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ORIGINAL PAPER

Breast-feeding and risk of epithelial ovarian cancer

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Abstract
Purpose Evidence suggests that breast-feeding may decrease the risk of epithelial ovarian cancer but it is not clear whether there is a relationship with duration of breast-feeding, patterns of breast-feeding, or particular histological subtypes of ovarian cancer. We sought to investigate these issues in detail.
Methods Data from participants in a population-based study of ovarian cancer in western Washington State, USA (2002–2007) who had had at least one birth (881 cases and 1,345 controls) were used to assess relations between patterns of breast-feeding and ovarian cancer. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI).
Results Women who ever breast-fed had a 22 % reduction in risk of ovarian cancer compared with those who never breast-fed (OR = 0.78, 95% CI 0.64–0.96) and risk reduction appeared greater with longer durations of feeding per child breast-fed (OR = 0.56, 95% CI 0.32–0.98 for 18 months average duration breast-feeding versus none). Introduction of supplementary feeds did not substantially alter these effects. The overall risk reduction appeared greatest for the endometrioid and clear cell subtypes (OR per month of average breast-feeding per child breast-fed = 0.944, 95% CI 0.903–0.987).
Conclusions Among women who have had the opportunity to breast-feed, ever breast-feeding and increasing durations of episodes of breast-feeding for each breast-fed child are associated with a decrease in the risk of ovarian cancer independent of numbers of births, which may be strongest for the endometrioid subtype.

Keywords Ovarian cancer · Breast-feeding · Histological subtype

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Introduction

The weight of evidence strongly suggests a role for ovulation or associated reproductive hormones in the development of epithelial ovarian cancer [1, 2] and as breast-feeding can have substantial impact upon both of these [3], it might be expected to influence ovarian cancer risk. Indeed, a meta-analysis of nine case–control studies published prior to 2004 found that women who had ever breast-fed had a 30 % reduction in risk of ovarian cancer [4] and more recent publications have supported this finding [5–9]. What is less clear is how the duration of breast-feeding influences ovarian cancer risk and whether factors such as the timing of

introduction of supplementary feeds can modify the relationship. It has also been suggested that other variations in breast-feeding practices such as the number of children breast-fed [10, 11] or whether the last born child is breast-fed may influence the effect of lactation on ovarian cancer risk [9].

Clarification of these issues is required in order to be able to provide women with the best advice about the possible preventive benefits of breast-feeding. We therefore sought to explore in depth the relationship between ovarian cancer and breast-feeding using data from a large case–control study based in Washington State, USA.

Materials and methods

Female residents of a thirteen county area of western Washington State, USA who were diagnosed with a primary invasive or borderline epithelial ovarian tumor from 2002 to 2007 were eligible for the study. From 2002 to 2005, women aged 35–74 years were included, while in 2006–2007 only women aged 35–69 years were included. Case women were identified through the cancer surveillance system (CSS), a population-based registry that is part of the surveillance, epidemiology, and end results (SEER) program of the US National Cancer Institute. The methods for case ascertainment and for case and control recruitment for 2002–2005 have previously been described [12]; similar methods were used for 2006–2007. Eligible cases were limited to English-speaking women who had a residential telephone at the time of cancer diagnosis, because random digit dialing (RDD) was the method used to select controls. Of 1,556 eligible cases identified, 1,170 (75.2 %) were interviewed. Tumor histologies were coded from pathology reports by the registry staff according to the third edition of the International Classification of Diseases for Oncology (ICD-O) [13]; for analysis, these were grouped into subtypes of serous, mucinous, endometrioid/clear cell, and other invasive tumors; and into serous, mucinous, and other borderline tumors. Control women (with at least one ovary and no history of ovarian cancer) were sampled via RDD within 5-year age categories, 1-year calendar intervals, and two (urban versus suburban/rural) county strata; list-assisted RDD methods were used for 2006–2007. We interviewed 1,584 control women, with a screening response proportion of 80.3 % and an interview response proportion of 81.6 %, for an overall response proportion (screening × interview) of 65.5 %. For the current analyses, we restricted to women who had had at least one live birth (881 cases and 1,345 controls).

