Review

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The Effect of Breastfeeding Duration and Parity on the Risk of Epithelial Ovarian Cancer: A Systematic Review and Meta-analysis

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Objectives: We conducted a systematic review and meta-analysis to summarize current evidence regarding the association of parity and duration of breastfeeding with the risk of epithelial ovarian cancer (EOC).

Methods: A systematic search of relevant studies published by December 31, 2015 was performed in PubMed and EMBASE. A random-effect model was used to obtain the summary relative risks (RRs) and 95% confidence intervals (CIs).

Results: Thirty-two studies had parity categories of 1, 2, and ≥3. The summary RRs for EOC were 0.72 (95% CI, 0.65 to 0.79), 0.57 (95% CI, 0.49 to 0.65), and 0.46 (95% CI, 0.41 to 0.52), respectively. Small to moderate heterogeneity was observed for one birth ($p<0.01$; $Q=59.46$; $I^2=47.9\%$). Fifteen studies had breastfeeding categories of <6 months, 6-12 months, and >13 months. The summary RRs were 0.79 (95% CI, 0.72 to 0.87), 0.72 (95% CI, 0.64 to 0.81), and 0.67 (95% CI, 0.56 to 0.79), respectively. Only small heterogeneity was observed for <6 months of breastfeeding ($p=0.17$; $Q=18.79$, $I^2=25.5\%$). Compared to nulliparous women with no history of breastfeeding, the joint effects of two births and <6 months of breastfeeding resulted in a 0.5-fold reduced risk for EOC.

Conclusions: The first birth and breastfeeding for <6 months were associated with significant reductions in EOC risk.

Key words: Ovarian neoplasms, Parity, Breast feeding, Reproduction, Risk factors, Meta-analysis

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INTRODUCTION

Worldwide, ovarian cancer is the seventh most common cancer in women. Furthermore, it is the sixth leading cause of cancer deaths in women and the second most common cause of death among those with gynecologic cancers [1]. Approximately 90% of ovarian cancers are of epithelial origin [2], with the remaining 10% composed of sex cord-stromal tumors (5%

to 8%), germ cell tumors (3% to 5%), and other rare types of ovarian cancer [3].

Most ovarian cancers are life-threatening and are notorious for having a poor prognosis, as they are usually diagnosed at an advanced stage. Moreover, screening results based on pelvic imaging or tumor markers for early detection remain unsatisfactory [4]. Therefore, to reduce the risk of ovarian cancer, primary prevention, such as avoiding risk factors or strengthening exposure to preventive factors, is important.

Reproductive risk factors for epithelial ovarian cancer (EOC) have been extensively explored in epidemiologic studies. For instance, a pooled analysis of 12 US case-control studies in 1992 showed that parous women and those who had breastfed had a lower risk of EOC [5,6]. The protective effect of parity and breastfeeding against EOC is biologically plausible and can be explained by two hypotheses: (1) the incessant ovulation hypothesis, in which monthly ovulation might increase the odds of genetic mutations, potentially leading to subsequent malignant changes [7], and (2) the gonadotropin hypothesis, in which ovarian overstimulation by elevated gonadotropins might trigger hyperproliferation, including subsequent malignant transformation [8]. A pooled analysis in 1992 showed that the greatest protection was associated with the first birth and the first few months of breastfeeding [5]. However, this was only observed in a pooled analysis of six population-based case-control studies, not in hospital-based case-control studies.

Since 1992, many studies from around the world have reported associations of parity and breastfeeding with ovarian cancer. However, findings concerning the protective role of increasing parity and duration of breastfeeding remain inconsistent. For parity, some studies have indicated that the first birth reduces ovarian cancer risk more than subsequent births [9-13]. In contrast, other studies have reported that the second birth was associated with a greater protective effect [14-16]. Likewise, for breastfeeding, some studies have indicated that the first six months of breastfeeding reduce risk more than a month of subsequent breastfeeding [17,18], whereas other studies have reported that each additional six months of breastfeeding confer approximately the same level of additional risk reduction [12,19].

Therefore, we conducted a systematic review and meta-analysis to summarize the current evidence regarding the association of parity and duration of breastfeeding with EOC risk. The aim of this study was to clarify the threshold for risk reduction among the studies without heterogeneity across the results. An additional aim was to perform a meta-analysis to estimate the joint risk reductions associated with parity and breastfeeding.

METHODS

Search Strategy

We performed a literature search including studies published through December 2015 using the following search terms in the PubMed and EMBASE databases (1) (parity or "number of live births") and (ovary or ovarian) and (cancer or tumor or neoplasm or malignancy) or (2) (breastfeeding or lactation) and (ovary or ovarian) and (cancer or tumor or neoplasm or malignancy). Furthermore, to find any additional published studies, a manual search was performed by checking all references of prior meta-analyses [5,6.8,20-23] and of all the original studies. This systematic review was planned, conducted, and reported in adherence to the standards of quality for reporting meta-analyses [24,25].

Study Selection

To be included, studies had to meet the following criteria: (1) the studies were observational (case-control or cohort studies), (2) the exposures of interest were the number of live births and the total duration of breastfeeding, (3) the outcome of interest was EOC, (4) odds ratios (ORs) or relative risk (RR) estimates with 95% confidence intervals (CIs) were reported or sufficient data were present to allow the calculation of these effect measures, and (5) articles were published in the English language. In the case of overlapping data, the study with the largest number of cases was included. As fertility treatments and *BRCA* mutation effects on EOC may alter the association between parity/breastfeeding and EOC [26], we excluded studies conducted on specific populations, such as *BRCA*-1 or *BRCA*-2 mutation carriers or infertile women treated with fertility drugs. The detailed steps of our literature search are shown in Figure 1.

Data Extraction

Data extraction was conducted independently by two authors. Disagreements were discussed and resolved by consensus. The following data were collected from each study: the first author's last name, publication year, study region and design, study period, participant age, sample size (cases and

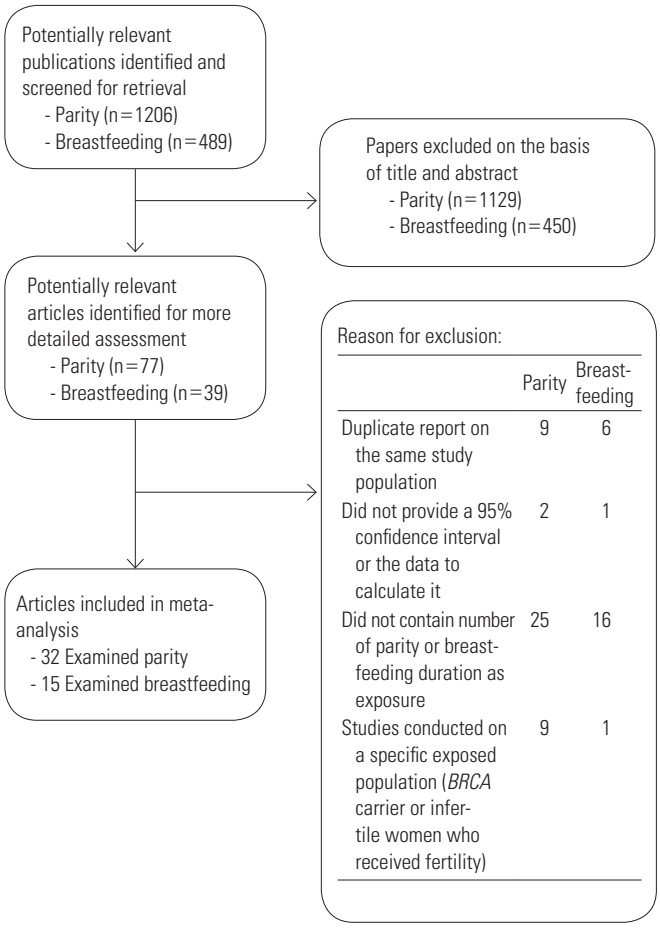

Figure 1. Literature search algorithm.

