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Systematic Reviews and Meta- and Pooled Analyses

Smoking Before the First Pregnancy and the Risk of Breast Cancer: A Meta-Analysis

Lisa A. DeRoo*, Peter Cummings, and Beth A. Mueller

* Correspondence to Dr. Lisa A. DeRoo, Epidemiology Branch, National Institute of Environmental Health Sciences, P.O. Box 12233, MD A3-05, 111 T. W. Alexander Drive, Research Triangle Park, NC 27709 (e-mail: DeRooL@niehs.nih.gov).

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The authors conducted a meta-analysis of the association between smoking before a first pregnancy, when undifferentiated breast tissue may be vulnerable to tobacco carcinogens, and the risk of breast cancer. A search of the published literature through August 2010 identified 23 papers reporting on associations between smoking before a first pregnancy and breast cancer. Odds ratios or hazard ratios and 95% confidence intervals, adjusted for known or suspected breast cancer risk factors, were abstracted from each study. Data were pooled using both fixed- and random-effects models. The fixed-effect summary risk ratio for breast cancer among the women who smoked before their first pregnancy versus women who had never smoked was 1.10 (95% confidence interval: 1.07, 1.14); the random-effects estimate was similar. The separate fixed-effect risk ratios for smoking only before the first pregnancy (5 studies) or only after the first pregnancy (16 studies) were both 1.07, providing no evidence that breast tissue is more susceptible to malignant transformation from smoking before the first pregnancy. While these small summary risk ratios may represent causal effects, residual confounding could readily produce estimates of this size in the absence of any causal effect.

breast neoplasms; pregnancy; smoking

Abbreviations: CI, confidence interval; RR, risk ratio.

Although many investigators report no association between smoking and breast cancer, it is possible that smoking during susceptible periods may increase risk (1). According to studies on breast development and cancer susceptibility, the relatively undifferentiated breast epithelial cells present before a first pregnancy may be particularly vulnerable to the carcinogenic effects of cigarette smoke (2, 3). Animal models have shown that cancer initiation can occur when chemical carcinogens come into contact with undifferentiated, highly proliferating mammary epithelium and is less likely after a full-term pregnancy, during which the mammary gland undergoes differentiation (2). In humans, the mammary gland is composed of developing lobules at menarche, and a first pregnancy and lactation trigger breast growth and differentiation.

We conducted a meta-analysis to examine the association between smoking before a first pregnancy and the risk of breast cancer. A previous meta-analysis by Lawlor et al. (4) used data from 11 papers; we used 23 studies and somewhat different selection criteria. We estimated the summary risk ratios for breast cancer among women who smoked before their first pregnancies, regardless of whether or not they continued to smoke after the pregnancy, compared with those who had never smoked. We also calculated separate summary risk ratio estimates for breast cancer among women who had smoked only before their first pregnancies and those who had smoked only after their first pregnancies to determine whether there were differences for these exposure periods. If cancer initiation by tobacco smoke were more likely in undifferentiated mammary gland epithelium, then the risk ratio for women who smoked only before their first pregnancy should be larger than the risk ratio for women who smoked only after, compared with otherwise similar women who had never smoked.

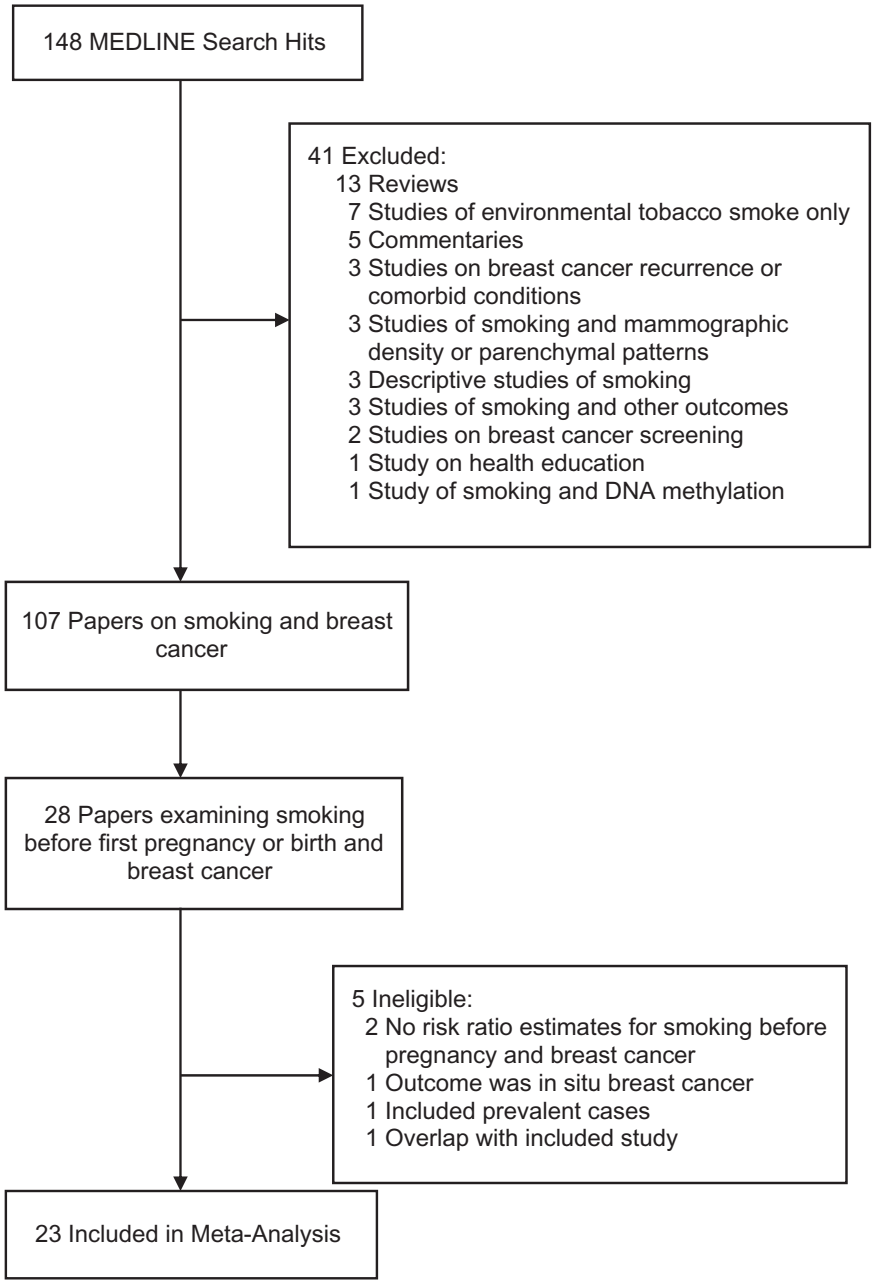

Figure 1. Search strategy and study selection process used in a meta-analysis of the association between smoking before the first pregnancy and risk of breast cancer, 1988–2009.