The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, and all women provided signed informed consent. In-person interviews were undertaken with cases and controls. The women were asked to provide information that pertained to the time before diagnosis (for case patients) or before an assigned comparable reference date (for control subjects). On average, the diagnosis or reference date was nine - months before interview for case patients and 11 months before interview for control subjects. The interview covered demographic and lifestyle characteristics; medical history; family and personal cancer history; and reproductive history. To aid recall, interviewers used a calendar to record life events and provided photographs of commonly used medicines including oral contraceptive and menopausal hormone preparations. Women were asked about each of their pregnancies in detail, including the outcome of the pregnancy. If the pregnancy resulted in a live birth women were asked about whether they had initiated breast-feeding for that child. They were asked the duration of the feeding for each child and asked to recall how old the child was when he/she regularly began to take any food, formula or milk other than breast milk. Women with diagnosis/reference dates after 2005 were not asked about supplementary feeding.

Statistical analysis

Only women who had had a live birth were included in the analysis and we only considered women who had breast-fed a child for two weeks or more to have ever breast-fed. Total duration of breast-feeding was calculated by summing the duration of feeding after each birth (resulting in a live-born child). We calculated average duration of breast-feeding per breast-fed child by dividing by the total duration of breast-feeding by the number of children each woman reported having breast-fed (considering multiple births as one). As we were also interested in durations of exclusive breast–feeding, we assessed the duration of breast-feeding up until the point at which the child regularly began to take food or milk other than breast milk and summed that quantity across all children that a woman breast-fed. Similar to the approach described for total duration of breast-feeding, the duration of exclusive breast-feeding was also divided by the number of children breast-fed to give an average duration of exclusive breast-feeding per breast-fed child.

Odds ratios (OR) and 95% confidence intervals (95% CI) for the risk of epithelial ovarian cancer associated with various aspects of breast-feeding were calculated using unconditional logistic regression. The reference group for all analyses was women who had had a live birth but had never breast-fed a child for more than two weeks. Linear trends were assessed by the inclusion of the relevant continuous term in the model (excluding the women who had never breast-fed).

Subtype-specific analyses were conducted for the major tumor groups; invasive mucinous cancers ($n = 24$) and borderline cancers of "other" subtype ($n = 12$) were excluded from these analyses because of the small case numbers.

All results shown are adjusted for the frequency matching variables of age (5-year intervals), county of residence (two strata, as described previously), and calendar year of diagnosis/reference date (1-year strata), as well as number of live births (categorical variables for 1, 2, 3, and 4 or more), duration of hormonal contraception (categorical variables of never users and users of <6, 6–59, 60–119, and ≥120 months), level of education (high school graduate or less, some college or technical college, college graduate, or postgraduate). Adjustment for other potential confounding variables (race/ethnicity, body mass index (BMI), age at menarche, history of breast cancer, family history of breast and/or ovarian cancer, smoking, tubal ligation, and hysterectomy) did not substantively change odds ratios. All analyses were conducted using SAS statistical software (SAS 9.2, SAS Institute Inc., Cary, NC, USA).

Results

Table 1 shows demographic, lifestyle, and reproductive factors of case and control women who had had at least one live birth. Compared to controls, women with ovarian cancer were more likely to report a personal history of breast cancer; have had fewer children; have a higher body mass index (BMI); have been a smoker; and have a lower level of education. They were less likely to have taken hormonal contraceptives.

Among women with at least one live birth, those who had ever breast-fed a child for more than two weeks had a 22 % decreased risk of ovarian cancer (OR = 0.78, 95% CI, 0.64–0.96; Table 2) relative to those who had not and it appeared that the risk reduction was greatest for those with the longest total duration of breast-feeding (e.g., OR = 0.70, 95% CI 0.53–0.93, for 18 months or more of breast-feeding versus never breast-fed (Table 2)). When we looked at the longest individual episode of breast-feeding women reported, we found that those who had breast-fed at least one child for 18 months or more had a 43 % reduction in risk compared with those who never breast-fed (p-trend per month of breast-feeding among women who had ever breast-fed = 0.1). Similarly, those who on average breast-fed each child for 18 months or more had a 44 % reduction in risk compared with those who never breast-fed (OR = 0.56, 95% CI 0.32–0.98).

