Breastfeeding and ovarian cancer risk: a meta-analysis of epidemiologic studies[1–4]

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ABSTRACT

Background: Epidemiologic studies have yielded inconsistent findings between breastfeeding and epithelial ovarian cancer (EOC) risk.

Objective: We performed a meta-analysis to summarize available evidence of the association between breastfeeding and breastfeeding duration and EOC risk from published cohort and case-control studies.

Design: Relevant published studies were identified by a search of MEDLINE through December 2012. Two authors (T-TG and Q-JW) independently performed the eligibility evaluation and data abstraction. Study-specific RRs from individual studies were pooled by using a random-effects model, and heterogeneity and publication-bias analyses were conducted.

Results: Five prospective and 30 case-control studies were included in this analysis. The pooled RR for ever compared with never breastfeeding was 0.76 (95% CI: 0.69, 0.83), with moderate heterogeneity ($Q = 69.4$, $P < 0.001$, $I^2 = 55.3\%$). Risk of EOC decreased by 8% for every 5-mo increase in the duration of breastfeeding (RR: 0.92; 95% CI: 0.90, 0.95). The risk reduction was similar for borderline and invasive EOC and was consistent within case-control and cohort studies.

Conclusions: Results of this meta-analysis support the hypothesis that ever breastfeeding and a longer duration of breastfeeding are associated with lower risks of EOC. Additional research is warranted to focus on the association with cancer grade and histologic subtypes of EOC.   *Am J Clin Nutr* 2013;98:1020–31.

INTRODUCTION

Epithelial ovarian cancer (EOC) is the second most-common cause of gynecologic cancer mortality worldwide, which accounted for almost 4.2% of all female cancer deaths in 2008 (1). Because EOC is often diagnosed at an advanced stage, has a poor prognosis with an overall 5-y survival rate of just 45% (2), and early detection efforts have not yet been successful (3), the identification of modifiable risk factors is necessary to reduce the burden of disease (4).

Two well-established risk factors for EOC [ie, the use of oral contraceptives (OCs) and parity] have been hypothesized to decrease risk by suppressing ovulation, which has been explained by the ''incessant ovulation'' hypothesis (5) or related to decreasing gonadotropin concentrations (6–8). Our recent meta-analysis (9) supported this hypothesis because later menarcheal age was inversely associated with EOC risk. Breastfeeding also causes gonadotrophin suppression. This suppression leads to low estrogen concentrations and anovulation with a resulting period of lactational amenorrhea and, therefore, has been investigated as a potential factor related to EOC development (10).

A report from the World Cancer Research Fund identified breastfeeding as "limited suggestive" for protection from EOC (11). Although a collaborative pooled analysis of 12 case-control studies in North America showed an inverse relation between ever breastfeeding and EOC risk (7), several prospective cohort studies have shown no association (12, 13). Analyses by histologic subtypes also showed conflicting results (14–16). Moreover, findings on the protective role of a longer duration of breastfeeding have been still inconsistent in recent studies (4, 14, 16, 17). A previous meta-analysis that included 15 case-control studies from developed countries published through 2005 was done by Ip et al (18) and was published in 2009, which showed a significant inverse association between ever breastfeeding and EOC risk. Since this meta-analysis, several relevant studies, including prospectively designed studies on the association between breastfeeding and EOC risk, have been published. Therefore, we conducted a meta-analysis of all observational studies published up to December 2012 to summarize available evidence on the association between both ever breastfeeding and breastfeeding duration with risk of EOC.

METHODS

Literature search

We performed a comprehensively literature search including published studies from database initiation until December 31, 2012 with the use of MEDLINE (PubMed; http://www.ncbi.nlm. nih.gov/pubmed). The search was limited to published studies in English and studies of humans by using the following search key words and Medical Subject Headings terms: (breastfeeding OR breast feed OR lactation OR infant nutrition OR breast milk OR milk human) AND (ovary OR ovarian) AND (cancer OR neoplasm OR carcinoma OR tumor). We also reviewed references of all included studies for additional publications. We followed standard criteria for conducting and reporting meta-analyses (19, 20).

Study selection

To be included, studies had to use a case-control or cohort study design and investigate the association between ever breastfeeding or the total duration of breastfeeding and incident EOC. The publication had to present the HR, OR, or RR with 95% CIs or data necessary to calculate these. When multiple publications from the same study were available, we used the publication with the largest number of cases and most-applicable information. We identified 35 potentially relevant full-text publications (4, 12–17, 21–45) from 6892 articles (**Figure 1**). Four publications (46–49) only reported the longest compared with shortest categories of total duration of breastfeeding and were, therefore, only included in the breastfeeding duration and dose-response analysis. For the cancer histology subgroup analysis, we included 2 publications (50, 51) that were duplicate reports from an already-represented study population but reported information on EOC histology.

Data abstraction

For each eligible study, 2 investigators (T-TG and Q-JW) independently performed the eligibility evaluation and data abstraction.

Disagreements were discussed and resolved by consensus. Data abstracted from each study were as follows: author list, year of publication, study region and design, study sample size (number of cases and controls or cohort size), range of follow-up for cohort studies, exposure and outcome assessment including ever breastfeeding and the total or average breastfeeding-duration categories, study-specific adjusted estimates with their 95% CIs for ever compared with never breastfeeding and longest compared with shortest of the total or average duration category of breastfeeding, and factors matched by or adjusted for in the design or data analysis. If multiple estimates of the association were available, we abstracted the estimate that adjusted for the most covariates. If no adjusted estimates were presented, we included the crude estimate. If no estimate was presented in a given study, we calculated it and its 95% CI according to the raw data presented in the article.

We did not use the Newcastle-Ottawa Scale (9, 52, 53) to assess the methodologic quality of all included studies because quality scoring in a meta-analysis of observational studies is controversial, lacks demonstrated validity, and sometimes results may not be associated with quality (54, 55). Instead, we carried out numerous subgroup and sensitivity analyses.

