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Linda Titus-Ernstoff,
Department of Community & Family Medicine, Dartmouth Medical School, 1 Medical Center Drive, 7927 Rubin Building, Lebanon, NH 03756, USA, Linda.titus-ernstoff@dartmouth.edu

Department of Pediatrics, Dartmouth Medical School, Lebanon, New Hampshire, USA

Judy R. Rees,
Department of Community & Family Medicine, Dartmouth Medical School, 1 Medical Center Drive, 7927 Rubin Building, Lebanon, NH 03756, USA

Kathryn L. Terry, and
Ob-Gyn Epidemiology Center, Brigham and Women's Hospital, Boston, MA, USA

Daniel W. Cramer
Ob-Gyn Epidemiology Center, Brigham and Women's Hospital, Boston, MA, USA

Abstract

Conflicting reports regarding the relationship between breast-feeding and ovarian cancer risk suggest a possible influence of patterns of breast-feeding. We used logistic regression to examine breast-feeding in a large population of parous women who participated in a case–control study of ovarian cancer in New Hampshire and MA, USA. Risk of ovarian cancer was reduced in parous women who ever breast-fed (OR: 0.75; 95% CI: 0.62, 0.92), but evidence was limited for an influence of duration of breast-feeding and the number of children breast-fed. Compared to never breast-feeding, inverse associations were seen for breast-feeding all children (OR: 0.72; 95% CI: 0.58, 0.91) and for breast-feeding some children when the last born child was breast-fed (OR: 0.58; 95% CI: 0.37, 0.91). There was little evidence of reduced risk for those who breast-fed some children when the last born child was not breast-fed (OR: 0.91; 95% CI: 0.66, 1.26). Similar findings were noted in women with exactly two children and in those with two or more children. The protective influence of breast-feeding on ovarian cancer risk may be limited to women who breast-feed their last born child. These findings, which require confirmation by future studies, imply that breast-feeding resets pregnancy-related states that mediate ovarian cancer risk.

Keywords

Ovarian cancer; Breast-feeding; Parity

Introduction

Parity and oral contraceptive use are strong and well-established protective factors for ovarian cancer. Pooled analyses have shown a decreasing risk with higher parity [1,2] and with longer duration of oral contraceptive use [1-4]. An early pooled analysis [1] and a subsequent study [5] showed an inverse relationship between ovarian cancer and ever having breast-fed, but several recent studies have found no association [6-10]. Findings have been inconsistent for

Correspondence to: Linda Titus-Ernstoff.

the duration of breast-feeding, which is inversely associated with ovarian cancer risk in some [5,11,12] but not all reports [6,13-15]. Study results have also been inconsistent with regard to a role for the number of children breast-fed [5,6].

Inconsistencies in findings across studies suggest the possibility that risk of ovarian cancer might be influenced by other patterns of breast-feeding, such as whether some or all children were breast-fed. We assessed this possibility using data from a large population-based, case–control study conducted in New England, USA. The size of our study allowed us to examine breast-feeding, duration of breast-feeding, and patterns of breast-feeding according to levels of parity.

Methods

This population-based case–control study of ovarian cancer was approved by the Human Subjects Review Committees at both Brigham and Women's Hospital and Dartmouth Medical School; all participants provided a signed informed consent. The study methods have been described previously [16]. Data were collected during two enrollment phases; the first phase started in May 1992 and ended in March 1997, the second phase started in July 1998 and ended in July 2003. Case enrollment was similar in the two phases [16]. Briefly, eligible case women were residents of New Hampshire or eastern Massachusetts who had a new diagnosis of ovarian cancer ascertained through hospital tumor boards and statewide cancer registries. We identified 2,347 case women; of these, 502 could not be contacted because they had died (n = 210), moved, or had no telephone (n = 160), did not speak English (n = 37), had a non-ovarian primary tumor after review (n = 93), or lived outside the study area (n = 2). Physicians declined permission to contact 232 of the remaining cases, and 307 cases declined or were too ill to participate. Of the 1,306 enrolled cases, 1,231 cases had epithelial ovarian tumors, including tumors of borderline malignancy (563 in phase 1 and 668 in phase 2).

