Published in final edited form as:
*Cancer Epidemiol Biomarkers Prev*. 2008 June ; 17(6): 1316–1321. doi:10.1158/1055-9965.EPI-08-0108.

# Infant Feeding and the Incidence of Endometrial Cancer

**Fei Xue**[1,3], **Leena A. Hilakivi-Clarke**[4], **G. Larry Maxwell**[5], **Susan E. Hankinson**[2,3], and **Karin B. Michels**[1,2,3]

[1]Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics, Gynecology and Reproductive Biology, Boston, Massachusetts

[2]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts

[3]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts

[4]Lombardi Comprehensive, Cancer Center, Department of Oncology, Georgetown University

[5]U.S. Military Cancer Institute, Walter Reed, Army Medical Center, Washington, District of Columbia

## Abstract

Biological mechanisms could support both an inverse and a direct association between exposure to breast milk in infancy and the risk of cancer. Having been breast-fed has been investigated in relation to the risk of breast and other cancer sites, and conflicting results have been reported. The association between infant feeding and the risk of endometrial cancer has not been explored. From 1976 to 2004, we followed 74,757 cancer-free participants in the Nurses' Health Study who had not undergone hysterectomy. Information on infant feeding was self-reported by study participants. A total of 708 incident cases of endometrial cancer were diagnosed during follow-up. After adjusting for age, family history of endometrial cancer, birth weight, premature birth, and birth order, the incidence of endometrial cancer was not associated with ever having been breast-fed (hazards ratio, 0.94; 95% confidence interval, 0.79–1.11) or duration of having been breast-fed [hazards ratio (95% confidence interval): 1.11 (0.80–1.54), 0.84 (0.62–1.13), 1.02 (0.79–1.31), respectively, for ≤3, 4–8, and ≥9 months of having been breastfed; *P* for trend = 0.88]. There was no significant effect modification by menopausal status, anthropometric factors (somatotype at age 5 or 10 years, body mass index at age 18 years, or current body mass index), or by other early-life exposures (birth weight, premature birth or exposure to parental smoking in childhood). Additional adjustment for adulthood risk factors of endometrial cancer did not materially change the results. Having been breast-fed was not associated with the incidence of endometrial cancer in this cohort, but statistical power for analyses restricted to premenopausal women was limited.

## Introduction

Endometrial cancer is the most common invasive gynecologic cancer among U.S. women, with 39,080 new cases projected to occur in 2007 (1). Incidence of endometrial cancer is highest in North America and lowest in Asian countries (2). Most epidemiologic investigations of the



**Requests for reprints:** Fei Xue, Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115. Phone: 781-472-8662; Fax: 781-472-8464. n2fei@channing.harvard.edu.

**Note:** The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

**Disclosure of Potential Conflicts of Interest**
No potential conflicts of interest were disclosed.

etiology of endometrial cancer have concentrated on events during women's reproductive years. In these studies, late menopause, anovulation, nulliparity, obesity, metabolic syndrome, endogenous estrogens, estrogen-only postmenopausal hormone use, and tamoxifen use have been associated with an increased risk of endometrial cancer, and smoking and combined oral contraceptive use have been associated with a decreased risk of endometrial cancer (2). Observations of a link between intrauterine exposure to radiation and the incidence of leukemia and other tumors in childhood (3), as well as the association between intrauterine exposure to diethylstilbestrol and vaginal adenocarcinoma in adolescence (4), suggested that carcinogenesis may begin as early as the prenatal period. Birth weight, one of the most frequently studied early-life exposures, has been associated with the risk of breast cancer (5), testicular cancer (6), and leukemia (7), possibly because birth weight is a marker of intrauterine exposure to estrogen and insulin-like growth factor-I, or epigenetic programming (5).