As noted earlier, assessment of supplementary feeding was limited to cases and controls with diagnosis/reference dates 2002–2005, representing approximately 60 % of the women who breast-fed for more than two weeks (Table 2). We found no convincing evidence that the timing of introduction of supplementary feeds had an impact on the overall effects of breast-feeding.

We found no material difference in the effect of breast-feeding between women who breast-fed their last child and those who did not; or between those who used hormonal contraceptives at some stage during lactation and those who did not (data not shown).

Also, our overall results were broadly similar when women were considered in strata of live births and the interaction between the number of live births and having ever breast-fed was not statistically significant (Table 3). Among women with only one live birth, 18 months or more of breast-feeding was associated with an almost 70 % reduction in ovarian cancer risk. An average duration of six or more months of breast-feeding per child was associated with a 27–35 % reduction in risk of ovarian cancer in women with one, two and four births but was not apparent among women with three births. The number of women in categories beyond four live births was too small to produce meaningful estimates.

We also stratified our analyses by hormonal contraceptive use, age (less than or greater than 50) and histological subtype (Tables 4, 5). There was a suggestion that the effects of breast-feeding were more pronounced among women who had ever used hormonal contraception (e.g., OR = 0.981, 95% CI 0.962–1.000) per month of average breast-feeding per child breast-fed among contraceptive users compared with OR = 1.002, 95% CI 0.961–1.045 for never users of hormonal contraceptives) but the interaction terms was not significant (p = 0.6). Our results also suggest that longer durations of breast-feeding are associated with greater risk reduction for invasive endometrioid/clear cell ovarian cancer compared with invasive serous cancer (OR per month of average breast-feeding per child breast-fed = 0.944, 95% CI 0.903–0.987 for endometrioid/clear cell versus OR = 0.989, 95% CI 0.965–1.013 for serous invasive cancers.

Discussion

Our results suggest that among parous women, ever breast-feeding and longer durations of breast-feeding per breast-fed child are associated with decreased risks of ovarian cancer independent of numbers of births. We had expected that exclusive breast-feeding would confer greater risk reduction than breast-feeding after supplementary food/milk was introduced but our results did not support that hypothesis. We did, however, find some evidence that the effects of breast-feeding might vary according to ever use

Table 1 Demographic, lifestyle, and reproductive factors among case and control women with at least one live birth who participated in a case–control study of epithelial ovarian cancer, in Washington State, USA 2002–2007

	Cases $N = 881$ N (%)	Controls $N = 1{,}345$ N (%)	p Value
Age at diagnosis or reference date (years)			
35–44	99 (11.2)	151 (11.2)	0.3
45–54	263 (29.9)	381 (28.3)	
55–64	326 (37.0)	470 (34.9)	
65–74	193 (21.9)	343 (25.5)	
Race/ethnicity			
White, non-Hispanic	790 (89.7)	1,218 (90.6)	0.1
Non-White, non-Hispanic	59 (6.7)	92 (6.8)	
Hispanic	32 (3.6)	35 (2.6)	
Duration of use of hormonal contraceptives (months)			
Never used	206 (23.4)	231 (17.2)	0.0005
<6	77 (8.8)	98 (7.3)	
6 to <59	325 (36.9)	509 (37.8)	
60 to <119	157 (17.8)	275 (20.5)	
≥120	115 (13.1)	232 (17.3)	
Number of live births			
1	187 (21.2)	213 (15.8)	0.01
2	344 (39.1)	539 (40.1)	
3	209 (23.7)	351 (26.1)	
≥4	141 (16.0)	242 (18.0)	
Tubal ligation			
No	673 (76.4)	994 (73.9)	0.2
Yes	208 (23.6)	351 (26.1)	
Family history of breast and ovarian cancer[a]			
None	510 (58.3)	800 (60.1)	0.01
Breast cancer only	264 (30.2)	432 (32.4)	
Ovarian cancer only	59 (6.7)	60 (4.5)	
Breast and ovarian cancer	42 (4.8)	40 (3.0)	
Prior breast cancer			
No	818 (92.9)	1,278 (95.0)	0.03
Yes	63 (7.2)	67 (5.0)	
Body mass index at age 30 (kg/m^2)			
<18.5	45 (5.1)	91 (6.8)	0.07
18.5–24.9	657 (75.3)	1,031 (77.3)	
25–29.9	110 (12.6)	139 (10.4)	
≥30	61 (7.0)	72 (5.4)	
Smoking status			
Never	419 (47.6)	717 (53.4)	0.02
Former	346 (39.3)	459 (34.2)	
Current	116 (13.2)	168 (12.5)	
Level of education			
High School grad or less	267 (30.4)	325 (24.2)	0.0001
Some college or tech.	343 (39.0)	507 (37.8)	
College graduate	180 (20.5)	301 (22.4)	
Postgraduate	89 (10.1)	210 (15.6)	

