

Breastfeeding and Endometrial Cancer Risk

An Analysis From the Epidemiology of Endometrial Cancer Consortium

Susan J. Jordan, MBBS, PhD, Renhua Na, PhD, Sharon E. Johnatty, PhD, Lauren A. Wise, PhD, Hans Olov Adami, MD, PhD, Louise A. Brinton, PhD, MPH, Chu Chen, PhD, Linda S. Cook, PhD, Luigino Dal Maso, PhD, Immacolata De Vivo, PhD, MPH, Jo L. Freudenheim, PhD, MS, Christine M. Friedenreich, PhD, MSc, Carlo La Vecchia, MD, MSc, Susan E. McCann, PhD, RD, Kirsten B. Moysich, PhD, MS, Lingeng Lu, PhD, MD, Sara H. Olson, PhD, Julie R. Palmer, ScD, MPH, Stacey Petruzella, MPH, Malcolm C. Pike, PhD, Timothy R. Rebbeck, PhD, Fulvio Ricceri, PhD, Harvey A. Risch, MD, PhD, Carlotta Sacerdote, PhD, Veronica Wendy Setiawan, PhD, Todd R. Sponholtz, PhD, Xiao Ou Shu, MD, PhD, Amanda B. Spurdle, PhD, Elisabete Weiderpass, MD, PhD, Nicolas Wentzensen, MD, PhD, Hannah P. Yang, ScM, PhD, Herbert Yu, MD, PhD, and Penelope M. Webb, MA, DPhil

OBJECTIVE: To investigate the association between breastfeeding and endometrial cancer risk using pooled data from 17 studies participating in the Epidemiology of Endometrial Cancer Consortium.

METHODS: We conducted a meta-analysis with individual-level data from three cohort and 14 case-control studies.

Study-specific odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for the association between breastfeeding and risk of endometrial cancer using multivariable logistic regression and pooled using random-effects meta-analysis. We investigated between-study heterogeneity with I^2 and Q statistics and metaregression.

From the QIMR Berghofer Medical Research Institute, and the University of Queensland, School of Public Health, Brisbane, Australia; the Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts; the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; the Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; the Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington; the Department of Internal Medicine and UNM Comprehensive Cancer Center, University of New Mexico, Albuquerque, New Mexico; the Department of Cancer Epidemiology and Prevention Research, CancerControl Alberta, Alberta Health Services, Calgary, Alberta, Canada; the Unit of Cancer Epidemiology, CRO Aviano, National Cancer Institute, IRCCS, Aviano, Italy; Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; the Department of Epidemiology and Environmental Health, University at Buffalo, Buffalo, New York; the Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milano, Italy; Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, New York; Yale School of Public Health, New Haven, Connecticut; the Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York; Slone Epidemiology Center, Boston University, Boston, Massachusetts; the Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California; Harvard TH Chan School of Public Health and Dana Farber Cancer Institute, Boston, Massachusetts; the Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital and Center for Cancer Prevention (CPO), Turin, Italy; the Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Centre, Vanderbilt University School of Medicine, Nashville, Tennessee; the Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway; the Genetic Epidemiology Group, Folkhälsan Research Center, Helsinki, Finland; the Department of Community Medicine, University of Tromsø, and the Arctic University of Norway, Tromsø, Norway; and the Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii.

The Alberta Case-control Study on Endometrial Cancer was funded by The Canadian Cancer Society. C. Friedenreich received career awards from the Canadian Institutes of Health Research and the Alberta Heritage Foundation for Medical Research (AHFMR)

during the conduct of this study. L. Cook held a Canada Research Chair and also received career award funding from AHFMR. The Australian National Endometrial Cancer Study was funded by the National Health and Medical Research Council (NHMRC) of Australia (#339435) and Cancer Council Tasmania (#403031 and 457636). S. Jordan, A. Spurdle, and P. Webb are supported by fellowships from the NHMRC of Australia. The National Cancer Institute/National Institutes of Health funded The Black Women's Health Study (grant numbers: R01-CA058420, UMI-CA164974, and R03-CA169888), The Connecticut Endometrial Cancer Study (R01CA098346), The Estrogen, Diet, Genetics, and Endometrial Cancer (R01 CA83918, P30 CA008748), and The Fred Hutchinson Cancer Research Center (R35 CA39779, R01 CA47749, R01 CA75977, N01 HD 2 3166, K05 CA 92002, R01 CA105212, and R01 CA87538), The Nurses' Health Study (2R01 CA082838), The Polish Endometrial Cancer Study, U.S. Endometrial Cancer Study (in part by intramural funds), The Shanghai Endometrial Cancer Study (R01 CA092585), The USC LA case control study (R01 CA48774 and P30 CA14089), and the Women's Insight and Shared Experience (P01-CA77596). The Italian Multi Centre Study was funded by The Italian Association for Cancer Research (AIRC). C. LaVecchia was supported by the Italian Foundation for Research in Cancer. The Swedish Women's Lifestyle and Health Study was funded by The Swedish Research Council (521-2011-2955). The Turin Case Control Study: The Italian Association for Cancer Research (AIRC) and the Ricerca Finalizzata Regione Piemonte.

Each author has indicated that he or she has met the journal's requirements for authorship.

