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Breastfeeding factors and risk of epithelial ovarian cancer☆

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HIGHLIGHTS

- Breastfeeding for as few as 3 months – the duration of a maternity leave – is associated with reduced ovarian cancer risk.
- This association decreases over time but persists for more than 30 years.
- Longer duration, greater number of offspring nursed, and earlier age at first breastfeeding associate with reduced risk.
- This association is similar in magnitude and duration to that observed for oral contraceptive use and bearing children.

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ABSTRACT

Objective. Previous studies suggest that breastfeeding reduces epithelial ovarian cancer (EOC) risk. However, the effects of age, timing and episode details on the EOC-breastfeeding relationship have not been examined. The objective of this study was to examine the association between breastfeeding factors and epithelial ovarian cancer.

Methods. We examined breastfeeding factors among parous women in a population-based, case-control study conducted in Pennsylvania, Ohio, and New York from 2003 to 2008. We compared 689 incident EOC cases to 1572 community controls. Multivariable unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) associated with breastfeeding patterns adjusting for potential confounders.

Results. Compared to never breastfeeding, breastfeeding any offspring was associated with a 30% reduction in EOC risk (OR = 0.70; 95%CI = 0.58–0.85). That association lasted more than 30 years (OR = 0.69, 95%CI = 0.53–0.88). An average breastfeeding episode of 3 months was also associated with reduced risk (OR = 0.73, 95%CI = 0.58–0.80). A greater number of breastfeeding episodes was associated with greater risk reduction (OR = 0.78, 95%CI = 0.64–0.96 and OR = 0.49, 95%CI = 0.36–0.68 1–2 and 3+ episodes, respectively, compared to never breastfed, trend p = 0.01). Longer breastfeeding duration was also associated with reduced risk (OR = 0.75 and 0.62 for less than and greater than 1-year total duration, respectively, compared to never breastfed). An earlier age at first breastfeeding was further associated with increased protection (OR = 0.50–0.80, for first episode at age <25, 25–29, and 30+, respectively, trend p = 0.001).

Conclusions. Breastfeeding for as few as 3 months is associated with reduced EOC risk. Although this association decreases over time, it persists for more than 30 years. Longer cumulative duration, increasing number of breastfeeding episodes, and earlier age at first breastfeeding episode are each associated with increased benefit.

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1. Introduction

Ovarian cancer is the most lethal gynecologic malignancy [1]. In 2018, approximately 22,240 women in the United States will be diagnosed with the disease and over 14,000 women will die from it [1]. When diagnosed at an early stage, 5-year survival is more than 90% [1]. Unfortunately, more than 70% of cases are diagnosed at a late stage, when 5-year survival is <30% [1]. This high fatality rate, coupled with the lack of a screening test for early detection [2], makes it critical to identify modifiable risk factors to reduce disease burden [3].

Epithelial ovarian cancer (EOC), which accounts for 90% of ovarian cancers [4], is believed to arise from the ovary or fallopian tubes [5]. Oral contraceptive (OC) use and bearing children have consistently been shown to reduce the risk of EOC. Each factor is associated with about a 30% decrease in risk, with greater protection conferred by increasing duration of OC use [6] and greater parity [7]. The benefits of OCs persist for more than 30 years, although the reduction in risk decreases as time since last use increases [6]. A similarly durable, but somewhat attenuated protective effect remains after the last live birth [8]. OC use and child bearing are hypothesized to reduce risk via several ways, although the exact mechanisms remain unknown. Both factors suppress ovulation, thereby reducing repetitive trauma to ovarian surface or tubal epithelium that can result in aberrant repair and subsequent malignant transformation [9,10]. Both factors also reduce gonadotropin levels, which result in lower estrogen levels. Estrogen can increase ovarian surface and tubal epithelial proliferation, potentially leading to malignant transformation [11,12]. Finally, pregnancy and OCs alter endogenous estrogen and progesterone levels, two hormones that have been implicated in EOC risk [13].

Breastfeeding also suppresses ovulation, reduces gonadotropin levels, and alters the hormonal milieu [14]; thus, it may reduce EOC risk. Most case-control studies report a protective association with ever breastfeeding [7,15,16]. Some also report an increasing reduction in risk associated with increasing cumulative duration [7,15,16]. In contrast, the handful of cohort studies examining breastfeeding found a weak, statistically non-significant reduction in risk [15], except for the Nurses' Health Study, which reported a statistically significant protective effect only after 18 cumulative months of breastfeeding [17].