Statistical analysis

Study-specific adjusted RRs were used as measures of the association across studies. Because absolute risk of EOC is low, we assumed that estimates of ORs from case-control studies and risk, rate, or HRs from cohort studies were all valid estimates of the RR, and therefore, we reported all results as the RR for simplicity (9). For studies that did not use the category with the shortest-duration breastfeeding as the reference, we used the effective-count method proposed by Hamling et al (56) to recalculate RRs.

For the dose-response analysis, we used the method proposed by Greenland et al (57) and Orsini et al (58) to compute study-specific slopes (linear trends) and 95% CIs from the ln of RRs and
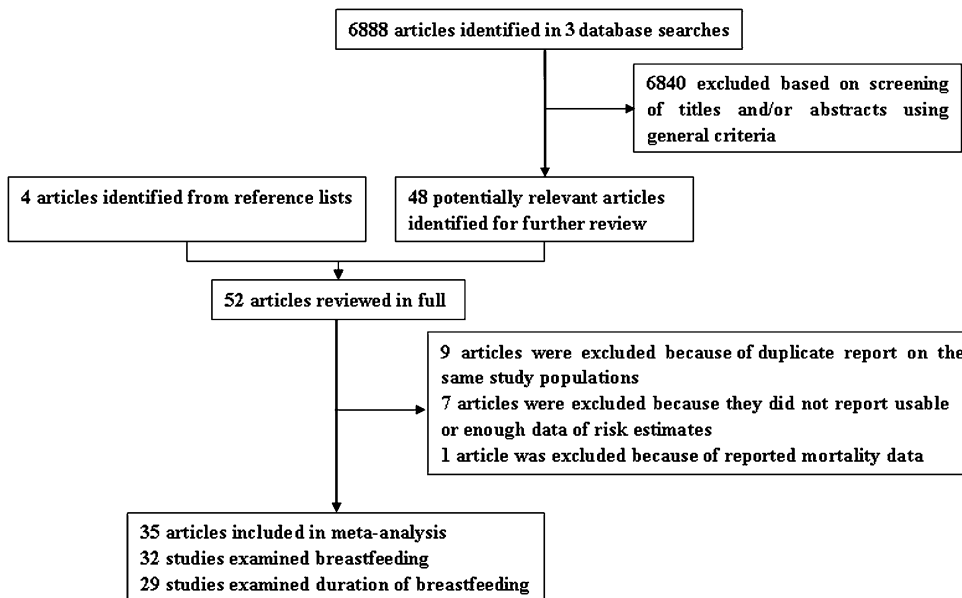

FIGURE 1. Selection of studies for inclusion in the meta-analysis.

TABLE 1
Characteristics of studies of breastfeeding and ovarian cancer risk[1]

First author (reference), publication year, country, study design	Cases/subjects (age), duration of follow-up	Lactation categories (exposure/case assessment)	RR/OR (95% CI)	Matched/adjusted factors
Prospective study				
Weiderpass et al (12), 2012, Japan, CS	86/45,748 (40–69 y), 16 y	Ever compared with never (Self-questionnaire/cancer registry)	1.0 (0.5, 1.9)	Age, study center, parity, age at first birth, use of exogenous hormones, menopausal status at enrollment, height, BMI, smoking status, exposure to second-hand smoke, physical activity during leisure time, usual sleep duration, and family history of cancer in first-degree relatives
Tsilidis et al (21), 2011, European, CS	878/327,396 (NA), 9 y	Ever compared with never Total >13 compared with ≤1 mo (Self-questionnaire/medical records)	0.86 (0.70, 1.07) 0.88 (0.69, 1.13)	Participating center and age at recruitment, smoking status, BMI, unilateral ovariectomy, simple hysterectomy, menopausal HRT, duration of OC use, age at menopause, and no. of full-term pregnancies
Antoniou et al (22), 2009, European, CS	253/3319 (>18 y), 8 y	Ever compared with never Total ≥24 mo compared with never (Self-questionnaire/NA)	0.88 (0.62, 1.26) 0.71 (0.29, 1.70)	Duration of OC use
Danforth et al (4), 2007, United States, CS	342/121,701 (30–55 y), 16 y 49/116,671 (25–42 y), 10 y	Ever compared with never Total ≥18 mo compared with never (Self-questionnaire/medical record)	0.86 (0.76, 1.06) 0.66 (0.46, 0.96)	Age, parity, duration of OC use, tubal ligation, and age at menarche
Mink et al (13), 1996, United States, CS	97/31,396 (55–69 y), 7 y	Ever compared with never (Self-questionnaire/cancer registry)	1.03 (0.66, 1.61)	Age
Case-control study				
Jordan et al (23), 2012, United States, PC-CS	881/1345 (35–74 y)	Ever compared with never Total ≥18 mo compared with none Average ≥18 mo compared with none (Interviewer/cancer registry)	0.78 (0.64, 0.94) 0.70 (0.53, 0.93) 0.56 (0.32, 0.98)	Reference year, education, no. of live births, and duration of hormonal contraception
Titus-Ernstoff et al (17), 2010, United States, PC-CS	829/1009 (mean: 54.5/52.6 y)	Ever compared with never Average ≥12 mo compared with never (Interviewer/medical records)	0.75 (0.62, 0.92) 0.58 (0.37, 0.93)	Age, study center, OC use, parity, and age at most recent birth
Jordan et al (14), 2010, Australia, PC-CS	1092/1288 (mean: 58.4/57.0 y)	Ever compared with never Total >42 mo compared with never Average >42 mo compared with never (Self-questionnaire/medical records)	0.77 (0.61, 0.96) 0.45 (0.25, 0.82) 0.61 (0.43, 0.82)	Age, state of residence, parity, age at first full-term birth, duration of hormonal contraceptive use (in mo), menopausal status, smoking, previous tubal ligation or hysterectomy, alcohol consumption, education, and family history of ovarian or breast cancer (result of average duration only adjusted for parity)

(Continued)

TABLE 1 (*Continued*)