Corresponding author: Susan J. Jordan, MBBS, PhD, QIMR Berghofer MRI, Locked Bag 2000, PO Royal Brisbane Hospital, Herston 4029, Queensland, Australia; email: susan.jordan@qimrberghofer.edu.au.

Financial Disclosure

The authors did not report any potential conflicts of interest.

© 2017 by The American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0029-7844/17



RESULTS: After excluding nulliparous women, the analyses included 8,981 women with endometrial cancer and 17,241 women in a control group. Ever breastfeeding was associated with an 11% reduction in risk of endometrial cancer (pooled OR 0.89, 95% CI 0.81–0.98). Longer average duration of breastfeeding per child was associated with lower risk of endometrial cancer, although there appeared to be some leveling of this effect beyond 6–9 months. The association with ever breastfeeding was not explained by greater parity and did not vary notably by body mass index or histologic subtype (grouped as endometrioid and mucinous compared with serous and clear cell).

CONCLUSION: Our findings suggest that reducing endometrial cancer risk can be added to the list of maternal benefits associated with breastfeeding. Ongoing promotion, support, and facilitation of this safe and beneficial behavior might therefore contribute to the prevention of this increasingly common cancer.

(*Obstet Gynecol* 2017;129:1059–67)

DOI: 10.1097/AOG.0000000000002057

Endometrial cancer is the fourth most common cancer in women in high-income countries such as the United States, Canada, and Australia where collectively more than 57,000 women are diagnosed each year¹ and the incidence has been increasing over the

past 20–30 years. A better understanding of its causes and ways it could be prevented is therefore required.

Exclusive breastfeeding generally suppresses ovulation and therefore maternal estrogen levels.² Reduced estrogen levels reduce endometrial mitoses³ and might therefore reduce risk of endometrial cancer; however, clear evidence for this association is lacking. The most recent World Cancer Research Fund and American Institute for Cancer Research endometrial cancer report classified the evidence for an association with lactation as “limited–no conclusion.”⁴

Some previous studies indicate risk reduction with longer breastfeeding durations⁵; some show risk reduction only for recent breastfeeding episodes^{6,7}; and others found no association.^{8,9} So, although two meta-analyses of published data suggest risk reduction with longer total durations of breastfeeding, they were unable to account for significant heterogeneity across studies.^{10,11} They also could not investigate factors that might modify breastfeeding associations such as body mass index (BMI, calculated as weight (kg)/[height (m)]²), time since last pregnancy, or menopausal status or how the duration of individual breastfeeding episodes might influence endometrial cancer associations. We hypothesize that, because estrogen levels during lactation are lowest while ovulation is

Table 1. Characteristics of 17 Studies From the Epidemiology of Endometrial Cancer Consortium Pooled to Investigate the Association Between Breastfeeding and Endometrial Cancer Risk Among Parous Women

Study Name	Acronym	Country	Years of Recruitment or Diagnosis	Women in the Case Group (n=8,981)
Case-control studies				
Alberta Case-Control Study on Endometrial Cancer ¹⁷	ALTA	Canada	2002–2006	441
Australian National Endometrial Cancer Study ²⁷	ANECs	Australia	2005–2007	1,119
Connecticut Endometrial Cancer Study ¹⁸	CONN	United States	2004–2009	505
Estrogen, Diet, Genetics, and Endometrial Cancer ¹⁹	EDGE	United States	2001–2005	370
Fred Hutchinson Cancer Research Center ²⁵	FHCRC	United States	1994–2005	703
Italian Multi Centre Study ²⁰	IMS	Italy	1992–2006	386
Patient Epidemiologic Data System ³⁰	PEDS	United States	1982–1998	401
Polish Endometrial Cancer Study ²¹	PECS	Poland	2000–2003	447
Shanghai Endometrial Cancer Study ²²	SECS	China	1997–2004	1,089
Turin Case Control Study	TURIN	Italy	1998–2008	219
USC LA case control ²⁴	USC	United States	1987–1993	660
US Endometrial Cancer Study ⁸	USE	United States	1987–1990	316
Western New York Diet Study ²³	WNYDS	United States	1986–1991	185
Women’s Insight and Shared Experience ³¹	WISE	United States	1999–2002	512
Cohort studies				
Black Women’s Health Study ¹⁵	BWHS	United States	1995–2013	202
Nurses’ Health Study ¹⁶	NHS	United States	1986–2012	1,197
Swedish Women’s Lifestyle and Health Study ¹⁴	SWLHS	Sweden	1993–2012	229

Data are n or n (%) unless otherwise specified.

* Among women who breastfed.



suppressed, ongoing breastfeeding beyond this point might not confer additional benefit.

To more comprehensively assess the association between breastfeeding and endometrial cancer risk, we pooled data from 17 studies participating in the Epidemiology of Endometrial Cancer Consortium.¹²

MATERIALS AND METHODS

Ethical approval was obtained from each study's institutional review board. All participants provided informed consent to take part in the respective studies.

We conducted a meta-analysis with individual participant data from 17 independent studies (14 case-control, three cohort) from the Epidemiology of Endometrial Cancer Consortium (Table 1) that provided data on breastfeeding and confounding factors. Cohort studies were analyzed as nested case-control studies with four women matched on birth year randomly selected for each woman with endometrial cancer from among cohort members who had not had a hysterectomy or an endometrial cancer diagnosis (or, in The Nurses' Health Study, any other invasive cancer) by the woman's diagnosis date.