Beyond the association with ever breastfeeding and breastfeeding duration, there has been little exploration of factors that may influence the breastfeeding-EOC association. Questions remain about the effects of age at breastfeeding, time since breastfeeding, and influence of birth order among offspring breastfed. We used data from a large, population-based case-control study to examine these questions.

2. Material and methods

2.1. Subjects

Details of the Hormones and Ovarian cancer PrEdiction (HOPE) Study are described elsewhere [18]. Cases were women diagnosed with incident, histologically-confirmed epithelial ovarian, peritoneal, or fallopian tube cancer from February 2003 to November 2008 in the contiguous regions of western Pennsylvania, eastern Ohio, and southwestern New York. Eligible participants were at least 25 years old, residing within the catchment region, and within 9 months of diagnosis at the time of interview. Women were identified through a network of hospital and physician practices using pathology records, physician practice records, and hospital cancer registries. Among 2878 potentially eligible cases, 1608 were excluded due to ineligibility (time since diagnosis more than 9 months, residence outside catchment region, prior diagnosis of ovarian cancer, inability to speak English, deceased). Of the 1270 remaining eligible cases, 902 (71%) consented to study participation.

Controls were identified through random-digit dialing and were frequency-matched to cases by 5-year age groups and 3-digit telephone exchange in a 2:1 ratio. Among 3922 women screened by phone, 2501 met eligibility requirements, and 1802 (72%) consented to study participation.

Institutional Review Board approval for the study was obtained from hospitals in which cases were identified and from the University of Pittsburgh. All participants provided written, informed consent.

2.2. Data collection and exposure assessment

Trained interviewers conducted a standardized 2-hour in-person interview to obtain detailed information on reproductive, medical, and demographic data from birth until a reference date. To aid recall, a life events calendar with milestones, such as marriages, births, and deaths, was used [19]. Each pregnancy was denoted on the calendar by coloring the month of pregnancy initiation until pregnancy end. Breastfeeding episodes were similarly noted on the calendar. For each pregnancy, a woman was asked the outcome (live birth, still birth, miscarriage, abortion). For each live birth, she was asked detailed information, including "Did you ever breastfeed this baby?" If she responded "yes", the total number of months breastfed was elicited by asking "For how many months did you nurse?"

The reference date was calculated as 9 months prior to diagnosis (cases) or interview (controls) to ensure that exposures occurred before ovarian cancer diagnosis in cases and within a similar time frame for controls.

Pathology data were extracted from pathology reports by two independent readers. Differences were reviewed by study staff to assign final pathology data.

2.3. Statistical analyses

Analyses were limited to the 1572 controls and 689 cases who reported at least one live birth. A woman was classified as having ever breastfed if she responded positively to the question "Did you breastfeed this baby?" for any live birth she reported. Total duration of breastfeeding was calculated by summing the number of months breastfed across all breastfeeding episodes. Age at first breastfeeding episode was calculated using the month and year of the pregnancy end corresponding to the first breastfeeding episode and the month and year of a subject's birth. Age at last breastfeeding episode was similarly calculated using the month and year of the pregnancy end corresponding to the last breastfeeding episode. Time since the first breastfeeding episode was obtained by calculating the time elapsed since the end of the first breastfeeding episode until the reference date. Time since the last breastfeeding episode was similarly obtained using the time elapsed since the end of the last breastfeeding episode.

We assessed total number of breastfeeding episodes, breastfeeding some or all offspring, average duration of breastfeeding per breastfeeding episode (defined as total breastfeeding duration divided by total number of offspring breastfed), and the duration of breastfeeding for the first and last breastfeeding episodes.

Case-control differences in demographic and other factors were initially assessed using X^2 tests. Multivariable unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between each breastfeeding factor and EOC (separate models for each factor). Age at reference date, total OC duration, parity, race, education, tubal ligation status, hysterectomy status, and family history of breast or ovarian cancer were selected a priori as potential confounders. A variable was retained if its removal resulted in at least a 10% change in the effect estimate. Family history of breast and ovarian cancer, tubal ligation, and hysterectomy did not affect the relationship between breast feeding and ovarian cancer risk and were not included in the final models. Sensitivity analyses showed estimates were not changed when including factors that may influence a woman's decision to breastfeed in our models (body mass index (BMI), smoking history, ever use of alcohol, and ever use of aspirin or