controls or cohort size), exposure variables (parity or total breastfeeding duration), study-specific adjusted RR or OR with 95% CIs for each exposure category, and factors matched or adjusted for in the design or data analysis. If no adjusted RR or OR was presented, we included crude estimates. If no RRs or ORs were presented in a given study, we calculated them and the 95% CIs according to the raw frequencies presented in the article. The quality of the study was assessed independently by two authors using the 9-star Newcastle-Ottawa Scale (range, 0 to 9 stars) [27]. This measure assesses aspects of methodology in observational studies related to study quality, including the selection of cases, comparability of populations, and ascertainment of exposure to risks.

Statistical Analysis

The study-specific RRs or ORs with 95% CIs were used to determine the principal outcome. Because the OR closely approximates the RR for rare diseases, the RR can be estimated from a case-control study using the OR as an approximation [28]. Ovarian cancer is relatively rare and its absolute risk is low, with an incidence of 6.1 per 100 000 women [1]. Therefore, in the meta-analysis, ORs from case-control studies were used as an equivalent of RRs from cohort studies; we reported all results as RRs [22.29]. Mantel-Haenszel crude estimates of the RRs and corresponding 95% CIs were calculated when the RRs were not present but enough data were available. Logit RR estimates were calculated when the data were sparse. A random-effect model was used to obtain the summary RR and 95% CI. To assess whether the risk of EOC decreased with increasing parity or duration of breastfeeding, we categorized parity (1, 2, or ≥3; 1, 2, 3, or ≥4; and 1, 2, 3, 4, or ≥5) relative to nulliparity and total breastfeeding duration (<6 months, 6-12 months, or ≥13 months; and <6 months, 6-12 months, 13-24 months, or ≥25 months) relative to never having breastfed, as reported by most of the studies.

One study did not provide the required risk estimates for analysis or separate the risk estimates for different categories of parity or breastfeeding duration. For this study, we used the method proposed by Fleiss and Gross [30]. This method allows adjusted effect estimates and CIs to be calculated for any alternative comparison of levels and can help in a dose-response meta-analysis. Briefly, we combined risk estimates obtained through a simple fixed-effects meta-analysis wherein the subjects were divided into unexposed groups ($i=0$) and exposed groups ($i=1, \ldots, n$), and estimates (Ri) with lower and upper 95% CIs were available. To obtain the R_{1+}, we meta-analyzed R_1, R_2, R_3, …, R_n using a fixed-effect model. The categories of parity or breastfeeding duration varied across studies; accordingly, the number of studies included in each meta-analysis and the summary RRs in each meta-analysis were different depending upon the number of categories.

Statistical heterogeneity among studies was evaluated with the Cochran Q and I-squared statistics [31]. The significance level for the Q statistic was defined as p-value<0.1. The I-squared value represents the proportion of total variation composed of between-study variation [31]. I-squared values ≤25%, 25.1-50%, 50.1-75%, and >75% were interpreted as indicating no, small, moderate, and significant heterogeneity, respectively [32]. Subgroup analyses were conducted to explore the potential sources of heterogeneity, according to the following characteristics: (1) study design (cohort, case-control studies); (2) the quality of study methodology across studies, with studies with ≥8 stars considered high-quality and those

with ≤7 stars considered low-quality as per the 9-star Newcastle-Ottawa Scale; and (3) year of publication (<2000, ≥ 2000), respectively.

Publication bias was evaluated using the Begg rank correlation and the Egger linear regression test, in which p-vlaue <0.05 were considered representative of statistically significant publication bias [33].

From the meta-analyzed result, to calculate the RR for the joint effect of parity and breastfeeding, we applied the log-linear dose-response model proposed by Berlin et al. [34].

We configured the following formula for the multivariate linear logit regression of two factors:

Logit $P = \alpha + \beta_1\chi_1 + \beta_2\chi_2$;

where P is the probability of a particular outcome (EOC risk), α is the intercept from the linear regression equation, β is the regression coefficient multiplied by some value of the predictor, and χ is the risk factor (parity and breastfeeding).

Using this equation yields the value of the RR for the joint effects of parity and breastfeeding duration. For example, in the case of a subject who has no risk factors, logit(P) is α. In this case, the probability of EOC is exp(α)=1.0. In the case of a subject with only χ_1, logit(P) is $\alpha+\beta_1$. In the case of a subject with both χ_1 and χ_2, logit(P) is $\alpha+\beta_1+\beta_2$. Accordingly, the probability of EOC is exp($\beta_1+\beta_2$)=$OR_1 \times OR_2$.

Since the category of parity and breastfeeding duration varied across studies, to calculate the RR for the joint effect of parity and breastfeeding, we used the summary RR for parity and breastfeeding duration that contained the largest number of studies.

All statistical analyses were performed with Stata version 12.0 (StataCorp., College Station, TX, USA).

RESULTS

Study Characteristics

The characteristics of the 32 studies included with data regarding parity and the 15 studies included with data regarding breastfeeding are shown in Supplemental Tables 1 and 2. For parity, six cohort studies and 26 case-control studies were included. The included studies were conducted between 1973 and 2008. Of the 32 studies, 14 were performed in North America, 12 in Europe, four in Asia, one in Australia, and one in

Table 1. Summary risk estimates for the association of epithelial ovarian cancer with parity and breastfeeding duration

		No. of studies[1]	Summary RR (95% CI)[2]	*p*-heterogeneity	Q-statistic	I-squared (%)
Parity (n)	1	32	0.72 (0.65, 0.79)	<0.01	59.46	47.9
	2		0.57 (0.49, 0.65)	<0.01	175.09	82.3
	≥3		0.46 (0.41, 0.52)	<0.01	186.20	81.7
	1	21	0.70 (0.62, 0.80)	<0.01	52.97	56.6
	2		0.53 (0.45, 0.62)	<0.01	146.32	84.3
	3		0.48 (0.42, 0.54)	<0.01	69.26	66.8
	≥4		0.39 (0.36, 0.42)	<0.01	80.00	71.3
	1	12	0.68 (0.58, 0.81)	<0.01	35.60	66.3
	2		0.50 (0.41, 0.61)	<0.01	94.17	87.3
	3		0.43 (0.40, 0.46)	<0.01	47.20	74.6
	4		0.34 (0.29, 0.41)	0.01	27.19	55.9
	≥5		0.33 (0.29, 0.37)	0.01	26.72	55.1
Breastfeeding duration (mo)	< 6	15	0.79 (0.72, 0.87)	0.17	18.79	25.5
	6-12		0.72 (0.64, 0.81)	0.24	17.41	19.6
	≥13		0.67 (0.56, 0.79)	<0.01	39.30	64.4
	< 6	6	0.87 (0.72, 1.04)	0.16	7.91	36.8
	6-12		0.71 (0.58, 0.87)	0.30	6.05	17.3
	13-24		0.75 (0.60, 0.93)	0.28	6.34	21.1
	≥25		0.53 (0.36, 0.77)	<0.01	21.16	73.4

RR, relative risk; CI, confidence interval.
[1]No publication bias in each category (p>0.05 in both the Begg and Egger tests).
[2]The summary RRs (95% CIs) in each meta-analysis were estimated using a random effect model.

