RESEARCH ARTICLE

Breastfeeding and Ovarian Cancer Risk: a Systematic Review and Meta-analysis of 40 Epidemiological Studies

Da-Peng Li[1&], Chen Du[2&], Zuo-Ming Zhang[1], Guang-Xiao Li[1], Zhi-Fu Yu[1], Xin Wang[1], Peng-Fei Li[1], Cheng Cheng[3], Yu-Peng Liu[1], Ya-Shuang Zhao[1]

Abstract

The present systematic review and meta-analysis was conducted to assess any association between breastfeeding and the risk of ovarian cancer. A systematic search of published studies was performed in PUBMED and EMBASE and by reviewing reference lists from retrieved articles through March 2013. Data extraction was conducted independently by two authors. Pooled relative risk ratios were calculated using random-effect models. Totals of 5 cohort studies and 35 case-control studies including 17,139 women with ovarian cancer showed a 30% reduced risk of ovarian cancer when comparing the women who had breastfed with those who had never breastfed (pooled RR = 0.70, 95% CI: 0.64-0.76; $p = 0.00$), with significant heterogeneity in the studies ($p = 0.00$; $I^2 = 76.29\%$). A significant decreasd in risk of epithelial ovarian cancer was also observed (pooled RR = 0.68, 95% CI: 0.61-0.76). When the participants were restricted to only parous women, there was a slightly attenuated but still significant risk reduction of ovarian cancer (pooled RR = 0.76, 95% CI: 0.69-0.83). For total breastfeeding duration, the pooled RRs in the < 6 months, 6-12 months and > 12 months of breastfeeding subgroups were 0.85 (95% CI: 0.77-0.93), 0.73 (95% CI: 0.65-0.82) and 0.64 (95%CI: 0.56-0.73), respectively. Meta-regression of total breastfeeding duration indicated an increasing linear trend of risk reduction of ovarian cancer with the increasing total breastfeeding duration ($p = 0.00$). Breastfeeding was inversely associated with the risk of ovarian cancer, especially long-term breastfeeding duration that demonstrated a stronger protective effect.

Keywords: Breastfeeding - ovarian cancer - risk reduction - meta-analysis

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Introduction

Breastfeeding is the most common method by which mothers provide nutrition to newborn infants. Based on the latest National Immunization Survey data in 2012, the overall rate of initiation of breastfeeding in the United States is 76.9% (CDC). The most significant effect of breastfeeding on maternal health is the reduced risk of developing breast cancer (Bernier et al., 2000; Collaborative Group on Hormonal Factors in Breast, 2002; do Carmo Franca-Botelho et al., 2012). Studies of the overall effect of breastfeeding on maternal outcomes also suggest that breastfeeding decreases the risk of developing hypertension, hyperlipidemia, cardiovascular disease and diabetes (Schwarz et al., 2009). Infant could also benefit from long-term breastfeeding, e.g. prevention of Childhood Hodgkin Lymphoma (Wang et al., 2013).

Ovarian cancer is the sixth most common cancer and the seventh-leading cause of cancer-related deaths among women. The prognosis for ovarian cancer is poor, with a 5-year survival rate of less than 45% (Jemal et al., 2011), and the causes of the disease are not understood. There are several hypotheses regarding the etiology of ovarian cancer, including the ''incessant ovulation'' hypothesis (Fathalla, 1971), the gonadotropin hypothesis (Stadel, 1975), the retrograde transportation hypothesis (Cramer and Xu, 1995) and apoptosis (Adami et al., 1994; Risch, 1998). A protective effect of breastfeeding on ovarian cancer risk may be linked to all of these hypotheses, as proposed by McNeilly AS (McNeilly, 2001).

However, findings from studies that examined the association between breastfeeding and ovarian cancer risk are inconsistent (Cramer et al., 1983; Risch et al., 1983; CSHS, 1987; Harlow et al., 1988; Mori et al., 1988; Booth et al., 1989; Hartge et al., 1989; Gwinn et al., 1990; Chen et al., 1992; Whittemore et al., 1992; Rosenblatt and Thomas, 1993; Risch et al., 1994; Purdie et al., 1995; Mink et al., 1996; Siskind et al., 1997; Hirose et al., 1999; Salazar-Martinez et al., 1999; Greggi et al., 2000; Ness et al., 2000; Modugno et al., 2001; Titus-Ernstoff et al., 2001; Riman et al., 2002; Tung et al., 2003; Yen et al., 2003; Mills et al., 2004; Rossing et al., 2004; Zhang et al., 2004; Zhang et al., 2004; Chiaffarino et al., 2005; Gronwald et al., 2006; Huusom et al., 2006; Danforth et al., 2007;

*[1]Department of Epidemiology, School of Public Health, Harbin Medical University, [2]The Third Affiliated Hospital, Harbin Medical University, [3]Heilongjiang Entry-Exit Inspection and Quarantine Bureau, Harbin, China [&]Equal contributors *For correspondence: liuyupeng@ems.hrbmu.edu.cn, zhao_yashuang@263.net*