First author (reference), publication year, country, study design	Cases/subjects (age), duration of follow-up	Lactation categories (exposure/case assessment)	RR/OR (95% CI)	Matched/adjusted factors
Moorman et al (24), 2008, United States, PC-CS[2]	896/967 (20–74 y)	Ever compared with never Total >12 mo compared with never (Trained interviewer/cancer registry)	0.77 (0.63, 0.96) 0.84 (0.51, 1.40)	Age, race, family history of breast or ovarian cancer, age at menarche, tubal ligation, infertility, BMI, duration of OC use, and age at last oral contraceptive use
McLaughlin et al (25), 2007, multinational study, PC-CS	799/2424 (27–82 y)	Ever compared with never Average >12 mo compared with never (Self-questionnaire/cancer registry)	0.74 (0.56, 0.97) 0.64 (0.47, 0.91)	Parity, OC use, tubal ligation, ethnicity, year of birth, mutation type, and country of residence
Huusom et al (15), 2006, Denmark, PC-CS	202/1564 (35–79 y)	Ever compared with never Total ≥25 mo compared with never (Self-questionnaire/cancer registry)	0.79 (0.47, 1.35) 0.33 (0.10, 1.10)	Age, childbirth, no. of additional births, age at first birth, duration of OC use, smoking, and intake of milk
Gronwald et al (26), 2006, Poland, HC-CS[2]	150/150 (NA)	Ever compared with never Total >12 mo compared with never (Self-questionnaire/medical records)	1.00 (0.52, 1.93) 1.0 (0.4, 2.6)	Year of birth
Chiaffarino et al (16), 2005, Italy, HC-CS	1031/2411 (median: 56/57 y)	Ever compared with never Total ≥17 mo compared with never Average ≥8 compared with<3 mo (Trained interviewer/cancer registry)	1.16 (0.93, 1.43) 1.21 (0.85, 1.71) 1.18 (0.93, 1.50)	Age, study center, education, parity, OC use, and family history of ovarian or breast cancer in first-degree relatives
Zhang et al (29, 46), 2004, China, C-CS	254/652 (mean: 46.8/48.0 y)	Ever compared with never Total >12 compared with ≤4 mo Average >12 compared with 0 mo (Trained interviewer/cancer registry)	0.50 (0.30, 0.82) 0.51 (0.30, 0.89) 0.63 (0.31, 1.31)	Age, locality, education, family income, BMI, total energy intake, tobacco smoking, alcohol consumption, ovarian cancer in first-degree relatives, parity (for duration of lactation), and OC use (for duration of lactation)
Rossing et al (27), 2004, United States, PC-CS[2]	378/1637 (35–54 y)	Ever compared with never Total >12 mo compared with never (Trained interviewer/cancer registry)	0.76 (0.58, 0.99) 0.5 (0.3, 0.7)	Age, race, study site, duration of OC use, and no. of full-term births
Mills et al (28), 2004, United States, PC-CS[2]	256/1122 (mean: 56.6/55 y)	Ever compared with never Total >12 mo compared with never (Trained interviewer/cancer registry)	0.52 (0.38, 0.71) 0.29 (0.17, 0.49)	Age, race-ethnicity, and OC use
Yen et al (31), 2003, Taiwan, HC-CS[2]	86/369 (median: 47/44 y)	Ever compared with never Total ≥24 mo compared with never (Trained interviewer/medical records)	0.61 (0.35, 1.07) 0.55 (0.29, 1.01)	Age, treatment hospital, date of admission, and no. of live births
Tung et al (30), 2003, United States, PC-CS	558/607 (NA)	Ever compared with never Average >16 mo compared with never (Trained interviewer/cancer registry)	0.6 (0.4, 0.7) 0.6 (0.4, 0.8)	Age, ethnicity, study site, education, OC use, tubal ligation, and parity
Riman et al (47), 2002, Sweden, PC-CS[2]	655/3899 (mean: 62.4/63.4 y)	Total ≥12 compared with <1 mo (Self-questionnaire/cancer registry)	0.87 (0.56, 1.35)	Age, parity, BMI, age at menopause, duration of OC use, and ever use of hormone replacement treatment
Riman et al (32), 2001, Sweden, PC-CS[2]	193/3899 (mean: 61.8/63.4 y)	Ever compared with never Total ≥12 mo compared with never (Self-questionnaire/cancer registry)	0.48 (0.28, 0.83) 0.47 (0.24, 0.94)	Age, parity, BMI, and age at menopause and ever use of OC, unopposed estrogens with cyclic progestin, and estrogens with continuous progestin
Ness et al (34), 2000, United States, PC-CS[2]	767/1367 (20–69 y)	Ever compared with never Total ≥24 mo compared with never (Trained interviewer/cancer registry)	0.85 (0.68, 1.06) 0.7 (0.4, 1.0)	Age, parity, family history of ovarian cancer, and race

(*Continued*)

TABLE 1 (*Continued*)