[a] Family history was defined as having an affected first- or second-degree relative

Table 2 Adjusted odds ratios and 95% confidence intervals for the association between breast-feeding and invasive and borderline epithelial ovarian cancer among women with at least one live birth

	Cases $N = 881$ N (%)	Controls $N = 1{,}345$ N (%)	OR (95% CI)	
Ever breast-fed				
No[a]	286 (32.5)	356 (26.5)	1.00	
Yes	595 (67.5)	988 (73.5)	0.78 (0.64–0.96)	
Total duration of breast-feeding (months)				
None[a]	286 (32.5)	356 (26.5)	1.00	
<6	217 (24.6)	335 (24.9)	0.80 (0.63–1.02)	
6 to <18	210 (23.8)	334 (24.9)	0.81 (0.63–1.05)	
≥18	168 (19.1)	319 (23.7)	0.70 (0.53–0.93)	
Per month			0.997 (0.991–1.003)	$p = 0.3$
Longest individual episode of breast-feeding (months)				
None[a]	286 (32.5)	356 (26.5)	1.00	
<3	157 (17.8)	253 (18.8)	0.81 (0.62–1.06)	
3 to <6	116 (13.2)	183 (13.6)	0.77 (0.57–1.04)	
6 to <12	168 (19.1)	268 (19.9)	0.81 (0.62–1.07)	
12 to <18	98 (11.1)	159 (11.8)	0.81 (0.58	
≥18	56 (6.4)	125 (9.3)	0.57 (0.39	
Per month			0.990 (0.976–1.003)	$p = 0.1$
Average duration of breast-feeding per child breast-fed (months)				
None[a]	286 (32.5)	356 (26.5)	1.00	
<6	341 (38.7)	537 (40.0)	0.81 (0.65–1.01)	
6 to <9	123 (14.0)	213 (15.9)	0.76 (0.55–1.01)	
9 to <12	71 (8.1)	116 (8.6)	0.80 (0.55–1.16)	
12 to < 18	37 (4.2)	76 (5.7)	0.65 (0.41–1.02)	
≥18	23 (2.6)	46 (3.4)	0.56 (0.32–0.98)	
Per month			0.985 (0.968–1.002)	$p = 0.09$
Average duration of exclusive breast-feeding (months) in strata of average months of breast-feeding per child breast-fed[b]				
No breast-feeding[a]	286 (44.6)	356 (33.5)	1.00	
Average duration/child breast-fed 0–6 months				
<3 months exclusive	180 (28.1)	344 (32.3)	0.83 (0.64–1.08)	
3 to ≤6 months exclusive	80 (12.5)	144 (13.5)	0.86 (0.61–1.21)	
Average duration/child breast-fed > 6–12 months				
<3 months exclusive	20 (3.1)	57 (5.4)	0.59 (0.34–1.04)	
3 to ≤6 months exclusive	65 (10.1)	135 (12.7)	0.80 (0.55–1.16)	
>6 months exclusive	10 (1.6)	28 (2.6)	0.57 (0.27–1.22)	

Adjusted for matching variables, reference year, education (high school graduate or less, some college or tech, college graduate, postgraduate), number of live births (1, 2, 3, or ≥4), duration of hormonal contraception (never used, <6 months, 6 months to <5 years, 5 to <10 years, 10 years or more)

[a] Women who never breast-fed at least one child for two or more weeks were included in this group

[b] Only women recruited between 2002 and 2005 provided information about timing of introduction of supplementary feeds

of hormonal contraceptives and histological subtype of ovarian cancer.

