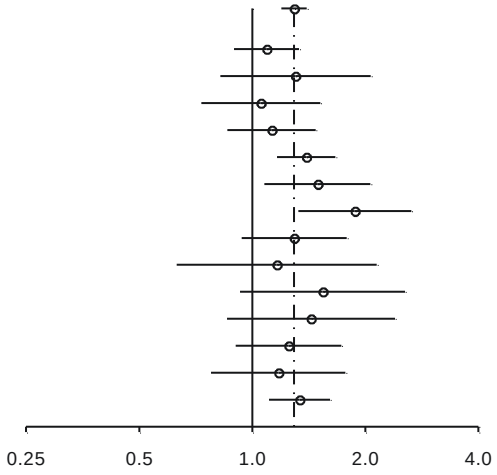
1.68) was higher than if OCs were used after FFTP (OR, 1.15; 95% CI, 1.06-1.26). The association between OC use and breast cancer risk was highest for parous women who used OCs 4 or more years before FFTP (OR, 1.52; 95% CI, 1.26-1.82; 99% CI, 1.19-1.93).

DISCUSSION

The results of this meta-analysis suggest that use of OCs is associated with an increase in breast cancer risk among premenopausal women or women younger than 50 years. The greatest risk appears to be for parous women who use OCs before FFTP.

Our results are consistent with other early meta-analyses and pooled analyses using studies conducted primarily in the 1970s and 1980s. Thomas[12] noted an increase in risk of 40% (OR, 1.4; 95% CI, 1.2-1.7) in premenopausal and postmenopausal women who used OCs before FFTP. Studies that focused on women who experienced high exposure to prolonged OC use at a young age (premenopausal women or women younger than 50 years) also showed elevated risks. Rushton and Jones[15] noted that women younger than 45 years who used OCs were not at an increased risk of breast cancer when analyzing studies conducted before 1982 (OR, 0.90; 95% CI, 0.77-1.05). However, when analyzing studies conducted after 1982, a small

Reference	Cases/controls: OC users	Cases/controls: OC nonusers	OR (95% CI)	*P* value
All			1.29 (1.2-1.4)	8.4×10^{-11}
Wingo,[72] 1993*	949/858	249/246	1.09 (0.9-1.33)	.41
Wingo,[72] 1993†	317/383	33/52	1.3 (0.82-2.07)	.31
Ursin,[70] 1999	402/399	66/69	1.05 (0.73-1.52)	.85
Tavani,[30] 1999	176/163	273/285	1.13 (0.86-1.48)	.42
Rosenberg,[75] 1996*	389/460	464/765	1.39 (1.17-1.66)	.00029
Rosenberg,[75] 1996†	132/265	83/249	1.49 (1.08-2.07)	.019
Palmer,[62] 1995	99/199	79/298	1.88 (1.33-2.65)	.00046
Meirik,[57] 1986	282/331	81/123	1.29 (0.94-1.79)	.14
Marubini,[54] 1988	66/72	26/33	1.16 (0.63-2.15)	.74
Gomes,[48] 1995	35/60	64/169	1.54 (0.93-2.56)	.12
Ewertz,[47] 1992	154/149	31/43	1.43 (0.86-2.4)	.21
Clavel,[46] 1991	185/175	115/136	1.25 (0.9-1.73)	.20
UK National,[45] 1989	550/562	45/54	1.17 (0.78-1.77)	.51
Brinton,[43] 1995	965/848	274/322	1.34 (1.11-1.61)	.0025



Reference	Cases/controls: OC users	Cases/controls: OC nonusers	OR (95% CI)	*P* value
All			1.15 (1.06-1.26)	.0015
Yuan,[74] 1988	68/71	122/145	1.14 (0.76-1.72)	.61
Wingo,[72] 1993*	631/611	249/246	1.02 (0.83-1.26)	.89
Wingo,[72] 1993†	137/158	33/52	1.37 (0.84-2.24)	.26
White,[73] 1994	149/193	34/46	1.04 (0.64-1.71)	.96
Weinstein,[71] 1991	101/92	124/151	1.34 (0.92-1.93)	.15
Tavani,[30] 1999	95/98	273/285	1.01 (0.73-1.4)	.99
Rosenberg,[75] 1996*	219/335	464/765	1.08 (0.88-1.32)	.51
Rosenberg,[75] 1996†	57/149	83/249	1.15 (0.77-1.7)	.56
Palmer,[62] 1995	76/156	79/298	1.84 (1.27-2.66)	.0016
Olsson,[61] 1989	60/179	29/111	1.28 (0.78-2.12)	.40
Ewertz,[47] 1992	68/77	31/43	1.22 (0.7-2.16)	.58
Clavel,[46] 1991	148/142	115/136	1.23 (0.88-1.73)	.26
Chie,[44] 1998	10/21	73/182	1.19 (0.53-2.64)	.83
Brinton,[43] 1995	240/246	274/322	1.15 (0.9-1.46)	.29