MATERIALS AND METHODS

Relevant studies were identified by querying MEDLINE (US National Library of Medicine) for articles published from 1949 through August 2010. To be included in the meta-analysis, a study had to 1) present data on incident cases of clinically diagnosed breast cancer and 2) examine the association between active smoking before a woman's first pregnancy and breast cancer. An advanced search was conducted in PubMed using the following Medical Subject Headings: (''smoking'' [major:noexplode] *or* ''tobacco smoke pollution'' [major:noexplode]) *and* (''breast neoplasms/etiology'' [major:noexplode] *or* ''breast neoplasms/epidemiology'' [major:noexplode] *or* ''breast neoplasms/genetics'' [major:noexplode]) *and* Journal Article [Publication Type], *not* males *not* animals. Of the 148 manuscripts identified, 41 were excluded and 107 were examined for analyses of smoking before pregnancy and breast cancer (Figure 1).

Of 28 papers that examined smoking before the first pregnancy, 5 were deemed ineligible. Two examined smoking before pregnancy and breast cancer but did not report

Table 1. Characteristics of Studies Included in a Meta-Analysis of the Association Between Smoking Before the First Pregnancy and Risk of Breast Cancer, by Study Design and Publication Year, 1988–2009

First Author, Year (Reference No.)	Year(s) of Data Collection	Location of Study	Source of Information on Smoking	Source of Information on Breast Cancer	Age of Subjects, years	Potential Confounders Examined in the Analyses	Comments
Case-control studies							
Adami, 1988 (15)	1984–1985	Sweden and Norway	In-person interview	Cancer registry	<45	Age at menarche, age at first full-term pregnancy, parity, menopausal status, OC use, alcohol consumption, education, history of surgery for BBD, and family history of breast cancer	Cases and controls were matched on date of birth and country of residency
Morabia, 1996 (16)	1992–1993	Geneva, Switzerland	In-person interview	Cancer registry	<75	Age, age at menarche, age at first livebirth, OC use, alcohol consumption, BMI[a], education, and family history of breast cancer	Referent group was never-active, never-passive smokers
Lash, 1999 (17)	1983–1986	Massachusetts, United States	Telephone (86%) and in-person interviews	Cancer registry	All	Age, age at first birth, parity, menopausal status, HRT, BMI, history of BBD, history of breast cancer other than the index diagnosis, history of radiation therapy, and family history of breast cancer	Referent group was never-active, never-passive smokers
Band, 2002 (12)	1988–1989	British Columbia, Canada	Mailed questionnaire	Cancer registry	<75	Age at menarche, no. of pregnancies, no. of livebirths, age at first pregnancy, age at first full-term pregnancy, breastfeeding, age at menopause, OC use, estrogen replacement therapy, cumulative alcohol score, weight and BMI at age 18 years and currently, change in BMI from age 18 years to the present, education, marital status, history of biopsy for BBD, ethnic origin, and family history of breast cancer	Cases and controls were matched on age
Kropp, 2002 (18)	1992–1995	Rhein-Neckar-Odenwald and Freiburg, Germany	Computer-assisted telephone interview	Hospital surveillance	≤50	Age, months of breastfeeding, menopausal status, average daily alcohol intake, BMI, education, and family history of breast cancer	Cases and controls were matched on age and study region Referent group was never-active, never-passive smokers
Lash, 2002 (19)	1987–1993	Massachusetts, United States	Interviews	Cancer registry	All	Age at first birth, parity, alcohol consumption, BMI, history of BBD, history of radiation therapy, and family history of breast cancer	Cases and controls were matched on age and vital status Referent group was never-active, never-passive smokers
Egan, 2003 (20)	1997–1998	Massachusetts and Wisconsin, United States	Telephone interviews	State tumor registries	20–69	Age, age at menarche, parity, age at first birth, menopausal status, age at menopause, alcohol consumption, BMI, education, state, history of BBD, and family history of breast cancer	