The data harmonization process for the Consortium was described elsewhere¹³ but, briefly, studies provided information on participants' demo-

graphics (patients' diagnosis age, reference date for women in the control group, race, education) and reproductive, health, and lifestyle factors (eg, parity, oral contraceptive use, height, weight) according to specified definitions. Studies also provided information on whether women breastfed, their total duration of breastfeeding (sum of duration of all of their breastfeeding episodes), and, for some studies, breastfeeding duration for each child. For women in the case group, studies provided tumor histology information, where available. Women with sarcomas were excluded.

For the cohort studies, the data were collected in slightly different ways. For one,¹⁴ data were mostly obtained from baseline questionnaires (1991–1992) with BMI data updated in 2003 for women diagnosed after this and their matched controls. For the other two,^{15,16} most data were from questionnaires returned in the period before a participant become a case or was selected as a control, although breastfeeding data were collected only once (1986) in the Nurses' Health Study.¹⁶

Analyses were restricted to parous women with breastfeeding information. Less than 2% of participants were missing breastfeeding or covariate data so a complete case analysis was undertaken. Study-specific odds ratios (ORs) and 95% confidence intervals (CIs) were

Women in the Control Group (n=17,241)	Ever Breastfed		Median Total Breastfeeding (mo)*	
	Women in the Case Group	Women in the Control Group	Women in the Case Group	Women in the Control Group
922	298 (68)	692 (75)	6	9
659	913 (82)	561 (85)	10	12
558	218 (43)	299 (54)	8	12
407	159 (43)	188 (46)	6	9
737	452 (64)	514 (70)	6	7
780	303 (79)	592 (76)	9	10
423	195 (49)	261 (62)	6	7
1,701	366 (82)	1,388 (82)	8	7
1,161	896 (83)	1,003 (86)	14	13
260	170 (78)	196 (75)	8	6.5
709	411 (63)	468 (66)	3	5
290	191 (60)	181 (62)	4	6
532	91 (49)	277 (52)	3	6
1,418	217 (42)	677 (48)	6	8
899	79 (39)	388 (43)	5	5
4,788	771 (64)	3,069 (64)	5	5
997	202 (88)	921 (92)	8	9



estimated for the associations between breastfeeding variables (see subsequently) and risk of endometrial cancer using multivariable logistic regression (conditional logistic regression for matched studies). Models were adjusted for parity (continuous), oral contraceptive pill use, BMI (around reference age; continuous) and education level. Study-specific ORs were pooled using random-effects models giving overall pooled ORs and 95% CIs. Between-study heterogeneity was assessed using I^2 and Q statistics.

The women were classified as having breastfed or not. Total breastfeeding duration was modeled continuously and in categories: never breastfed, 3 months or less, greater than 3 to 6 months or less, greater than 6 to 9 months or less, greater than 9 to 12 months or less, and then in 6-month categories up to greater than 36 months.

Because we hypothesized that risk reduction with breastfeeding might plateau as duration of a breastfeeding episode increased (beyond return of ovulation), we examined associations with duration of individual breastfeeding episodes. First, to allow inclusion of all the studies, we divided total breastfeeding duration by the number of births for each woman to give average duration of breastfeeding per child. Then, for studies with information on individual breastfeeding episodes^{8,14,17–25} (plus Turin Study), we divided total breastfeeding duration by the number of children actually breastfed. Both variables were analyzed in categories (as previously but with the highest category 12–18 months) weighting the first variable by the number of births and the second by the number of children breastfed to give the risk per child for each average duration.

We assessed whether associations differed between case-control and cohort studies by stratifying the meta-analysis by study type. We also stratified analyses by number of births to assess potential for residual confounding by parity and by BMI at reference age (less than 30 kg/m² compared with 30 or greater) and early adulthood (less than 25 compared with 25 or greater, where available), because this measure was generally closer to the time of breastfeeding) to assess whether associations varied by BMI. We conducted analyses in strata of histologic subtype (type I-endometrioid and mucinous adenocarcinomas compared with type II-serous and clear cell cancers) because etiology may vary by subtype.¹³ Differences between strata were assessed using random-effects meta-regression.²⁶

We explored heterogeneity between studies by assessing whether associations varied by participant characteristics, including those already mentioned

plus race (white, black, Asian); menopausal status; participant's birth year (before 1950 compared with 1950 or later); and years since last pregnancy (less than 30 compared with 30 years or greater). We used random-effects meta-regression²⁶ to evaluate whether these factors explained between-study heterogeneity.

We estimated the proportion of endometrial cancers (population-attributable fraction) that could be attributed to breastfeeding for 6 months or less per child using the standard formula:

$$\text{Population Attributable Fraction} = \frac{\sum(p_x \times \text{ERR}_x)}{1 + \sum p_x \times \text{ERR}_x},$$

where ERR was the excess relative risk for each category of average breastfeeding per child breastfed below the greater than 6–9 months category. The prevalence (p_x) was the proportion of women in each category. Sensitivity analyses were conducted using prevalence estimates from the studies with the lowest²³ and highest prevalence²² of breastfeeding greater than 6 months per child.