Early nutrition is an important stimulus for lifelong programming of metabolism and growth and may have important effects on chronic disease processes (8,9). Infant feeding is another early-life exposure that may influence subsequent cancer risk. It was hypothesized in 1930 that an oncogenic virus transmitted in milk may cause subsequent breast cancer among offspring (10). Besides, children who were breast-fed during infancy were found to have taller stature in childhood and adulthood (11,12) and higher circulating levels of insulin-like growth factor-I (13) later in childhood than infants who were bottle-fed; both tall stature and high insulin-like growth factor-I levels may affect future cancer risk. On the other hand, as a source of balanced nutrient composition and a number of conditionally essential nutrients, human breast milk also provides different types of bioactive factors, such as enzymes and hormones, which may decrease future risk of cancer. For instance, human breast milk contains multimeric α-lactalbumin, a potent apoptosis-inducing agent (14,15). Human breast milk also contains progesterone and gonadotropin-releasing hormones, which may counteract prenatal exposure to estrogen and suppress premature development of female reproductive organs (16). Studies investigating the association between being breast-fed during infancy and the risk of cancer later in life (including all cancer in general, breast cancer, testicular cancer, prostate cancer, colorectal cancer, and gastric cancer) have reported conflicting results but largely null associations (17). To our knowledge, the association between being breast-fed in infancy and the incidence of endometrial cancer has not yet been studied.

Using data from 28 years of follow-up of women participating in the Nurses' Health Study (NHS), we examined the association between being breast-fed in infancy and the incidence of endometrial cancer later in life and whether this association was modified by menopausal status, subsequent anthropometric factors, or early-life exposures.

## Materials and Methods

### Study Population: NHS

NHS was established in 1976, initially to investigate the potential long-term consequences of the use of oral contraceptives, potent drugs that were being prescribed to hundreds of millions of normal women. Participants were married registered nurses ages 30 to 55 years in 1976, who lived in the 11 most populous U.S. states. Of 170,000 female registered nurses, 121,700 responded to the baseline questionnaire on their health status and on major illnesses. Participants have received follow-up questionnaires biennially by mail to update information on demographic factors, anthropometric factors, lifestyle factors, and newly diagnosed disease. For the present analysis, we excluded women with missing data on being breast-fed in infancy, women with prevalent endometrial cancer cases at baseline, and women with hysterectomy before or at baseline. During follow-up, we censored women with *in situ* endometrial cancer or invasive endometrial cancer, women with hysterectomy, and women who died or were lost to follow-up. Among all women who met the other eligibility criteria ($n$ = 103,183), 74,757

(72.5%) who provided information on whether they have ever been breast-fed were included in the study at baseline in 1976, and 1,747,137 eligible person-years of follow-up accumulated among them from 1976 to 2004. Of the 74,757 women with information on ever being breast-fed, 46,719 (62.5%) provided information on the duration of being breast-fed and were included in the analysis of duration of being breast-fed. Based on eligible person-years, the follow-up rate for the entire eligible cohort in our study from 1976 to 2004 was 92%. This study was approved by the institutional review board at the Brigham and Women's Hospital.

### Assessment of Being Breast-fed in Infancy

On the 1992 questionnaire, we asked participants whether they were breast-fed during infancy. For those who reported that they were breast-fed, we assessed the duration of breast feeding in four categories, that is, not sure, 3 months or less, 4 to 8 months, and 9 months or more. A considerable number of women who reported that they were breast-fed did not report duration. The accuracy of self-reports of having been breast-fed has been examined in a validation study in the cohort of NHS II, which has been organized and followed using the same strategy as NHS (18). When comparing self-report of the nurse participants of ever having been breast-fed with their mothers' report in a sample of 538 participants and their mothers, the sensitivity was 82% and the specificity was 86%. For duration of being breast-fed, the Spearman correlation coefficient between mothers' and daughters' reports was 0.74.

### Assessment of Endometrial Cancer

On each biennial questionnaire, all participants were asked whether they had been newly diagnosed with endometrial cancer during the previous 2 years. The National Death Index was also routinely searched for deaths among women who did not respond to the questionnaires. For endometrial cancer cases reported by women or reported by the next of kin for those who had died, permission was requested to review the relevant medical records. Study physicians reviewed all the medical records and pathologic reports to confirm their diagnosis. Cases included in our study were invasive epithelial endometrial cancer patients with stage equal to or greater than IB in the International Federation of Gynecology and Obstetrics staging system.