First author (reference), publication year, country, study design	Cases/subjects (age), duration of follow-up	Lactation categories (exposure/case assessment)	RR/OR (95% CI)	Matched/adjusted factors
Greggi et al (33), 2000, Italy, HC-CS	440/868 (median: 54/55 y)	Ever compared with never Total >12 mo compared with never (Trained interviewer/medical records)	0.58 (0.42, 0.81) 0.5 (0.4, 0.8)	Age, education, parity, OC use, family history of ovarian cancer, and age at first birth
Salazar-Martinez et al (35), 1999, Mexico, HC-CS	84/668 (mean: 52.8/54.6 y)	Ever compared with never Total ≥25 mo compared with never (Trained interviewer/medical records)	0.31 (0.18, 0.53) 0.36 (0.19, 0.69)	Age, hormonal use, no. of pregnancies, smoking, diabetes mellitus, hypertension, physical activity, menopausal status, and body build index
Hirose et al (36), 1999, Japan, HC-CS	99/25,488 (≥30 y)	Ever compared with never Average ≥12 mo compared with never (Self-questionnaire/cancer registry)	0.89 (0.43, 1.85) 0.70 (0.31, 1.55)	Age and BMI
Mori et al (37), 1998, Japan, HC-CS	89/323 (30–85 y)	Ever compared with never (Trained interviewer/medical records)	0.59 (0.21, 1.72)	Age
Siskind (38), 1997, Australia, PC-CS[2]	824/855 (18–79 y)	Ever compared with never Total >36 mo compared with never (Self-questionnaire/medical records)	0.79 (0.61, 1.03) 0.77 (0.34, 1.75)	No. of live-born children, age, use of OC, education, smoking history, and for all women, menopausal status
Rosenblatt et al (39), 1993, multinational study, HC-CS[3]	393/2565 (40–79 y)	Ever compared with never Total >48 compared with ≤4 mo Average ≥13 compared with 0–2 mo (Trained interviewer/medical records)	0.86 (0.57, 1.28) 0.80 (0.45, 1.42) 0.68 (0.43, 1.07)	Age, center, date of diagnosis, and no. of live births (only for total duration)
Chen et al (40), 1992, China, PC-CS[2]	112/224 (mean: 48.5/49 y)	Ever compared with never Total ≥36 mo compared with never (Trained interviewer/cancer registry)	0.92 (0.41, 2.07) 1.1 (0.4, 2.9)	Age, education, street office or township and parity
Gwinn et al (41), 1990, United States, PC-CS[3]	436/3833 (20–54 y)	Ever compared with never Total ≥24 mo compared with never (Trained interviewer/medical records)	0.52 (0.42, 0.64) 0.27 (0.13, 0.58)	Age
Hartge et al (43), 1989, United States, HC-CS[2]	296/343 (mean: 54.4/54.7 y)	Ever compared with never Total 19–110 mo compared with never (Trained interviewer/medical records)	0.84 (0.55, 1.28) 1.1 (0.5, 2.6)	Age, race, hospital, and parity
Booth et al (42), 1989, United Kingdom, HC-CS[2]	235/451 (mean: 52.4/51.4 y)	Ever compared with never Total ≥25 mo compared with never (Interviewer/medical records)	1.23 (0.79, 1.93) 3.4 (1.1, 10.8)	Age, social class, and no. of live births
Mori et al (44), 1988, Japan, HC-CS	110/220 (NA)	Ever compared with never (Interviewer/medical records)	0.7 (0.3, 1.9)	Year of birth and year of survey
Harlow et al (48), 1988, United States, PC-CS	116/158 (20–79 y)	Total >9 compared with <1 mo (Interviewer/cancer registry)	0.3 (0.1, 0.7)	Parity, age at diagnosis, and use of OC
Cramer et al (45), 1983, United States, PC-CS[2]	215/215 (mean: 53.2/53.5 y)	Ever compared with never (Interviewer/NA)	0.90 (0.57, 1.43)	Age, race, and place of residence
Risch et al (49), 1983, United States, PC-CS[3]	284/705 (20–74 y)	Total ≥36 compared with ≤24 mo (Trained interviewer/cancer registry)	0.82 (0.62, 1.09)	NA

[1] C-CS, case-control study; CS, cohort study; HC-CS, hospital-based case-control study; HRT, hormone-replacement therapy; NA, not available; OC, oral contraceptive; PC-CS, population-based case-control study.

[2] RR was recalculated by the method proposed by Hamling et al (56).

[3] OR and 95% CI were calculated from published data with EpiCalc 2000 software (version 1.02; Brixton Health).

CIs across categories of the total duration of breastfeeding. The method requires that the distribution of cases and person-years of noncases and RRs with the variance estimates for ≥3 quantitative exposure categories are known. For studies that reported the duration by ranges, we estimated the midpoint in each category by calculating the average of the lower and upper bounds. When the highest category did not have an upper bound, we assumed the length of the open-ended interval to be the same as that of the adjacent interval. When the lowest category did not have a lower bound, we set the lower bound to zero. Dose-response results in forest plots are presented on the basis of 5-mo increments for the total duration of breastfeeding.

We evaluated the heterogeneity of RRs across studies by using the Cochrane Q statistic, where $P < 0.1$ was indicative of statistically significant heterogeneity, and I^2 statistic. The summary estimate was based on the fixed-effects model (59) for no detected heterogeneity or the random-effects model (60) when substantial heterogeneity was detected. In both methods, the weight of each study depended on the inverse of the variance of log OR, which was estimated by the 95% CI from each study. Because limited studies (14, 16, 17, 23, 25, 30, 36, 39, 46) reported results of the average duration of breastfeeding per child, summary estimates were calculated for ever breastfeeding and the total duration of breastfeeding. Subgroup analyses were carried out based on the study design (cohort compared with case-control studies), type of controls within case-control studies (population-based compared with hospital-based controls), exposure assessment (self-administered questionnaire compared with trained interviewers), geographic location (Europe, America, and Asia), cancer grading (invasive compared with borderline), and cancer histotype (serous, mucinous, endometrioid, and clear cell). We also stratified the meta-analysis by potentially important confounders (ie, parity, BMI, OC use, and smoking status). Heterogeneity between subgroups was evaluated by using a meta-regression. Finally, we carried out sensitivity analyses by

TABLE 2
Summary risk estimates of the association between breastfeeding and ovarian cancer risk