NSAIDs); therefore, they were not included in the final models. Sensitivity analyses showed estimates were also unchanged by adjusting for age at first live birth, age at last live birth, decade of subject's birth, and year of birth as being pre vs post 1950 and therefore we not included in the final models. Thus, the final models included age at reference date, total OC duration, and parity as continuous variables, and race and education as categorical variables. Tests for trend were performed by coding the exposure of interest as a grouped linear variable. Analyses were repeated examining only women age 50 or over and restricting cases to women with invasive disease only. Further analyses examined the associations limiting to high grade serous EOC (the most common histotype); limited cases of other histotypes precluded meaningful analyses. All p-values were two-sided and considered statistically significant at $p < 0.05$. Analyses were conducted using Stata version 9.1 (StataCorp).

3. Results

Cases were more likely to be non-white and less educated, as well as to have an increased family history of breast or ovarian cancer (Table 1). They were less likely to have used OCs, borne children, or had a tubal ligation.

Cases were less likely to have breastfed, and breastfeeding was associated with a statistically significant 30% decrease in EOC risk (OR = 0.70, 95%CI = 0.58–0.85; Table 2). The magnitude of this association was similar whether all (OR = 0.71) or only some (OR = 0.69) offspring were breastfed, as well as whether the first (OR = 0.69) or last (OR = 0.72) offspring was breastfed. Greater number of breastfeeding episodes was associated with increased protection (OR = 0.78 and 0.49 for nursing 1–2 and 3+ episodes, respectively, compared to never breastfed, trend p = 0.01).

Longer total breastfeeding duration across all breastfeeding episodes was also associated with increased protection (OR = 0.75 and 0.62 for less than and greater than 1-year total duration, respectively; Table 3). An average duration of 3 months per breastfeeding episode was associated with statistically significant risk reduction (OR = 0.73, 95%CI = 0.58–0.93). Longer average duration per breastfeeding episode appeared more protective although the difference was not statistically significant (OR = 0.73 and OR = 0.67 for 1–3 and 4 or more months average per episode, respectively). Longer duration for both the first (OR = 0.75 and OR = 0.66 for 1–3 and 4 or more months, respectively) and last (OR = 0.75 and OR = 0.65) breastfeeding episodes was associated with statistically significant reduced risk.

An earlier age at first breastfeeding episode was associated with a statistically significant 37% reduction in EOC risk (OR = 0.63, 95%CI = 0.50–0.80, Table 4). Increasing age at first breastfeeding was associated with a decreasing protective effect (OR = 0.63, 0.71, 0.92, for first episode at age <25, 25–29, and 30+, respectively, trend p = 0.001). In contrast, age at last breastfeeding episode did not have a substantial impact on risk; last breastfeeding episode at any age provided a similar protective effect (OR = 0.66, 0.76, 0.70, for last episode at age <25, 25–29, and 30+, respectively).

More recent breastfeeding was associated with a statistically significant 44% reduction in EOC risk (OR = 0.56, 95%CI = 0.32–0.95 for time since last breastfeeding within the last 10 years, Table 4). Although the association with reduced risk decreased over time, the effect persisted for more than 30 years after the last breastfeeding episode (OR = 0.69, 95%CI = 0.53–0.88).

Results were similar when examining women over 50 (Supplemental Tables S1a–S1c), when restricting cases to women with invasive disease (Supplemental Tables S2a–S2c), and when restricting cases to high grade serous histotype (Supplemental Tables S3a–S3c).

Table 1
Characteristics of HOPE Study participants, 2003–2008.