### Assessment of Other Covariates

At baseline and during follow-up, we inquired about a variety of personal characteristics, including reproductive factors and lifestyle factors, many of which are risk factors of endometrial cancer. Age, age at menarche, age at first birth, and height were queried at baseline in 1976. Other early-life exposures, including premature birth (2+ weeks premature) and birth weight, were assessed in 1992, and birth order was queried in 2004. Contraceptive use and pregnancy history were updated biennially until 1984, when most women had passed reproductive age. Age at last birth was derived from updated pregnancy history. Menopause status, postmenopausal hormone use, and amount and status of current smoking were updated biennially until 2002. Pack-years of smoking were derived by multiplying the number of packs per day (1 pack = 20 cigarettes) by the number of years over which that quantity was smoked. Tamoxifen use was updated biennially from 1994 to 1998. Frequency and duration of leisure-time physical activities were assessed and updated biennially from 1980 to 2000. Current weight was assessed biennially from 1976 to 2002. Weight at age 18 years was assessed in 1980. Current body mass index (BMI) and BMI at age 18 years were calculated as weight (kg) / height$^2$ ($m^2$) using updated current weight and weight at age 18 years, respectively. Somatotype (body fatness) at ages 5 and 10 years was indicated on the 1988 questionnaire, when participants were asked to recall their body shape using a nine-level figure drawing originally developed by Stunkard et al. (19). Maternal vital status and family history of endometrial cancer was asked only once in 1996. All variables assessed repeatedly were updated in the analysis.

### Statistical Analysis

The association between being breast-fed in infancy and the incidence of endometrial cancer was analyzed using a Cox proportional hazards model. Being breast-fed in infancy was assessed as ever being breast-fed (yes/no) and duration of being breast-fed (never, ≤3 months, 4–8 months, ≥9 months). Women with missing data on or who were unsure about how long they were breast-fed were excluded from the analysis on duration of being breast-fed. Linear trend of the association between duration of being breast-fed and the incidence of endometrial cancer was assessed using an ordinal variable valued according to the approximate midpoint of each duration category (0, 2, 6, and 12 months). Both age-adjusted and covariate-adjusted analyses were done. Three covariate-adjusted models were pursued in the analysis. In the first model (covariate-adjusted I), we adjusted only for family history of endometrial cancer and other early-life exposures, including birth order (1st, 2nd, 3rd, 4th or above), birth weight (<5.5, 5.5–6.9, 7–8.4, ≥8.5 lb), and premature birth (yes, no), in addition to age (continuous). In the second covariate-adjusted model (covariate-adjusted II), we also included other established or potential risk factors of endometrial cancer, including age at menarche (≤10, 11, 12, 13, 14, 15+ years), current and past contraceptive use (never, past <5 years, past ≥5 years, current <5 years, current ≥5 years), parity (1, 2, 3, 4+), age at first birth (≤24, 25–30, 30+ years), age at last birth (≤24, 25–29, 30–34, 35–40, >40 years), physical activity [<3, 3–8, 9–17, 18–26, 27–41, 42+ metabolic equivalents (20) per week], cigarette smoking (never, 1–20, 21–40, 41+ pack-years), tamoxifen use (never, past and <5 years, past and ≥5 years, current and<5 years, current and ≥5 years), menopause status (yes, no), age at menopause (<50, 50–52, 53+ years), and postmenopausal hormone use (never, past and<5 years, past and ≥5 years, current and <5 years, current and ≥5 years), in addition to covariates in multivariate-adjusted I. In the third model (multivariate-adjusted III), we additionally adjusted for anthropometric factors later in life, including somatotype at ages 5 and 10 years (ranked from 1 to 9), BMI at age 18 years, and current BMI (continuous in $kg/m^2$). Although multivariate-adjusted II and III models have better goodness of fit due to additional adjustment for potential risk factors for endometrial cancer, these factors occur after being breast-fed during infancy and may mediate the effect of being breast-fed on endometrial cancer risk. Therefore, we rely on multivariate-adjusted II and III analysis to assess the direct effect of being breast-fed during infancy independent of these subsequent events. Adjustment for early-life exposures preceding infant feeding and for family history provides an estimate of the overall effect of being breast-fed during infancy.

Because being breast-fed during infancy was not queried until 1992, the follow-up from 1976 to 1992 is retrospective regarding the evaluation of exposure. To assess the potential recall bias as a result of retrospective assessment of being breast-fed, we restricted our analysis to follow-up from 1992 to 2004 in a sensitivity analysis and compared the results with the primary analysis using the entire follow-up from 1976 to 2004.