During phase 1, control women were selected using random digit dialing (RDD) supplemented with residents lists for older controls. In 10% of households contacted through RDD, the answerer declined to provide a household census and in 80% of households, an age- and sex-matched control for a case could not be made, or was ineligible due to a previous oophorectomy. Of the remaining 10% of screened households containing a potentially eligible control, 72% agreed to participate. Because RDD proved inefficient for identifying controls >60 years old in Massachusetts, we identified older controls in Massachusetts by randomly selecting women from the residents' lists (townbooks) matched to cases by community and age within 4 years. Of 328 sampled townbook controls, 21% could not be reached, 18% were ineligible, and 30% declined to participate. A total of 523 (421 RDD and 102 townbook) controls were enrolled from phase 1 of the study. During phase 2, controls were identified through townbooks in Massachusetts and drivers' license lists in New Hampshire. Age matching was accomplished by sampling controls based upon the age distribution of cases in the previous phase of the study with adjustment as current cases were enrolled. Of the 1,843 potential controls identified in the second phase, 576 were ineligible because they had died, moved, or had no telephone, did not speak English, had no ovaries, or were seriously ill. Of the remaining 1,267 potential controls, 546 declined participation either by telephone or by returning an "opt out" postcard, and 721 were enrolled.

Participants were interviewed in-person at a location of their choosing. The questionnaire included demographic characteristics as well as medical, family, hormone use, including use of oral contraceptives (OC), and a complete reproductive history, including the number of live births and the date of birth for each child. For each live birth, the woman was asked whether the child was breast-fed and the duration of breast-feeding.

Statistical analyses

In all, 1,231 cases of ovarian cancer and 1,244 controls were enrolled in the study. The analysis of breast-feeding (defined as breast-feeding for at least one month) was based on 829 cases and 1,009 controls who reported at least one live birth (parous women), allowing for the possibility of breast-feeding. Four parous women who did not provide breast-feeding information were omitted, leaving 828 cases and 1,006 controls for analysis. In addition to assessing ever breast-feeding, we examined the number of children breast-fed as well as the total duration (in months) of breast-feeding over all live births, the average duration of breast-feeding per live birth and per breast-fed child. We also assessed patterns of breast-feeding, including whether some or all children were breast-fed, whether the last born child was breast-fed, and the duration of breast-feeding the last born child. Analyses were conducted overall and within subgroups of interest, for example, among uniparous women (those with one live birth), parous women (women with one or more live births), multiparous women (women with two or more live births), and women with exactly two live births. We also assessed breast-feeding in relation to the histologic subgroups of ovarian cancer.

We calculated odds ratios (OR) and 95% confidence intervals (CI) using unconditional logistic regression models to estimate the association between breast-feeding and ovarian cancer risk. Unless stated otherwise, ORs reported here were minimally adjusted for age, study center, OC use, and age at the most recent live birth. ORs based on women with more than one child additionally were adjusted for parity. Preliminary analyses indicated that ORs were unchanged by adjustment for age at first live birth, the difference between the age at first and last birth, or duration of breast-feeding, whether assessed as total duration of breast-feeding over all live births or the average duration of breast-feeding per live birth. Tests of trend were based on the continuous form of variables among those with the exposure of interest. T-tests were used to compare the average number of months of breast-feeding for cases and controls. All statistical tests were two-sided (alpha = 0.05).

Results

In this study, population of parous women the mean age of cases was slightly greater than that of controls, and women who had ever breast-fed were younger than those who had not (Table 1). Use of OC was more common in controls than in cases overall, and among women who had breast-fed and those who had not. The average number of live births was slightly lower in cases than in controls, and this was true regardless of breast-feeding status. Women’s age at their most recent birth was somewhat greater in controls than in cases, and this was evident among those who had breast-fed and those who had not.