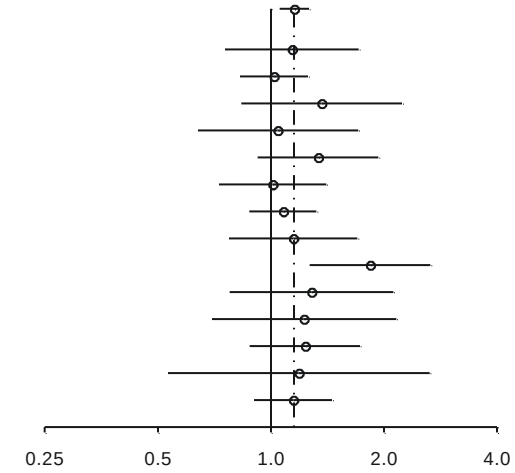
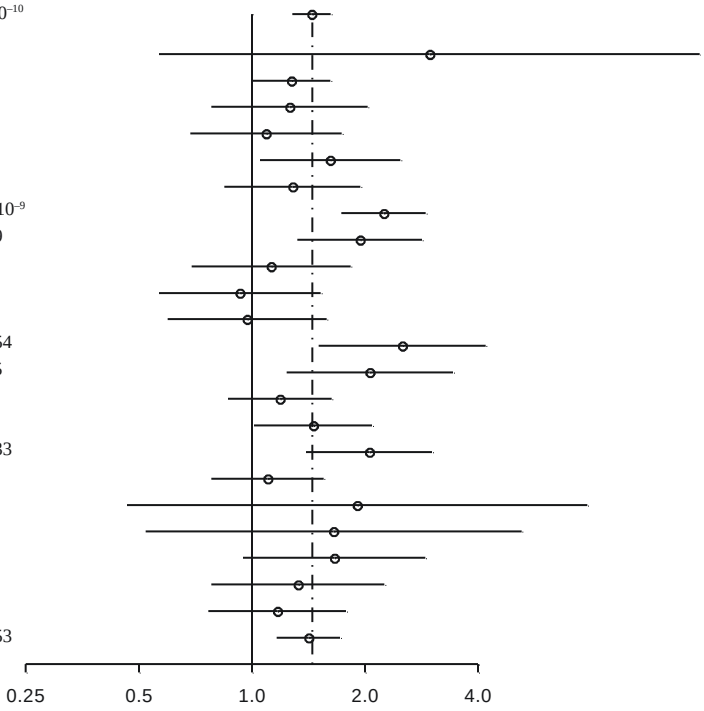


FIGURE 3. Summary estimates of risk of breast cancer in parous premenopausal women and women younger than 50 years associated with use of oral contraceptives (OCs). *Subset of women 35 years and older. †Subset of women younger than 35 years. CI = confidence interval; OR = odds ratio. Only first author mentioned because of space constraints.
Top, Among the 39 eligible studies listed in Table 1, 14 provided data on ever or never use of OCs in parous women. Includes case-control studies of parous premenopausal women (or those <50 years) who used OCs at any time vs parous women with no use. For each study, most patients developed breast cancer after 1980.
Bottom, Among the 39 eligible studies listed in Table 1, 14 provided data on OC use after a first full-term pregnancy (FFTP) in parous women. Includes case-control studies of parous premenopausal women (or those <50 years) who used OCs after FFTP vs parous women with no use. For each study, most patients developed breast cancer after 1980.

but significant risk was noted (OR, 1.25; 95% CI, 1.15-1.36). Delgado-Rodriguez et al[14] analyzed studies from 1966 to 1990 and reported an OR of 1.60 (95% CI, 1.14-2.24) for premenopausal women who used OCs for 96 months or more before FFTP. Romieu et al[10] reported that women younger than 46 years who used OCs for 4 or more years before FFTP experienced a significant 72% increase in risk (OR, 1.72; 95% CI, 1.36-2.19).