Strengths of this study include the large number of cases and controls, its population-based design, the relatively high-response proportions among both cases and controls and the detailed information available about women's breast-feeding practices and potential confounding factors. A weakness is that all the information was recalled, often from many years in the past, so it is likely that there is some error in the estimates. However, highly structured

Table 3 Adjusted odds ratios and 95% confidence intervals for the association between breast-feeding and ovarian cancer in strata of number of live births

	One birth Case = 187 (21.2) Cont = 213 (15.8) OR and 95% CI	Two births Case = 344 (39.1) Cont = 539 (40.1)	Three births Case = 209 (23.7) Cont = 351 (26.1)	Four births Case = 87 (9.9) Cont = 150 (11.2)
Ever breast-fed				
No[a]	1.00	1.00	1.00	1.00
Yes	0.72 (0.44–1.15)	0.75 (0.54–1.04)	0.88 (0.57–1.35)	0.83 (0.42–1.63)
Total duration of breast-feeding (months)				
None[a]	1.00	1.00	1.00	1.00
<6	0.70 (0.41–1.20)	0.96 (0.65–1.42)	0.69 (0.41–1.17)	0.39 (0.16–0.96)
6 to <18	0.87 (0.48–1.57)	0.57 (0.38–0.85)	1.06 (0.62–1.80)	1.89 (0.81–4.40)
≥18	0.32 (0.11–0.90)	0.72 (0.46–1.14)	1.01 (0.57–1.79)	0.73 (0.31–1.70)
Per month	0.975 (0.942–1.010)	0.992 (0.977–1.007)	1.000 (0.992–1.007)	0.998 (0.982–1.014)
Average duration of breast-feeding per child breast-fed (months)				
None[a]	1.00	1.00	1.00	1.00
<6	0.70 (0.41–1.21)	0.81 (0.57–1.15)	0.81 (0.52–1.28)	1.94 (0.46–1.93)
≥6	0.73 (0.42–1.29)	0.66 (0.44–0.98)	1.05 (0.61–1.82)	0.65 (0.28–1.50)
Per month	0.975 (0.942–1.010)	0.983 (0.955–1.012)	0.990 (0.951–1.032)	0.996 (0.933–1.063)

Adjusted for matching variables, reference year, education (high school graduate or less, some college or tech, college graduate, postgraduate), duration of hormonal contraceptive use (never used, <6 months, 6 months to <5 years, 5 to <10 years, 10 years or more)

[a] Women who breast-fed for <2 weeks were included in this group

Table 4 Adjusted odds ratios and 95% confidence intervals for the association between breast-feeding and epithelial ovarian cancer stratified by (a) ever use of hormonal contraceptives, (b) age greater or less than 50 years

	Never used OCs Case = 206 (23.4) Cont = 231 (17.2) OR and 95% CI	Ever used OCs Case = 674 (76.6) Cont = 1,114 (82.8)	Age < 50 Case = 214 (24.3) Cont = 327 (24.3)	Age ≥ 50 Case = 667 (75.7) Cont = 1,018 (75.7)
Ever breast-fed				
No[a]	1.00	1.00	1.00	1.00
Yes	1.10 (0.70–1.72)	0.71 (0.56–0.90)	0.81 (0.48–1.34)	0.77 (0.61–0.96)
Total duration of breast-feeding (months)				
None[a]	1.00	1.00	1.00	1.00
<6	1.14 (0.66–1.97)	0.73 (0.55–0.96)	0.97 (0.53–1.76)	0.75 (0.58–0.98)
6 to <18	1.33 (0.72–2.43)	0.73 (0.55–0.96)	0.79 (0.44–1.41)	0.83 (0.63–1.10)
≥18	0.82 (0.44–1.54)	0.65 (0.47–0.90)	0.68 (0.38–1.24)	0.70 (0.50–0.98)
Per month	1.003 (0.990–1.017)	0.994 (0.987–1.002)	0.994 (0.982–1.006)	0.998 (0.991–1.005)
Average duration of breast-feeding per child breast-fed (months)				
None[a]	1.00	1.00	1.00	1.00
<6	1.16 (0.72–1.86)	0.74 (0.58–0.95)	0.96 (0.56–1.66)	0.77 (0.61–0.98)
≥6	1.03 (0.58–1.83)	0.66 (0.50–0.87)	0.66 (0.38–1.16)	0.76 (0.57–1.02)
Per month	1.002 (0.961–1.045)	0.981 (0.962–1.000)	0.983 (0.956–1.011)	0.985 (0.963–1.008)