	Studies	Summary RR (95% CI)	Q statistic	I^2	$P_h{}^1$	$P_h{}^2$
	n			%		
Overall	32	0.76 (0.69–0.83)	69.40	55.3	<0.001	—
Subgroup analyses						
Study design						0.090
Cohort studies	5	0.88 (0.78, 0.99)	0.73	0	0.947	
Case-control studies	27	0.74 (0.67, 0.82)	62.36	58.3	<0.001	
Exposure assessment						0.065
Trained interviewer	15	0.68 (0.57, 0.80)	51.59	72.9	<0.001	
Self-administered questionnaire	12	0.82 (0.75, 0.90)	7.06	0	0.794	
Type of control subjects						0.158
Population based	16	0.73 (0.68, 0.78)	22.91	34.5	0.086	
Hospital based	10	0.78 (0.60, 1.02)	31.01	71.0	<0.001	
Study population						0.862
Asians	7	0.69 (0.53, 0.89)	3.99	0	0.678	
Americans	13	0.71 (0.63, 0.81)	35.90	66.6	<0.001	
Europeans	8	0.85 (0.69, 1.06)	19.75	64.6	0.006	
Cancer grading						0.645
Invasive	5	0.62 (0.53, 0.72)	6.14	34.9	0.189	
Borderline	4	0.57 (0.44, 0.74)	2.53	0	0.470	
Cancer histotype						0.267
Serous	7	0.82 (0.68, 0.99)	13.91	56.9	0.031	
Mucinous	6	0.80 (0.64, 1.00)	7.10	29.6	0.213	
Endometrioid	3	0.65 (0.47, 0.89)	2.10	5.0	0.349	
Clear cell	2	0.67 (0.39, 1.15)	0.92	0	0.336	
Adjustment for confounders						
Parity						0.285
Yes	22	0.78 (0.71, 0.85)	42.23	50.3	0.004	
No	10	0.70 (0.57, 0.87)	18.55	51.5	0.029	
BMI						0.803
Yes	5	0.79 (0.69, 0.91)	4.43	9.7	0.351	
No	27	0.75 (0.68, 0.83)	64.71	59.8	<0.001	
OC^3 use						0.782
Yes	17	0.77 (0.70, 0.84)	32.56	50.9	0.008	
No	15	0.87 (0.69, 1.09)	34.97	60.6	0.001	
Smoking						0.505
Yes	7	0.71 (0.57, 0.88)	15.32	60.8	0.018	
No	25	0.77 (0.70, 0.85)	54.00	55.6	<0.001	

[1] P value for heterogeneity within each subgroup.
[2] P value for heterogeneity between subgroups with meta-regression analysis.
[3] OC, oral contraceptive.

excluding one study at a time to explore whether results were strongly influenced by a specific study.

Publication bias was evaluated via Egger's linear regression (61), Begg's rank-correlation methods (62), and funnel plots. $P < 0.05$ for Egger's or Begg's tests was considered representative of a significant statistical publication bias. Statistical analyses were performed with Stata software (version 11.2; StataCorp). P values were 2 sided with a significance level of 0.05.

RESULTS

Study characteristics

Characteristics of the 35 included articles are shown in **Table 1**. The included articles, which represented 14,465 cases and 706,152 noncases, were published between 1983 and 2012 and consist of 5 cohort studies (4, 12, 13, 21, 22) and 30 case-control studies (14–17, 23–45, 47–49). All of the studies only included parous women in analyses. Of the 5 cohort studies, 2 studies each were conducted in the United States (4, 13) and Europe (21, 22), and one study was conducted in Japan (12). Cohort sizes ranged from 3319 (22) to 327,396 (21), and the number of EOC cases varied from 86 (12) to 878 (21) cases. The longest total duration of breastfeeding varied from 13 mo (21) to >24 mo (22). The shortest total duration of breastfeeding varied from never (4, 22) to <1 mo (21).

Of 30 case-control studies, 12 studies were conducted in the United States (17, 23, 24, 27, 28, 30, 34, 41, 43, 45, 48, 49), 3 studies were conducted in China (29, 31, 40), 3 studies were conducted in Japan (36, 37, 44), 2 studies each were conducted in

Australia (14, 38), Sweden (32, 47), and Italy (16, 33), and one study each was conducted in Denmark (15), Poland (26), the United Kingdom (42), and Mexico (35). Two studies covered multiple countries (25, 39). The number of cases enrolled in these studies ranged from 84 (35) to 1092 (14) cases, and the number of control subjects varied from 150 (26) to 25,488 (36) subjects. Control subjects were drawn from the general population in 18 studies (14, 15, 17, 23–25, 27, 28, 30, 32, 34, 38, 40, 41, 45, 47–49), hospitals in 11 studies (16, 26, 31, 33, 35–37, 39, 42–44), and both places in one study (29). The longest total duration of breastfeeding varied from 9 mo (48) to >48 mo (39). The shortest total duration of breastfeeding varied from never (14–17, 23–28, 30–36, 38, 40–43) to <24 mo (49).

Breastfeeding

Five cohort (4, 12, 13, 21, 22, 48) and 27 case-control (14–17, 23–45) studies investigated the association between ever breastfeeding and EOC risk. The summary RR of EOC for the ever compared with never categories of breastfeeding was 0.76 (95% CI: 0.69, 0.83) with moderate heterogeneity ($Q = 69.4$, $P < 0.001$, $I^2 = 55.3\%$) (**Table 2**, **Figure 2**). There was no indication of a publication bias by using Egger's test (P-bias = 0.495) or Begg's test (P-bias = 0.538), and no asymmetry was observed in funnel plots when inspected visually.

Longest compared with shortest total durations of breastfeeding

Four case-control studies (17, 25, 36, 63) reported the average duration of breastfeeding, and these studies were excluded from
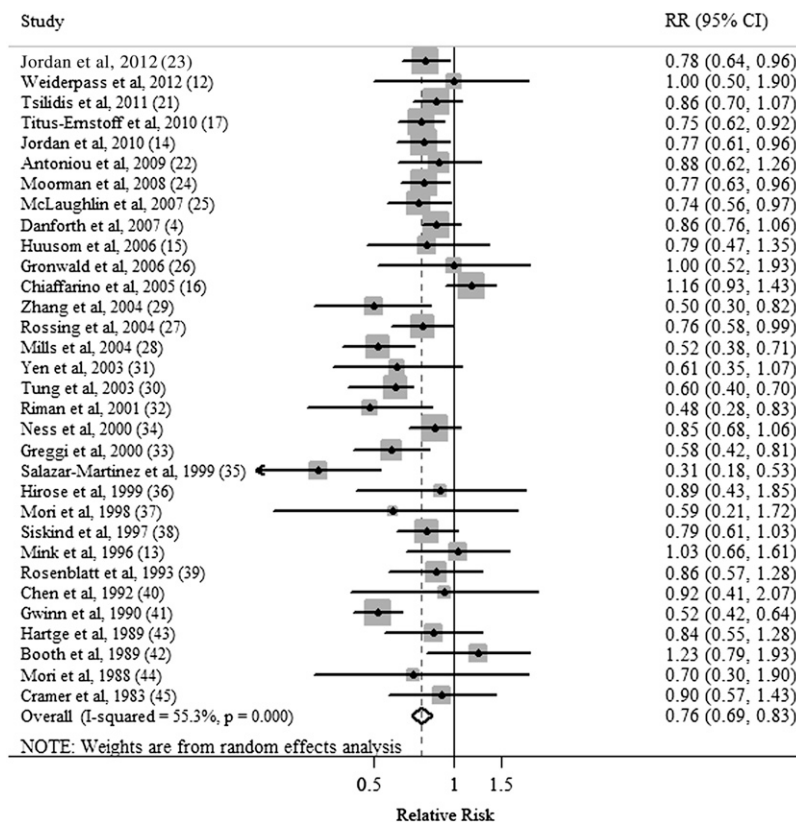