Africa. For breastfeeding, two cohort studies and 13 case-control studies were included. The included studies were conducted between 1978 and 2008. Of the 15 studies, seven were performed in North America, six in Europe, one in Asia, and one in Australia.

Parity and Epithelial Ovarian Cancer Risk

Thirty-two studies had parity categories of 1, 2, and ≥3. The summary RRs for the first, second, and third births were 0.72 (95% CI, 0.65 to 0.79), 0.57 (95% CI, 0.49 to 0.65), and 0.46 (95% CI, 0.41 to 0.52), respectively (Table 1). Small to moderate heterogeneity was observed for the first birth ($p<0.01$; Q=59.46, $I^2=47.9\%$), whereas significant heterogeneity was observed for the second ($p<0.01$; Q=175.09; $I^2=82.3\%$) and third ($p<0.01$; Q=186.20; $I^2=81.7\%$) births. Analyses gave no indication of publication bias. Similar results were also observed for parity categories of 1, 2, 3, and ≥4 and 1, 2, 3, 4, and ≥5.

Duration of Breastfeeding and Epithelial Ovarian Cancer Risk

Fifteen studies had breastfeeding categories of <6 months, 6-12 months, and ≥13 months. The summary RRs for these categories were 0.79 (95% CI, 0.72 to 0.87), 0.72 (95% CI, 0.64 to 0.81) and 0.67 (95% CI, 0.56 to 0.79), respectively (Table 1). Small or no heterogeneity was observed for <6 months ($p=0.17$; Q=18.79; $I^2=25.5\%$) and 6-12 months ($p=0.24$; Q=17.41; $I^2=19.6\%$), whereas moderate heterogeneity was observed for ≥13 months ($p<0.01$; Q=39.30; $I^2=64.4\%$). Analyses gave no indication of publication bias. Similar results were also observed for the breastfeeding categories of <6 months, 6-12 months, 13-24 months, and ≥25 months.

Subgroup Analysis According to Study Design, Study Quality, and Publication Year

The results from the subgroup analysis according to study design, study quality, and publication year are shown in Table 2. In high-quality studies, the summary RRs for the first, second, and third births were 0.73 (95% CI, 0.64 to 0.84), 0.60 (95% CI, 0.49 to 0.74), and 0.46 (95% CI, 0.41 to 0.52), respectively. The summary RRs for <6 months, 6-12 months, and ≥13 months of breastfeeding were 0.79 (95% CI, 0.68 to 0.91), 0.82 (95% CI, 0.69 to 0.97), and 0.79 (95% CI, 0.66 to 0.95), respectively. The summary RRs of the first birth and <6 months of breastfeeding from the analysis of high-quality studies were almost identical to the values from the analysis of all 32 and 15 studies, without heterogeneity ($I^2=0\%$).

The summary RR for the first birth in cohort studies was weaker, and only had a borderline significant effect on EOC risk (RR, 0.86; 95% CI, 0.75 to 1.00) relative to case-control studies (RR, 0.69; 95% CI, 0.61 to 0.77). In contrast, with regards to breastfeeding, the summary RRs for <6 months were similar between cohort studies and case-control studies (Table 2), with small heterogeneity.

Relative Risk for the Joint Effect of Parity and Breastfeeding

The RR for the joint effect of parity and breastfeeding, obtained using the summary RR from the analysis of 32 studies with parity categories of 1, 2, and ≥3 and 15 studies with breastfeeding categories of <6 months, 6-12 months, and ≥13 months, is shown in Table 3. Compared to nulliparous women who never breastfed, uniparous women with no history of breastfeeding had a nearly 30% reduced risk for EOC (Table 3). Without breastfeeding, two births and three or more births elicited 40% and 50% reduced risks for EOC, respectively. When breastfeeding <6 months was added to each parity category, an additional 10% reduction in EOC risk was found.

DISCUSSION

The findings of this meta-analysis indicate that parity and breastfeeding experiences in women can help prevent EOC, which is typically life-threatening and has a poor prognosis. In particular, the first birth and the first six months of breastfeeding had a greater protective effect than did subsequent births and/or additional breastfeeding, although multiparity and additional breastfeeding did provide some additional protection. The risk reduction effect of the first birth on EOC risk was almost 30%, and the combined effect of the first birth and <6 months of breastfeeding was 40%; thus, breastfeeding provided a nearly 10% greater risk reduction. In regards to parity, the EOC risk reduction was highest for the first birth, with some additional protection from the second birth. However, slightly less risk reduction was observed for the third birth (Figure 2). Although a prior meta-analysis suggested a continuous risk reduction of approximately 14% for each additional pregnancy after the first [5], the current findings show different results, with a gradually decreasing risk from additional parity and/or breastfeeding duration that eventually plateaus (Table 1).

Pregnancy and breastfeeding are thought to reduce EOC risk

Table 2. Subgroup analysis according to study design, study quality, and publication year

				No. of studies[1]	Summary RR (95% CI)[2]	*p*-heterogeneity	Q-statistic	I-squared (%)
Parity (n)	Quality	High[3]	1	8	0.73 (0.64, 0.84)	0.71	4.61	0.0
			2		0.60 (0.49, 0.74)	0.03	15.86	62.2
			≥3		0.46 (0.41, 0.52)	<0.01	28.06	75.1
		Low[4]	1	24	0.71 (0.63, 0.81)	<0.01	54.69	57.9
			2		0.56 (0.47, 0.66)	<0.01	155.48	85.2
			≥3		0.46 (0.40, 0.53)	<0.01	145.47	84.2
	Study design	Cohort	1	6	0.86 (0.75, 1.00)	0.77	2.54	0.0
			2		0.75 (0.66, 0.84)	0.88	1.79	0.0
			≥3		0.60 (0.54, 0.68)	0.34	5.63	11.1
		Case-control	1	26	0.69 (0.61, 0.77)	<0.01	52.56	52.4
			2		0.75 (0.66, 0.84)	<0.01	147.39	83.0
			≥3		0.43 (0.38, 0.49)	<0.01	132.57	81.1
	Year of publication	<2000	1	24	0.68 (0.60, 0.76)	0.01	40.29	42.9
			2		0.54 (0.45, 0.64)	<0.01	144.90	84.1
			≥3		0.45 (0.39, 0.52)	<0.01	136.78	83.2
		≥2000	1	8	0.84 (0.72, 0.98)	0.17	10.35	32.4
			2		0.64 (0.54, 0.76)	0.03	15.45	54.7
			≥3		0.49 (0.40, 0.61)	<0.01	34.34	79.6
Breastfeeding duration (mo)	Quality	High[3]	< 6	4	0.79 (0.68, 0.91)	0.43	2.76	0.0
			6-12		0.82 (0.69, 0.97)	0.39	2.99	0.0
			≥13		0.79 (0.66, 0.95)	0.33	39.30	13.0
		Low[4]	< 6	11	0.78 (0.68, 0.90)	0.06	17.65	43.3
			6-12		0.69 (0.60, 0.79)	0.31	11.69	14.5
			≥13		0.63 (0.52, 0.78)	<0.01	28.38	64.8
	Study design	Cohort	< 6	2	0.77 (0.63, 0.93)	0.22	1.53	34.6
			6-12		0.87 (0.71, 1.06)	0.43	0.63	0.0
			≥13		0.81 (0.67, 0.98)	0.33	0.97	0.0
		Case-control	< 6	13	0.79 (0.70, 0.90)	0.09	18.97	36.8
			6-12		0.69 (0.61, 0.77)	0.39	12.69	8.8
			≥13		0.64 (0.53, 0.77)	<0.01	31.53	61.9
	Year of publication	<2000	< 6	11	0.78 (0.70, 0.86)	0.28	12.11	17.4
			6-12		0.70 (0.61, 0.82)	0.12	15.26	34.5
			≥13		0.63 (0.53, 0.76)	<0.01	25.58	60.9
		≥2000	< 6	4	0.80 (0.57, 1.12)	0.04	8.39	64.2
			6-12		0.75 (0.60, 0.94)	0.56	2.04	0.0
			≥13		0.81 (0.51, 1.27)	0.01	11.77	74.5