Jordan et al., 2007; Jordan et al., 2007; McLaughlin et al., 2007; Antoniou et al., 2009; Moorman et al., 2009; Jordan et al., 2010; Titus-Ernstoff et al., 2010; Permuth-Wey et al., 2011; Tsilidis et al., 2011; Jordan et al., 2012; Kurta et al., 2012; Le et al., 2012; Pieta et al., 2012; Weiderpass et al., 2012; Wilailak et al., 2012; Su et al., 2013). Some studies indicate that breastfeeding lowers risk of developing ovarian cancer (Risch et al., 1983; CSHS, 1987; Harlow et al., 1988; Gwinn et al., 1990; Whittemore et al., 1992; Siskind et al., 1997; Salazar-Martinez et al., 1999; Greggi et al., 2000; Modugno et al., 2001; Tung et al., 2003; Mills et al., 2004; Rossing et al., 2004; Zhang et al., 2004; Huusom et al., 2006; McLaughlin et al., 2007; Moorman et al., 2009; Jordan et al., 2010; Titus-Ernstoff et al., 2010; Permuth-Wey et al., 2011; Jordan et al., 2012; Kurta et al., 2012; Pieta et al., 2012; Wilailak et al., 2012; Su et al., 2013), while many other studies observed no associations between breastfeeding and ovarian cancer risk (Mori et al., 1988; Booth et al., 1989; Chen et al., 1992; Rosenblatt and Thomas;1993; Mink et al., 1996; Hirose et al., 1999; Riman et al., 2002; Yen et al., 2003; Chiaffarino et al., 2005; Gronwald et al., 2006; Danforth et al., 2007; Antoniou et al., 2009; Tsilidis et al., 2011; Le et al., 2012; Weiderpass et al., 2012). A pooled analysis with 12 US-based case-control studies and a meta-analysis with 9 case-control studies among developed countries (excluding Japan) were published in 1992 and 2009, respectively (Whittemore et al., 1992, Ip et al., 2009). The results of the association between breastfeeding and ovarian cancer risk only based on a small part of published studies in both of the two previous published meta-analyses. The results of the association between breastfeeding and ovarian cancer risk in these analyses are based on a small subset of data previously published in two meta-analyses. Excluded in these results are 7 case-control studies which are newly published from developed countries since 2009 with inconsistent results and 7 studies that were conducted in developing countries. In addition, 5 cohort studies published from 1996 to 2012 examining the association between breastfeeding and the risk of ovarian cancer were not included in the previously published meta-analysis. Therefore, we conducted a systematic review and meta-analysis of the literature to update the current knowledge of the association between breastfeeding and ovarian cancer risk. This study includes both case-control study and cohort study, and also analyzes the dose-response relationship between breastfeeding duration and ovarian cancer risk.

Materials and Methods

Search strategy

We conducted the meta-analysis according to the Meta-analysis of Observational Studies in Epidemiology (Stroup et al., 2000). A systematic search of published studies was performed in PUBMED and EMBASE through March 2013. We used the following search terms: (Ovarian) and (cancer or malignant or tumor) and (Breastfeeding or breastfed or lactation). In addition, the reference lists of retrieved articles were thereafter hand-searched to identify additional studies.

Eligibility criteria

Studies were included in the meta-analysis if they met the following criteria: observational studies (case-control studies or cohort study) that assessed the association between breastfeeding (exposures) and the risk of ovarian cancer (outcomes), were published in the English language, and reported effect estimates of relative risk (RR) or odds ratio (OR) with 95% confidence intervals (CIs) or reported sufficient information to calculate these values. If data were duplicated among studies, the most recent or complete publications were included.

Data extraction

Data extraction was conducted independently by two authors (DaPeng Li and ZuoMing Zhang), and discrepancies were resolved by consensus. The following data were extracted from each retrieved article: name of the first author, publication year, country, mean age or age range of study subjects, methods of breastfeeding assessment, sample size (cases and controls or cohort size), study period or follow-up time, the fully adjusted RRs or ORs with 95%CIs, and confounding factors that were adjusted for individual studies. If available, both the total breastfeeding duration and average breastfeeding duration from each study were also extracted. Breastfeeding duration reported in years was converted into months for this analysis. The study quality was assessed independently by two authors using the 9-star Newcastle-Ottawa Scale (NOS) (Stang, 2010).

Statistical analysis

All of the meta-analytic estimates were derived using random-effect models. The maximally adjusted RRs or ORs with 95%CIs of each study, which compared women who have breastfed with those who have never breastfed, were used to determine the principal outcome. Maximally adjusted RR or OR estimates for the outcome of epithelial ovarian cancer patients and for the participation of parous women only were also collected. One study did not provide the required risk estimates for analysis or separate the risk estimates for different categories of the breastfeeding duration. We therefore combined the risk estimates in this study into a single required category and then calculated a study-specific effect size with the fixed effect model (Dong et al., 2011).

To assess whether increased duration of breastfeeding could lead to a further decrease in risk of ovarian cancer in later life, we categorized total breastfeeding duration as>6 months, 6-12 months, >12 months and>24 months as included by most of the studies reported. We then plotted the meta-regression analysis between the correlated logarithm of RR or OR estimates with total breastfeeding duration and average breastfeeding duration based on the random-effect method. In the meta-regression analysis, the breastfeeding duration associated with each risk estimate was computed as the midpoint of each category, and the open-ended upper category was defined as 1.2 times its lower bound (Berlin et al., 1993). For example, if the breastfeeding duration was categorized as 0-4 months, 5-18 months, 19-48 months and >48 months, values of 2, 11.5, 33.5 and 57.6 months were assigned, respectively.