FIGURE 2. Forest plot (random-effects model) of ever breastfeeding and ovarian cancer risk. Squares indicate study-specific RRs (the size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; the diamond indicates the summary RR estimate with its 95% CI.

the analysis. Three cohort (4, 21, 22) and 23 case-control (14–16, 23, 24, 26–29, 31–35, 38–43, 47–49) studies investigated the association between the total duration of breastfeeding and EOC risk. The summary RR of EOC for the longest compared with shortest total duration categories of breastfeeding was 0.65 (95% CI: 0.55, 0.78) with significant heterogeneity ($Q = 70.26$, $P < 0.001$, $I^2 = 64.4\%$) (**Table 3**). There was no indication of a publication bias by using Egger's test (P-bias = 0.068) or Begg's test (P-bias = 0.741), and no asymmetry was seen in funnel plots when inspected visually.

Dose-response analysis of total duration of breastfeeding

Three cohort (4, 21, 22) and 22 case-control (14–16, 23, 24, 26–28, 31–35, 38–43, 46–48) studies were included in the dose-response analysis. The summary RR for each increase by 5 mo for breastfeeding duration was 0.92 (95% CI: 0.90, 0.95) with

significant heterogeneity ($Q = 74.12$, $P < 0.021$, $I^2 = 67.6\%$) (**Table 4**, **Figure 3**). Publication bias was not evident by using Egger's test ($P = 0.090$) or Begg's test ($P = 0.161$) or by visual inspection of the funnel plot.

Subgroup and sensitivity analyses

In subgroup analyses of ever breastfeeding and EOC risk, all strata showed inverse associations, and there was no evidence of significant heterogeneity between subgroups with meta-regression analyses (Table 2). Similar results were also observed in dose-response analyses of the relation between the total duration of breastfeeding and EOC risk (Table 4). We further focused on the difference between studies in which associations with breastfeeding were of primary interest (4, 14–17, 21–25, 29, 30, 34, 35, 38, 39, 41, 44–46, 48, 49) and studies that mainly dealt with other associations (12, 13, 26–28, 31–33, 36, 37, 40, 42, 43, 47).

TABLE 3
Summary risk estimates of the association between the total duration of breastfeeding and ovarian cancer risk: longest compared with shortest durations[1]

	Studies	Summary RR (95% CI)	Q statistic	I^2	$P_h{}^2$	$P_h{}^3$
	n			%		
Overall	26	0.65 (0.55, 0.78)	70.26	64.4	<0.001	—
Subgroup analyses						
Study design						0.511
Cohort studies	3	0.80 (0.66, 0.98)	1.69	0	0.429	
Case-control studies	23	0.63 (0.52, 0.78)	67.25	67.3	<0.001	
Exposure assessment						0.790
Trained interviewer	14	0.61 (0.49, 0.76)	49.54	73.8	<0.001	
Self-administered questionnaire	9	0.75 (0.63, 0.88)	9.33	14.3	0.315	
Type of control subjects						0.185
Population based	14	0.57 (0.45, 0.71)	27.98	53.5	0.009	
Hospital based	8	0.81 (0.53, 1.21)	31.11	77.5	<0.001	
Study population						0.365
Asians	3	0.66 (0.43, 1.00)	1.36	0	0.505	
Americans	11	0.55 (0.43, 0.71)	25.93	61.4	0.004	
Europeans	9	0.81 (0.59, 1.10)	27.46	70.9	0.001	
Cancer grading						0.291
Invasive	4	0.55 (0.36, 0.84)	7.95	62.3	0.047	
Borderline	5	0.41 (0.28, 0.60)	1.67	0	0.797	
Cancer histotype						0.258
Serous	6	0.75 (0.59, 0.96)	1.78	0	0.879	
Mucinous	4	0.61 (0.19, 1.94)	12.04	75.1	0.007	
Endometrioid	3	0.59 (0.35, 0.98)	2.64	24.4	0.267	
Clear cell	1	0.24 (0.06, 0.97)	NA	NA	NA	
Adjustment for confounders						
Parity						0.318
Yes	21	0.68 (0.59, 0.82)	50.60	60.5	<0.001	
No	5	0.53 (0.30, 0.94)	17.53	77.2	0.002	
BMI						0.406
Yes	5	0.81 (0.67, 0.98)	3.44	0	0.486	
No	21	0.63 (0.50, 0.78)	64.46	69.0	<0.001	
OC use						0.428
Yes	16	0.62 (0.50, 0.77)	48.25	68.9	<0.001	
No	10	0.73 (0.53, 1.00)	22.00	59.1	0.009	
Smoking						0.521
Yes	6	0.58 (0.40, 0.85)	11.15	55.1	0.049	
No	20	0.67 (0.55, 0.83)	59.07	67.8	<0.001	

[1] NA, not available; OC, oral contraceptive.
[2] P value for heterogeneity within each subgroup.
[3] P value for heterogeneity between subgroups with meta-regression analysis.