We also evaluated whether the association between being breast-fed and endometrial cancer risk varied by menopausal status, anthropometric factors including somatotype at age 5 and 10 years, BMI at age 18 years and current BMI, and other early-life exposures, including birth weight and parental smoking in childhood through stratified analysis. The Wald test on the cross-products between being breast-fed and potential effect modifiers was used to assess the statistical significance of interactions.

## Results

In the age-standardized analysis, when compared with women who were not breast-fed, women who were breast-fed were slightly more likely to have a family history of endometrial cancer (3.4% versus 2.8%) and to have been born before 1930 (35.9% versus 23.6%), and were less likely to have been born after 1940 (17.8% versus 29.0%), to have been born prematurely (3.3%

versus 6.8%), to be first-born (31.9% versus 41.4%), and to have ever smoked (54.0% versus 58.4%; Table 1).

A total of 708 incident cases of endometrial cancer were identified during the 28 years of follow-up. In the overall analysis among the entire cohort, the incidence of endometrial cancer was not associated with whether they had ever been breast-fed [hazards ratio (HR), 0.93; 95% confidence interval (95% CI), 0.79–1.10] or duration of being breast-fed [HR (95% CI): 1.13 (0.81–1.57), 0.85 (0.63–1.15), 1.03 (0.80–1.32) for ≤3, 4–8, and ≥9 months, respectively; *P* for trend = 0.93] in age-adjusted analysis (Table 2). When restricting the analysis to the follow-up from 1992 to 2004, the effect estimates in age-adjusted analysis did not appreciably differ from the primary analysis based on follow-up from 1976 to 2004 with respect to ever being breast-fed (HR, 1.05; 95% CI, 0.86–1.29) or duration of being breast-fed [HR (95% CI): 1.30 (0.88, 1.91), 0.84 (0.57, 1.23), and 1.18 (0.87, 1.61) for ≤3, 4–8, and ≥9 months, respectively; *P* for trend = 0.48]. Test for interaction also did not suggest significant heterogeneity with regard to period of follow-up (1976–2004 versus 1992–2004) in the association between endometrial cancer incidence and ever being breast-fed (*P* for interaction = 0.46) or duration of being breast-fed (*P* for interaction = 0.29). When analyzing premenopausal (*n* = 99 cases) and postmenopausal endometrial cancer (*n* = 601 cases) separately, women who were breast-fed had a lower incidence of premenopausal endometrial cancer (HR, 0.70; 95% CI, 0.46–1.07) although the difference was not statistically significant (Table 2). Being breast-fed during infancy was not associated with postmenopausal endometrial cancer (HR, 1.01; 95% CI, 0.84–1.21). The test for interaction with menopausal status was not statistically significant for ever being breast-fed (*P* = 0.99) or duration of being breast-fed (*P* = 0.28). When the analysis was restricted to the follow-up from 1992 to 2002, results remained essentially the same for ever being breast-fed (HR, 0.77; 95% CI, 0.37–1.61) among premenopausal women, and for ever being breast-fed (HR, 1.12; 95% CI, 0.90–1.40) and the duration of being breast-fed [HR (95% CI): 1.39 (0.92–2.09), 0.93 (0.63–1.37), and 1.27 (0.92–1.75) for ≤3, 4–8, and ≥9 months, respectively; *P* for trend = 0.23] among postmenopausal women (*P* for interaction = 0.46 and 0.09 for ever being breast-fed and duration of being breast-fed, respectively). The limited number of cases among premenopausal women during follow-up from 1992 to 2004 (*n* = 4) precluded further analysis on duration of being breast-fed among this subgroup. Results did not differ substantially after additional adjustment for family history of endometrial cancer and other early-life exposures (covariate-adjusted I), other potential risk factors of endometrial cancer (covariate-adjusted II), or anthropometric factors later in life (covariate-adjusted III).