We performed a sensitivity analysis by removing a study that had the most weight in the analysis to evaluate whether the pooled results were affected markedly. In addition, we also repeated the analysis using fixed-effect models. We further conducted subgroup analyses according to study design (cohort studies and case-control studies), type of controls (population-based and hospital-based), study quality score (higher-quality and lower-quality), sample size (≥1500 and <1500) and study population (North American, European, Asian and Australian) to explore the potential sources of the heterogeneity between studies. We also conducted a cumulative analysis by publication year. Statistical heterogeneity between studies was evaluated by using the Q and I^2 statistics. Publication bias was evaluated with the use of a funnel plot for asymmetry and was further examined quantitatively using the Begg's rank correlation and Egger's linear regression tests. In this meta-analysis, all statistical analyses were performed with the Comprehensive Meta Analysis v.2.0 (Biostat, Englewood, NJ, USA). For all comparisons, a two-tailed P value of less than 0.05 was considered statistically significant.

Results

Literature search

The results of the literature search are shown in Figure 1. We retrieved 375 articles from PUBMED and 138 articles using EMBASE for our preliminary search. After screening titles and abstracts, 48 articles were considered potentially eligible and were retrieved in full text (Cramer et al., 1983; Risch et al., 1983; CSHS, 1987; Harlow et al., 1988; Mori et al., 1988; Booth et al., 1989; Hartge et al., 1989; Gwinn et al., 1990; Chen et al., 1992; Whittemore et al., 1992; Rosenblatt and Thomas, 1993; Risch et al., 1994; Purdie et al., 1995; Mink et al., 1996; Siskind et al., 1997; Hirose et al., 1999; Salazar-Martinez et al., 1999; Greggi et al., 2000; Ness et al., 2000; Modugno et al., 2001; Titus-Ernstoff et al., 2001; Riman et al., 2002; Tung et al., 2003; Yen et al., 2003; Mills et al., 2004; Rossing et al., 2004; Zhang et al., 2004; Zhang et al., 2004; Chiaffarino et al., 2005; Gronwald et al., 2006; Huusom et al., 2006; Danforth et al., 2007; Jordan et al., 2007; Jordan et al., 2007; McLaughlin et al., 2007; Antoniou et al., 2009; Moorman et al., 2009; Jordan et al., 2010; Titus-Ernstoff et al., 2010; Permuth-Wey et al., 2011; Tsilidis et al., 2011; Jordan et al., 2012; Kurta et al., 2012; Le et al., 2012; Pieta et al., 2012; Weiderpass et al., 2012; Wilailak et al., 2012; Su et al., 2013). A pooled analysis with 12 US-based case-control studies was included as two studies: a hospital-based study and a population-based study. Nine duplicates were excluded (Cramer et al., 1983; Hartge et al., 1989; Risch et al., 1994; Purdie et al., 1995; Ness et al., 2000; Titus-Ernstoff et al., 2001; Zhang et al., 2004; Jordan et al., 2007; Jordan et al., 2007). Finally, the 40 remaining articles were included in this systematic review.

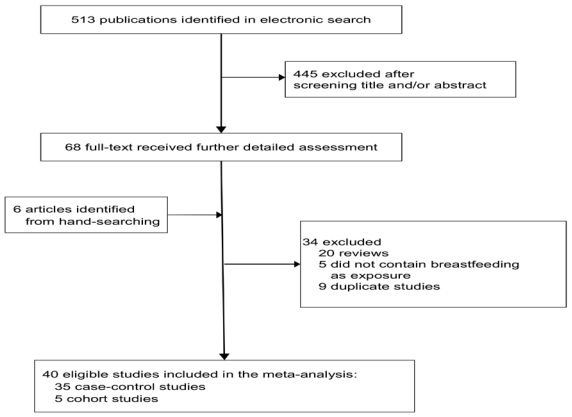

Figure 1. Selection of Studies for Inclusion in Meta-Analysis

Characteristics of the included studies

The characteristics of the included 35 case-control studies and 5 cohort studies are shown in Table 1 and Table 2, respectively. Overall, this meta-analysis included 17139 women with ovarian cancer and 398810 women without ovarian cancer. The age range of participants was from 15 to 79 years. The 40 included studies were published between 1983 and 2013. Nineteen studies were conducted in the North America, 10 in Asia, 9 in Europe and 2 in Australia. The participants of 26 studies were selected from parous women only and the data for parous women was only separated among 6 studies. The outcome was ovarian cancer as confirmed by histology in 33 studies..

Breastfeeding and ovarian cancer risk

The results from the random-effect meta-analysis of the relationship between breastfeeding and the risk of ovarian cancer are shown in Figure 2. Overall, women who have breastfed showed statistically significant reduction of ovarian cancer risk by 30% compared to women that had never breastfed (pooled RR=0.70, 95%CI: 0.64-0.76; p=0.00).

When participants were restricted to parous women, we found a slightly attenuated but still statistically significant risk reduction (pooled RR=0.76, 95%CI: 0.69-0.83; p=0.00; Table 3) from 32 included studies involving 12765 cases.