Our results vary in some ways from those of the Oxford pooled analysis.[83] First, the Oxford study concluded that women who began OC use before the age of 20 years had higher relative risks than women who began use after the

Reference	Cases/controls: OC users	Cases/controls: OC nonusers	OR (95% CI)	*P* value
All			1.44 (1.28-1.62)	8.1×10^{-10}
Yuan,[74] 1988	5/2	122/145	2.97 (0.57-15.59)	.34
Wingo,[72] 1993*	318/247	249/246	1.27 (1-1.62)	.059
Wingo,[72] 1993†	180/225	33/52	1.26 (0.78-2.03)	.41
White,[73] 1994	363/450	34/46	1.09 (0.69-1.74)	.80
Weinstein,[71] 1991	69/52	124/151	1.62 (1.05-2.49)	.038
Tavani,[30] 1999	59/48	273/285	1.28 (0.85-1.94)	.28
Rosenberg,[75] 1996*	170/125	464/765	2.24 (1.73-2.9)	1.0×10^{-9}
Rosenberg,[75] 1996†	75/116	83/249	1.94 (1.32-2.84)	.0009
Rookus,[65] 1994	267/279	34/40	1.13 (0.69-1.83)	.72
Primic-Zakelj,[64] 1995	33/37	288/300	0.93 (0.57-1.53)	.87
Paul,[63] 1990	137/535	24/91	0.97 (0.6-1.58)	.99
Palmer,[62] 1995	32/48	79/298	2.51 (1.51-4.19)	.00054
Olsson,[61] 1989	63/117	29/111	2.06 (1.24-3.44)	.0075
Moorman,[58] 2001	221/173	129/120	1.19 (0.86-1.63)	.33
Meirik,[57] 1986	143/149	81/123	1.46 (1.01-2.09)	.052
McPherson,[56] 1987	90/51	226/263	2.05 (1.4-3.02)	.00033
McCredie,[55] 1998	239/185	102/87	1.1 (0.78-1.56)	.64
Lee,[51] 1992	4/4	87/166	1.91 (0.47-7.82)	.59
Gomes,[48] 1995	5/8	64/169	1.65 (0.52-5.23)	.59
Ewertz,[47] 1992	86/72	31/43	1.66 (0.95-2.9)	.10
Clavel,[46] 1991	37/33	115/136	1.33 (0.78-2.26)	.36
UK National,[45] 1989	348/357	45/54	1.17 (0.77-1.78)	.53
Brinton,[43] 1995	725/602	274/322	1.42 (1.17-1.72)	.00053



Reference	Cases/controls: OC users	Cases/controls: OC nonusers	OR (95% CI)	*P* value
All			1.52 (1.26-1.82)	1.0×10^{-5}
Rosenberg,[75] 1996*	34/39	464/765	1.44 (0.9-2.31)	.17
Rosenberg,[75] 1996†	23/30	83/249	2.3 (1.27-4.18)	.0089
Paul,[63] 1990	31/143	24/91	0.82 (0.45-1.49)	.62
Palmer,[62] 1995	5/14	79/298	1.35 (0.47-3.85)	.79
Meirik,[57] 1986	51/48	81/123	1.61 (1-2.62)	.069
McPherson,[56] 1987	31/12	226/263	3.01 (1.51-5.99)	.002
Ewertz,[47] 1992	31/37	31/43	1.16 (0.6-2.26)	.78
Clavel,[46] 1991	9/10	115/136	1.06 (0.42-2.71)	.91
UK National,[45] 1989	129/103	45/54	1.5 (0.94-2.41)	.12
Brinton,[43] 1995	296/224	274/322	1.55 (1.23-1.97)	.00033