We used SAS 9.4 and STATA 13 for statistical analyses. All statistical significance tests are two-sided.

RESULTS

Table 1 shows details of the included studies. The analyses included 8,981 parous women with endometrial cancer and 17,241 parous control women. Overall, 68% of the control women had breastfed at least one child, but the percentage varied considerably across studies ranging from 43%¹⁵ to 92%.¹⁴ Median total duration of breastfeeding among women in the control group who had ever breastfed ranged across studies from 5^{15,16,24} to 13 months.²² As expected, compared with women in the case group, the women in the control group had higher parity, were more likely to have used oral contraceptive pills, and, on average, had a lower BMI (Table 2). Women in the control group were also somewhat more likely to have posthigh school education.

Table 3 shows the crude and adjusted associations between the various breastfeeding measures and endometrial cancer risk; for brevity, we refer only to the adjusted pooled ORs in this section. Having ever breastfed was associated with a statistically significant 11% reduced risk of endometrial cancer compared with never breastfeeding (pooled OR 0.89, 95% CI 0.81–0.98) (Fig. 1), although there was moderate between-study heterogeneity ($I^2=45\%$, $P=.02$). For total duration of breastfeeding, estimates for durations beyond 3 months suggested an inverse association that became more pronounced for very long durations (pooled OR 0.67, 95% CI 0.53–0.83 for greater than 36 months' total duration compared with never



Table 2. Prevalence of Covariates Among Parous Women in the Pooled Analysis

Covariate	Women in the Case Group (n=8,981)	Women in the Control Group (n=17,241)*	<i>P</i> [†]
Age (y)	61±8.9	60±8.8	<.001
BMI (kg/m ²)	29.3±7.0	25.9±5.0	<.001
Race			
White	77.4	73.1	
Black	4.1	4.7	
Asian	12.6	12.4	
Other	3.8	3.0	
Missing	2.1	6.8	<.001
Education			
High school or less	49.4	46.0	
Post-high school	49.5	52.5	
Missing	1.1	1.5	<.001
Parity			
1	21.7	18.2	
2	36.1	35.5	
3	23.3	24.7	
4	11.3	12.0	
5	7.6	10.5	<.001
Oral contraceptive use			
No	57.5	50.4	
Yes	41.9	49.0	
Missing	0.6	0.6	<.001

BMI, body mass index.

Data are mean±standard deviation or % unless otherwise specified.

* Percentages weighted by numbers of women in the case group in each study.

[†] Differences between women in the case group and those in the control group were tested with *t* tests for continuous variables and χ^2 tests for categorical variables.

breastfeeding). However, the risk reduction associated with increasing total duration of breastfeeding was not clearly linear. Our analyses of individual episodes of breastfeeding (average breastfeeding per child, average breastfeeding per child breastfed) also showed that individual breastfeeding durations beyond 3 months were associated with statistically significant reductions in risk. However, beyond the greater than 6–9 months category, the ORs did not appear to decrease much further, although the numbers of women who breastfed individual children for longer than this were small and therefore these estimates are less precise.

Figure 2 shows the results of analyses of ever breastfeeding stratified by participant characteristics. The association did not vary substantially by tumor type (I compared with II), parity, recent BMI, or menopausal status. The magnitude of association differed somewhat by race–ethnicity, BMI in early adulthood (no association in heavier women), and time since last

pregnancy, but the differences were not statistically significant. For the race analyses, the number of studies included in each stratum was small; only two studies contributed to the estimate for Asian women,^{22,27} including one in which all women were Asian. Estimates for ever breastfeeding differed significantly by women's birth year (*P*=.03). For women born since 1950 (likely to have breastfed after approximately 1970), ever breastfeeding was associated with a 28% reduction in endometrial cancer risk (OR 0.72, 95% CI 0.59–0.87) compared with never breastfeeding, whereas, for women born before 1950, the risk reduction was smaller and no longer statistically significant (OR 0.93, 95% CI 0.85–1.02). It is notable that the study with the highest OR associated with ever breastfeeding (OR 1.12, 95% CI 0.97–1.29)¹⁶ included no women born after 1950 and the participants had the highest mean age at diagnosis (65 years). Removing this study from the pooled analysis reduced the *I*² from 45% to 24%.

Results from univariable meta-regression to evaluate potential sources of between-study heterogeneity in estimates for ever breastfeeding are shown in Table 4. Of the factors considered, only the proportion of women whose last birth was less than 30 years before study participation (*P*=.02, adjusted *R*²=82.3%) and the median age at diagnosis of women in the case group in each study (*P*=.03, adjusted *R*²=68.5%) were significantly associated with the strength of association. Although these factors were no longer statistically significant in a meta-regression excluding the Nurses' Health Study, the adjusted *R*² for each (last birth 30 years prior or greater; median age at diagnosis) remained high at 41% and 68%, respectively. No factors remained statistically significant when included in multivariable meta-regression, likely because of the relatively small number of studies involved.

We estimated the proportion of endometrial cancers among parous women (population-attributable fraction) that could be attributed to breastfeeding for 6 months or less per child to be 11% (range from sensitivity analyses 5–15%). The prevalence of nulliparity across the studies was 16% giving a population-attributable fraction for all women of approximately 9% (possible range 4–13%).