Gammon, 2004 (21)	1996–1997	Long Island Breast Cancer Study Project, New York, United States	In-person interview	Pathology reports confirmed by a physician	24–98	Age, age at menarche, age at first birth, parity, no. of livebirths, months of lactation, no. of miscarriages, history of fertility problems, OC use, HRT, alcohol intake, physical activity, fruit and vegetable intake, BMI at reference date and at age 20 years, education, race, ethnicity, religion, marital status, screening history, history of BBD, and family history of breast cancer	Referent group was never-active, never-passive smokers
Li, 2005 (22)	1997–1999	Washington, United States	In-person interview	Cancer registry	65–79	Age at first full-term pregnancy, parity, age at menopause, type of menopause, HRT (unopposed and combined estrogen/progestin), alcohol consumption, BMI, education, and family history of breast cancer	Cases and controls were matched on age
Lissowska, 2006 (23)	2000–2003	Warsaw and Lodz, Poland	Personal interview	Hospitals and cancer registry	20–74	Age at menarche, age at first full-term birth, no. of full-term births, age at menopause, OC use, HRT, alcohol consumption, BMI, education, prior benign breast biopsy, and family history of breast cancer	Cases and controls were matched on age and study site
Magnusson, 2007 (24)	1993–1995	Sweden	Mailed questionnaire	Cancer registry	50–74	Age at menarche, age at first birth, parity, age at menopause, HRT, alcohol consumption, BMI, socioeconomic position, history of BBD, and family history of breast cancer	Cases and controls were matched on age
Prescott, 2007 (25)	1998–2003	Los Angeles, California, United States	In-person interviews	Cancer registry	20–49	Age, age at menarche, no. of full-term pregnancies, alcohol consumption, education, race, and family history of breast or ovarian cancer	Cases and controls were matched on age and race
Rollison, 2008 (26)	2000–2002	Delaware, United States	Telephone interviews	Cancer registry	40–79	Age, age at menarche, age at first livebirth, menopausal status, OC use, other hormone use, alcohol consumption, BMI, education, and family history of breast cancer	Cases and controls were frequency-matched on age
Slattery, 2008 (27)	1999–2004	Arizona (7 counties), Colorado, New Mexico, and Utah, United States	Interviewer-administered computer questionnaire	Cancer registry	25–79	Age, center, age at menarche, age at first birth, parity, age at menopause, OC use, alcohol consumption, long-term physical activity, use of aspirin/nonsteroidal antiinflammatory drugs, and BMI	Cases and controls were matched on age
Young, 2009 (28)	1996–1998	Ontario Women's Health Study, Ontario, Canada	Mailed questionnaire	Cancer registry	25–75	Age at menarche, age at first livebirth, parity, menopausal status, OC use, HRT, alcohol consumption, BMI, household income, history of BBD, and family history of breast cancer	Cases and controls were matched on age Referent group was never-active, never-passive smokers
Cohort studies							

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Year(s) of Data Collection	Location of Study	Source of Information on Smoking	Source of Information on Breast Cancer	Age of Subjects, years	Potential Confounders Examined in the Analyses	Comments
Egan, 2002 (11)	1982–1996	Nurses' Health Study, United States	Mailed questionnaire	Self-report confirmed by medical record review	36–61	Age, age at menarche, age at first birth, parity, menopausal status, age at menopause, HRT, alcohol consumption, weight at age 18 years and adult weight change, adult height, total carotenoid intake, duration of postpartum smoking, history of BBD, and family history of breast cancer	
Al-Delaimy, 2004 (29)	1989–1999	Nurses' Health Study II, United States	Mailed questionnaire	Self-report confirmed by hospital record and pathology reports	25–42	Age, age at menarche, age at first birth, parity, menopausal status, OC use, recent alcohol consumption, BMI, height, history of BBD, and family history of breast cancer	
Lawlor, 2004 (4)	1999–2001	British Women's Heart and Health Cohort Study, United Kingdom	Self-administered questionnaire	Cancer and mortality registries	60–79	Age, age at menarche, age at first birth, parity, age at menopause, hysterectomy and/or oophorectomy, OC use, HRT, alcohol consumption, BMI, and childhood and adult social class	Results for incident cases were used
Reynolds, 2004 (30)	1995–2000	California Teachers Study, California, United States	Mailed questionnaire	Cancer registry	All	Age, age at menarche, age at first full-term pregnancy, parity, menopausal status, HRT, alcohol consumption, physical activity, BMI, race, and family history of breast cancer	
Gram, 2005 (31)	1991–1992	Norwegian-Swedish Women's Lifestyle and Health Cohort Study, Sweden and Norway	Mailed questionnaire	Cancer registry	30–50	Age, age at menarche, age at first birth, parity, menopausal status, hormonal contraceptive use, alcohol consumption, BMI, and family history of breast cancer	Results for long-term smokers ($\geq$20 years) were used
Olson, 2005 (32)	1986	Iowa Women's Health Study, Iowa, United States	Mailed questionnaire	Cancer registry	55–69	Age at menarche, age at menopause, OC use, HRT, alcohol consumption, physical activity, waist-to-hip ratio, height, BMI at age 18 years and currently, education, and family history of breast cancer	
Cui, 2006 (33)	1980–1985	Canadian National Breast Cancer Screening Study, Canada	Self-administered questionnaire	Cancer registry and mortality database	40–59	Age, randomization group, study center, age at menarche, parity, menopausal status, OC use, HRT, alcohol consumption, physical activity, BMI, education, breast self-examination, history of BBD, and family history of breast cancer	Cohort was created from a randomized controlled trial
Ha, 2007 (34)	1983–1989	US Radiologic Technologists Study, United States	Mailed questionnaire	Self-report (most validated) and National Death Index Plus	22–92	Age, birth cohort, year first worked as a radiologic technologist, age at menarche, age at first birth, parity, menopausal status, HRT, alcohol consumption, BMI, and family history of breast cancer	

Abbreviations: BBD, benign breast disease; BMI, body mass index; HRT, hormone replacement therapy; OC, oral contraceptive.
[a] Weight (kg)/height $(m)^2$.

estimated associations from those analyses (5, 6). One studied in situ breast cancer only, excluding cases with invasive cancer (7). One study included prevalent cases (8) and was excluded because estimates might have been biased if some eligible case subjects did not survive to take part in the study or if smoking is related to survival time (9). Finally, we excluded a case-control study (10) nested within the Nurses' Health Study because the same subjects were also part of an included cohort study by Egan et al. (11). In addition, our eligibility criteria differed from those of the previous meta-analysis (4) as follows: We used 1 summary estimate from Band et al. (12) in our calculation of pooled estimates, whereas Lawlor et al. (4) used 2, and we did not include 2 studies of smoking during the first pregnancy that used linked birth and cancer registry data (13, 14) because nonsmokers in those studies included both never smokers and smokers who quit before the first pregnancy.