RR, relative risk; CI, confidence interval.
[1]No publication bias in each category ($p>0.05$ in both the Begg and Egger test).
[2]The summary RRs (95% CIs) in each meta-analysis were estimated using a random effect model.
[3]Studies with ≥8 stars were considered high-quality as per the 9-star Newcastle-Ottawa Scale.
[4]Studies with ≤7 stars were considered low-quality as per the 9-star Newcastle-Ottawa Scale.

by decreasing pituitary gonadotropin levels and inducing anovulation [7,35]. Pregnancy and breastfeeding are expected to decrease the likelihood of spontaneous genetic mutation under the incessant ovulation hypothesis and of the hyperproliferation of inclusion cysts under the gonadotropin hypothesis. However, the observation that multiparity and additional breastfeeding did not provide an equal amount of protection does not provide evidence for either of these hypotheses. Nev-

Table 3. Relative risks (RRs) for the joint effect of parity and breastfeeding

Parity (n)		Breastfeeding (mo)				
Category	**RR[1,2]**		**0**	**<6**	**6-12**	**≥13**
		RR[1,2]	1.00	0.79	0.72	0.67
0	1.00	Joint RR	1.0			
1	0.72		0.7	0.6	0.5	0.5
2	0.57		0.6	0.5	0.4	0.4
≥3	0.46		0.5	0.4	0.3	0.3

[1]The RRs in each category were estimated using a random effect model.
[2]We used the summary RR from the analysis of 32 studies with parity categories of 1, 2, and ≥3 and 15 studies with breastfeeding categories of <6, 6-12, and ≥13 months (as shown in Table 1).

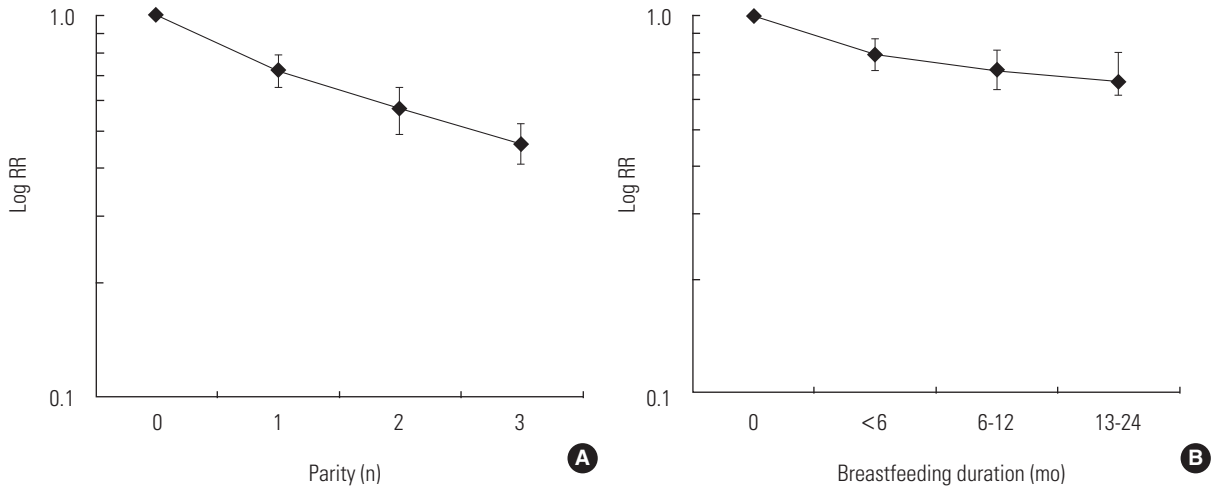

Figure 2. Decreasing epithelial ovarian cancer (EOC) risk with increasing parity and breastfeeding duration. (A) Decreasing EOC risk with increasing parity[1,2]. (B) Decreasing EOC risk with increasing breastfeeding duration[1,2]. [1]The relative risks (RRs) in each category were estimated using a random effect model. [2]We used summary RRs from 32 studies for parity and 15 studies for breastfeeding (shown in Table 1).

ertheless, the results of two experimental studies provide biological evidence for the relatively weaker protective effect of additional parity and breastfeeding [36,37]. For instance, high progesterone levels during pregnancy can increase apoptosis, which may clear transformed cells from the ovarian epithelium, meaning that all the accumulated transformed cells are washed fully out by the first pregnancy. Therefore, the first pregnancy provides a stronger protective effect than subsequent pregnancies [36]. In regards to breastfeeding, breastfeeding in the first few months completely inhibits the pulsatile secretion of gonadotropin-releasing hormone and luteinizing hormone, leading to suppression of ovulation [37]. After a couple of months, ovulatory activity may return, even though breastfeeding continues [37]; thus, a longer duration of breastfeeding does not provide an additional protective effect.

Our finding of decreased EOC risk with longer breastfeeding is similar to that reported by prior meta-analyses in 2013 and 2014 [22,23], but differs from that of a meta-analysis of nine case-control studies conducted in developed countries in 2001, in which breastfeeding for ≥12 months was associated with a significant 0.72-fold reduced risk of EOC compared to never having breastfed, while breastfeeding <12 months did not show such an association (OR, 0.95; 95% CI, 0.80 to 1.12) [21].

Based on the RR for the joint effect of parity and breastfeeding, women who had two births and breastfed for <6 months had a 0.5-fold reduced risk of EOC. Our findings may provide evidence for developing guidelines for EOC prevention.