DISCUSSION

We observed a modest reduction in risk of endometrial cancer associated with breastfeeding that was not explained by greater parity and did not vary by BMI or endometrial cancer type (type I compared with type II). The association appeared stronger with increasing duration of breastfeeding episodes up to



Table 3. Associations Between Breastfeeding and Endometrial Cancer Risk Among Parous Women in the Pooled Analysis

Breastfeeding Variable	Women in the Case Group*	Women in the Control Group*	Crude Pooled OR (95% CI)	Adjusted Pooled OR [†] (95% CI)	I ² % [‡]
Ever breastfed					
No	3,049 (33.9)	5,566 (32.3)	1.00	1.00	
Yes	5,932 (66.1)	11,675 (67.7)	0.82 (0.75–0.90)	0.89 (0.81–0.98)	45
Total duration of breastfeeding (mo)					
Never breastfed	3,049 (34.1)	5,566 (32.3)	1.00	1.00	
0–3	1,647 (18.4)	3,059 (17.8)	0.98 (0.88–1.09)	1.01 (0.91–1.12)	18
3–6	915 (10.2)	2,017 (11.7)	0.83 (0.74–0.92)	0.84 (0.73–0.98)	39
6–9	710 (7.9)	1,555 (9.0)	0.81 (0.70–0.95)	0.90 (0.77–1.05)	32
9–12	667 (7.5)	1,000 (5.8)	0.89 (0.73–1.07)	0.96 (0.79–1.16)	47
12–18	723 (8.1)	1,413 (8.2)	0.82 (0.73–0.93)	0.93 (0.82–1.05)	0
18–24	506 (5.7)	998 (5.8)	0.74 (0.64–0.85)	0.80 (0.69–0.93)	3
24–30	248 (2.8)	598 (3.5)	0.66 (0.51–0.84)	0.67 (0.51–0.87)	40
30–36	179 (2.0)	319 (1.9)	0.65 (0.53–0.81)	0.69 (0.54–0.88)	0
Greater than 36	309 (3.5)	686 (4.0)	0.58 (0.48–0.70)	0.67 (0.53–0.83)	18
Per 3 mo of total breastfeeding			0.97 (0.96–0.98)	0.97 (0.96–0.98)	26
Average duration of breastfeeding per child (mo) [§]					
Never breastfed	3,049 (34.3)	5,566 (32.6)	1.00	1.00	
0–3	2,777 (31.3)	5,603 (32.9)	0.99 (0.96–1.02)	1.01 (0.98–1.03)	0
3–6	1,230 (13.9)	2,618 (15.4)	0.92 (0.89–0.97)	0.95 (0.91–0.99)	25
6–9	844 (9.5)	1,649 (9.7)	0.92 (0.88–0.97)	0.93 (0.88–0.98)	31
9–12	752 (8.5)	1,184 (6.9)	0.90 (0.85–0.95)	0.92 (0.86–0.97)	7
12–18	225 (2.5)	430 (2.5)	0.86 (0.78–0.95)	0.88 (0.79–0.97)	22
Average duration of breastfeeding per child breastfed (mo)					
Never breastfed	1,793 (32.9)	2,335 (26.4)	1.00	1.00	
0–3	1,394 (25.6)	2,324 (26.3)	0.98 (0.92–1.04)	0.99 (0.93–1.05)	29
3–6	798 (14.6)	1,674 (18.9)	0.92 (0.86–0.98)	0.93 (0.88–0.98)	15
6–9	616 (11.3)	1,200 (13.6)	0.90 (0.85–0.96)	0.89 (0.83–0.95)	17
9–12	673 (12.3)	993 (11.2)	0.88 (0.81–0.96)	0.87 (0.80–0.95)	21
12–18	176 (3.2)	310 (3.5)	0.86 (0.77–0.96)	0.86 (0.78–0.95)	1

OR, odds ratio; CI, confidence interval.

Data are n (%) unless otherwise specified.

* May not add to total as a result of missing data.

[†] Adjusted for age (years), parity (continuous), oral contraceptive duration (continuous; or ever use [yes or no]^{17,23}), body mass index (around reference age, continuous), education (level achieved or number of years).

[‡] From random effects meta-analysis models. The I²% measures variation across studies that is the result of heterogeneity rather than chance.

[§] OR is for the risk change per child or per child breastfed.

^{||} Included data only from 12 studies (Turin Study^{8,14,17–25}).

between 6 and 9 months per child breastfed, but thereafter the decline in risk was smaller. These results suggest that reduction in endometrial cancer risk could be added to the list of maternal benefits associated with breastfeeding for more than 6 months.