TABLE 4
Summary risk estimates of the association between the total duration of breastfeeding and ovarian cancer risk: a dose-response analysis (per 5-mo increase)[1]

	Studies	Summary RR (95% CI)	Q statistic	I^2	$P_h{}^2$	$P_h{}^3$
	n			*%*		
Overall	25	0.92 (0.90, 0.95)	74.12	67.6	<0.001	—
Subgroup analyses						
Study design						0.686
Cohort studies	3	0.95 (0.90, 0.99)	2.57	22.1	0.277	
Case-control studies	22	0.92 (0.90, 0.95)	71.35	70.6	<0.001	
Exposure assessment						0.160
Trained interviewer	13	0.90 (0.85, 0.95)	55.21	78.3	<0.001	
Self-administered questionnaire	9	0.94 (0.92, 0.96)	9.77	18.1	0.281	
Type of control subjects						
Population based	14	0.57 (0.45, 0.71)	27.98	53.5	0.009	
Hospital based	8	0.81 (0.53, 1.21)	31.11	77.5	<0.001	
Study population						0.925
Asians	3	0.89 (0.77, 1.04)	6.45	69.0	0.040	
Americans	10	0.89 (0.85, 0.93)	27.48	67.3	0.001	
Europeans	9	0.96 (0.90, 1.01)	24.07	66.8	0.002	
Cancer grading						0.770
Invasive	4	0.88 (0.84, 0.92)	4.99	39.9	0.172	
Borderline	5	0.89 (0.82, 0.96)	11.43	65.0	0.022	
Cancer histotype						0.074
Serous	6	0.94 (0.90, 0.98)	2.17	0	0.824	
Mucinous	4	0.84 (0.72, 0.99)	8.46	64.6	0.037	
Endometrioid	3	0.86 (0.79, 0.95)	2.63	24.0	0.268	
Clear cell	1	0.62 (0.41, 0.94)	NA	NA	NA	
Adjustment for confounders						
Parity						0.169
Yes	21	0.93 (0.91, 0.96)	55.55	64.0	<0.001	
No	4	0.86 (0.82, 0.90)	4.93	39.2	0.177	
BMI						0.438
Yes	5	0.89 (0.82, 0.97)	10.79	62.9	0.029	
No	20	0.93 (0.90, 0.96)	63.04	69.9	<0.001	
OC use						0.219
Yes	16	0.91 (0.88, 0.94)	46.58	67.8	<0.001	
No	9	0.95 (0.90, 1.00)	22.37	64.2	0.004	
Smoking						0.521
Yes	6	0.93 (0.89, 0.98)	12.85	61.1	0.025	
No	19	0.92 (0.88, 0.96)	61.15	70.6	<0.001	

[1] NA, not available; OC, oral contraceptive.
[2] *P* value for heterogeneity within each subgroup.
[3] *P* value for heterogeneity between subgroups with meta-regression analysis.

However, results of the meta-regression and tests for heterogeneity did not show a significant difference in the analyses of ever breastfeeding or in breastfeeding duration (data not shown). When stratified by the adjustment for potential confounders, we did not shown a significant difference between estimates adjusted and those not adjusted for specific factors (Tables 2–4).

In a sensitivity analysis, we sequentially removed one study at a time and reanalyzed the data. The 32 study-specific RRs of ever breastfeeding ranged from a low of 0.74 (95% CI: 0.68, 0.80) after omission of the study by Chiaffarino et al (16) to a high of 0.77 (95% CI: 0.71, 0.84) after omission of the study by Gwinn et al (41). Similar analyses were also carried out in the dose-response analysis of total breastfeeding duration, with study-specific RRs ranging from a low of 0.92 (95% CI: 0.89, 0.95) after omission of the study by Chiaffarino et al (16) to a high of 0.93 (95% CI: 0.90, 0.96) after omission of the study by Mills et al (28).

DISCUSSION

The findings from this meta-analysis of epidemiologic studies indicated that ever breastfeeding had an almost 24% reduction in EOC risk compared with that for never breastfeeding. The risk reduction was similar for borderline and invasive EOC, and was consistently reported in case-control and cohort studies. In addition, results of dose-response analyses suggested that risk of EOC decreased by 8% for each 5-mo increase in total breastfeeding duration.

The inverse association between breastfeeding and risk of borderline EOC as well as invasive EOC is biologically plausible. Recently, 2 hypotheses have dominated when the cause of ovarian pathogenesis has been considered. One of these hypotheses proposes that, because of incessant ovulation, repeated trauma to the ovary caused by ovulation may increase ovarian cancer risk (5). The other hypothesis suggests that excessive concentrations of gonadotropins increase EOC risk through increased estrogen
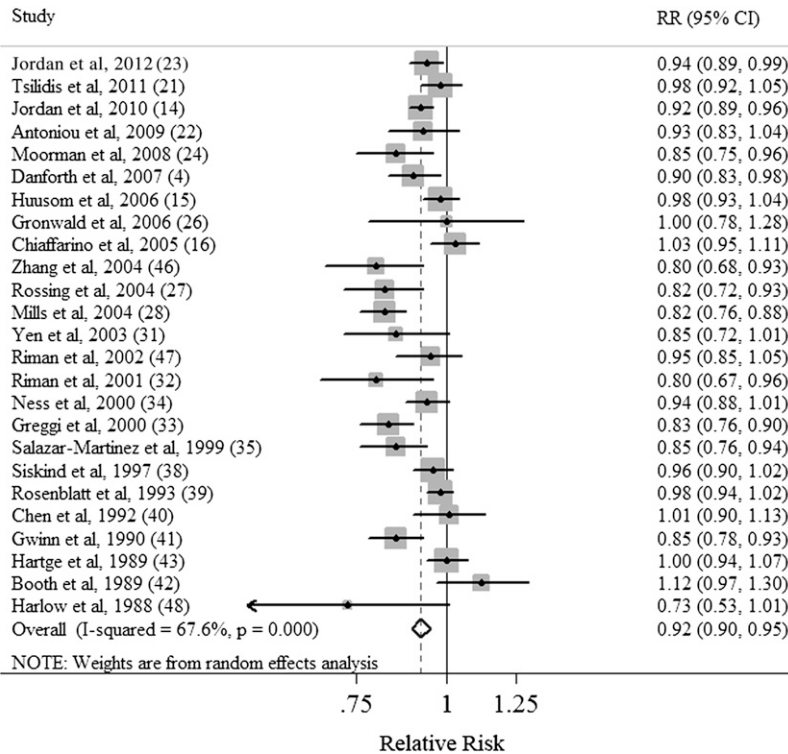
FIGURE 3. Forest plot (random-effects model) of the total duration of breastfeeding (dose-response analyses on the basis of increases of 5 mo in duration) and ovarian cancer risk. Squares indicate study-specific RRs (the size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; the diamond indicates the summary RR estimate with its 95% CI.