In age-adjusted analysis, the association between being breast-fed and endometrial cancer did not vary by somatotype at age 5 years (*P* for interaction = 0.62 and 0.51 for ever being breast-fed and duration of being breast-fed, respectively), somatotype at age 10 years (*P* for interaction = 0.94 and 0.47 for ever being breast-fed and duration of being breast-fed, respectively), BMI at age 18 years (*P* for interaction = 0.19 and 0.82 for ever being breast-fed and duration of being breast-fed, respectively), or current BMI (*P* for interaction = 0.14 and 0.77 for ever being breast-fed and duration of being breast-fed, respectively). When the analysis was stratified by other early-life exposures, the association between being breast-fed and the incidence of endometrial cancer was not modified by birth weight (*P* for interaction = 0.20 and 0.32 for ever being breast-fed and duration of being breast-fed, respectively), premature birth (*P* for interaction = 0.67 and 0.66 for ever being breast-fed and duration of being breast-fed, respectively), or exposure to parental smoking in childhood (*P* for interaction = 0.19 and 0.20 for ever being breast-fed and duration of being breast-fed, respectively). The association also did not differ between women who were first-born and women who were not (*P* for interaction = 0.29 and 1.00 for ever being breast-fed and duration of being breast-fed, respectively). Results were not substantially changed in age-adjusted analysis or covariate-adjusted analysis I to III.

## Discussion

We found no association between being breast-fed and the incidence of endometrial cancer. Women who were breast-fed seemed to have a lower incidence of premenopausal endometrial cancer than those who were never breast-fed, but the association was not statistically significant. To our knowledge, this is the first study in which the association between having been breast-fed in infancy and the risk of endometrial cancer has been addressed. Previous studies have provided data regarding the association between being breast-fed and the risk of cancer at other sites. Breast cancer has been intensively studied (17,21–31). A protective effect of being breast-fed during infancy for breast cancer was reported by two population-based case-control studies (24,25), but in subsequent studies, including two prospective cohort studies (17,21), no association was found. Similarly, in studies on testicular cancer (32,33), prostate cancer (17), colorectal cancer (17), gastric cancer (17), and all cancers combined (17,29,34), no association with ever having been breast-fed or duration of being breast-fed during infancy was detected. A meta-analysis by Martin et al. also supported a null association between being breast-fed during infancy and the risk of all assessed cancer sites, except a slightly reduced risk of premenopausal breast cancer among breast-fed women (summary RR, 0.88; 95% CI, 0.79–0.98; ref. 17).

Being breast-fed seemed to be associated with a decreased incidence of premenopausal but not postmenopausal endometrial cancer, although the association was not statistically significant and based on small number of premenopausal endometrial cancer cases. The same pattern has been found in the birth weight–breast cancer association: birth weight was more strongly associated with premenopausal than postmenopausal breast cancer (5). As carcinogenesis is a multistage process that usually takes a long period of time, early-life exposures trigger or delay the onset of this process at a young age and therefore may be more relevant to cancer with early onset.

Based on 28 years of follow-up of 74,757 women in the NHS and 708 cases of endometrial cancer, the present study has sufficient statistical power to detect a modest association, if it exists. We also assessed a wide variety of potential risk factors of endometrial cancer and several other early-life exposures as potential confounders or effect modifiers, and the association was unchanged after adjusting for potential confounders or stratification by anthropometric factors or other early-life exposures.

The incomplete assessment of infant feeding history, such as breast-feeding for more than 9 months and mixed feeding of breast milk and other supplement or solid food, may also limit inference about the effect of long-term breast-feeding and exclusive breast-feeding. Another potential limitation of the current study is the assessment of being breast-fed through retrospective self-report of nurses, which is susceptible to random misclassification. Our previous comparison of self-report of ever having been breast-fed with mother's report showed a high sensitivity (82%) and specificity (86%; ref. 18). For duration of being breast-fed, the correlation between mothers' and daughters' reports was also high ($r = 0.74$; ref. 18). When the data on being breast-fed were collected (1992), any potential link between being breast-fed and the risk of endometrial cancer would not have been suspected; therefore, it is not likely that endometrial cancer patients would have reported their history of being breast-fed differentially from women without endometrial cancer. It is possible that cases of endometrial cancer before 1992 may have been lost to follow-up and did not report the history of infant feeding due to death or symptoms of the cancer. Nevertheless, because endometrial cancer was shown not to be related to the history of infant feeding in the analysis based on prospective follow-up from 1992 to 2004, loss to follow-up among cases in 1976 to 1992 should not result in a bias in the effect estimate for being breast-fed in relation to the incidence of endometrial

cancer. Compared with results from the analysis restricted to prospective follow-up from 1992 to 2004, our primary analysis results (follow-up from 1976 to 2004) did not differ substantially.