The inverse association between parity (treated as a continuous variable) and ovarian cancer risk was comparable for women who had ever breast-fed (OR: 0.85; 95% CI: 0.75, 0.96) and those who had not (OR: 0.84; 95% CI: 0.75, 0.93) (results not shown in table). Among all parous women, 43.0% of cases and 54.0% of controls had ever breast-fed; the adjusted OR was 0.75 (95% CI, 0.62, 0.92) for ever having breast-fed compared to never (Table 2). On average, parous cases breast-fed 0.8 children and controls breast-fed 1.1. Among women who had breast-fed, the OR was 0.97 (95% CI: 0.82, 1.14) for each additional child who was breast-fed (Table 2; p for trend = 0.69). In all parous women, 29.0% of cases and 36.5% of controls breast-fed all their live born children. Compared to breast-feeding none, the ORs were 0.72 (95% CI: 0.58, 0.91) for breast-feeding all live born children and 0.91 (95% CI: 0.66, 1.26) for breast-feeding some children but not the last born (Table 2). Also compared to breast-feeding none, the OR was 0.58 (95% CI: 0.37, 0.91) for breast-feeding some children including the last born child. This finding was comparable when breast-feeding some children including the last born was directly compared to breast-feeding some children excluding the last born (OR: 0.58; 95% CI: 0.34, 0.99). Using the same comparison, exploratory stratified analyses produced

ORs of 0.46 (95% CI: 0.21, 1.03) in women who were 31 years of age or older at the time of their last birth and 0.70 (95% CI: 0.33, 1.45) in women who were age <31 at the time of their last birth (data not shown in table). Finally, the OR was 0.56 (95% CI: 0.38, 0.83) when we compared breast-feeding the last born child to nulliparity (not shown in table).

Among parous women who ever breast-fed, cases breast-fed for a total duration of 11.6 months, and controls for 13.3 months. The mean duration of breast-feeding per live birth (or per breast-fed child) in all parous women was 2.3 (5.9) for cases and 3.1 (6.4) months for controls. Compared to never breast-feeding, the adjusted ORs for the mean duration of breast-feeding per live birth in parous women were 0.77 (95% CI: 0.62, 0.95) for breast-feeding fewer than 6 months, 0.77 (95% CI: 0.56, 1.06) for breast-feeding at least 6 months, but fewer than 12, and 0.58 (95% CI: 0.37, 0.93) for breast-feeding at least 12 months (Table 3). Among parous women who ever breast-fed, the adjusted OR was 0.99 (95% CI: 0.97, 1.02) for each additional month of breast-feeding per live birth (Table 3). The findings were similar for each additional month of breast-feeding over all births (OR: 1.00; 95% CI: 0.99, 1.01; data not shown in table). In parous women, who had breast-fed their last born child, the OR was 1.00 (95% CI: 0.97, 1.02) for each additional month the last born child was breast-fed (Table 3). Findings with regard to breast-feeding generally were similar for parous and multiparous women (Tables 2, 3).

We also examined breast-feeding in women with exactly one live birth. Among uniparous women, 44.0% of cases and 59.7% of controls ever breast-fed. The adjusted OR was 0.77 (95% CI: 0.47, 1.26) for ever breast-feeding when compared with never (Table 2). The mean durations of breast-feeding among uniparous women who breast-fed were 6.6 months in cases and 8.4 months in controls. Compared to never breast-feeding, the adjusted ORs were 0.91 (95% CI: 0.52, 1.62); 0.76 (95% CI: 0.39, 1.50) and 0.35 (95% CI: 0.13, 0.94), respectively, for breast-feeding on average fewer than 6 months per live birth; at least 6 months but fewer than 12 months, and at least 12 months. Among uniparous women, who ever breast-fed, the OR was 1.00 (95% CI: 0.95, 1.04) for each additional month of breast-feeding (p for trend = 0.83; Table 3).

In order to examine the influence of breast-feeding the first or last child in the simplest setting, we conducted analyses in women who had exactly two live born children. In this subgroup, 35.0% of cases and 45.3% of controls had breast-fed both children, 52.9% of cases and 44.2% of controls had breast-fed neither, and 12.1% of cases and 10.5% of controls had breast-fed one of the two. In women with exactly two children, the OR for ever breast-feeding, compared to never, was 0.79 (95% CI: 0.57, 1.10; Table 2). The OR was 0.70 (95% CI: 0.42, 1.19) for breast-feeding both children compared to breast-feeding only one. The OR was 0.73 (95% CI: 0.51, 1.04) for breast-feeding both (all) children, compared to breast-feeding neither (Table 2). Also compared to breast-feeding neither child, the ORs were 1.33 (95% CI: 0.74, 2.41) for breast-feeding only the first child and 0.53 (95% CI: 0.22, 1.28) for breast-feeding only the second child. The OR was 0.36 (95% CI: 0.13, 1.02) when breast-feeding only the second born was directly compared to breast-feeding only the first born.