stimulation, which promotes cell proliferation and increases the opportunity for malignant transformation (8). Research also has indicated that breastfeeding may reset pregnancy-related changes, possibly through hypothalamic-pituitary–regulated mechanisms that mediate EOC risk (17). Breastfeeding also causes gonadotrophin suppression, which leads to low estrogen concentration and induces a state of relative quiescence in women's ovaries by suppressing the release of luteinizing hormone and, thereby, preventing ovulation. Thus, according to these hypotheses, ever breastfeeding and a longer duration of breastfeeding would be expected to decrease EOC risk through their effects on ovulation and gonadotropin concentrations.

Significant inverse associations for the duration of breastfeeding on EOC risk were only observed in American populations (Tables 3 and 4), which could have been attributed to a greater variation in breastfeeding patterns and duration. Rosenblatt et al (39) reported that nearly 90% of the study population breastfed for ≥1 mo in a multinational case-control study, which resulted in a referent group of women who breastfed for 0–4 mo instead of women who never breastfed. However, populations in which more than one-half of the women had never breastfed were observed in several population-based case-control studies in United States (24, 27). By comparison, Salazar-Martinez et al (35) reported mean breastfeeding duration of 12.7 mo/child in 668 hospital-based controls in Mexico, whereas Mori et al (37) reported a mean breastfeeding duration of 8.5 mo/child in 323 hospital-based controls in Japan.

Although the average duration of breastfeeding per child has more public health applicability than the total duration, only 9 case-control studies (14, 16, 17, 23, 25, 30, 36, 39, 46) reported

the results of this average measurement; therefore, we only carried out analyses for the total duration in the main study. Dose-response results for the average duration of breastfeeding per child (summary RR for a 5-mo increase in duration: 0.91 (95% CI: 0.85, 0.98), which was calculated from 7 (16, 17, 23, 25, 36, 39, 46) of these 9 studies) was similar to the results of the total duration, which also supported our findings. Besides, the majority of included studies adjusted for parity or the number of live births.

Although not all the studies presented results by histologic subtype and cancer grade, our meta-analysis suggested a significant inverse association for breastfeeding with invasive, borderline, serous, and endometrioid EOC. These results were consistent in the dose-response analyses of breastfeeding duration. However, because of the limited number of studies that reported histologic subtypes, the results should be interpreted with caution.

The strengths of this meta-analysis included the large sample size of 14,465 cases and 706,152 noncases. This sample size should have provided sufficient statistical power to detect the putative association between ever breastfeeding and the duration of breastfeeding with risk of EOC. In addition, our study considered a number of subgroups to evaluate heterogeneity. Our study also has several limitations. First, as a meta-analysis of observational studies, it was prone to biases (eg, recall and selection bias) inherent in the original studies. Cohort studies are less susceptible to bias than case-control studies because, in the prospective design, information on exposures is collected before the diagnosis of the disease. Although the results of the meta-regression showed no evidence of significant heterogeneity between subgroups, summary association estimates were slightly different in subgroup analyses by study design and exposure

assessment. It is possible that the relations reported by case-control studies may have been overstated as a result of recall or interviewer bias. In addition, some recent cohort studies provided detailed information of adjustment for confounders, whereas some early case-control studies adjusted for fewer factors. Thus, more large studies, especially prospective studies, are warranted in the future.

A second limitation was that individual studies may have failed to control for potential confounders, which may have introduce bias in an unpredictable direction. Ever breastfeeding and a longer duration of breastfeeding are often associated with other hormone-dependent or reproductive factors, including lower levels of BMI (64), a lower prevalence of OC use (65), a higher parity number, and a lower prevalence of smoking (66). Many, but not all, of the studies adjusted for potential confounding factors. However, an inverse association was still observed when we stratified results according to the adjustment for confounding factors, and the evidence of meta-regression analyses indicated that the adjustment for these confounders was not a source of heterogeneity.

Third, significant heterogeneity and a possible publication bias must be considered. There was significant heterogeneity in the pooled analysis of ever breastfeeding ($Q = 69.40$, $P < 0.001$, $I^2 = 55.3\%$) and in the dose-response analysis of the total breastfeeding duration ($Q = 74.12$, $P < 0.021$, $I^2 = 67.6\%$). Despite the numerous subgroup and sensitivity analyses that were carried out, heterogeneity still existed in our study. To our knowledge, the category of duration of breastfeeding, especially the longest duration, differed between studies and may have contributed to the heterogeneity in results. However, few of the included studies reported how they categorized the duration of breastfeeding, and thus, we hardly considered this point in the subgroup analysis and ruled out the heterogeneity thoroughly. Publication bias can be a problem in meta-analyses of published studies; however, we showed no statistical evidence of a publication bias in the meta-analysis, and there did not appear to be asymmetry in funnel plots when inspected visually.

In conclusion, findings from this meta-analysis suggest that breastfeeding, particularly a longer duration of breastfeeding, was inversely associated with risk of EOC. The results were consistent with benefits of breastfeeding proposed by the US National Institute of Child Health and Human Development (67) and may have implications for women's decisions regarding breastfeeding in the future.

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