Adjusted for matching variables, reference year, education (High School graduate or less, some college or tech, college graduate, postgraduate), duration of hormonal contraceptive use (never used, <6 months, 6 months to <5 years, 5 to <10 years, 10 years or more)

[a] Women who breast-fed for <2 weeks were included in this group

interviews and lifetime calendars were used to aid recall and, as the association between breast-feeding and ovarian cancer is not well established or widely known, it is likely that any error would be non-differential.

Although the World Cancer Research Fund report from 2007 [14] concluded that "there is limited evidence suggesting that lactation protects against ovarian cancer," a meta-analysis of nine case–control studies reported a 30 %

Table 5 Adjusted odds ratios and 95% confidence intervals for the association between breast-feeding and epithelial ovarian cancer by histological subtype

	Invasive				Borderline		
	All invasive $N = 658$ OR (95% CI)	Serous $N = 405$ OR (95% CI)	Endo/ccc $N = 122$ OR (95% CI)	Other $N = 107$ OR (95% CI)	All borderline $N = 223$ OR (95% CI)	Serous $N = 121$ OR (95% CI)	Mucinous $N = 90$ OR (95% CI)
Ever breast-fed							
No[a]	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Yes	0.80 (0.64–1.00)	0.85 (0.65–1.11)	0.73 (0.46–1.14)	0.71 (0.46–1.12)	0.70 (0.50–0.99)	0.73 (0.46–1.14)	0.68 (0.41–1.13)
Total duration of breast-feeding (months)							
None[a]	1.00	1.00	1.00	1.00	1.00	1.00	1.00
<6	0.82 (0.63–1.07)	0.80 (0.58–1.10)	0.99 (0.60–0.64)	0.72 (0.42–1.23)	0.70 (0.46–1.06)	0.71 (0.41–1.23)	0.75 (0.41–1.38)
6 to <18	0.86 (0.66–1.13)	0.95 (0.69–1.32)	0.61 (0.34–1.09)	0.87 (0.50–1.51)	0.66 (0.42–1.02)	0.71 (0.41–1.25)	0.51 (0.25–1.02)
≥18	0.65 (0.47–0.89)	0.80 (0.55–1.16)	0.43 (0.22–0.86)	0.45 (0.21–0.94)	0.77 (0.49–1.22)	0.76 (0.42–1.38)	0.76 (0.39–1.48)
Per month	0.993 (0.986–1.001)	0.999 (0.991–1.007)	0.974 (0.954–0.995)	0.979 (0.957–1.001)	1.004 (0.994–1.014)	1.00 (0.986–1.014)	1.008 (0.994–1.022)
Average duration of breast-feeding per child breast-fed (months)							
None[a]	1.00	1.00	1.00	1.00	1.00	1.00	1.00
<6	0.84 (0.66–1.07)	0.86 (0.64–1.14)	0.89 (0.55–1.44)	0.72 (0.44–1.18)	0.70 (0.48–1.02)	0.77 (0.48–1.26)	0.66 (0.38–1.16)
≥6	0.72 (0.55–0.95)	0.84 (0.61–1.17)	0.48 (0.27–0.87)	0.70 (0.39–1.23)	0.71 (0.47–1.07)	0.65 (0.38–1.12)	0.70 (0.38–1.30)
Per month	0.975 (0.955–0.995)	0.989 (0.965–1.013)	0.944 (0.903–0.987)	0.970 (0.926–1.016)	1.003 (0.978–1.028)	0.997 (0.965–1.030)	1.010 (0.974–1.048)