	Controls (N = 1572)	Cases (N = 689)	p-Value
	N (%)	N (%)	
Age, years			<0.001
<50	450 (28.6)	133 (19.3)	
50–54	211(13.4)	96 (13.9)	
55–59	279 (17.8)	113 (16.4)	
60–64	178 (11.3)	93 (13.5)	
65–69	175 (11.1)	83 (12.1)	
70+	279 (17.8)	171 (24.8)	
Race			0.001
White	1530 (97.3)	652 (94.6)	
Black	27 (1.7)	31 (4.5)	
Other	15 (1.0)	6 (0.9)	
Education			<0.001
Less than high school	75 (4.8)	74 (10.7)	
High school	488 (31.0)	249 (36.1)	
Post high school training	495 (31.5)	191 (27.7)	
College graduate	514 (32.7)	175 (25.4)	
Menopausal status			0.003
Pre-menopausal	481 (30.6)	168 (24.4)	
Post-menopausal	1039 (66.1)	505 (73.3)	
Unknown	52 (3.3)	16 (2.3)	
Body mass index (BMI), kg/m^2			0.409
<25	595 (37.9)	243 (35.3)	
25–29	466 (29.7)	204 (29.7)	
≥30	510 (32.5)	241 (35.0)	
Oral contraceptive use			<0.001
Never	451 (28.7)	271 (39.3)	
Ever	1121 (71.3)	418 (60.7)	
Duration of oral contraceptive use, years			<0.001
0	451 (28.7)	271 (39.3)	
<1	247 (15.7)	126 (18.3)	
1–4	425 (27.0)	156 (22.6)	
5–9	267 (17.0)	94 (13.6)	
10+	182 (11.6)	42 (6.1)	
Number of full births			0.212
1	231 (14.7)	120 (17.4)	
2	601 (38.2)	264 (38.3)	
3+	740 (47.1)	305 (44.3)	
Tubal ligation			<0.001
No	979 (62.3)	496 (72.0)	
Yes	593 (37.7)	193 (28.0)	
Hysterectomy			0.002
No	1284 (81.7)	523 (75.9)	
Yes	288 (18.3)	166 (24.1)	
Hormone replacement therapy use			0.984
Never	982 (62.5)	432 (62.7)	
Ever	540 (34.4)	236 (34.3)	
Unknown	50 (3.2)	21 (3.1)	
Smoking status			0.473
Never smoker	779 (49.6)	340 (49.4)	
Current smoker	298 (19.0)	118 (17.1)	
Former smoker	495 (31.4)	231 (33.5)	
Alcohol use			0.887
Never	935 (59.5)	412 (59.8)	
Ever	637 (40.5)	277 (40.2)	
Aspirin/NSAID use			0.270
Never	743 (47.3)	343 (49.8)	
Ever	829 (52.7)	346 (50.22)	
Family history of breast or ovarian cancer			0.02
No	1301 (82.9)	541 (78.8)	
Yes	269 (17.1)	146 (21.3)	
History of endometriosis			0.318
No	1465 (93.2)	634 (92.0)	
Yes	107 (6.8)	55 (8.0)	

4. Discussion

In the HOPE Study, breastfeeding was associated with a 30% reduction in EOC risk. While this association decreased over time, it persisted for more than 30 years. Breastfeeding for as little as three months was associated with statistically significant reduction in risk. Longer breastfeeding duration, greater number of breastfeeding episodes, and earlier age at first breastfeeding were each associated with increased protection.

Our results are consistent with the majority of studies that have shown an inverse association between ever breastfeeding and EOC

Table 2
Association of breastfeeding patterns with epithelial ovarian cancer, the HOPE Study 2003–2008.

Factor	Controls	Cases	Odds ratio	95% confidence interval	Adjusted odds ratio[a]	95% confidence interval
	N (%)	N (%)				
Ever breastfed						
No	684 (43.5)	386 (56.0)	1		1	
Yes	888 (56.5)	303 (44.0)	0.6	0.50–0.72	0.70	0.58–0.85
Breastfed all offspring						
Never breastfed	684 (43.5)	386 (56.0)	1		1	
Breastfed some, but not all	328 (20.9)	119 (17.3)	0.64	0.50–0.82	0.69	0.53–0.89
Breastfed all	560 (35.6)	184 (26.7)	0.58	0.47–0.72	0.71	0.57–0.89
Breastfed first offspring						
Never breastfed	684 (43.5)	386 (56.0)	1		1	
Breastfed some, but not first	122 (7.8)	46(6.7)	0.67	0.47–0.96	0.77	0.52–1.11
Breastfed first offspring	766 (48.7)	257 (37.3)	0.59	0.49–0.72	0.69	0.57–0.85
Breastfed last offspring						
Never breastfed	684 (43.5)	386 (56.0)	1		1	
Breastfed some, but not last	198 (12.6)	71 (10.3)	0.64	0.47–0.86	0.65	0.47–0.89
Breastfed last	690 (43.9)	232 (33.7)	0.60	0.49–0.72	0.72	0.58–0.89
Number of breastfeeding episodes						
Never breastfed	684 (43.5)	386 (56.0)	1		1	
1 or 2 episodes	619 (39.4)	238 (34.5)	0.68	0.56–0.83	0.78	0.64–0.96
3 or more episodes	269 (17.1)	65 (9.4)	0.43	0.32–0.58	0.49	0.36–0.68
					Trend p = 0.01	