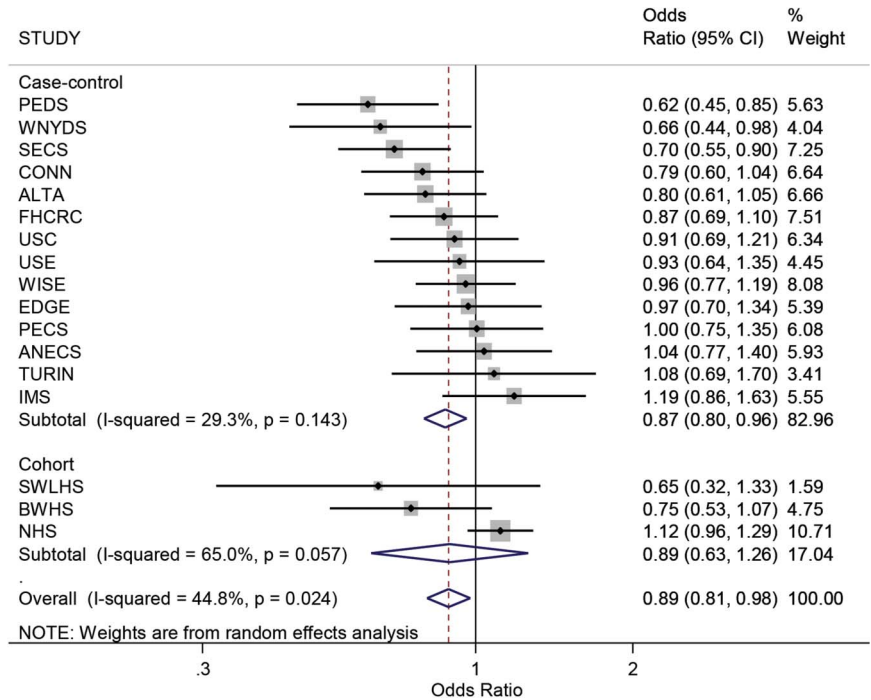
Strengths of our study include the large sample size, our ability to define exposure levels consistently across studies, to adjust consistently for potential confounders, and the inclusion of studies from different U.S. populations and different countries. However, some limitations should be considered. We had no information on factors that predispose women to breastfeed or data on when menstruation recommenced so we could not consider these in our

analyses. Most of the studies were of case-control design with potential self-selection of more health-conscious women in the control group, perhaps more likely to have breastfed. Nevertheless, the pooled estimates for ever breastfeeding did not vary by study design (cohort compared with case-control) making selection bias less likely. Also, all studies relied on retrospective self-report of breastfeeding, which for many women occurred years before study participation and thus was possibly subject to recall error. This would be nondifferential for the cohort studies and, again, the lack of difference in pooled estimates by study design makes substantial recall bias unlikely. Finally, despite the inclusion of greater



Fig. 1. Forest plot showing study-specific estimates and 95% confidence intervals (CIs) for the association between ever breastfeeding and endometrial cancer risk among parous women. Estimates are stratified by study design (case-control or cohort) and ordered smallest to largest. The *box size* indicates the study weight, the *line* represents the 95% confidence interval, and the *diamonds* represent the pooled estimates. Higher I^2 values and P values $<.05$ suggest statistically significant between-study heterogeneity. Study acronyms are defined in Table 1.

Jordan. Breastfeeding and Risk of Endometrial Cancer. *Obstet Gynecol* 2017.



than 26,000 women, relatively few women breastfed for long durations making estimates for these categories less precise.

An inverse association between breastfeeding and endometrial cancer risk is biologically plausible. Breastfeeding can suppress gonadotrophin-releasing

Fig. 2. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for the association between ever breastfeeding and endometrial cancer risk stratified by participant characteristics. The number of studies included in each stratum varies because some studies did not have information on the variable of interest or because there were too few women in specific strata to calculate study-specific estimates. ^aOnly case group was stratified. ^bIncludes five studies in which all women were white. ^cIncludes one study in which all women were black. ^dIncludes one study in which all women were Asian. ^eThe estimate for ever breastfed in women born before 1950, including only the 11 studies that also included women who were born after 1950 is 0.93 (95% CI 0.84–1.03).

Jordan. Breastfeeding and Risk of Endometrial Cancer. *Obstet Gynecol* 2017.