The 23 studies included in our meta-analysis were published between 1988 and 2009 and included 15 case-control studies (12, 15–28) and 8 cohort studies (4, 11, 29–34). Adjusted odds ratios or hazard ratios and 95% confidence intervals for the association between smoking before a first pregnancy and breast cancer were abstracted from each paper. Some investigators reported estimates stratified by years of smoking or pack-years of smoking before the first pregnancy (11, 15, 25, 26, 28–30, 33, 34), menopausal status (12, 27), *N*-acetyltransferase 2 acetylation genotype (20), or race/ethnicity (27). Others separated smokers into categories according to whether they smoked only before their first pregnancy or both before and after their first pregnancy (17–19, 21). When necessary, we created within-study estimates for the association between ever smoking before the first pregnancy and breast cancer risk by using inverse-variance weighting of the stratum-specific adjusted estimates reported in each study. When available, we also abstracted association estimates for women who had smoked only before their first pregnancy (11, 17–19, 21) and those who had smoked only after their first pregnancy (11, 12, 16–19, 21, 23–25, 27, 28, 30–32), and we used the same methods to calculate within-study estimates for stratified results.

We summarized risk ratios across the studies using inverse-variance weighting to calculate fixed-effect summary estimates. Random-effects estimates were also calculated using the method of DerSimonian and Laird (35). We used Cochran's Q statistic (36) to test the null hypothesis that risk ratios were homogeneous across studies (37). We set a conservative cutoff (10%) for significance because the Q statistic is poor at detecting heterogeneity under certain conditions, such as when the number of studies is small (38). We also calculated I^2, a quantitative estimate of the percentage of total variation between studies that is due to heterogeneity rather than chance (39, 40). Funnel plots (41) and Begg's tests (42) were used to assess potential publication bias. Analyses were conducted using Stata software (43, 44).

RESULTS

Of the 23 studies used for this review, 13 were conducted in the United States (11, 17, 19–22, 25–27, 29, 30, 32, 34), 3 in Canada (12, 28, 33), 2 in Sweden and Norway combined (15, 31), and 1 each in Switzerland (16), Germany (18), the United Kingdom (4), Poland (23), and Sweden (24) (Table 1). Nearly all of the case-control studies identified breast cancer patients through population-based registries, and controls were selected using population registries (15, 16, 18, 23, 24, 28), random digit dialing (17, 19, 21), voter's lists (12), lists of licensed drivers (20, 26, 27), Health Care Financing Administration records of Medicare beneficiaries (17, 19–22, 26, 27), mortality registers (17, 19), and a neighborhood walk algorithm (25). The cohort studies drew subjects from population-based samples (4, 31, 32), women undergoing mammographic screening (33), and occupational groups, including nurses (11, 29), teachers (30), and radiologic technologists (34). Breast cancer cases were identified in the cohorts using self-reports validated by medical records (11, 29, 34), cancer registries (4, 30–33), and mortality databases (4, 33, 34). In all studies, information on smoking and possible confounders was collected using self-administered questionnaires (4, 11, 12, 24, 28–34) or interviews (15–23, 25–27). In most of the studies, investigators used breast cancer patients and controls who were alive at the time of the study; however, in 2 studies (17, 19), they also collected information on deceased subjects by interviewing their next of kin. Each study examined numerous covariates, including alcohol use, pregnancy history, and age at first pregnancy. For 15 studies, the published article specified that nulliparous women were excluded from analyses of smoking before pregnancy (11, 12, 15, 18, 19, 21–23, 25, 26, 28, 30–33).

Smoking before the first pregnancy

The 23 adjusted within-study odds ratios or hazard ratios ranged from 0.70 to 3.0 (Table 2, Figure 2). The fixed-effect summary risk ratio for breast cancer among the women who had smoked before their first pregnancy as compared with women who had never smoked was 1.10 (95% confidence interval (CI): 1.07, 1.14) across the 23 studies; the random-effects summary risk ratio was 1.11 (95% CI: 1.06, 1.16) (Table 3). Stratifying by study type, the 15 case-control studies had a fixed-effect summary risk ratio (risk ratio (RR) = 1.08, 95% CI: 1.03, 1.13) similar to that of the 8 cohort studies (RR = 1.12, 95% CI: 1.07, 1.17) (test of heterogeneity: $P = 0.21$). There was evidence of heterogeneity across the 23 studies (Cochran's Q test $P = 0.06$; $I^2 = 34.0\%$) but no evidence of publication bias based on funnel plots or Begg's test ($P = 0.48$). Removing the results of 2 studies that included deceased subjects (17, 19) reduced the heterogeneity (Cochran's Q test $P = 0.26$; $I^2 = 15\%$), and the summary risk ratio estimate for the remaining 21 studies was 1.11 (95% CI: 1.07, 1.14) using the fixed-effect method and 1.11 (95% CI: 1.07, 1.15) using the random-effects method. Fourteen studies (4, 11, 15, 20–26, 28, 30, 31, 34) used the outcome of first birth, first livebirth, or first full-term pregnancy (as opposed to a first pregnancy, which could end in abortion). The pooled fixed-effect risk ratio from these 14 studies was 1.10 (95% CI: 1.05, 1.14). For the other 9 studies that used first pregnancy as an outcome (12, 16–19, 27, 29,

Table 2. Within-Study Subgroup and Summary Estimates for Risk of Breast Cancer Among Women Who Smoked Before Their First Pregnancy, Women Who Smoked Only Before Their First Pregnancy, and Women Who Smoked Only After Their First Pregnancy as Compared With Women Who Had Never Smoked, 1988–2009