The strength of this meta-analysis is that it included all available studies, and the large number of EOC cases allowed for the investigation of the risk associated with different categories of parity and breastfeeding duration. However, the current study also has several limitations. First, our meta-analysis was

restricted to studies published in indexed journals and might not have included unpublished studies. Second, some residual confounders may not have been excluded and may have influenced the protective effect of parity and breastfeeding, although a large number of potential confounding factors, such as age, race, and use of oral contraceptives, were adjusted for in most of the included studies. Third, significant heterogeneity must be considered. Significant heterogeneity was present in the analysis assessing whether the risk of EOC decreased with increasing parity or duration of breastfeeding, especially for higher parity and longer duration of breastfeeding. Despite the subgroup analyses, heterogeneity still existed in the results of the highest category of parity and longest duration of breastfeeding. Categories of parity and duration of breastfeeding, especially the highest parity and longest duration of breastfeeding, differed among studies and may have contributed to the heterogeneity in the results. However, the first birth and <6 months of breastfeeding showed little heterogeneity, and similar results were found in the subgroup analysis to those of the high-quality studies. Fourth, as a meta-analysis of observational studies, the data were prone to biases such as recall and selection bias inherent in the original studies. Cohort studies are less susceptible to bias than case-control studies because information is collected before the diagnosis of the disease. However, only a small number of cohort studies have been published; therefore, it was not possible to analyze the various categories of parity and breastfeeding duration using cohort studies alone. Fifth, the included studies were primarily from North America and Europe. Therefore, the findings may not apply to Asian populations with a low incidence of ovarian cancer.

CONCLUSION

In conclusion, our findings indicated that the first birth and breastfeeding for <6 months were associated with significant reductions in EOC risk. As a modifiable reproductive risk factor, two childbirths and additional breastfeeding, regardless of breastfeeding duration, can reduce EOC risk by 50%. These findings may help to generate recommendations for the prevention of EOC.

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CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

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Supplemental Table 1. Details of studies on parity and ovarian cancer risk

Author (year of publication) [Ref]	Country	Age (y)	Study period	No. of cases	No. of controls (cohort[1])	Outcome	Parity	RR/OR (95% CI)	Study quality[2]	Comments
Cohort study										
Hankinson et al. (1995) [A01]	USA	30-55	1976-1988	260	(121 700)	EOC	Nulliparous 1 2 3 4 5 ≥6	1.00 (reference) 0.96 (0.58, 1.60) 0.73 (0.47, 1.12) 0.58 (0.37, 0.90) 0.49 (0.30, 0.81) 0.45 (0.25, 0.84) 0.39 (0.20, 0.74)	7	The Nurses' Health Study cohort Study quality: [Selection: 2, Comparability: 2, Outcome: 3] Adjusted for age, duration of oral contraceptive use, tubal ligation, age at menarche, age at menopause, smoking status, Quetelet Index
Kumle et al. 2004 [A02]	Norway/ Sweden	30-49	1991-2000	214	(103 551)	EOC	Nulliparous 1 2 ≥3	1.0 (reference)[3] 0.7 (0.4, 1.1)3 0.6 (0.4, 0.9)3 0.5 (0.4, 0.8)3	8	The Norwegian-Swedish Women's Lifestyle and Health cohort Study quality: [Selection: 3, Comparability: 2, Outcome: 3] Adjusted for age
Lacey et al. 2006 [A03]	USA	31-89	1973-1998	346	(46 026)	Total OC	Nulliparous 1 2 ≥3	1.00 (reference) 1.04 (0.79, 1.65) 0.61 (0.60, 1.17) 0.73 (0.54, 1.00)	9	The Breast Cancer Detection Demonstration Project cohort Diet and Health Study Cohort Study quality: [Selection: 4, Comparability: 2, Outcome: 3] Adjusted for age, calendar time
Tsilidis et al. 2011 [A04]	10 European countries	50.45	1992-2006	878	(327 396)	EOC	Nulliparous 1 2 3 ≥4	1.00 (reference) 0.80 (0.63, 1.02) 0.74 (0.61, 0.91) 0.64 (0.50, 0.81) 0.62 (0.46, 0.93)	8	The European Prospective Investigation into Cancer and Nutrition cohort Study quality: [Selection: 4, Comparability: 2, Outcome: 2] Adjusted for age and oral contraceptive use
Weiderpass et al. 2012 [A05]	Japan	40-69	1990-2008	86	(45 748)	EOC	Nulliparous 1 2 3 >3	1.0 (reference)[3] 1.5 (0.5, 4.5)[3] 0.8 (0.3, 2.1)[3] 0.6 (0.2, 1.8)[3] 0.6 (0.2, 1.8)[3]	8	The Japan Public Health Center-Based Prospective Study cohort Study quality: [Selection: 4, Comparability: 2, Outcome: 2] Adjusted for age and study area, age at menarche, age at first birth, use of exogenous hormones, menopausal status, height, body mass index, smoking status, physical activity, sleep duration, family history of cancer
Yang et al. 2012 [A06]	USA	62.85	1995-2006	849	(169 391)	EOC	Nulliparous 1 2 ≥3	1.00 (reference) 0.93 (0.73, 1.19) 0.76 (0.62, 0.93) 0.64 (0.53, 0.77)	7	NIH-AARP Diet and Health Study Study quality: [Selection: 3, Comparability: 2, Outcome: 2] Adjusted for age and oral contraceptive use, menopausal hormone therapy
Case-control study										
Booth et al. 1989 [A07]	UK	(52.4/ 51.4)[5]	1978-1983	235	451	EOC	Nulliparous 1 2 3 4 ≥5	1.0 (reference)[3] 0.7 (0.4, 1.2)[3] 0.6 (0.4, 1.0)[3] 0.6 (0.3, 1.0)[3] 0.5 (0.2, 1.0)[3] 0.3 (0.1, 0.7)[3]	6	Unmatched Study quality: [Selection: 3, Comparability: 2, Outcome: 1] Adjusted for age, social class
Hartge et al. 1989 [A08]	USA	20-79	1978-1981	296	343	EOC	Nulliparous 1 2 3 ≥4	1.0 (reference)[3] 1.0 (0.6, 1.7)[3] 0.8 (0.5, 1.3)[3] 0.7 (0.4, 1.2)[3] 0.6 (0.4, 1.1)[3]	7	Matched for hospital, age, race Study quality: [Selection: 3, Comparability: 2, Outcome: 2] Adjusted for age, race

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Supplemental Table 1. Continued from the previous page