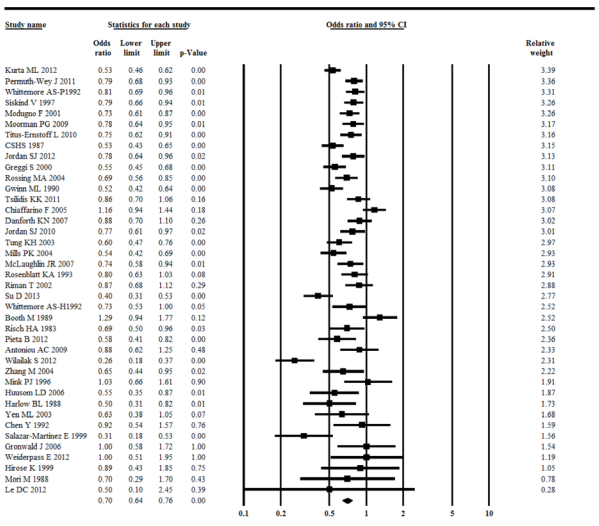

Figure 2. Summary Relative Risks (RRs) of Breastfeeding and Ovarian Cancer Risk. Test for heterogeneity: Q=164.47; p=0.00; I^2=76.29%; *The studies are ordered based on their relative weight in the random-effect model

Table 1. Characteristics of Included Case-control Studies on Breastfeeding and Ovarian Cancer

Study/year	Country	Time	No. cases/ controls	Age, yr Mean/range	Type of participant[d]	Duration of breastfeeding	Breastfeeding assessment[e]	Outcome[f]	Study quality
Hospital-based									
Su D 2013	China	2006-2008	493/472	≤75	P	≤10, 11-20, 21-30, ≥31 months	Questionnaire	EOC	7
Pięta B 2012	Poland	2007-2011	202/1144	NA b	P&N	<1 and ≥6 months	Questionnaire	OC	4
Wilailak S 2012	Thailand	2006-2008	311/772	20-70	P&N	Never and ever	Questionnaire	EOC	6
Gronwald J 2006	Poland	1998-	150/150	25-71	P&N	Never, ≤12, and >12months	Self-report	OC with BRCA1	5
Chiaffarino F 2005	Italy	1992-1999	1028/2390	17-79	P&N	Never,1-4, 5-8, 9-16 , and ≥17 months	Questionnaire	EOC	7
Zhang M 2004	China	1999-2000	275/623	< 75	P	0-4, 5-12, and >12 months	Questionnaire	EOC	5
Yen ML 2003	China	1993-1998	86/369	20-75	P&N	Never, ≤12 and >12 months	Questionnaire	invasive EOC	7
Greggi S 2000	Italy	1988-1998	330/721	13-80	P&N	Never, ≤12 and > 12 months	Questionnaire	EOC	7
Salazar-Martinez E 1999	Mexico	1995–1997	84/668	54.4 c	P&N	Never, 1-12, 13-24, and ≥25 months	Questionnaire	EOC	6
Hirose K 1999	Japan	1988-1995	83/20324	> 30	P	Never and ever	Self-report	EOC	5
Rosenblatt KA 1993	7 countries a	1979-1988	293/2565	≥15	P	0-4, 5-18, 19-48, and >48 months	Questionnaire	EOC	5
Whittemore AS-H 1992	USA	1956-1986	201/1081	NA	P	Never,1-5, 6-11, 12-23 , and ≥24 months	Questionnaire	invasive EOC	NA
Booth M 1989	UK	1978-1983	169/362	20-64	P	Never, ≤6, 7-12, 13-18, 19-24, and ≥25months	Questionnaire	EOC	6
Mori M 1988	Japan	1980-1981/1984-1985	90/205	51 c	P	Never and ever	Questionnaire	EOC	4
CSHS 1987	USA	1980-1982	489/4191	20-54	P&N	Never and ever	Questionnaire	EOC	5
Population-based									
Le DC 2012	Vietnam	2001-2006	225/714	< 59	P	Never and ever	Questionnaire	OC	6
Kurta ML 2012	USA	2003-2008	902/1802	≥25	P&N	Never, <6, 6-<12, and ≥12 months	Questionnaire	EOC	5
Jordan SJ 2012	USA	2002-2007	881/1345	35–74	P	Never, <3 , 3-<6, 6-< 12, 12-< 18, and ≥18 months	Questionnaire	EOC	7
Permuth-Wey J 2011	Canada and USA	1995-2011	1244/1348	18-80	P&N	Never and ever	Questionnaire	EOC	4
Titus-Ernstoff L 2010	USA	1992-2004	828/1006	53.4 c	P	Never and ever	Questionnaire	OC	6
Jordan SJ 2010	Australia	2002-2005	1092/1228	18-79	P	Never, 1-6 , 7-18, 19-30 , 31-42 and >42 months	Self-report	EOC	6
Moorman PG 2009	USA	1999-2008	857/1057	20-74	P&N	Never and ever	Questionnaire	EOC	6
McLaughlin JR 2007	10 countries	1994-2006	798/2423	24-75	P&N	Never, ≤12 and >12 months	Questionnaire/ telephone/self-report	OC with BRCA1 and BRCA2	6
Huusom LD 2006	Denmark	1995-1999	163/1416	35-79	P	Never,1-5, 6-11, 12-24, and ≥42 months	Questionnaire/telephone	BOT	6
Mills PK 2004	USA	2000-2001	203/1013	≥18	P	Never, <6, 6-11, 12-23,and ≥24 months.	Telephone interviews	EOC	6
Rossing MA 2004	USA	1994-1998	268/1284	35-54	P	Never, <6, 6-12, >12 moths	Questionnaire	OC	7
Tung KH 2003	USA	1993-1999	558/607	≥18	P&N	Never, ≤ 5, 6-16, and >16 months	Self-report	EOC	6
Riman T 2002	Sweden	1993-1995	459/2637	50-74	P	< 1, 1-5, 6-11, and≥12 months.	Self-report/telephone	EOC	5
Modugno F 2001	USA	1994-1998	531/1191	20-69	P	Never, < 1, 1-6 ,7-12, 13-<24 and ≥24 months	Questionnaire	invasive EOC	6
Siskind V 1997	Australia	1990-1993	618/724	18-79	P	Never,1-6, 7-12, 13-24 , 25-36, and >36 months	Questionnaire	EOC	7
Chen Y 1992	China	1984-1986	112/224	48.8 c	P&N	0,< 12, 12-24, 25-36, >36 months	Questionnaire	EOC	7
Whittemore AS-P 1992	USA	1956-1986	870/4734	NA	P	Never,1-5, 6-11, 12-23 , and ≥24 months	Questionnaire	invasive EOC	NA
Gwinn ML 1990	USA	1980-1982	436/3833	20-54	P&N	Never, 1-2, 3-5, 6-11, 12-23 and ≥24 months	Questionnaire	EOC	4
Harlow BL 1988	USA	1980-1985	84/125	20-79	P	<1, 1-2, 3-9, and >9 months	Questionnaire	BOT	6
Risch HA 1983	USA	1975-1979	284/705	20-74	P&N	0-2 and ≥3 months	Questionnaire	EOC	5