Smoking Exposure Variable and Study	Within-Study Subgroup Estimate		Within-Study Summary Estimate	
	OR or HR	95% CI	RR	95% CI
Smoked before first pregnancy				
Adami, 1988 (15)			0.8	0.6, 1.1
<5 years[a]	1.0	0.6, 1.6		
5–9 years	0.7	0.4, 1.1		
≥10 years	0.7	0.3, 1.4		
Morabia, 1996 (16)			3.0	1.7, 7.0
Lash, 1999[b] (17)			1.5	0.8, 2.5
Smoked only before first pregnancy	5.6	1.5, 21		
Smoked before and after first pregnancy	1.1	0.6, 2.0		
Band, 2002 (12)			1.11	0.90, 1.35
Premenopausal women	1.47	1.02, 2.10		
Postmenopausal women	0.97	0.76, 1.24		
Egan, 2002 (11)			1.12	1.01, 1.23
<5 years[a]	1.10	0.96, 1.26		
≥5 years	1.13	0.99, 1.30		
Kropp, 2002 (18)			1.16	0.82, 1.64
Smoked only before first pregnancy	0.92	0.52, 1.65		
Smoked before and after first pregnancy	1.32	0.86, 2.03		
Lash, 2002[b] (19)			0.70	0.52, 0.95
Smoked only before first pregnancy	0.73	0.42, 1.30		
Smoked before and after first pregnancy	0.69	0.49, 0.96		
Egan, 2003 (20)			1.22	0.87, 1.70
Slow *NAT2* acetylation genotype (>5 years[a])	1.38	0.87, 2.19		
Fast *NAT2* acetylation genotype (>5 years)	1.05	0.64, 1.72		
Al-Delaimy, 2004 (29)			1.18	1.05, 1.32
1–4 years[a]	1.02	0.72, 1.44		
5–9 years	1.12	0.91, 1.39		
10–14 years	1.19	0.97, 1.47		
15–19 years	1.42	1.10, 1.83		
≥20 years	1.10	0.80, 1.52		
Gammon, 2004 (21)			0.94	0.75, 1.17
Smoked only before first pregnancy	0.72	0.49, 1.05		
Smoked before and after first pregnancy	1.08	0.82, 1.43		
Lawlor, 2004 (4)			1.08	0.39, 2.55
Reynolds, 2004 (30)			1.09	0.98, 1.21
<5 years[a]	0.99	0.80, 1.21		
≥5 years	1.13	1.00, 1.28		
Gram, 2005 (31)			1.27	1.00, 1.62
Li, 2005 (22)			1.3	1.0, 1.6
Olson, 2005 (32)			1.21	1.07, 1.37
Cui, 2006 (33)			1.07	0.99, 1.15
≤5 years[a]	1.01	0.91, 1.13		
>5 years	1.13	1.01, 1.25		
Lissowska, 2006 (23)			1.14	0.98, 1.32
Ha, 2007 (34)			1.14	0.80, 1.61
<10 pack-years	0.97	0.61, 1.54		
≥10 pack-years	1.39	0.82, 2.35		
Magnusson, 2007 (24)			1.09	0.94, 1.26
Current smokers	1.2	0.9, 1.4		
Past smokers	1.0	0.8, 1.2		
Prescott, 2007 (25)			0.99	0.79, 1.22
≤10 years[a]	0.95	0.48, 1.95		
>10 years	1.03	0.75, 1.43		

Table continues

Table 2. Continued

Smoking Exposure Variable and Study	Within-Study Subgroup Estimate		Within-Study Summary Estimate	
	OR or HR	95% CI	RR	95% CI
Rollison, 2008 (26)			1.24	0.92, 1.66
<5 years[a]	1.25	0.73, 2.13		
5–9 years	1.37	0.87, 2.16		
10–14 years	0.69	0.33, 1.45		
15–39 years	1.99	0.76, 5.18		
Slattery, 2008 (27)			1.05	0.91, 1.22
Premenopausal women				
Non-Hispanic white	1.4	1.0, 1.9		
Hispanic/American Indian	1.1	0.8, 1.7		
Postmenopausal women				
Non-Hispanic white	1.0	0.8, 1.3		
Hispanic/American Indian	0.9	0.7, 1.2		
Young, 2009 (28)			1.07	0.98, 1.16
≤5 years[a]	0.96	0.84, 1.09		
>5 years	1.16	1.04, 1.31		
Smoked only before the first pregnancy				
Lash, 1999[b] (17)			5.6	1.5, 21.0
Egan, 2002 (11)			1.15	0.99, 1.34
<5 years[a]	1.18	0.95, 1.46		
≥5 years	1.12	0.90, 1.40		
Kropp, 2002 (18)			0.92	0.52, 1.65
Lash, 2002[b] (19)			0.73	0.42, 1.30
Gammon, 2004 (21)			0.72	0.49, 1.05
Smoked only after the first pregnancy				
Morabia, 1996 (16)			3.5	1.7, 7.0
Lash, 1999[b] (17)			2.1	1.1, 4.0
Band, 2002 (12)			0.68	0.47, 0.99
Premenopausal women	0.83	0.37, 1.85		
Postmenopausal women	0.64	0.42, 0.98		
Egan, 2002 (11)			1.01	0.78, 1.32
Kropp, 2002 (18)			1.64	0.90, 2.97
Lash, 2002[b] (19)			0.66	0.42, 1.00
Gammon, 2004 (21)			1.20	0.76, 1.89
Reynolds, 2004 (30)			0.89	0.65, 1.21
Gram, 2005 (31)			0.98	0.70, 1.62
Li, 2005 (22)			1.1	0.8, 1.5
Olson, 2005 (32)			1.03	0.88, 1.21
Lissowska, 2006 (23)			1.06	0.87, 1.29
Magnusson, 2007 (24)			1.13	0.88, 1.46
Current smokers	1.0	0.7, 1.4		
Past smokers	1.3	0.9, 1.9		
Prescott, 2007 (25)			0.97	0.48, 1.95
Slattery, 2008 (27)			1.08	0.86, 1.37
Premenopausal women				
Non-Hispanic white	1.2	0.6, 2.4		
Hispanic/American Indian	1.0	0.5, 2.1		
Postmenopausal women				
Non-Hispanic white	1.0	0.7, 1.4		
Hispanic/American Indian	1.2	0.8, 1.8		
Young, 2009 (28)			1.24	1.02, 1.52

Abbreviations: CI, confidence interval; HR, hazard ratio; NAT2, *N*-acetyltransferase 2; OR, odds ratio; RR, risk ratio.

[a] Categories refer to the number of years of smoking before the first pregnancy.

[b] Study included deceased subjects.