Author (year of publication) [Ref]	Country	Age (y)	Study period	No. of cases	No. of controls (cohort[1])	Outcome	Parity	RR/OR (95% CI)	Study quality[2]	Comments
Gwinn et al. 1990 [A09]	UK	20-54	1980-1982	436	3833	EOC	Nulliparous 1 2 3 4 ≥5	1.00 (reference) 0.66 (0.47, 0.93)[4] 0.52 (0.39, 0.69)[4] 0.45 (0.34, 0.62)[4] 0.28 (0.22, 0.48)[4] 0.24 (0.19, 0.37)[4]	7	Unmatched Study quality: [Selection: 4, Comparability: 1, Outcome: 2] Crude OR
Chen et al. 1992 [A10]	China	(48.5/49.0)[5]	1984-1986	112	224	EOC	Nulliparous 1 2 3 4-5 ≥6	1.0 (reference)[3] 0.5 (0.2, 1.8)[3] 0.3 (0.1, 1.2)[3] 0.1 (0.0, 0.6)[3] 0.1 (0.0, 0.5)[3] 0.1 (0.0, 0.6)[3]	8	Matched for age Study quality: [Selection: 4, Comparability: 2, Outcome: 2] Adjusted for education
Tavani et al. 1993 [A11]	Italy	18-45	1983-1992	194	710	EOC	Nulliparous 1 2 ≥3	1.00 (reference) 0.9 (0.6, 1.4)[3] 1.0 (0.6, 1.7)[3] 1.1 (0.6, 2.0)[3]	7	Study quality: [Selection: 3, Comparability: 2, Outcome: 2] Adjusted for age, education, family history, number of births, number of abortions
Adami et al. 1994 [A12]	Sweden	Not available	1960-1984	3486	19 980	Total OC	1 2 3 4 5 ≥6	1.00 (reference) 0.75 (0.67, 0.83) 0.61 (0.54, 0.70) 0.56 (0.46, 0.68) 0.37 (0.25, 0.55) 0.40 (0.25, 0.66)	6	Matched for age Study quality: [Selection: 2, Comparability: 2, Outcome: 1] Adjusted for age at diagnosis or enrollment and age at first birth
Risch et al. 1994 [A13]	Canada	35-79	1989-1992	450	564	EOC	Nulliparous 1 2 3 4 ≥5	1.00 (reference) 0.64 (0.41, 1.01) 0.37 (0.25, 0.56) 0.40 (0.26, 0.61) 0.27 (0.16, 0.46) 0.23 (0.13, 0.42)	8	Matched for age Study quality: [Selection: 4, Comparability: 2, Outcome: 2] Adjusted for age, oral contraceptive use
Purdie et al. 1995 [A14]	Australia	18-79	1990-1993	824	860	EOC	Nulliparous 1 2 3 4 ≥5	1.00 (reference) 1.38 (0.92, 2.08) 0.82 (0.59, 1.13) 0.61 (0.43, 0.86) 0.52 (0.35, 0.78) 0.84 (0.53, 1.33)	7	Matched for area of residence and age Study quality: [Selection: 4, Comparability: 2, Outcome: 1] Adjusted for age, education, talc use, body mass index, smoking, family history, hysterectomy, tubal ligation, duration of oral contraceptive use
Ness et al. 2000 [A15]	USA.	20-69	1994-1998	767	1367	EOC	Nulliparous 1 2 3 4 ≥5	1.0 (reference)[3] 0.6 (0.4, 0.9)[3] 0.4 (0.3, 0.6)[3] 0.4 (0.3, 0.5)[3] 0.3 (0.2, 0.4)[3] 0.3 (0.2, 0.4)[3]	7	Study quality: [Selection: 4 Comparability: 2, Outcome: 1] Adjusted for age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy and breast-feeding
Greggi et al. 2000 [A16]	Italy	13-80	1988-1998	440	868	EOC	Nulliparous 1 2 ≥3	1.0 (reference)[3] 0.8 (0.5, 1.3)[3] 0.9 (0.6, 1.4)[3] 0.7 (0.5, 1.2)[3]	7	Controls were identified in similar strata of age among women admitted to the same hospital Study quality: [Selection: 3, Comparability: 2, Outcome: 3] Adjusted for age, education, parity, oral contraceptive use, family history of ovarian cancer
Akhmedkhanov et al. 2001 [A17]	USA	31-70	1985-1996	68	680	EOC	Nulliparous 1 2 ≥3	1.00 (reference) 0.58 (0.27, 1.25) 0.53 (0.27, 1.01) 0.45 (0.22, 0.92)	7	Matched for age, menopausal status, date of enrollment, date of response Study quality: [Selection: 3, Comparability: 2, Outcome: 1] Adjusted for age at menarche, oral contraceptive use, first degree family history of breast cancer before 50

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Supplemental Table 1. Continued from the previous page

Author (year of publication) [Ref]	Country	Age (y)	Study period	No. of cases	No. of controls (cohort[1])	Outcome	Parity	RR/OR (95% CI)	Study quality[2]	Comments
Riman et al. 2001 [A18]	Sweden	50-74	1993-1995	193	3899	BOT	Nulliparous 1 2 3 4 ≥5	1.00 (reference) 0.68 (0.43, 1.12) 0.53 (0.34, 0.83) 0.44 (0.36, 0.73) 0.27 (0.12, 0.61) 0.33 (0.12, 0.87)	9	Frequency matched by age Study quality: [Selection: 4, Comparability: 2, Outcome: 3] Adjusted for age, body mass index, age at menopause, duration of oral contraceptive use
Titus-Ernstoff et al. 2001 [A19]	USA.	20-74	1992-1997	563	523	EOC	Nulliparous 1 2 3 4 ≥5	1.0 (reference)[3] 0.6 (0.4, 0.9)[3] 0.4 (0.3, 0.6)[3] 0.3 (0.2, 0.5)[3] 0.3 (0.2, 0.5)[3] 0.2 (0.1, 0.4)[3]	7	Matched to case women by age and telephone sampling unit Study quality: [Selection: 4, Comparability: 2, Outcome: 1] Adjusted for age, state
Riman et al. 2002 [A20]	Sweden	50-74	1993-1995	655	3899	Invasive EOC	Nulliparous 1 2 3 4 ≥5	1.00 (reference) 0.61 (0.46, 0.81) 0.55 (0.43, 0.70) 0.44 (0.33, 0.58) 0.35 (0.23, 0.53) 0.32 (0.18, 0.56)	9	Study quality: [Selection: 4, Comparability: 2, Outcome: 3] Adjusted for age, body mass index, age at menopause, duration of oral contraceptive use as categorized variables, any lifetime use of hormone replacement therapy
Tung et al. 2003 [A21]	USA.	≥18	1993-1999	558	607	EOC	Nulliparous 1 2 >2	1.0 (reference)[3] 0.6 (0.4, 0.9)[3] 0.6 (0.4, 0.9)[3] 0.6 (0.4, 0.8)[3]	7	Matched to cases with an approximate 1:1 ratio on the basis of specific ethnicity (e.g., Japanese), age (year of birth±5 y), and study site. Study quality: [Selection: 3, Comparability: 2, Outcome: 2] Adjusted for age, ethnicity, study site, education, tubal ligation, hormone replacement therapy, and ovulation variables
Mills et al. 2004 [A22]	USA.	≥18	2000-2001	256	1122	EOC	Nulliparous 1 2 3 ≥4	1.00 (reference) 0.37 (0.16, 0.83) 0.42 (0.20, 0.90) 0.41 (0.19, 0.90) 0.36 (0.16, 0.80)	7	Frequency matched on age and ethnicity Study quality: [Selection: 4, Comparability: 2, Outcome: 1] Adjusted for age, race, ethnicity, oral contraceptive use and breastfeeding
Pike et al. 2004 [A23]	USA	18-74	1992-1998	467	660	Invasive EOC	Nulliparous 1 2 3 ≥4	1.00 (reference) 0.62 (0.40, 0.96) 0.62 (0.42, 0.90) 0.55 (0.36, 0.84) 0.36 (0.22, 0.57)	7	Individually matched on race, ethnicity, date of birth Study quality: [Selection: 4, Comparability: 2, Outcome: 1] Adjusted for age, ethnicity, socioeconomic status, education, family history ovarian cancer, tubal ligation, use of genital area talc, body mass index, oral contraceptive use, menopausal status, age at menopause, age at last birth, hormone replacement therapy use
Rossing et al. 2004 [A24]	USA	35-54	1994-1998	378	1637	EOC	Nulliparous 1 2 ≥3	1.0 (reference)[3] 0.7 (0.5, 1.0)[3] 0.6 (0.5, 0.9)[3] 0.5 (0.3, 0.7)[3]	6	Matched for area of residence and age Study quality: [Selection: 3, Comparability: 2, Outcome: 1] Adjusted for age, race and study site
Chiaffarino et al. 2005 [A25]	Italy	18-79	1992-1999	1031	2411	EOC	Nulliparous 1 2 3 ≥4	1.0 (reference)[3] 1.1 (0.8, 1.5)[3] 1.0 (0.8, 1.3)[3] 0.6 (0.5, 0.9)[3] 0.5 (0.3, 0.7)[3]	7	Matched for age Study quality: [Selection: 3, Comparability: 2, Outcome: 2] Adjusted for age and study center, education, oral contraceptive use and family history