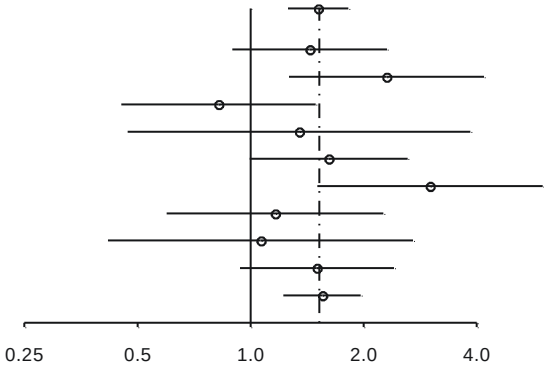


FIGURE 4. Summary estimates of risk of breast cancer in parous premenopausal women and women younger than 50 years associated with use of oral contraceptives (OCs). *Subset of women 35 years and older. †Subset of women younger than 35 years. CI = confidence interval; OR = odds ratio. Only first author mentioned because of space constraints.
Top, Among the 39 eligible studies listed in Table 1, 23 provided data on OC use before a first full-term pregnancy (FFTP) in parous women. Includes case-control studies of parous premenopausal women (or those <50 years) who used OCs before FFTP vs parous women with no use. For each study, most cases developed breast cancer after 1980.
Bottom, Among the 39 eligible studies listed in Table 1, 10 provided data on OC use for 4 or more years before FFTP in parous women. Includes case-control studies of parous premenopausal women (or those <50 years) who used OCs 4 or more years before FFTP vs parous women with no use. For each study, most cases developed breast cancer after 1980.

age of 20 years. This finding appears to support our results regarding increased risk for use before FFTP in parous women since many women who took OCs before the age of 20 years likely did so before FFTP. In addition, they noted

that parous women who used OCs within 4 years of entrance into the study and used them before FFTP had a significantly increased risk (relative risk, 1.30 for current use and 1.36 for last use 1-4 years ago).[83]

The Oxford pooled analysis also concluded that women who used OCs incurred no increased risk 10 years after last use (ie, they found the highest risk in current or recent OC users) and that cancer in women who used OCs was less advanced than those diagnosed in women who never used OCs. We note 2 distinctions in regard to these findings. First, these results cannot be directly compared with ours because of the different parameters of our analyses. We focused on premenopausal risk of early OC use in case-control studies in which cases developed breast cancer primarily after 1980; omitting 4 of 39 studies that collected some of their data before 1980 did not alter our findings (data not shown). The conclusions of the Oxford analysis in regard to the points of reference were based on OC use in both premenopausal and postmenopausal women; two thirds of the breast cancer patients in the Oxford analysis were older than 45 years.[84] Furthermore, they included several case-control studies whose database included primarily women who developed breast cancer before 1980.[19-25,85]

Second, we were unable to obtain data on timing of OC use (ie, current, recent, or 10 years after last use) for the specific subgroup of premenopausal parous women who used OCs before FFTP. A possible explanation for the Oxford study's conclusion that risks were higher in current and recent users involves the epidemiology of use. In their analysis, current or recent users would have been more likely to have used OCs in more recent decades than women whose last use was more than 10 years ago. We noted earlier that women used OCs for longer periods before FFTP in more recent decades (eg, 1980s and 1990s) vs older decades (eg, 1960s and 1970s); therefore, the increased risk of current or recent users noted in the Oxford analysis may reflect the increased risks of longer OC use before FFTP as we have observed.

We found that the risk in parous women who took OCs before FFTP (OR, 1.44; 95% CI, 1.28-1.62) was higher than in nulliparous women who took OCs (OR, 1.24; 95% CI, 0.92-1.67). We know of no reason why this difference exists.

We intentionally subdivided our analysis into different subgroups (eg, parous and nulliparous). We believe this was important because nulliparous women might experience potential risk factors (eg, infertility, use of infertility drugs, polycystic ovarian disease) more frequently than parous women.

Our analysis complements the existing body of literature by focusing on studies conducted since 1980 and examining the effect of OCs on premenopausal breast cancer. The results of prior studies and of ours are consistent with the hypothesis that OCs can be carcinogenic, especially when used before FFTP. The nulliparous breast is composed of undifferentiated structures, and it is only during a full-term pregnancy that the breast attains its maximum development.[16] This development occurs in 2 distinct phases, an early growth phase and a late phase of lobular differentiation.[16] The undifferentiated breast structures found in the nulliparous breast may be more susceptible to carcinogens than the more differentiated structures found in the fully developed breast. For example, in Hiroshima and Nagasaki, Japan, nulliparous women who were exposed to radiation from the atomic bomb developed breast cancer far more frequently than women who had already borne children at the time of exposure.[86] Although it is not possible to directly establish the carcinogenic potential of OCs in the human breast in vivo, animal studies suggest that the hormones contained in OCs have carcinogenic potential in rodents, dogs, and monkeys.[87-92] Moreover, OCs accelerate the rate of breast cell division in women who take them before FFTP.[93] Increased rates of cell division are associated with increased cancer risk.[94-96] In addition, there is evidence that OCs work at times by causing a postfertilization effect (ie, at times they work after fertilization by preventing nidation).[97] If this effect is associated with early hormonal shifts, as some data suggest,[98,99] it could be an alternative mechanism for the carcinogenic effect of OCs, especially if used before FFTP.