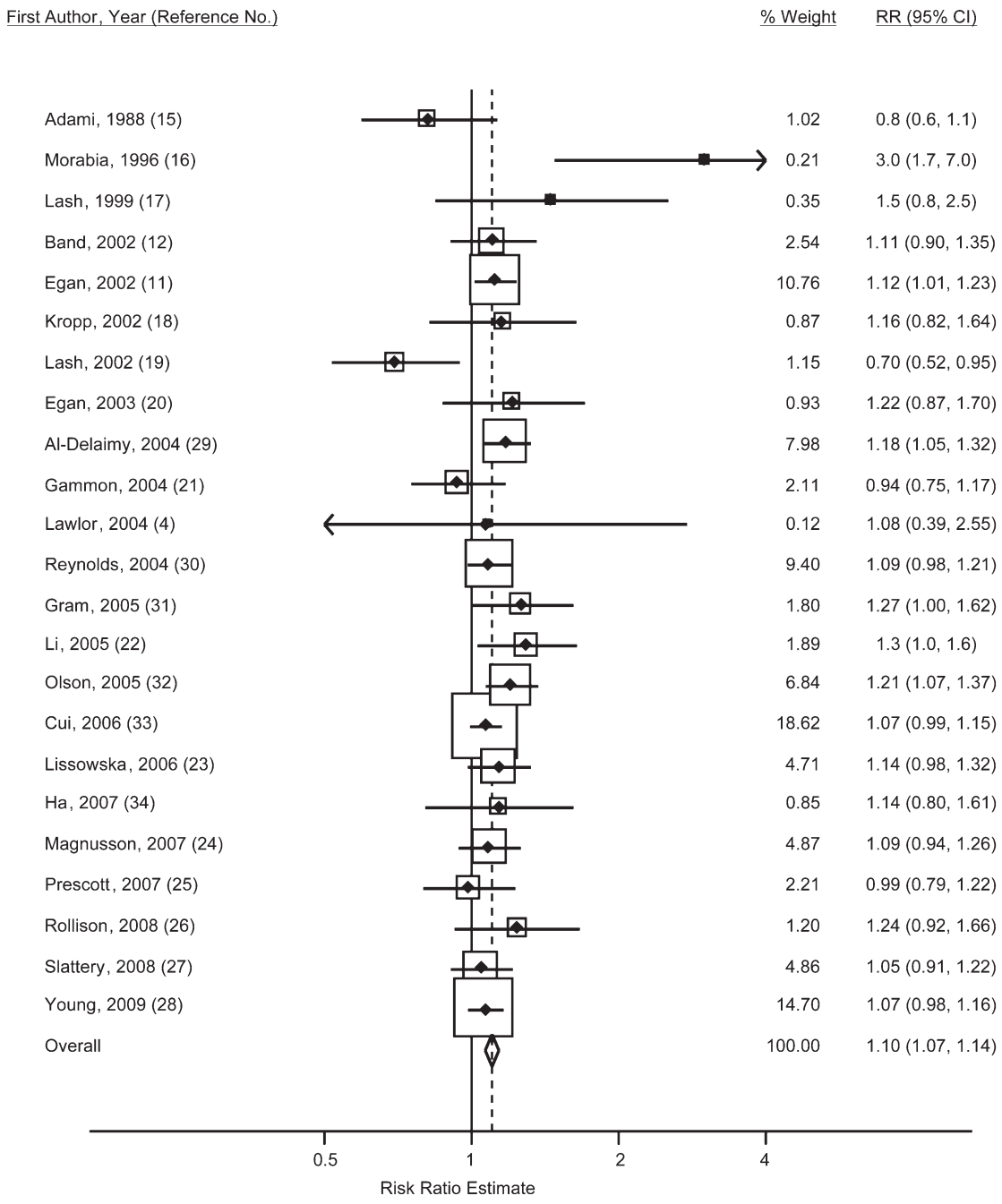

Figure 2. Study-specific odds and hazard ratios and fixed-effect summary risk ratio (RR) (diamond) for breast cancer among women who smoked before their first pregnancy as compared with women who had never smoked, 1988–2009. The size of each box indicates the relative weight of each study in the meta-analysis; the horizontal bars show the 95% confidence intervals (CIs).

32, 33), the fixed-effect risk ratio was 1.11 (95% CI: 1.06, 1.16).

Smoking only before the first pregnancy

Five studies examined the risk ratio for breast cancer among women who had smoked only prior to their first pregnancy and not afterward, in comparison with women who had never smoked (11, 17–19, 21). The adjusted within-study odds ratios or hazard ratios ranged from 0.72 to 5.6 (Table 2, Figure 3). The summarized fixed-effect risk ratio across the 5 studies was 1.07 (95% CI: 0.93, 1.22); the random-effects estimate was 1.00 (95% CI: 0.69, 1.44) (Table 3). There was evidence of heterogeneity of results

Table 3. Summary Risk Ratios for Breast Cancer Among Women Who Smoked Before Their First Pregnancy, Women Who Smoked Only Before Their First Pregnancy, and Women Who Smoked Only After Their First Pregnancy as Compared With Women Who Had Never Smoked, 1988–2009

Smoking Exposure Variable and No. of Studies (Reference Nos.)	Fixed Effects		Random Effects		Cochran's Q[a] P Value	I^2[b]		Begg's Test[c] P Value
	RR	95% CI	RR	95% CI		%	95% CI	
Smoked before the first pregnancy (4, 11, 12, 15–34)								
23	1.10	1.07, 1.14	1.11	1.06, 1.16	0.06	34	0, 60	0.48
21[d]	1.11	1.07, 1.14	1.11	1.07, 1.15	0.26	15	0, 45	0.43
Smoked only before the first pregnancy (11, 17–19, 21)								
5	1.07	0.93, 1.22	1.00	0.69, 1.44	0.01	69	22, 88	0.33
3[d]	1.07	0.93, 1.23	0.95	0.69, 1.32	0.07	62	0, 89	0.60
Smoked only after the first pregnancy (11, 12, 16–19, 21–25, 27, 28, 30–32)								
16	1.07	0.99, 1.15	1.08	0.96, 1.21	0.007	53	17, 73	0.21
14[d]	1.07	1.00, 1.16	1.08	0.97, 1.20	0.04	43	0, 70	0.30

Abbreviations: CI, confidence interval; RR, risk ratio.
[a] Test of the null hypothesis that risk ratios were homogeneous across studies.
[b] Estimate of the percentage of total variation between studies that was due to heterogeneity rather than chance.
[c] Assessment of potential publication bias.
[d] Two studies (17, 19) were eliminated to reduce heterogeneity.

across the 5 studies (Cochran's Q test $P = 0.01$; $I^2 = 69\%$) but no evidence of publication bias (Begg's test $P = 0.33$). Removing the 2 studies that included deceased subjects (17, 19) did not eliminate the heterogeneity (Cochran's Q test $P = 0.07$; $I^2 = 62\%$). The fixed-effect summary risk ratio estimate for the remaining 3 studies was 1.07 (95% CI: 0.93, 1.23), and the random-effects estimate was 0.95 (95% CI: 0.69, 1.32).