The average duration of breast-feeding per live birth (or per breast-fed child) in women with exactly two live births was 2.7 (6.0) months in cases and 3.5 (6.7) months in controls. The average total duration of breast-feeding was 2.8 months for women who breast-fed only the first child, 4.4 months in women who breast-fed only the second child, and 14.5 months in women who breast-fed both children. Compared to never breast-feeding, the ORs for the mean duration of breast-feeding per live birth were 0.77 (95% CI: 0.54, 1.11) for breast-feeding fewer than 6 months, 0.88 (95% CI: 0.54, 1.43) for at least 6 months but fewer than 12, and 0.73 (95% CI: 0.37, 1.44) for 12 or more months (Table 3). Among women with two children who ever breast-fed, the OR was 0.98 (95% CI: 0.94, 1.02) for each additional month of breast-feeding per live birth (Table 3). Among women with exactly two children who breast-fed the second child (regardless of whether the first child was breast-fed), the OR was 1.00 (95% CI: 0.97, 1.04) for each additional month of breast-feeding the second (last born) child.

Finally, we examined the association between breast-feeding and risk of five histologic subtypes of ovarian cancer (Table 4). An inverse association with ever breast-feeding was apparent for all histological subtypes, but was most striking and statistically significant only for the endometrioid/clear cell tumor type (OR: 0.48; 95% CI: 0.34, 0.68). The OR for breast-feeding some children including the last born child, compared to never breast-feeding, was similar for the mucinous and endometrioid/ clear cell subtypes but statistically significant only for the endometrioid/clear cell group (OR 0.28; 95% CI 0.10, 0.79). However, for the endometrioid/clear cell type, breast-feeding appeared to be inversely associated with risk, irrespective of pattern.

Discussion

Using data from a large, population-based study, we assessed patterns of breast-feeding which, to the best of our knowledge, have not been examined previously in relation to ovarian cancer risk. Our findings in parous women indicated an inverse association of ever having breast-fed overall and in subgroups defined by the number of live births. We found little evidence that the duration of breast-feeding or the number of children breast-fed was associated with reduced risk. However, our data suggested the provocative possibility that breast-feeding the last born child may be critical to eliciting the protective effect of breast-feeding.

In parous women, the inverse association with ovarian cancer risk was most apparent for those who breast-fed all children, and those who breast-fed some children including the last born child. There was little evidence of a protective effect of breast-feeding some children when the last born child was not breast-fed. Similar patterns were apparent in analyses confined to women with exactly two live births, representing the purest setting for assessing the effects of breast-feeding the last born child.

As in our previous report, which was based on an earlier phase of this study [15], our findings indicated a strong inverse association between breast-feeding and a combined category of endometrioid and clear cell tumors. Similarly, other studies have found an inverse association in relation to endometrioid tumors [12,17-19] and clear cell tumors [9,18]. One study found a reduced risk only for invasive serous tumors [18], while two others assessed the broader categories of mucinous and non-mucinous tumors, with inconsistent results [8,13].

Recall bias is a potential limitation of all case–control studies, but our findings with regard to ever breast-feeding are consistent with the results of a recent prospective study [12] which was not subject to recall bias. Also, it seems unlikely that cases and controls would differentially report whether they breast-fed their last child. Higher parity women might have more difficulty remembering which children were breast-fed. However, compared to never breast-feeding, the strong inverse association with breast-feeding the last born child was similar for women with exactly two children (OR: 0.53), all parous women (OR: 0.58) and multiparous women (OR: 0.57). Finally, we did not collect information about use of lactation suppressants. Possibly, use of these hormones after the birth of the last child offsets the protective effect of previous breast-feeding.