A number of methodologic issues are important to consider when interpreting our results alone and in comparison with previous work. First, we chose the random-effects method for this meta-analysis because we expected studies to differ significantly in many factors, including length and patterns of OC use and the available latency period, and these factors would be expected to affect the measured ORs. Second, because study populations differed substantially in race and culture, these 2 factors might lead to differences in bias in addition to having direct effects. Thus, although we consider the evidence for the association of OC use and cancer to be strong, we do not claim that each of the studies included in our analysis should have observed an effect. However, although it is biologically implausible that OC use would both increase risk and protect against breast cancer in premenopausal women, differences in study designs, variability, patient characteristics, and measurement devices could cause an individual study to find an association that appears to contradict the collective data available; thus, we consider the study by Traina et al[69] (OR, 0.61; P=.005) to be an outlier (although we included it in our analyses). In interpreting the results of our meta-analysis, it is important to understand the method and its shortcomings. The basic assumption underlying the ran-

dom-effects model is that the studies analyzed are a random sample from a large population of studies; the average OR in the population of studies is μ, and its (normally distributed) error is σ. The meta-analysis provides estimates of μ and σ, and from these we determine the CI for μ and the *P* value for no association between OC use and cancer. As noted before, we would not expect ORs to be both less than 1 and greater than 1 unless bias played a significant role; thus, the assumption that μ is distributed normally is a shortcoming. We also note that the CI computed in the random-effects model and the *P* value associated with it should be interpreted with caution when assessing the association of OC use and cancer; the random-effects model estimates properties of the population mean OR, but some of the subpopulations evaluated in the studies we considered in this meta-analysis may be at much greater risk than others.

Additional issues regarding our study design should be noted. First, by choosing to analyze studies of premenopausal women published in or after 1980, we structured this analysis to include a large portion of women exposed to OCs before FFTP to maximize the potential latent period between the exposure to OCs and breast cancer outcome.[100-103] Postmenopausal women included in studies conducted even as late as 1995 were unlikely to include many women exposed to OCs before FFTP. Moreover, there is precedent for the importance of an adequate latent period between an exposure and subsequent breast cancer development. Atomic bomb survivors experienced a radiation dose–related increase in breast cancer incidence that was first noted 15 years after exposure,[86] and the link between diethylstilbestrol use and subsequent breast cancer risk did not become evident for more than 22 years.[104] Hence, most previous analyses[10,11,13,14] that analyzed data on studies conducted before 1980 may not have included an adequate period between exposure to OCs and subsequent breast cancer development.

A second issue involves the relatively rapid change in the age of first use of OCs during the past few decades. Since the late 1970s, women have been using OCs at younger ages and for longer periods than women of similar reproductive age in the 1960s and early 1970s.[11] Hence, studies must closely match cases and controls by age so that case and control distributions within age strata are similar or any potential association may be obscured. For example, if the controls in the youngest age category are oversampled relative to the cases in that category, the control group will likely contain more women who had early and longer OC use, resulting in an underestimate of the OR. Notably, this stacking or clustering of controls in the younger age stratum relative to cases exists in many of the studies that examined OCs and breast cancer risk. Of the 34 studies included in our meta-analysis, 18 studies[30,43,45,46,48,50-52,55-57,60,62,63,69,72,73,75] provided information on frequency of age distribution of cases and controls. Eleven (61%)[30,43,46,50,60,62,63,69,72,73,75] of the 18 studies showed a stacking effect in the control group. Although individual studies can address this potential confounder by adjusting for participant age in their analyses or analyzing their data by small age strata, we were unable to do so because we did not have data on individual study participants. Moreover, because many of the individual studies did not perform analyses stratified by ever parous or OC use relative to FFTP, we could only use crude (rather than adjusted) estimates in our analyses. However, at least for the unstratified analyses (which were the only analyses for which we were able to obtain adjusted ORs), most of the crude ORs for OC use in parous women before FFTP that we calculated were similar to the adjusted ORs reported by the original authors.[30,43,45-47,51,55-57,61-63,66,71-73]

Survivor bias, that is, the exclusion of women with more aggressive breast cancer who may be too sick or die before study participation, is an important consideration since OC use early in life is associated with more aggressive disease.[105-108] Among the 13 studies[43-46,50,52,55,57,59,60,63,65,73] that reported appropriate data, 9 (69%)[45,50,52,55,57,59,63,65,73] had a potential for survivor bias, with 4 studies[45,50,59,73] of the 9 positive studies showing that more than 5% of patients died or were too sick to be interviewed. If most of these women were OC users, excluding them from the studies would yield results that attenuate any true association. An attenuated effect could also result from studies excluding younger women, such as those in their 20s and 30s, who would be more likely to have used OCs before FFTP.