In conclusion, the results from the current study suggest that being breast-fed during infancy does not play an important role in the etiology of endometrial cancer later in life; this finding is consistent with previous studies suggesting a lack of association with other malignancies. Although early-life exposures have been extensively studied in association with the risk of breast cancer and some other malignancies, few data exist on their influence on endometrial cancer risk. The current study is the first attempt to assess being breast-fed in relation to the risk of endometrial cancer. Despite the large sample size, statistical power was limited to assess the role of infant feeding for premenopausal women with endometrial cases. Further studies with more comprehensive assessment of infant feeding and other early life exposures are warranted to clarify the role of early life exposure in the etiology of endometrial cancer.

## Acknowledgments

**Grant support:** The Nurses' Health Study is supported by grant CA87969 from the National Cancer Institute, NIH. The current project was funded by the Department of Defense grant W81XWH.

## References

1. American Cancer Society. Detailed guide: endometrial cancer. Atlanta (GA): American Cancer Society, Inc.; [last visited: May 1, 2007]. Available from http://www.cancer.org/docroot/CRI/CRI_2_3x.asp?dt=11
2. Adami, H.; Hunter, D.; Trichopoulos, D. Textbook of cancer epidemiology. Oxford University Press; 2002. p. 359-377.
3. Macmahon B. Prenatal X-ray exposure and childhood cancer. J Natl Cancer Inst 1962;28:1173–1191. [PubMed: 14468031]
4. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 1971;284:878–881. [PubMed: 5549830]
5. Michels KB, Xue F. Role of birthweight in the etiology of breast cancer. Int J Cancer 2006;119:2007–2025. [PubMed: 16823839]
6. Michos A, Xue F, Michels KB. Birth weight and the risk of testicular cancer: a meta-analysis. Int J Cancer 2007;121:1123–1131. [PubMed: 17471572]
7. Tower RL, Spector LG. The epidemiology of childhood leukemia with a focus on birth weight and diet. Crit Rev Clin Lab Sci 2007;44:203–242. [PubMed: 17453918]
8. McCance RA. Food, growth and time. Lancet 1962;ii:271–272.
9. Mott, GE.; Lewis, DS.; McGill, HC. Programming of cholesterol metabolism by breast or formula feeding. In: Bock, GR.; Whelan, J., editors. The childhood environment and adult disease. Chichester: Wiley; 1991. p. 56-76.
10. Bittner JJ. Mammary tumors in mice in relation to nursing. Am J Cancer 1937;30:530.
11. Martin RM, Smith GD, Mangtani P, Frankel S, Gunnell D. Association between breast feeding and growth: the Boyd-Orr cohort study. Arch Dis Child Fetal Neonatal Ed 2002;87:F193–F201. [PubMed: 12390990]
12. Wadsworth ME, Hardy RJ, Paul AA, Marshall SF, Cole TJ. Leg and trunk length at 43 years in relation to childhood health, diet and family circumstances; evidence from the 1946 national birth cohort. Int J Epidemiol 2002;31:383–390. [PubMed: 11980800]
13. Martin RM, Holly JM, Smith GD, et al. Could associations between breastfeeding and insulin-like growth factors underlie associations of breastfeeding with adult chronic disease? The Avon Longitudinal Study of Parents and Children. Clin Endocrinol (Oxf) 2005;62:728–737. [PubMed: 15943836]
14. Hakansson A, Zhivotovsky B, Orrenius S, Sabharwal H, Svanborg C. Apoptosis induced by a human milk protein. Proc Natl Acad Sci U S A 1995;92:8064–8068. [PubMed: 7644538]