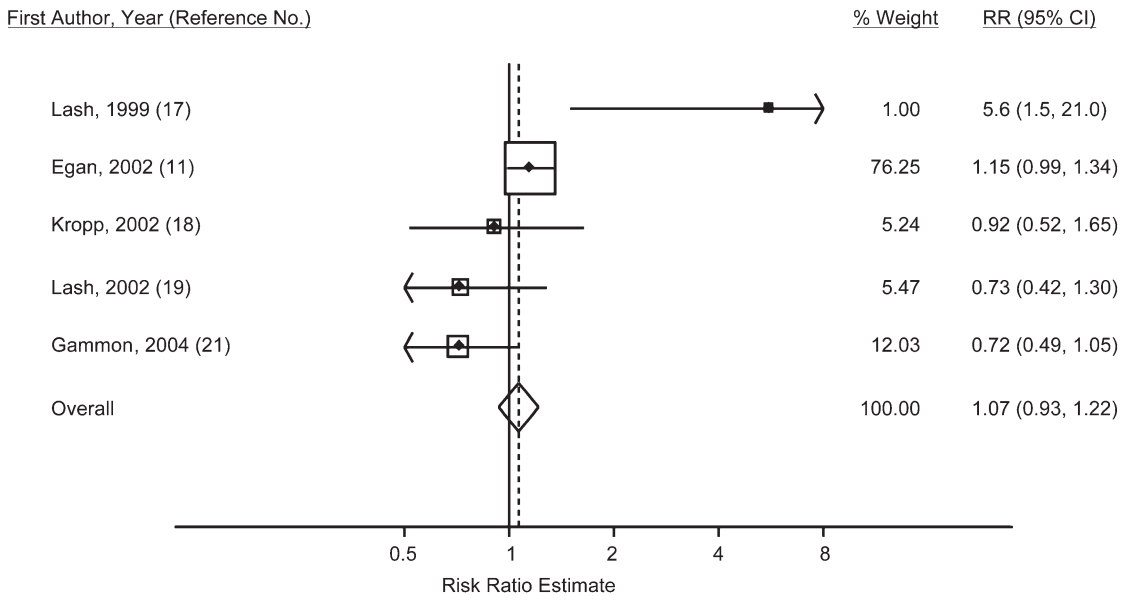

Figure 3. Study-specific odds and hazard ratios and fixed-effect summary risk ratio (RR) (diamond) for breast cancer among women who smoked only before their first pregnancy as compared with women who had never smoked, 1988–2009. The size of each box indicates the relative weight of each study in the meta-analysis; the horizontal bars show the 95% confidence intervals (CIs).