The definition of OC use might also affect any risk estimate. In particular, approximately 30% of women who start using OCs for the first time stop using them within 6 months because of adverse effects or for other reasons,[109,110] and many women discontinue use within 3 months.[111] These women are often included in the ever users or users before FFTP groups, although it is unclear whether this short-term exposure is associated with an increased breast cancer risk. Thus, including them in our analyses likely attenuated our derived ORs.

Several issues concerning our results warrant discussion. First, because we limited the included studies to those with a case-control design, a possibility of recall bias exists, which would inflate any OC–breast cancer association. However, this concern has been explicitly addressed in the literature: 3 separate studies compared patients' recall against prescription records, and no study found evidence of a significant recall bias effect.[45,65,112] The concern over recall bias could have been avoided by using prospective studies; however, we did not include prospective stud-

TABLE 2. **Risk of Breast Cancer Associated With Oral Contraceptive Use (Prospective Studies)***

Reference	Country	Year of entry	Last year of study	Age at entry (y)	RR (95% CI) for ever vs never use	Name
Alexander et al,[113] 1987	Scotland	1978-1985	1985	45-64	1.14 (0.75-1.73)	None given
Beral et al,[114] 1999	Britain	1968-1969	1993	18-40?	1.1 (0.8-1.4)	Royal College of General Practitioner's Study
Calle et al,[115] 1993	United States	1982	1988	30-80	1.02 (0.92-1.12)†	American Cancer Society Study
Dumeaux et al,[116] 2003	Norway	1991-1997	1999	30-70	1.25 (1.07-1.46)	Norwegian Woman and Cancer Study
Grabrick et al,[117] 2000	United States	1991-1996	1996	18-52	3.3 (1.6-6.7)‡	None given
Hankinson et al,[118] 1997	United States	1976-1992	1992	30-55	Between 1.01 and 1.12	Nurses' Health Study
Hiatt et al,[119] 1984	United States	1960-1979	1979	Postmenopausal	Unknown	Kaiser Permanente Study
Kay et al,[120] 1988	England	1968-1969	1985	~18-40	1.22 (0.93-1.60)	Royal College of General Practitioners
Kumle et al,[121] 2002	Norway and Sweden	1991-1992	1999	30-49	1.3 (1.1-1.5)	The Norwegian-Swedish Women's Lifestyle and Health Cohort Study
Miller et al,[122] 1992	Canada	1980-1985	1990	40-49	1.06 (0.99-1.13)†	Canadian National Breast Study
Mills et al,[123] 1989	United States	1976	1982	~55	1.54 (0.94-2.53)	Seventh-day Adventist Study
Schuurman et al,[124] 1995	United States	1986	1989	55-69	1.1 (0.8-1.5)	Netherlands Cohort Study
Tomasson & Tomasson,[125] 1996	Iceland	1965-1989	1989	25-69	0.92 (no CI given)	None given
Trapido,[126] 1981	United States	1970	1979	25-50	0.84 (0.7-1.1)	None given
Tryggvadottir et al,[127] 1997	Iceland	1975-1993	1993	18-43	0.9-1.3 (no CIs given)	Icelandic Cancer Society Study
Van Hoften et al,[128] 2000	Netherlands	1982-1984	1996	41-52	1.31 (0.96-1.79)	The DOM Cohort
Vessey et al,[129] 1989	England and Scotland	1968-1974	1987	25-39	0.69 (0.53-0.85)†	Oxford Family Planning Study

*CI = confidence interval; RR = relative risk.
†Data on RR taken from Oxford pooled analysis.[83]
‡RR for sisters/daughters of proband.