Our exploratory analysis suggested the protective effect of breast-feeding the last born child was stronger in women who were more than 30 years of age when their last child was born. While speculative, this association might contribute, in part, to an inverse association with later age at last birth [20], a finding ascribed to pregnancy-related clearance of transforming ovarian epithelial cells [20,21]. For the last few decades, two hypotheses have dominated thinking about ovarian pathogenesis. One implicates incessant ovulation [22] and the other proposes a role for excessive concentrations of gonadotropins [23]. Although both hypotheses are compatible with major ovarian risk factors, neither predicts a greater benefit with breast-feeding the last born child. Our findings, which show a protective effect of breast-feeding only when the last born child is breast-fed, suggest the involvement of central regulatory processes. From an evolutionary perspective, breast-feeding is a requisite sequela of giving birth. Consistent with our findings, lactation may re-set pregnancy-related changes, possibly involving hypothalamic–pituitary regulated mechanisms that mediate ovarian cancer risk.

In summary, our data indicate that breast-feeding the last born child is strongly and inversely associated with ovarian cancer risk, whereas little protection is conferred by breast-feeding when the last born child is not breast-fed. Although ovarian cancer is a rare disease, these findings, if replicated in future studies, have implications for women's decisions regarding breast-feeding.

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Table 1

Means and frequencies of select characteristics in all parous women, in parous women who breast-fed at least one child, and in parous women who never breast-fed

	All parous women		Breast-fed ≥1 child		Never breast-fed	
	Cases	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
Age (years)	54.5[a]	52.6	52.0[b]	50.1	56.3	55.4
OC use (ever) (%)	47.8[a]	60.9	57.0[a]	67.4	40.9[a]	53.4
Parity (no. of live births)	2.5[a]	2.7	2.4[b]	2.6	2.6[a]	2.9
Min/max # of live births	1–11	1–10	1–9	1–10	1–11	1–10
Maternal age at last birth	30.0[a]	31.0	31.0[a]	32.0	29.3	29.7

[a] Comparison of cases to controls (2-sided *t*-test or chi square test) $p < 0.01$

[b] Comparison of cases to controls (2-sided *t*-test) $p < 0.05$

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for the association between breast-feeding and ovarian cancer risk by parity

Breast-feeding	Parous (≥1 birth)		Uniparous (1 birth)		Exactly 2 births		Multiparous (≥2 Births)	
	Cases *n* = 828 *n* = 1,834	Controls *n* = 1,006	Cases *n* = 166 *n* = 325	Controls *n* = 159	Cases *n* = 314 *n* = 685	Controls *n* = 371	Cases *n* = 662 *n* = 1,509	Controls *n* = 847
Ever breast-fed								
No (Ref)	472	463	93	64	166	164	379	399
Yes	356	543	73	95	148	207	283	448
OR (95% CI)	0.75 (0.62, 0.92)		0.77 (0.47, 1.26)		0.79 (0.57, 1.10)		0.75 (0.60, 0.93)	
OR per child breast-fed[a]	0.97 (0.82, 1.14)				0.70 (0.42, 1.19)		0.96 (0.81, 1.13)	
Pattern of breast-feeding								
None (Ref)	472	463	–	–	166	164	379	399
All	240	367	–	–	110	168	167	272
OR (95% CI)	0.72 (0.58, 0.91)		–	–	0.73 (0.51, 1.04)		0.71 (0.55, 0.93)	
Some, excluding last	85	108	–	–	30	23	85	108
OR (95% CI)	0.91 (0.66, 1.26)		–	–	1.33 (0.74, 2.41)		0.91 (0.66, 1.26)	
Some, including last	31	68	–	–	8	16	31	68
OR (95% CI)	0.58 (0.37, 0.91)		–	–	0.53 (0.22, 1.28)		0.57 (0.36, 0.90)	
Pattern of breast-feeding[b]								
Some, excluding last (Ref)	85	108	–	–	30	23	85	108
Some, including last	31	68	–	–	8	16	31	68
OR (95% CI)	0.58 (0.34, 0.99)		–	–	0.36 (0.13, 1.02)		0.58 (0.34, 0.98)	

In parous women only; OR adjusted for age, study center, OC use, and age at most recent birth; OR additionally adjusted for parity in analyses of parous and of multiparous women

[a]The OR for each additional child breast-fed among women who breast-fed at least one

[b]Breast-feeding some (but not all) children including the last compared to breast-feeding some (but not all) excluding the last