Adjusted for matching variables, reference year, education (High School graduate or less, some college or tech, college graduate, postgraduate), number of live births (1, 2, 3, or 4 or more) duration of hormonal contraceptive use (never used, <6 months, 6 months to <5 years, 5 to <10 years, 10 years or more)

[a] Women who breast-fed for <two weeks were included in this group

reduction in risk of women who had ever breast-fed [4]. Also, as reviewed by Danforth et al. [7], most other more recently published population-based studies have found inverse associations with breast-feeding [5, 7, 15] although not all results have been statistically significant or shown trends of decreasing risk with increasing duration of lactation. Since the Danforth paper [7] a further three studies have investigated this association. A Danish study of borderline ovarian tumors found an overall reduction in risk of around 2 % per month of breast-feeding [6]. While we found some suggestion of risk reduction for this tumor group, our results were not statistically significant possibly reflecting the much higher proportions of never breast feeders in our study (26 % among our controls versus 6 % in the Danish study). An Australian study reported a similar risk reduction for ever breast-feeding and somewhat stronger inverse associations with total duration and average duration (per birth) of breast-feeding (1.4 and 3.5 % per month, respectively) compared with this study [8]. Again the proportion of never breast feeders was lower in that study (18 %). That study also considered duration of individual episodes of breast-feeding and these analyses suggested that breast-feeding a child beyond 12 months conferred no additional risk reduction. In contrast, our results for the longest episode of breast-feeding, for breast-feeding among women with only one child and for average duration per child breast-fed suggest that risk reduction continues for episodes of 18 months of lactation and beyond. Finally, a recent US-based case–control study found a decreased risk of ovarian cancer for ever breast feeders but little evidence of further risk reduction with increasing duration of lactation (of note, the proportion of never breast feeders among controls in that study was 46 %) [9]. These authors also reported that the risk-reducing effect of breast-feeding was restricted to women who breast-fed their last child—a finding that we did not replicate. They did, however, find, as we did, that the risk reduction associated with breast-feeding was greatest for the combined group of endometrioid and clear cell cancers. A specific benefit for endometrioid or clear cell cancers has now been reported by five [7, 9, 16, 17] of nine studies (including this study) that have investigated the subtype effects. A pooled analysis with the power to investigate the subtypes individually is required to definitively determine whether breast-feeding has particular risk-reducing effects for endometrioid and clear cell cancers but such an association is biologically plausible. Endometriosis is a likely precursor lesion for both subtypes [18] and endometriosis is effectively treated with drugs which induce a profound hypo-estrogenic state; breast-feeding can have a similar effect. Indeed, breast-feeding has been found to reduce the risk of endometriosis among parous women [19].

An overall effect of breast-feeding is also biologically plausible. Breast-feeding causes gonadotrophin suppression leading to low estrogen levels and anovulation with a resulting period of lactational amenorrhea (LAM) and should thus protect the ovary from most factors postulated to have a strong causative role in ovarian cancer development [20]. We did not directly ask about the duration of LAM, although we had information about factors such as supplementary feeding and maternal body mass index around the time of child-bearing, which can influence its duration [3, 21]. In our study, the timing of introduction of supplementary feeds did not appear to influence ovarian cancer risk; however, if extra food merely supplements breast milk intake without reducing it, then gonadotrophin suppression and anovulation may persist [21, 22]. The final indicator of duration of LAM that we have is duration of breast-feeding itself. Duration of episodes of breast-feeding is likely highly correlated with duration of LAM and our results do indicate that longer episodes of breast-feeding result in lower risks of ovarian cancer. Although recall difficulties may be problematic, direct assessment of the duration of lactational amenorrhea and other practices associated with its duration (e.g., night feeding) may help us understand how the benefits of breast-feeding for ovarian cancer reduction might best be achieved.

In conclusion, we have found that, among women who have had the opportunity to breast feed, ever breast-feeding and increasing durations of episodes of breast-feeding are associated with a decrease in the risk of ovarian cancer. In line with the general advice from the US National Institute of Child Health and Human Development [23], our results indicate maternal benefits for breast-feeding to 12 months and beyond.

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Conflict of interest The authors declare that they have no conflicts of interest.

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