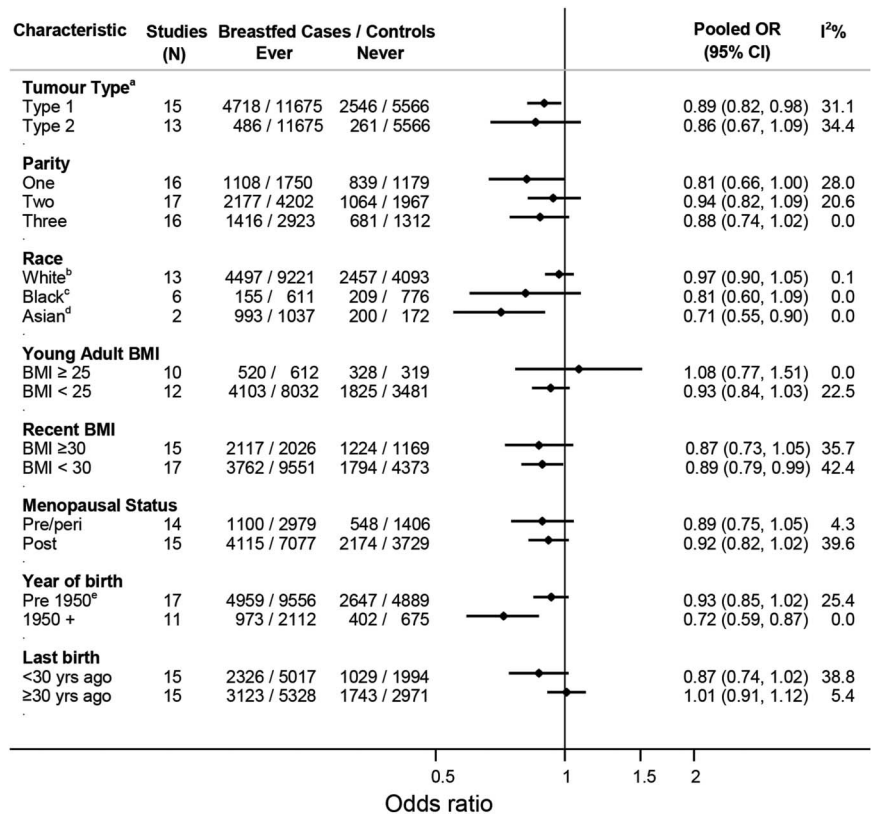


Table 4. Results of Univariable Metaregression Assessing Factors Associated With Between-Study Heterogeneity in Estimates for the Association Between Ever Breastfeeding and Endometrial Cancer Risk

Factor	Adjusted R^2 %*	P From Univariable Metaregression
Study design (case-control or cohort)	9.4	.48
Proportion of white women	31.0	.1
Median breastfeeding duration among women who breastfed	4.4	.5
Median age at diagnosis (y)	68.5	.03
Proportion of women whose last birth was less than 30 y before reference date	82.3	.02
Proportion of women born after 1950	24.9	.2

* Proportion of between-study variance explained.

hormone-inhibiting ovarian follicular growth and reduce estradiol levels to within the postmenopausal range.² At these levels, endometrial cell mitoses are virtually absent.³ Estrogen levels in breastfeeding women appear to depend on suckling stimuli with the lowest levels found in women breastfeeding exclusively.² Most guidelines recommend introduction of nonmilk foods when infants are approximately 6 months old, so, notwithstanding considerable variation in breastfeeding practices between women, it is likely that the suckling stimulus decreases around this time and estrogen levels increase. This is consistent with our finding of leveling in risk reduction with longer durations of individual episodes of breastfeeding.

We had expected that BMI might modify the association with breastfeeding because obesity lowers sex hormone-binding globulin levels, increasing bioavailable estrogen and testosterone. This, with estrone production in adipose tissue in more obese women, might negate the relative hypoestrogenic state induced by breastfeeding. We did not observe significant effect modification, but our BMI measures may not closely reflect adiposity during breastfeeding. Most BMI data were from around diagnosis, generally years after breastfeeding. We had BMI estimates from early adulthood from 12 studies, but this may have been poorly recalled because it was further in the past and may still not reflect a woman's BMI during breastfeeding. Furthermore, few women were overweight on early

adulthood measures so power may have been insufficient to detect effect modification.

We observed moderate between-study heterogeneity in some associations, most notably for ever breastfeeding ($I^2=45\%$). This is consistent with published meta-analyses investigating this relation,^{10,11} although only two studies^{8,20} included in those analyses were also in ours. We found the different proportions across studies of women who gave birth further in the past significantly contributed to heterogeneity. We also found the inverse association with breastfeeding was weaker in women born before 1950. These factors may reflect attenuation of breastfeeding effects over time or differences in breastfeeding practices across birth cohorts causing different physiologic effects in the endometrium. Breastfeeding rates, at least in the United States, were much lower in the 1950s and 1960s than more recently²⁸ but whether breastfeeding practices (eg, less demand or exclusive feeding with potentially less ovulation suppression²⁹) also differed is not clear.

Assuming the associations we observed are causal and that prevalence of breastfeeding and nulliparity among women diagnosed with endometrial cancer in 2015 is similar to our study, it may be that, of the estimated 345,000 women diagnosed with endometrial cancer worldwide in 2015,¹ approximately 31,000 (9%, possible range 14,500 [4%] to 43,500 [13%]) might have been prevented if all parous women had been able to breastfeed their infants for more than 6 months each.

For health practitioners, our study suggests that promoting breastfeeding and providing support to women to breastfeed for 6 months and beyond might have the added benefit of contributing to the prevention of this increasingly common cancer.

REFERENCES

1. International Agency for Research on Cancer. GLOBOCAN 2012: estimated cancer incidence, mortality, and prevalence worldwide. Available at: <http://globocan.iarc.fr>. Retrieved October 10, 2016.
2. McNeilly AS. Lactational control of reproduction. *Reprod Fert Dev* 2001;13:583-90.
3. Key TJ, Pike MC. The dose-effect relationship between 'unopposed' oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. *Br J Cancer* 1988;57:205-12.
4. World Cancer Research Fund/American Institute for Cancer Research. Continuous update project report: food, nutrition, physical activity and the prevention of endometrial cancer. Washington, DC: American Institute for Cancer Research; 2013.
5. Salazar-Martinez E, Lazcano-Ponce EC, Gonzalez Lira-Lira G, Escudero-De los Rios P, Salmeron-Castro J, Hernandez-Avila M. Reproductive factors of ovarian and endometrial cancer risk