[a]7 countries include Australia, Chile, China, Israel, Mexico, the Philippines, and Thailand; [b]NA= not available; [c]Value expressed as mean; [d]P= parous women, P&N= parous women and nulliparous women; [e]Questionnaire= face-to-face interviews of participants, Self-report= self-administered questionnaire; [f]OC= ovarian cancer, EOC= epithelial ovarian cancer, BOT= borderline ovarian tumor

Table 2. Characteristics of Included Cohort Studies on Breastfeeding and Ovarian Cancer

Study/year	Country	Study population	Time of follow-up	No. cases/ sample size	Age at baseline	Type of participant d	Duration of breastfeeding	Breastfeeding assessment	Outcome	Study quality
Weiderpass E 2012	Japan	JPHC	1990-2008	80/42844	40-69	P	Never and ever	Self-report	EOC	7
Tsilidis KK 2011	10 European countries a	EPIC	1992-2006	658/243297	55 c	P	1, 2-6, 7-12, and≥ 13 months	Questionnaire	EOC	7
Danforth KN 2007	USA	NHS and NHS II	1976-2002(NHS) 1989-2003(NHS II)	391/14693	30-55(NHS) 25-42(NHS II)	P	Never, 1-6, 7-11, 12-17, and > 17months.	Self-report	EOC	7
Antoniou AC 2009	3 European countries b	IBCCS	1997-2005	234/2605	46.5 c	P	Never, 1-5, 6-12, 1 3-24, and >24 months	Questionnaire/ telephone/self-report	OC with BRCA1 and BRCA2	6
Mink PJ 1996	USA	the Lowa women's health cohort study	1986-1992	79/31396	55-69	P	Never and ever	Self-report	EOC	7

[a]10 countries include Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom; [b]3 European countries include United Kingdom and Eire, the Netherlands, and France; [c]Value expressed as mean; [d]P= parous women, P&N= parous women and nulliparous women