[a] Separate models and analyses for each factor. Each model adjusted for age, race, education, duration of oral contraceptive use, and number of pregnancies.

risk. A meta-analysis of 35 studies [16] reported a summary relative risk of 0.76, which is similar in magnitude to the point estimate (0.70) we report. Data examining the effect of duration are less consistent. Some studies have reported a decrease in risk with increasing total or average duration, whereas others report no trend with increasing duration or no additional benefit from breastfeeding beyond a certain number of months [17,20–23]. Despite reporting inter-study heterogeneity, a recent meta-analysis of 40 studies [15] found a statistically significant point estimate of 0.64 (95%CI 0.56–0.73) for total breastfeeding duration of greater than one year, which is similar to the protective association we observed (OR = 0.62).

Only one previous study explored factors related to age and timing of breastfeeding, with no effects noted [20]. This stands in contrast to our findings in which an earlier age at first breastfeeding episode was associated with a statistically significant reduction in EOC risk. That protective association was evident but decreased with increasing age at first breastfeeding episode. We further found that while more recent breastfeeding was associated with greater protection, the reduced risk associated with breastfeeding persisted for more than 30 years.

A differential effect of age and recency of breastfeeding as well as a persistent effect of exposure is similar to what is observed with OC use [24]. Specifically, as we found for breastfeeding, earlier age at first OC use is associated with increased protection against EOC, with the magnitude of the protective effect decreasing with increasing age at first use [24]. More recent OC use is also associated with greater protection, and while the magnitude of that association decreases with time, it remains for more than 30 years after cessation [24]. The impact of age and timing of childbearing on EOC risk is less clear. Recent full-term birth has been associated with a greater decrease in risk in most studies. In contrast to our findings of greater EOC protection associated with an earlier age at first breastfeeding, a later age at last birth may provide the greatest protection. In particular, age at last pregnancy has been found to be more critical to EOC risk reduction than number of pregnancies [8,25,26]. This observation is often attributed to the apoptotic effect of high progesterone levels in pregnancy potentially "clearing" premalignant ovarian epithelial cells [26].

Only one study has examined the pattern of offspring breastfed and its association with EOC, reporting that while breastfeeding in general is associated with reduced EOC risk, this protective association was limited to women who breastfed their last child [22]. We did not replicate that finding. We observed that if breastfeeding any one child provides greater protection, it is the first child, which in our study was associated

Table 3
Association of breastfeeding duration with epithelial ovarian cancer, the HOPE Study 2003–2008.

Factor	Controls	Cases	Odds ratio	95% confidence interval	Adjusted odds ratio[a]	95% confidence interval
	N (%)	N (%)				
Total duration of breastfeeding (years)						
Never breastfed	684 (43.5)	386 (56.0)	1		1	
<1	502 (31.9)	192 (27.9)	0.68	0.55–0.83	0.75	0.61–0.94
1 or more	386 (24.6)	110 (16.0)	0.50	0.39–0.65	0.62	0.47–0.80
Duration of breastfeeding per breastfeeding episode (months)						
Never breastfed	684 (43.5)	386 (56.0)	1		1	
≤3	375 (23.9)	143 (20.8)	0.68	0.54–0.85	0.73	0.58–0.93
4 or more	513 (32.6)	159 (23.1)	0.55	0.44–0.60	0.67	0.53–0.85
Duration of breastfeeding first breastfeeding episode (months)						
Never breastfed	684 (43.5)	386 (56.0)	1		1	
≤3	396 (25.2)	151 (21.9)	0.68	0.54–0.85	0.75	0.59–0.94
4 or more	492 (31.3)	151 (21.9)	0.54	0.44–0.68	0.66	0.52–0.84
Duration of breastfeeding last breastfeeding episode (months)						
Never breastfed	684 (43.5)	386 (56.0)	1		1	
≤3	393 (25.0)	154 (22.4)	0.69	0.55–0.87	0.75	0.60–0.95
4 or more	495 (31.5)	148 (21.5)	0.53	0.42–0.66	0.65	0.51–0.83

[a] Separate models and analyses for each factor. Each model adjusted for age, race, education, duration of oral contraceptive use, and number of pregnancies.