Table 3

Odds ratios (OR) and 95% confidence intervals (CI) for the association between the duration of breast-feeding and ovarian cancer risk by parity

Breast-feeding	Parous (≥1 birth)		Uniparous (1 birth)		Exactly 2 births		Multiparous (≥2 Births)	
	Cases *n* = 828 *n* = 1,834	Controls *n* = 1,006	Cases *n* = 166 *n* = 325	Controls *n* = 159	Cases *n* = 314 *n* = 685	Controls *n* = 371	Cases *n* = 662 *n* = 1,509	Controls *n* = 847
Mean duration of breast-feeding per live birth[a]								
0 (Ref)	472	463	93	64	166	164	379	399
1 to <6 months	234	339	43	44	88	124	191	295
OR (95% CI)	0.77 (0.62, 0.95)		0.91 (0.52, 1.62)		0.77 (0.54, 1.11)		0.75 (0.59, 0.95)	
6 to <12 months	89	134	23	28	42	55	66	106
OR (95% CI)	0.77 (0.56, 1.06)		0.76 (0.39, 1.50)		0.88 (0.54, 1.43)		0.77 (0.54, 1.10)	
≥12 months	33	69	7	23	18	28	26	46
OR (95% CI)	0.58 (0.37, 0.93)		0.35 (0.13, 0.94)		0.73 (0.37, 1.44)		0.73 (0.42, 1.24)	
Mean duration of breast-feeding per live birth[b]	0.99 (0.97, 1.02)		1.00 (0.95, 1.04)		0.98 (0.94, 1.02)		0.99 (0.96, 1.02)	
p for trend	0.45		0.83		0.31		0.62	
Duration of breast-feeding the last born child[c]	1.00 (0.97, 1.02)		1.00 (0.95, 1.04)		1.00 (0.97, 1.04)		1.00 (0.97, 1.03)	
p for trend	0.74		0.83		0.94		0.97	

In parous women only; OR adjusted for age, study center, OC use, and age at the most recent birth; OR additionally adjusted for parity in analysis of parous and of multiparous women

[a] Mean duration of breast-feeding in months over all live births among women who ever breast-fed, compared to breast-feeding none

[b] The OR for each additional month of breast-feeding among women who breast-fed; based on the continuous form of the variable

[c] Duration in months of breast-feeding the last born child among women who breast-fed the last born child; based on the continuous form of the variable

Table 4

Odds ratios (OR) and 95% confidence intervals (CI) for the association between duration of breast-feeding and ovarian cancer risk by histologic subtype

Histology	No. of cases	Ever breast-fed OR (95% CI)[a]	OR (95% CI)[b]			OR (95% CI)
			Breast-fed some including last born child	Breast-fed some excluding last born child	Breast-fed all children	Breast-fed some including last compared to some excluding last born child
Serous borderline	108	0.95 (0.61, 1.48)	1.25 (0.53, 2.98)	1.23 (0.59, 2.58)	0.84 (0.51, 1.37)	0.83 (0.28, 2.42)
Serous invasive	371	0.87 (0.67, 1.12)	0.79 (0.45, 1.39)	1.14 (0.77, 1.68)	0.77 (0.57, 1.05)	0.67 (0.35, 1.28)
Mucinous	95	0.79 (0.50, 1.25)	0.29 (0.07, 1.22)	0.87 (0.41, 1.86)	0.87 (0.52, 1.45)	0.26 (0.05, 1.31)
Endometrioid/clear cell	196	0.48 (0.34, 0.68)	0.28 (0.10, 0.79)	0.48 (0.25, 0.94)	0.51 (0.35, 0.76)	0.55 (0.16, 1.84)
Other/undifferentiated	58	0.58 (0.33, 1.04)	c	0.49 (0.17, 1.43)	0.74 (0.39, 1.41)	c

In parous women only; OR adjusted for age, study center, OC use, and age at most recent birth; OR additionally adjusted for parity in women with more than one child

[a]OR for ever breast-fed compared to never

[b]OR for pattern of breast-feeding compared to never breast-fed and adjusted for age, center, OC use, parity, and age at most recent birth

[c]Not computed due to zero value cell