ies in our analyses because few prospective data exist on timing of OC use and breast cancer in parous premenopausal women. We identified 17 prospective studies[113-129] (Table 2). Two studies[114,115] examined the risks of OCs solely in regard to *fatal* breast cancer. One studied only women who had a positive family history of breast cancer.[117] Two Icelandic studies[125,127] had no information on early OC use because the national cancer registry did not collect information on age of use of OCs until the 1990s. Only 2 prospective studies[118,129] examined OC risk in women who used them before FFTP, and only one of these examined the risk of long-term use before FFTP in premenopausal women.[118] The latter study identified only 4 premenopausal women younger than 45 years who had used OCs for 5 or more years before FFTP, a number too small from which to draw any meaningful conclusions. Moreover, if OC use before FFTP is associated with more aggressive premenopausal breast cancers,[105-108] premenopausal women with breast cancer might not be included in prospective studies since they were absent from the population from which the cohort was chosen because of their early death or excluded from the original cohort because of study design. These factors would lead to an underestimation of any true effect.

A limitation of our analyses is that we used crude ORs instead of adjusted ORs because of the lack of available data on adjusted ORs for exposure by parity or FFTP. Hence, we could not adjust for potential confounders, such as age at menarche and age at first birth. However, if certain confounders played a significant effect, we might expect the ORs that we calculated based on the raw data to be significantly different from the adjusted ORs for OC use before FFTP reported in the original publications. This does not appear to be the case. Most studies[30,43,45-47,51,55-57,61-63,66,71-73] reported adjusted ORs similar to the crude ORs we calculated in our analyses, suggesting that it is unlikely that the lack of adjustments for potential confounders substantially affected our findings.

Second, we were not able to control for hormonal doses in the OC preparations. Hormonal content of OCs has changed throughout the years, and the results of studies in which women were exposed predominantly to high-dose estrogen and progestin OCs may not apply to low-dose OCs. Although low-dose OCs have less thrombotic risk than high-dose OCs, low-dose OCs have been associated with greater breast cancer risk compared with high-dose regimens.[21,60,65] For example, the Oxford pooled analysis reported a higher risk of metastatic breast cancer in women who took low-dose triphasic OCs vs the high-dose monophasic OCs.[11] Although the reason underlying this apparent contradiction is unknown, it could be due to the more potent progestins used in newer OCs. Although

the norethindrone-related progestins (eg, norethindrone, norethynodrel, ethynodiol) were exclusively used in the 1960s and 1970s, the gonanes (eg, desogestrel, norgestrel, norgestimate), which are far more potent than their predecessors,[130] have been used more frequently since the late 1970s. Progesterone levels rise in the luteal phase and have been hypothesized to be responsible for the increasing rate of breast cell division.[131] Oral contraceptives hyperstimulate breast cell division in the nulliparous breast but have their greatest effect in the luteal phase, when progestin doses within low-dose triphasic OCs are highest.[93] Synthetic progestins appear to increase breast cancer risk. Skegg et al[132] noted that women of young reproductive age who take injectable medroxyprogesterone acetate for 3 years or longer sustained a 190% increased risk in breast cancer (relative risk, 2.9; 95% CI, 1.2-7.1). Recently, the Women's Health Initiative reported that women randomized to take a combined estrogen-progestin formulation had an increased risk of breast cancer,[8] whereas women taking estrogen alone had no increased risk.[133] Hence, it is possible that the type and dose of OC progestin component might affect breast cancer risk.

Third, we noted earlier that we were not able to obtain specific data regarding timing since last use for premenopausal parous women who used OCs before FFTP. However, we believe it is reasonable to assume that most premenopausal patients who took OCs before FFTP took them at least 10 years ago since the average woman in the United States continues to take OCs for approximately 5 years.[134] In the future, the definition of timing of last OC use may become clouded as more perimenopausal women use newer low-dose OC regimens for noncontraceptive purposes. Another consideration is that we included all studies in the literature without applying any quality assessment criteria. This may explain some of the heterogeneity we observed in our analyses and might bias our findings toward the null. Although we noted heterogeneity in studies limited to nulliparous women, we were unable to identify the cause of the heterogeneity. Publication bias might also affect our results, although the smallest study included in our analysis had only 200 patients, and construction of a funnel plot showed no evidence of publication bias (data not shown).

CONCLUSION

Consistent with the recent International Agency for Research on Cancer classification of OCs as group 1 carcinogens, this meta-analysis suggests that OCs are associated with an increase in premenopausal breast cancer risk, especially among women who use OCs before FFTP.

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