Table 3. Subgroup Analyses and Publish Bias

Subgroup	No. of analyses	RR (95%CI)	*p* value	Heterogeneity		Publish bias (*p* value)	
				p value	I^2 (%)	For Begg's rank correlation test	For Egger's linear correlation test
Overall analysis	40	0.70 (0.64-0.76)	0	0	76.29	0.38	0.75
Parous women only	32	0.76(0.69-0.83)	0	0	75.59	0.69	0.65
Total breastfeeding duration							
< 6 months	16	0.85(0.77-0.93)	0	0.06	38.25	0.34	0.56
6-12 months	15	0.73(0.65-0.82)	0	0.16	26.72	1	0.3
>12 months	20	0.64(0.56-0.73)	0	0	61.87	0.42	0.31
> 24 months	10	0.60(0.42-0.86)	0	< 0.01	64.3	1	0.74
Average breastfeeding duration							
< 6 months	6	0.78(0.71-0.86)	0	0.99	0	0.26	0.14
6-12 months	5	0.69(0.58-0.84)	0	0.29	0	0.46	0.2
> 12 months	5	0.63(0.50-0.78)	0	0.99	0	0.81	0.5
EOC a	33	0.68(0.61-0.76)	0	0	79.5	0.36	0.74
Study design							
Cohort studies	5	0.89(0.78-1.01)	0.08	0.96	0	0.09	0.08
Case–control studies	35	0.67(0.61-0.74)	0	0	77.4	0.21	0.48
Hospital based	15	0.64(0.51-0.80)	0	0	86.39	0.92	0.81
Population based	20	0.70(0.64-0.76)	0	0	57.86	0.13	0.66
Study population							
North American	19	0.68(0.61-0.74)	0	0	69.53	0.18	0.51
Asian	10	0.62(0.45-0.84)	0	0	75.58	0.86	0.58
European	9	0.83(0.67-1.02)	0.08	0	79.69	0.92	0.96
Australian	2	0.78(0.68-0.90)	0	0.88	0	-	-
Study quality							
Higher-quality studies	26	0.70(0.62-0.79)	0	0	79.59	0.54	0.44
Lower-quality studies	12	0.67(0.58-0.76)	0	0	67.06	0.73	0.53
Sample size							
<1500	19	0.62(0.53-0.73)	0	0	78.18	0.94	0.68
>1500	21	0.75(0.68-0.83)	0	0	71.76	0.38	0.28
Adjustment for parity							
Yes	26	0.70 (0.63-0.79)	0	0	78.56	0.35	0.22
No	14	0.68(0.59-0.77)	0	0	68.02	0.83	0.46
Cancer grading							
Invasive	7	0.70(0.61-0.82)	0	0.01	63.78	0.76	0.71
Borderline	5	0.58(0.48-0.70)	0	0.7	0	1	0.2
Cancer histotype							
Serous	9	0.67(0.51-0.87)	0	0	86.28	0.35	0.78
Mucinous	9	0.76(0.64-0.90)	0	0.89	0	0.47	0.51
Endometrioid/clear cell	7	0.60(0.50-0.72)	0	0.21	28.93	0.23	0.33

[a]EOC=epithelial ovarian cancer

Breastfeeding duration and the risk of ovarian cancer

For total breastfeeding duration, the pooled RRs in the<6 months, 6-12 months and>12 months of breastfeeding subgroups were 0.85 (95%CI: 0.77-0.93), 0.73 (95%CI: 0.65-0.82) and 0.64 (95%CI: 0.56-0.73), respectively (Figure 3). We further noted a strong inverse association (pooled RR=0.60, 95%CI: 0.42-0.86) in the subgroup including women that breastfed for >24 months (Table 3). We found similar inverse associations between breastfeeding and reduced risk of developing ovarian cancer in subgroups including average breastfeeding duration of<6 months, 6-12 months and>12 months compared to those who had never breastfed (Figure 3).

Meta-regression analysis indicated an increasing linear trend of reduced ovarian cancer risk with increased breastfeeding duration for both total breastfeeding duration (p=0.00; Figure 3) and average breastfeeding duration (p<0.01; Figure 3).

Subgroup analyses and cumulative analysis

Results varied among differently designed studies. In case-control studies, the pooled RR was 0.67 (95%CI: 0.61-0.74; Table 3), and the protective effects were consistently observed in both population-based (pooled RR=0.70, 95%CI: 0.64-0.76) and hospital-based case-control studies (pooled RR=0.64, 95%CI: 0.51-0.80). However, in cohort studies, a weaker but borderline significant effect of breastfeeding on ovarian cancer risk was found (pooled RR=0.89, 95%CI: 0.78-1.01). The effects of breastfeeding

on ovarian cancer risk were different among studies performed in North American, European, Asian and Australian. In North American (pooled RR=0.68, 95%CI: 0.61-0.74), Asian (pooled RR=0.62, 95%CI: 0.45-0.84) and Australian (pooled RR=0.78, 95%CI: 0.68-0.90), breastfeeding significantly decreased the ovarian cancer risk for women who had breastfed for any length of time, while breastfeeding was associated with a borderline significant risk reduction of ovarian cancer in Europe (pooled RR=0.83, 95%CI: 0.67-1.02).

Thirty-three studies used epithelial ovarian cancer as the only outcome, and a significant decrease in the risk of epithelial ovarian cancer was observed (pooled RR=0.68, 95%CI: 0.61-0.76; p=0.00; Table 3). Subgroup analysis by cancer histotypes revealed that there were also inverse associations for serous (pooled RR=0.67, 95%CI: 0.51-0.87), mucinous (pooled RR=0.76, 95%CI: 0.64-0.90) and endometrioid/clear cell (pooled RR=0.60, 95%CI: 0.50-0. 72) cancers (Table 3). Separate risk estimates were used for different grades of cancers. The risk estimates for invasive and borderline ovarian cancer were 0.70 (95%CI: 0.61-0.82; Table 3) and 0.58 (95%CI: 0.48-0.70; Table 3), respectively.

The cumulative analysis by publication year showed that the pooled results trend toward an inverse significant association with an increasing number of studies in overall results, cohort studies and case-control studies .