Table 4
Timing of breastfeeding and epithelial ovarian cancer, the HOPE Study 2003–2008.

Factor	Controls	Cases	Odds ratio	95% confidence interval	Adjusted odds ratio[a]	95% confidence interval
	N (%)	N (%)				
Age at first breastfeeding episode (years)						
Never breastfed	684 (43.5)	386 (56.0)	1		1	
<25	415 (26.4)	141 (20.5)	0.60	0.48–0.76	0.63	0.50–0.80
25–29	295 (18.8)	91 (13.2)	0.55	0.42–0.71	0.71	0.54–0.95
30+	178 (11.3)	71 (10.3)	0.71	0.52–0.96	0.92	0.67–1.27
					Trend p = 0.001	
Age at last breastfeeding episode (years)						
Never Breastfed	684 (43.5)	386 (56.0)	1		1	
<25	199 (12.7)	75 (10.9)	0.67	0.50–0.90	0.66	0.49–0.89
25–29	246 (15.7)	90 (13.1)	0.65	0.49–0.85	0.76	0.57–1.00
30+	443 (28.2)	138 (20.0)	0.55	0.44–0.69	0.70	0.55–0.90
Time since first breastfeeding episode (years)						
Never breastfed	684 (43.5)	386 (56.0)	1		1	
<10	71 (4.5)	12 (1.7)	0.30	0.16–0.56	0.56	0.28–1.10
10–19	150 (9.5)	41 (5.9)	0.48	0.34–0.70	0.76	0.50–1.14
20–29	253 (16.1)	92 (13.4)	0.64	0.49–0.84	0.85	0.63–1.14
30+	414 (26.3)	158 (22.9)	0.68	0.54–0.84	0.64	0.51–0.80
Time since last breastfeeding episode (years)						
Never breastfed	684 (43.5)	386 (56.0)	1		1	
<10	114 (7.3)	21 (3.1)	0.33	0.20–0.53	0.56	0.32–0.95
10–19	209 (13.3)	58 (8.4)	0.49	0.36–0.67	0.70	0.49–0.99
20–29	224 (14.3)	82 (11.9)	0.65	0.49–0.86	0.80	0.59–1.07
30+	341 (21.7)	142 (20.6)	0.74	0.59–0.93	0.69	0.53–0.88

[a] Separate models and analyses for each factor. Each model adjusted for age, race, education, duration of oral contraceptive use, and number of pregnancies.

with a (statistically non-significant) increased protection relative to breastfeeding any child but the first.

A protective effect of breastfeeding is biologically plausible. Although the pathogenesis of EOC remains unclear, two prevailing theories have dominated the literature. The incessant ovulation hypothesis posits that ovulation results in repeated trauma to ovarian surface epithelial cells, and subsequent repair opens the door for malignant transformation [9]. More recently, data suggest that some ovarian cancers may arise from the fimbreated end of the fallopian tube [5], where release of follicular fluid from ovulation may result in inflammation and DNA damage to tubal epithelial cells [10]. These transformed cells may then migrate and implant on the ovarian surface or within the peritoneal cavity [27]. Regardless of whether EOC arises in the ovary or fallopian tube, factors that decrease ovulation would reduce EOC risk. The gonadotropin hypothesis posits that high levels of gonadotropins increase ovarian estrogen stimulation, thereby promoting ovarian surface and tubal epithelial cell proliferation and increasing the chance for malignant transformation [11]. Thus, factors that decrease gonadotropins would also reduce EOC risk. Breastfeeding suppresses gonadotropins (particularly luteinizing hormone), which reduces estrogen levels and leads to anovulation and amenorrhea [14]. In the absence of breastfeeding, ovulation typically resumes six weeks postpartum, whereas ovulation can be suppressed for several months with lactation [28,29].

Alterations in the maternal hormonal milieu and/or metabolism are other potential biologic mechanisms whereby breastfeeding may impact EOC risk. Weaning, not birth, is the natural end to a pregnancy episode in terms of pregnancy-associated physiologic changes [30]. Therefore, lactation may reset pregnancy-associated hormonal mechanisms, which could influence EOC risk [22]. It may also reset pregnancy-associated metabolic changes, such as insulin resistance and visceral fat accumulation, that may increase EOC risk [31,32]. Longer breastfeeding duration reduces accumulated fat stores and results in other favorable metabolic changes that persist long after weaning [28]. In contrast, in women who do not breastfeed, adverse metabolic changes associated with EOC risk persist [30].