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Supplemental Table 1. Continued from the previous page

Author (year of publication) [Ref]	Country	Age (y)	Study period	No. of cases	No. of controls (cohort[1])	Outcome	Parity	RR/OR (95% CI)	Study quality[2]	Comments
El-Khwsky et al. 2006 [A26]	Egypt	20-79	2000-2003	172	441	EOC	Nulliparous 1 2 3 ≥4	1.00 (reference) 0.36 (0.16, 0.78) 0.36 (0.19, 0.68) 0.52 (0.27, 0.97) 0.56 (0.34, 0.94)	5	Matched by age and address Study quality: [Selection: 2, Comparability: 2,Outcome: 1] Crude OR
Huusom et al. 2006 [A27]	Denmark	35-79	1995-1999	202	1564	BOT	1 2 3 ≥4	1.00 (reference) 0.51 (0.33, 0.79) 0.41 (0.23, 0.72) 0.51 (0.24, 1.08)	7	Frequency matched in 5 y intervals by using age distribution women with ovarian cancer Study quality: [Selection: 4, Comparability: 2,Outcome: 1] Adjusted for age, age at first birth, duration of oral contraceptives smoking, intake of milk
Soegaard et al. 2007 [A28]	Denmark	35-79	1995-1999	554	1564	EOC	1 2 ≥3	1.00 (reference) 0.63 (0.45, 0.87) 0.51 (0.37, 0.69)	7	Frequency-matched in 5 y intervals by age using computerized civil registration data Study quality: [Selection: 4, Comparability: 2, Outcome: 1] Adjusted for age, pregnancy and duration of oral contraceptive use
Fujita et al. 2008 [A29]	Japan	≥30	1997-2003	141	2016	Total OC	Nulliparous 1 2 ≥3	1.00 (reference) 0.57 (0.28, 1.17) 0.39 (0.22, 0.69) 0.31 (0.17, 0.57)	7	Unmatched Study quality: [Selection: 3, Comparability: 2, Outcome: 2] Adjusted for age, year of survey, referral base, area of residence, smoking history, history of alcohol drinking, family history of index cancer, occupation, age at menarche
Moorman et al. 2008 [A30]	USA	20-74	1999-2006	869	967	EOC	Nulliparous 1 2 3 >3	1.00 (reference)[4] 0.66 (0.46, 0.90)[4] 0.37 (0.28, 0.49)[4] 0.53 (0.39, 0.72)[4] 0.66 (0.47, 0.92)[4]	7	Frequency matched by age and race Study quality: [Selection: 4, Comparability: 2, Outcome: 2] Crude OR
Kurta et al. 2012 [A31]	USA	≥25	2003-2008	902	1802	EOC	Nulliparous 1 2 3 4 ≥5	1.00 (reference) 0.51 (0.38, 0.68) 0.45 (0.35, 0.57) 0.39 (0.30, 0.51) 0.32 (0.23, 0.45) 0.32 (0.22, 0.47)	7	Frequency matched by age (5 y categories). Telephone area code through random digit dialing Study quality: [Selection: 4, Comparability: 2, Outcome: 1] Adjusted for age, race, education
Le et al. 2012 [A32]	Vietnam	40-59	2001-2006	262	755	Total OC	Nulliparous 1 2 3 4 ≥5	1.0 (reference)[3] 0.8 (0.4, 1.7)[3] 0.5 (0.2, 0.9)[3] 0.4 (0.2, 0.7)[3] 0.2 (0.1, 0.3)[3] 0.2 (0.1, 0.4)[3]	7	Matched for age Study quality: [Selection: 4, Comparability: 2, Outcome: 1] Adjusted for age, education level, body mass index, menopausal status, age at menarche, oral contraceptive use

EOC, epithelial ovarian cancer; OC, ovarian cancer; BOT, borderline ovarian tumor; OR, odds ratio; RR, relative risk; CI, confidence interval.
[1]Number of total cohort.
[2]Study quality was judged based on the Newcastle-Ottawa Scale (range, 1-9 points).
[3]Values is listed to one decimal point in the original data.
[4]Mantel-Haenszel crude estimates of the ORs/RRs and corresponding 95% CIs were calculated when the ORs/RRs were not presented.
[5]Mean age.

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Supplemental Table 2. Details of studies on breastfeeding and ovarian cancer risk

Author (year of publication) [Ref]	Country	Age (y)	Study period	No. of cases	No. of controls (cohort[1])	Outcome	Breast-feeding (mo)	RR (95% CI)	Study quality[2]	Comment
Cohort study										
Danforth et al. 2007 [B01]	USA	30-55 /20-42	1986-2002 /1993-2003	391	(149 693)	EOC	Never 1-6 7-11 12-17 18+	1.00 (reference) 0.96 (0.76, 1.21) 0.76 (0.52, 1.11) 0.82 (0.54, 1.24) 0.66 (0.46, 0.96)	8	The Nurses' Health Study and Nurses' Health Study II Study quality: [Selection: 2, Comparability: 2, Outcome: 3] Adjusted for age, parity, duration of oral contraceptive use, tubal ligation, age at menarche
Tsilidis et al. 2011 [B02]	10 European countries	50.4[5]	1992-2006	878	(327 396)	EOC	≤1 2-6 7-12 >3	1.00 (reference) 0.84 (0.68, 1.03) 0.91 (0.72, 1.14) 0.66 (0.46, 0.96)	8	The European Prospective Investigation into Cancer and Nutrition cohort Study quality: [Selection: 4, Comparability: 2, Outcome: 2] Adjusted for age and oral contraceptive use
Case-control study										
Booth et al. 1989 [B03]	UK	(52.4/51.4)[5]	1978-1983	235	451	EOC	Never ≤6 7-12 13-18 19-24 ≥25	1.0 (reference)[3] 0.3 (0.8, 2.2)[3] 0.9 (0.5, 1.6)[3] 1.2 (0.5, 2.5)[3] 2.1 (0.7, 6.7)[3] 3.4 (1.1, 10.8)[3]	6	Unmatched Study quality: [Selection: 3, Comparability: 2, Outcome: 1] Adjusted for age, number of live births
Gwinn et al. 1990 [B04]	UK	20-54	1980-1982	436	3833	EOC	Never 1-2 3-5 6-11 12-23 ≥24	1.0 0.6[4] 0.8[4] 0.8[4] 0.7[4] 0.3[4]	7	Unmatched Study quality: [Selection: 4, Comparability: 1, Outcome: 2] Adjusted for pregnancy, oral contraceptive use. age
Siskind et al. 1997 [B05]	Australia	18-79	1990-1993	824	855	EOC	Never 1-6 7-12 13-24 25-36 >36	1.00 (reference) 0.89 (0.65, 1.21) 0.68 (0.49, 0.94) 0.84 (0.59, 1.20) 0.69 (0.38, 1.27) 0.77 (0.34, 1.75)	7	Matched for age and residence Study quality: [Selection: 4, Comparability: 2, Outcome: 1] Adjusted for number of live born children, age, use of oral contraceptives, education, smoking history
Hirose et al. 1999 [B06]	Japan	(51.8/48.5)[5]	1998-1995	95	25 488	EOC	Never 1-5 6-11 ≥12	1.00 (reference) 0.89 (0.39, 2.03) 1.18 (0.54, 2.60) 0.70 (0.31, 1.55)	5	Unmatched Study quality: [Selection: 4 Comparability: 2, Outcome: 1] Adjusted for age, body mass index
Ness et al. 2000 [B07]	USA	20-69	1994-1998	767	1367	EOC	Never 1-5 6-11 12-23 ≥24	1.0 (reference)[3] 0.9 (0.7, 1.2)[3] 0.9 (0.6, 1.3)[3] 0.7 (0.5, 1.1)[3] 0.6 (0.4, 1.0)[3]	7	Study quality: [Selection: 4 Comparability: 2, Outcome: 1] Adjusted for age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy and breast-feeding
Riman et al. 2001 [B08]	Sweden	50-74	1993-1995	193	3899	BOT	Never 1-5 6-11 ≥12	1.00 (reference) 0.72 (0.38, 1.36) 0.52 (0.28, 1.00) 0.47 (0.24, 0.94)	9	Frequency matched by age Study quality: [Selection: 4, Comparability: 2, Outcome: 3] Adjusted for age, body mass index, age at menopause, duration of oral contraceptive use