Heterogeneity and meta-regression analysis

There was significant heterogeneity among 40 studies of the association between breastfeeding and the risk of ovarian cancer (p=0.00; I^2=77.40%). To explore the sources of the observed heterogeneity among studies, we conducted subgroup analyses by study design, sample size and study quality score, and performed meta-regression analysis according to publication year, sample size and study quality score. Significant heterogeneity remained among the case-control studies (p=0.00; I^2=77.40; Table 3) but not among the cohort studies (p=0.97; I^2=0.00%; Table 3). Therefore, heterogeneity was unlikely to be associated with sample size, study quality score and publication year (Table 3).

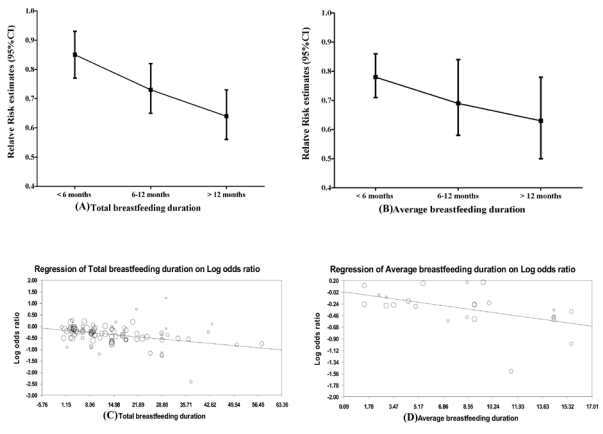

Figure 3. Stratified Analysis of (A) Total Breastfeeding Duration (months) and (B) Average Breastfeeding Duration (months) in Relation to Ovarian Cancer and Meta-Regression Analysis by (C) Total Breastfeeding Duration (months) and (D) Average Breastfeeding Duration (months) and Risk of Ovarian Cancer. The meta-regression analysis between (C) total breastfeeding duration with Log Relative Ratios (RRs) in 29 studies, p value for meta-regression=0.00, (D) average breastfeeding duration with Log Relative Ratios (RRs) in 8 studies, p value for meta-regression < 0.01

Sensitivity analyses and publication bias

The summarized estimates were consistent when the analysis was repeated using fixed-effect models. Omitting a single study that had the most relative weight and then recalculating the pooled effect estimates showed that none of the individual studies substantially influenced the pooled results for any of the outcomes. We found no evidence of publication bias by using funnel plots, Begg's rank correlation test or Egger's regression test (Table 3).

Discussion

The present systematic review and meta-analysis indicated that breastfeeding was associated with a significant risk reduction of ovarian cancer in women who had breastfed compared to those who did not. A significant decrease in the risk of epithelial ovarian cancer was also observed. For parous women, the risk of ovarian cancer was slightly attenuated but still significant. From stratified and meta-regression analyses according to breastfeeding duration, the protective effect of breastfeeding increases with breastfeeding duration.

There are a number of physiological mechanisms that may account for the protective effect of breastfeeding against ovarian cancer. Breastfeeding suppresses ovulation and causes suppression of gonadotrophins, resulting in depressed production of plasma estradiol anovulation and lactation amenorrhea (LAM) (McNeilly, 2001, Riman et al., 2004). In the absence of breastfeeding, ovulation normally resumes within six weeks postpartum but can be suppressed for several months in women who are breastfeeding (McNeilly, 2001). Breastfeeding was expected to lower the ovarian cancer risk during the suppression of ovulatory cycles (Short et al., 1991, McNeilly, 2001). Chemosignals present in human milk modulate ovarian cycle length (Jacob et al., 2004). However, ovulation will resume upon supplementary feeding and reduce the intensity of breastfeeding (Short et al., 1991; Li and Qiu, 2007). Breastfeeding also reduced the levels of gonadotropins, especially luteinizing hormone (McNeilly, 2001), which are considered to be a potential causal mechanism of ovarian cancer when present at high levels (Stadel, 1975).

Our results are similar to those presented in the pooled analysis with 12 US case-control studies and the meta-analysis with 9 case-control studies in developed countries (Whittemore et al., 1992). A recent meta-analysis was published in 2013 and also showed an inverse association between breastfeeding and ovarian cancer risk (Luan et al., 2013).

In a stratified analysis of total breastfeeding duration, we noted that breastfeeding has a significant protective effect even for women who have breastfed for a short duration (< 6 months). However, the risk of ovarian cancer

was significantly decreased ($p<0.01$) in women who breastfed>12 months over women who breastfed for<6 months and 6-12 months. The meta-regression analysis also revealed a linear decrease in risk with an increase in the total breastfeeding duration. A weak but significant reduction of ovarian cancer risk was observed in parous women only and increased with total breastfeeding duration (meta-regression analysis for parous women only not shown). The average breastfeeding duration can better reflect the duration of LAM. The results from the analysis of subgroups defined by the average breastfeeding duration also indicated that an increased average duration of breastfeeding resulted in a lower risk of ovarian cancer. Consistently, the meta-regression analysis between average breastfeeding duration and ovarian cancer risk showed a statistically significant decrease. According to the pooled analysis of 12 case-control studies, breastfeeding within the initial months after delivery has stronger protective effects on ovarian cancer risk than breastfeeding at later time periods. For example, breastfeeding for 6 months post-delivery reduces risk more than does a month of subsequent breastfeeding (Whittemore et al., 1992). However, we found that women who breastfed for ≥12 months were at a lower risk for ovarian cancer than those who breastfed for<6 months and 6-12 months. The current WHO guidelines recommend exclusive breastfeeding for a minimum of 6 months up to the first 2 years of life for each infant (Section on, 2012). Our findings that women benefit from an average breastfeeding duration up to 12 months and beyond are supported by this WHO recommendation.