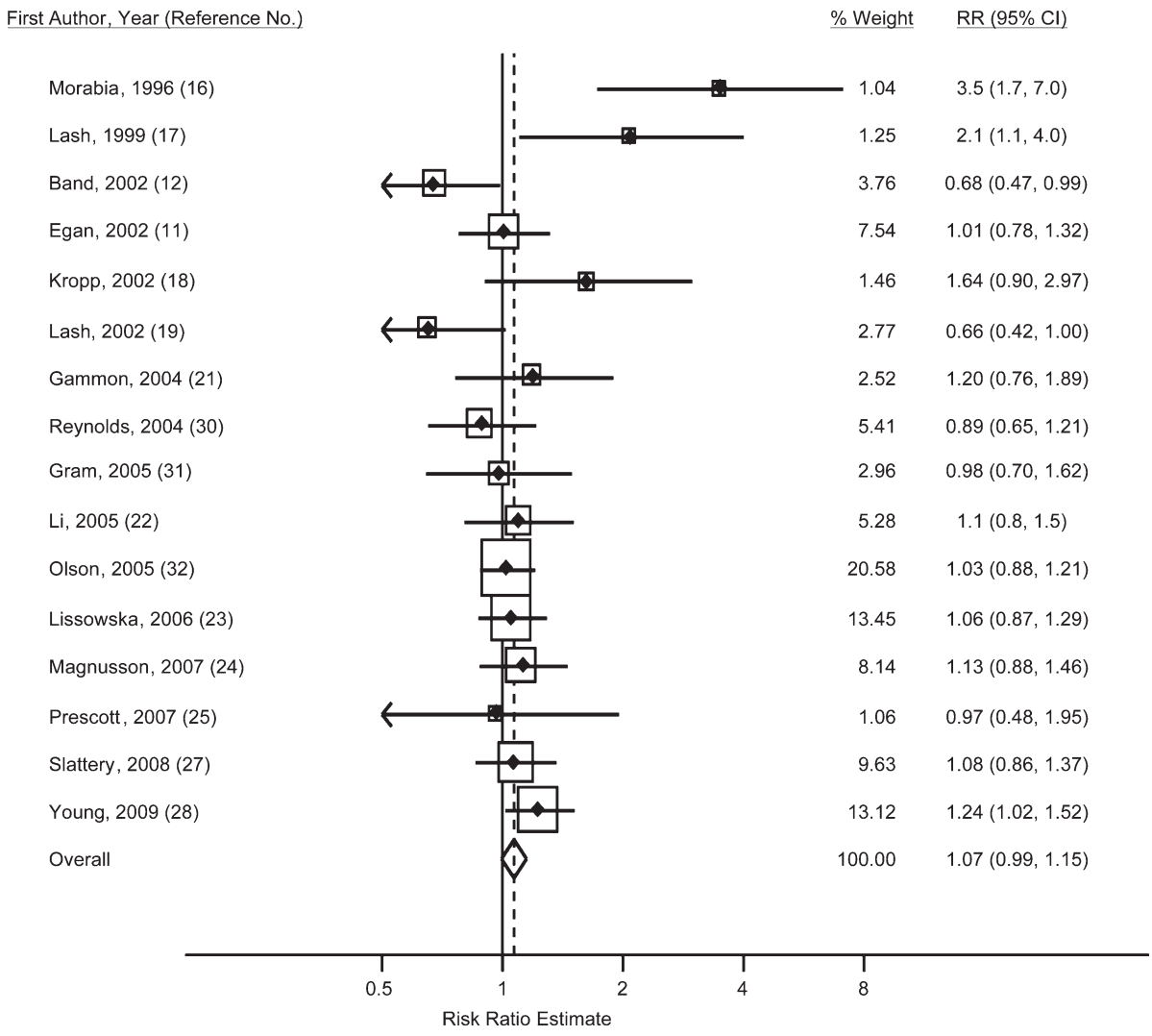

Figure 4. Study-specific odds and hazard ratios and fixed-effect summary risk ratio (RR) (diamond) for breast cancer among women who smoked only after their first pregnancy as compared with women who had never smoked, 1988–2009. The size of each box indicates the relative weight of each study in the meta-analysis; the horizontal bars show the 95% confidence intervals (CIs).

Smoking only after the first pregnancy

For 16 studies, authors reported the risk ratio for breast cancer among women who smoked only after their first pregnancy compared with women who had never smoked (11, 12, 16–19, 21–25, 27, 28, 30–32). The adjusted within-study odds ratio or hazard ratio ranged from 0.66 to 3.5 (Table 2, Figure 4). The fixed-effect summary risk ratio was 1.07 (95% CI: 0.99, 1.15), and the random-effects estimate was similar (RR = 1.08, 95% CI: 0.96, 1.21) (Table 3). There was evidence of heterogeneity across studies (Cochran's Q test $P = 0.007$; $I^2 = 53\%$) but little evidence of publication bias (Begg's test $P = 0.21$). Eliminating the 2 studies that included deceased subjects (17, 19) did not eliminate the heterogeneity (Cochran's Q test $P = 0.04$; $I^2 = 43\%$), and the summary risk ratio estimates for the remaining 14 studies were similar using the fixed-effect (RR = 1.07, 95% CI: 1.00, 1.16) and random-effects (RR = 1.08, 95% CI: 0.97, 1.20) methods.

DISCUSSION

We found a weak association between smoking before a first pregnancy and breast cancer, with a 10% greater risk observed among women who smoked before their first pregnancy (regardless of whether or not they continued to smoke after the pregnancy) in comparison with women who had never smoked (summary RR = 1.10, 95% CI: 1.07, 1.14). Despite inclusion of 15 additional studies and exclusion of 3 studies, our results using 23 studies were consistent with a previous meta-analysis of 11 studies that calculated a

pooled risk ratio estimate of 1.07 (95% CI: 0.94, 1.22) (4). The summary fixed-effect estimates for smoking only before or only after the first pregnancy were both 1.07, which does not support the idea that undeveloped mammary epithelium before a first pregnancy is more vulnerable to tobacco carcinogens than the more differentiated epithelium present after a first pregnancy.

A limitation of this meta-analysis was the small number of studies ($n = 5$) that specifically examined smoking only before the first pregnancy. Most of the analyses pertaining to smoking before a first pregnancy and breast cancer risk were not the main focus of the studies but instead were subgroup analyses reported in papers that focused primarily on current or lifetime smoking and breast cancer risk. Publication bias was a concern, because researchers may be more likely to report the results of subgroup analyses when they are statistically significant (45); however, we found little evidence of this.

Subjects who smoked before pregnancy may have also smoked at some time during the pregnancy, making it difficult to disentangle the possible effects of smoking prior to the first pregnancy and smoking during the first pregnancy. Three of the published studies used linked birth record and cancer registry data to specifically examine smoking during the first pregnancy and subsequent risk of breast cancer. One of these studies (13) found an increased risk ratio of 4.8 (95% CI: 1.6, 14.6) for breast cancer among women who smoked during the first pregnancy compared with those who did not. However, 2 larger studies using similar methods but with better control for age and other confounders (14, 46) did not find an increased risk ratio (RR = 0.9 (95% CI: 0.7, 1.3) and RR = 1.0 (95% CI: 0.8, 1.1), respectively), suggesting that smoking during the first pregnancy is not associated with an increased risk of breast cancer. If that is the case, then our inability to account for the fact that some women who smoked prior to their first pregnancy also smoked during their first pregnancy may not have been a source of bias for this meta-analysis. However, we acknowledge that for many of the studies whose data we summarized, we could not separate out any possible association between later breast cancer and the exposures of smoking prior to a first pregnancy and smoking during a first pregnancy.

Removing the results of 2 studies that collected information from the next of kin of deceased subjects (17, 19) reduced the heterogeneity between studies but did not substantially change the summary risk ratio estimates. In both of these studies, the percentage of information obtained from surrogate respondents was greater for controls (45%) than for cases (33%). The surrogate respondents' recall of smoking habits before the subject's first pregnancy may have been less accurate than information collected from subjects themselves. This may have resulted in differential misclassification of exposure, which could have biased the study estimates (47).

Despite extensive study (48), there is little evidence that smoking increases the risk of breast cancer after taking confounders into account. An International Agency for Research on Cancer Working Group concluded that the cumulative evidence weighed against there being a causal association between smoking and breast cancer (49). The weak association (RR = 1.10) estimated in this meta-analysis does little to contradict that view.

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Author affiliations: Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington (Lisa A. DeRoo, Beth A. Mueller); and Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington (Lisa A. DeRoo, Peter Cummings, Beth A. Mueller).

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