(Continued to the next page)

Supplemental Table 2. Continued from the previous page

Author (year of publication) [Ref]	Country	Age (y)	Study period	No. of cases	No. of controls (cohort[1])	Outcome	Breastfeeding (mo)	RR (95% CI)	Study quality[2]	Comment
Riman et al. 2002 [B09]	Sweden	50-74	1993-1995	655	3899	Invasive EOC	Never 1-5 6-11 ≥12	1.00 (reference) 0.99 (0.64, 1.52) 0.77 (0.50, 1.19) 0.87 (0.56, 1.35)	9	Study quality: [Selection: 4, Comparability: 2, Outcome: 3] Adjusted for age, body mass index, age at menopause, duration of oral contraceptive use as categorized variables, any lifetime use of hormone replacement therapy
Tung et al. 2003 [B10]	USA.	≥18	1993-1999	558	607	EOC	Never ≤5 6-12 >12	1.0 (reference)[3] 0.6 (0.4, 0.7)[3] 0.6 (0.4, 0.9)[3] 0.6 (0.4, 0.9)[3]	7	Matched to cases with an approximate 1:1 ratio on the basis of specific ethnicity (e.g., Japanese), age (year of birth ±5 y), and study site Study quality: [Selection: 3, Comparability: 2, Outcome: 2] Adjusted for age, ethnicity, study site, education, tubal ligation, hormone replacement therapy, and ovulation variables
Mills et al. 2004 [B11]	USA.	≥18	2000-2001	256	1122	EOC	Never <6 6-11 12-23 ≥24	1.00 (reference) 0.37 (0.16, 0.83) 0.42 (0.20, 0.90) 0.41 (0.19, 0.90) 0.36 (0.16, 0.80)	7	Frequency matched on age and ethnicity Study quality: [Selection: 4, Comparability: 2, Outcome: 1] Adjusted for age, race, ethnicity, oral contraceptive use and breastfeeding
Rossing et al. 2004 [B12]	USA	35-54	1994-1998	378	1637	EOC	Never <6 6-12 ≥12	1.0 (reference)[3] 0.9 (0.7, 1.3)[3] 0.8 (0.5, 1.2)[3] 0.5 (0.3, 0.7)[3]	6	Matched for area of residence and age Study quality: [Selection: 3, Comparability: 2, Outcome: 1] Adjusted for age, race and study site
Huusom et al. 2006 [B13]	Denmark	35-79	1995-1999	202	1564	BOT	Never 1-5 6-11 12-24 ≥25	0.97 (0.50, 1.86) 1.00 (reference) 0.73 (0.48, 1.13) 0.93 (0.57, 1.50) 0.32 (0.11, 0.95)	7	Frequency matched in 5 y intervals by using age distribution women with ovarian cancer Study quality: [Selection: 4, Comparability: 2,Outcome: 1] Adjusted for age, age at first birth, duration of oral contraceptives smoking, intake of milk
Moorman et al. 2008 [B14]	USA	20-74	1999-2006	869	967	EOC	Never <6 6-12 >12	1.00 (reference) 0.78 (0.68, 1.12) 0.74 (0.43, 0.80) 0.92 (0.51, 1.40)	7	Frequency matched by age and race Study quality: [Selection: 4, Comparability: 2, Outcome: 2] Crude OR
Kurta et al. 2012 [B15]	USA	≥25	2003-2008	902	1802	EOC	Never <6 6-11 ≥12	1.00 (reference) 0.60 (0.47, 0.76) 0.54 (0.40, 0.72) 0.46 (0.36, 0.59)	7	Frequency matched by age (5 y categories) Telephone area code through random digit dialing Study quality: [Selection: 4, Comparability: 2, Outcome: 1] Adjusted for age, race, education

EOC, epithelial ovarian cancer; OC, ovarian cancer; BOT, borderline ovarian tumor; OR, odds ratio; RR, relative risk; CI, confidence interval.

[1]Number of total cohort.

[2]Study quality was judged based on the Newcastle-Ottawa Scale (range, 1-9 points).

[3]Values is listed to 1 decimal point in the original data.

[4]The 95% CI was not presented in the original article.

[5]Mean age.

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B03. Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. Br J Cancer 1989;60(4):592-598.

B04. Gwinn ML, Lee NC, Rhodes PH, Layde PM, Rubin GL. Pregnancy, breast feeding, and oral contraceptives and the risk of epithelial ovarian cancer. J Clin Epi-

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B11. Mills PK, Riordan DG, Cress RD. Epithelial ovarian cancer risk by invasiveness and cell type in the Central Valley of California. Gynecol Oncol 2004;95(1):215-225.
B12. Rossing MA, Tang MT, Flagg EW, Weiss LK, Wicklund KG. A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. Am J Epidemiol 2004;160(11):1070-1078.
B13. Huusom LD, Frederiksen K, Høgdall EV, Glud E, Christensen L, Høgdall CK, et al. Association of reproductive factors, oral contraceptive use and selected lifestyle factors with the risk of ovarian borderline tumors: a Danish case-control study. Cancer Causes Control 2006;17(6):821-829.
B14. Moorman PG, Calingaert B, Palmieri RT, Iversen ES, Bentley RC, Halabi S, et al. Hormonal risk factors for ovarian cancer in premenopausal and postmenopausal women. Am J Epidemiol 2008;167(9):1059-1069.
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