- in a high fertility population in Mexico. *Cancer Res* 1999;59:3658–62.
6. Newcomb PA, Trentham-Dietz A. Breast feeding practices in relation to endometrial cancer risk, USA. *Cancer Causes Control* 2000;11:663–7.
 7. Rosenblatt KA, Thomas DB. Prolonged lactation and endometrial cancer. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Epidemiol* 1995;24:499–503.
 8. Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, et al. Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. *Am J Obstet Gynecol* 1992;167:1317–25.
 9. Dossus L, Allen N, Kaaks R, Bakken K, Lund E, Tjonneland A, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2010;127:442–51.
 10. Wang L, Li J, Shi Z. Association between breastfeeding and endometrial cancer risk: evidence from a systematic review and meta-analysis. *Nutrients* 2015;7:5697–711.
 11. Ma X, Zhao LG, Sun JW, Yang Y, Zheng JL, Gao J, et al. Association between breastfeeding and risk of endometrial cancer: a meta-analysis of epidemiological studies. *Eur J Cancer Prev* 2015 [Epub ahead of print].
 12. Olson SH, Chen C, De Vivo I, Doherty JA, Hartmuller V, Horn-Ross PL, et al. Maximizing resources to study an uncommon cancer: E2C2—Epidemiology of Endometrial Cancer Consortium. *Cancer Causes Control* 2009;20:491–6.
 13. Setiawan VW, Yang HP, Pike MC, McCann SE, Yu H, Xiang YB, et al. Type I and II endometrial cancers: have they different risk factors? *J Clin Oncol* 2013;31:2607–18.
 14. Roswall N, Sandin S, Adami HO, Weiderpass E. Cohort profile: the Swedish Women's Lifestyle and Health cohort. *Int J Epidemiol* 2015 [Epub ahead of print].
 15. Rosenberg L, Adams-Campbell L, Palmer JR. The Black Women's Health Study: a follow-up study for causes and preventions of illness. *J Am Med Womens Assoc* (1972) 1995;50:56–8.
 16. Viswanathan AN, Feskanich D, De Vivo I, Hunter DJ, Barbieri RL, Rosner B, et al. Smoking and the risk of endometrial cancer: results from the Nurses' Health Study. *Int J Cancer* 2005;114:996–1001.
 17. Friedenreich CM, Cook LS, Magliocco AM, Duggan MA, Courneya KS. Case-control study of lifetime total physical activity and endometrial cancer risk. *Cancer Causes Control* 2010;21:1105–16.
 18. Lu L, Risch H, Irwin ML, Mayne ST, Cartmel B, Schwartz P, et al. Long-term overweight and weight gain in early adulthood in association with risk of endometrial cancer. *Int J Cancer* 2011;129:1237–43.
 19. Fortuny J, Sima C, Bayuga S, Wilcox H, Pulick K, Faulkner S, et al. Risk of endometrial cancer in relation to medical conditions and medication use. *Cancer Epidemiol Biomarkers Prev* 2009;18:1448–56.
 20. Zucchetto A, Serraino D, Polesel J, Negri E, De Paoli A, Dal Maso L, et al. Hormone-related factors and gynecological conditions in relation to endometrial cancer risk. *Eur J Cancer Prev* 2009;18:316–21.
 21. Brinton LA, Sakoda LC, Lissowska J, Sherman ME, Chatterjee N, Peplonska B, et al. Reproductive risk factors for endometrial cancer among Polish women. *Br J Cancer* 2007;96:1450–6.
 22. Shu XO, Brinton LA, Zheng W, Gao YT, Fan J, Fraumeni JF Jr. A population-based case-control study of endometrial cancer in Shanghai, China. *Int J Cancer* 1991;49:38–43.
 23. McCann SE, Freudenheim JL, Marshall JR, Brasure JR, Swanson MK, Graham S. Diet in the epidemiology of endometrial cancer in western New York (United States). *Cancer Causes Control* 2000;11:965–74.
 24. Pike MC, Peters RK, Cozen W, Probst-Hensch NM, Felix JC, Wan PC, et al. Estrogen-progestin replacement therapy and endometrial cancer. *J Natl Cancer Inst* 1997;89:1110–6.
 25. Doherty JA, Weiss NS, Fish S, Fan W, Loomis MM, Sakoda LC, et al. Polymorphisms in nucleotide excision repair genes and endometrial cancer risk. *Cancer Epidemiol Biomarkers Prev* 2011;20:1873–82.
 26. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions* version 5.1.0. Available at: www.handbook.cochrane.org. Retrieved September 15, 2016.
 27. Neill AS, Nagle CM, Protani MM, Obermair A, Spurdle AB, Webb PM, et al. Aspirin, nonsteroidal anti-inflammatory drugs, paracetamol and risk of endometrial cancer: a case-control study, systematic review and meta-analysis. *Int J Cancer* 2013;132:1146–55.
 28. Martinez GA, Nalezienski JP. The recent trend in breast-feeding. *Pediatrics* 1979;64:686–92.
 29. Rogers IS. Lactation and fertility. *Early Hum Dev* 1997;49 (suppl):S185–90.
 30. Moysich KB, Baker JA, Rodabaugh KJ, VILLELLA JA. Regular analgesic use and risk of endometrial cancer. *Cancer Epidemiol Biomarkers Prev* 2005;14:2923–8.
 31. Strom BL, Schinnar R, Weber AL, Bunin G, Berlin JA, Baumgarten M, et al. Case-control study of postmenopausal hormone replacement therapy and endometrial cancer. *Am J Epidemiol* 2006;164:775–86.