When analyzing the case-control study and cohort study separately, we found a significant inverse association between breastfeeding and the risk of ovarian cancer in the case-control studies (both population-based and hospital-based), but this association was a borderline significant risk reduction in the cohort studies. While this discrepancy is difficult to explain, it should be noted that, in all 5 of the cohort studies, questionnaires were only collected once at baseline to assess breastfeeding. Therefore, the possibilities for young women planning to breastfeed after giving birth may lead to an underestimated number of women who breastfeed and may also underestimate the protective effect of breastfeeding (Danforth et al., 2007; Antoniou et al., 2009; Weiderpass et al., 2012). In addition, older participants may have more recall bias (Mink et al., 1996; Tsilidis et al., 2011). The cumulative analysis by publication year in cohort studies suggested an inverse significant association with the increasing numbers of studies in pooled results. Additional prospective studies are needed to quantify the association between breastfeeding and ovarian cancer risk.

We found a significant reduction in the risk of ovarian cancer in Asian populations, an attenuated risk reduction in American and Australian populations and a borderline significant risk reduction in Europeans. Based on the GLOBOCAN 2008 database, the highest incidences of ovarian cancer were reported in Europe and North America (Canada and USA), while lower incidences were reported in Asia (Ferlay J). Although data on breastfeeding rates in Europe were not available, the breastfeeding pattern in Europe might be reflected by the results of the European Prospective Investigation into Cancer and Nutrition (EPIC) in 10 European countries, which reported that the cumulative duration of breastfeeding was relatively short (the mean duration was 6 months; 95%CI: 3-13 months) (Tsilidis et al., 2011). It is therefore not surprising that a borderline significant reduction in ovarian cancer risk was observed in Europe, given that short-term breastfeeding was expected to have a weak protective effect on ovarian cancer risk.

Two potential confounders, which may influence the summary results for the protective effects of breastfeeding on ovarian cancer risk, should be discussed. Childbirth is a known protective factor for the ovarian cancer risk, and women breastfeed only after experiencing childbirth. However, 12 studies included in the analysis reported the association for both parous women and nulliparous women. To minimize the possibility that our results were influenced by childbirth, we restricted the participants to parous women only and found a slightly attenuated but significant reduction in the risk of ovarian cancer. This result confirmed the finding from a previous pooled analysis of 12 case-control studies in 1992, which also found a significant inverse association between breastfeeding and the risk of ovarian cancer for parous women (Whittemore et al., 1992).

The total breastfeeding duration increases with parity, which is closely related to the decreased risk of ovarian cancer (Whittemore et al., 1992). To illustrate the influence of parity on decreased ovarian cancer risk due to breastfeeding, we conducted a repetition analysis restricted to 26 studies in which parity adjusted or controlled and found a similar significant protective effect (pooled RR=0.70, 95%CI: 0.63-0.79; Table 3). We also conducted a meta-regression analysis based on the average parity in the included studies and found that the magnitudes of reduced risk of ovarian cancer increased along with the increasing average parity, but this trend was not statistically significant ($p=0.23$). Taken together, the findings from both subgroup analysis and meta-regression analysis indicated that parity might not substantially influence the summarized results. In other words, the protective effect of breastfeeding from ovarian cancer is likely to be independent of parity.

Our analysis reviewed all available studies, and the large number of ovarian cancer cases allowed for the investigation of the risk associated with different categories of breastfeeding duration. Moreover, we carried out meta-regression analysis between breastfeeding duration and the ovarian cancer risk. There were some limitations in our meta-analysis. First, as there are inherent practical and ethical challenges to carry out a randomized intervention study, the current findings are all based on observational epidemiological studies, which are likely to have biases. However, the participants enrolled in the included case-control studies, all of which were population-based case-control studies, were all newly diagnosed ovarian cancer patients, and the included cohort studies have a relatively large sample size (from 2605 to 243297). All of these factors could have partly eliminated the selection bias or recall bias. Second, some residual

confounders may not be ruled out and may influence the protective effect of breastfeeding, although a large number of potential confounding factors, such as age, race, use of oral contraceptives and especially parity, have been adjusted for in most of the included studies. Third, the classification and measurement methods of breastfeeding varied across the included studies. The total duration of breastfeeding was classified into only two levels in two cohort and ten case-control studies; the reported interval values of total breastfeeding duration were usually 6 or 12 months, and only one study reported the category of more than 48 months (Rosenblatt and Thomas, 1993). Therefore, we cannot evaluate the long-term effect in terms of total breastfeeding duration.

In conclusion, the findings from our meta-analysis suggested that women who had breastfed for any amount of time benefited from a decreased risk of ovarian cancer by 30% compared to women who did not breastfeed. Furthermore, the protective effect of breastfeeding from ovarian cancer occurs in a duration-dependent manner. Women having breastfed for a longer duration were likely to have stronger protective benefits. Therefore, women should be encouraged to breastfeed, and awareness may increase the number of women who choose to breastfeed.

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