A major strength of this study is that it is one of the largest population-based studies of EOC ever conducted in the US. In addition, data were collected through a standardized, structured interview administered by trained personnel, ensuring consistent and high-quality exposure measurements.

Despite these strengths, limitations must be noted. First, although the original HOPE subject population frequency matched cases and controls by 5-year age groupings, when restricting the data set to women reporting at least one live birth, controls were younger than cases (Table 1). Thus, because younger controls were overrepresented in the subset of participants included in the breastfeeding analyses reported herein, some of our findings may reflect the structure of the restricted dataset rather than a true association. For example, younger women may be more likely to breastfeed more recently. To address this concern, we controlled for age in our models. In addition, we repeated our analyses limiting subjects to women over 50 years of age, which showed similar results to analyses in the overall population.

Because of the large age range in our study population, we cannot eliminate the possible influence of cohort effects. We controlled for age in our models and our analyses restricting subjects to women 50 + years of age produced findings similar to those of the overall population. In addition, including a term for decade of birth (as a marker for cohorts) and analyses including a term for subject birth year pre- or post-1950 (as a more gross marker for cohorts) did not impact effect estimates.

As in all case-control studies, we cannot eliminate the possibility of recall bias. However, participants were not aware of the study hypotheses since questions regarding breastfeeding were collected as part of a more detailed interview regarding various aspects of reproductive health and behavior. In addition, trained interviewers used structured, standardized interview questions and prompts, including life event calendars, which provided graphical time frames to help improve respondents' long-term recall. Selection bias is also a concern. The population-based design and frequency-matching by three-digit telephone prefix, a marker of geographical location, increased the likelihood that controls were representative of the population from which the cases arose. However, we cannot exclude the possibility that controls who chose to participate in HOPE differed in important exposure or confounding factors from potential controls who did not, thereby over- or under-estimating the true association. The lack of information on lactational amenorrhea, exclusive breastfeeding, and effects of breastfeeding on maternal anthropometry are also limitations. Our inability to control for total estrogen exposure prior to diagnosis and cumulative months of pregnancy in our models are additional limitations. Finally, because more than 97% of controls and 94% of cases were white women from western PA, eastern

OH, and southwestern NY, the generalizability of our findings to other races or ethnicities cannot be assumed.

Approximately 82% of U.S. women give birth to at least one child [33]. The American Academy of Pediatrics (AAP) recommends exclusive breastfeeding for 6 months and continued breastfeeding for at least 1 year [34]. The American College of Obstetricians and Gynecologists (ACOG) affirms this recommendation [35]. Despite these recommendations, <20% of infants are exclusively breastfed for 6 months, <50% are breastfed for 6 months, and only 27% are still breastfeeding at 1 year [36]. Our findings suggest that improving compliance with AAP and ACOG recommendations could impact EOC risk in the vast majority of U.S. women.

In conclusion, interventions to encourage and support women in breastfeeding may help reduce EOC risk. Breastfeeding any offspring for as little as 3 months is associated with a statistically significant protective effect. Thus, encouraging women to breastfeed even if only during a maternity leave may provide benefit. Notably, this association persists for more than 30 years and is similar to the magnitude and duration of protection associated with oral contraceptive use and bearing children, the two well-established EOC protective factors. Studies examining the biological bases for the observations presented in this and other work examining the EOC-breastfeeding link can potentially shed light on EOC etiology and open pathways to identifying new prevention modalities, which are critical in overcoming this highly fatal malignancy.

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Conflict of interest

The authors report no conflicts of interest.

Author contributions

Francesmary Modugno: Contributed to the conception and design of the study, analysis, and interpretation of data, drafted the article, and approved the final version submitted for publication.

Sharon L. Goughnour: Contributed to the analysis and interpretation of data, revision of the article, and approved the final version submitted for publication.

Danielle Wallack: Contributed to the analysis and interpretation of data, revision of the article, and approved the final version submitted for publication.

Robert P. Edwards: Contributed to the collection of study data, revision of the article, and approved the final version submitted for publication.

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Roberta B. Ness, MD: Contributed to the collection of study data, conception and design of the study, revision of the article, and approved the final version submitted for publication.

Maria Mori Brooks: Contributed to the analysis and interpretation of data, revision of the article, and approved the final version submitted for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.01.017.

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