15. Hakansson A, Andreasson J, Zhivotovsky B, Karpman D, Orrenius S, Svanborg C. Multimeric α-lactalbumin from human milk induces apoptosis through a direct effect on cell nuclei. Exp Cell Res 1999;246:451–460. [PubMed: 9925761]
16. Rodriguez-Palmero M, Koletzko B, Kunz C, Jensen R. Nutritional and biochemical properties of human milk: II. Lipids, micronutrients, and bioactive factors. Clin Perinatol 1999;26:335–359. [PubMed: 10394491]
17. Martin RM, Middleton N, Gunnell D, Owen CG, Smith GD. Breast-feeding and cancer: the Boyd Orr cohort and a systematic review with meta-analysis. J Natl Cancer Inst 2005;97:1446–1457. [PubMed: 16204694]
18. Troy LM, Michels KB, Hunter DJ, et al. Self-reported birthweight and history of having been breast-fed among younger women: an assessment of validity. Int J Epidemiol 1996;25:122–127. [PubMed: 8666479]
19. Stunkard, A.; Sorensen, T.; Schulsinger, F. Use of the Danish Adoption Register for the study of obesity and thinness. In: Kety, S.; Rowland, L.; Sidman, S.; Mathysee, S., editors. The genetics of neurological and psychiatric disorders. New York: Raven Press; 1983. p. 115-120.
20. Ainsworth BE, Halkell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25:71–80. [PubMed: 8292105]
21. Michels KB, Trichopoulos D, Rosner BA, et al. Being breast-fed in infancy and breast cancer incidence in adult life: results from the two Nurses' Health Studies. Am J Epidemiol 2001;153:275–283. [PubMed: 11157415]
22. Titus-Ernstoff L, Egan KM, Newcomb PA, et al. Exposure to breast milk in infancy and adult breast cancer risk. J Natl Cancer Inst 1998;90:921–924. [PubMed: 9637142]
23. Sanderson M, Williams MA, Daling JR, et al. Maternal factors and breast cancer risk among young women. Paediatr Perinat Epidemiol 1998;12:397–407. [PubMed: 9805713]
24. Weiss HA, Potischman NA, Brinton LA, et al. Prenatal and perinatal risk factors for breast cancer in young women. Epidemiology 1997;8:181–187. [PubMed: 9229211]
25. Freudenheim JL, Marshall JR, Graham S, et al. Exposure to breast-milk in infancy and the risk of breast cancer. Epidemiology 1994;5:324–331. [PubMed: 8038247]
26. Ekbom A, Hsieh CC, Trichopoulos D, Yen YY, Petridou E, Adami HO. Breastfeeding and breast cancer in the offspring. Br J Cancer 1993;67:842–845. [PubMed: 8471443]
27. Brinton LA, Hoover R, Fraumeni JF Jr. Reproductive factors in the aetiology of breast cancer. Br J Cancer 1983;47:757–762. [PubMed: 6860545]
28. Henderson BE, Powell D, Rosario I, et al. An epidemiologic study of breast cancer. J Natl Cancer Inst 1974;53:609–614. [PubMed: 4369771]
29. Tokuhata GK. Morbidity and mortality among offspring of breast cancer mothers. Am J Epidemiol 1969;89:139–153. [PubMed: 5765954]
30. Bucalossi P, Veronesi U. Some observations on cancer of the breast in mothers and daughters. Br J Cancer 1957;11:337–347. [PubMed: 13499783]
31. Penrose LS, MacKenzie HJ, Karn MN. A genetic study of human mammary cancer. Br J Cancer 1948;2:168–176. [PubMed: 18099716]
32. Coupland CAF. Maternal risk factors for testicular cancer: a population-based case-control study (UK). Cancer Causes Control 2004;15:277–283. [PubMed: 15090722]
33. Henderson BE, Benton B, Jing J, Yu MC, Pike MC. Risk factors for cancer of the testis in young men. Int J Cancer 1979;23:598–602. [PubMed: 37169]
34. Wingard DL, Criqui MH, Edelstein SL, et al. Is breast-feeding in infancy associated with adult longevity? Am J Public Health 1994;84:1458–1462. [PubMed: 8092371]

*Cancer Epidemiol Biomarkers Prev*. Author manuscript; available in PMC 2010 March 9.

**Table 1**

Age-adjusted distribution of demographic characteristics according to ever being breast-fed and duration of being breast-fed based on entire person-years of follow-up from 1976 to 2004 (*N* = 1,747,137 person-years)

| Demographic characteristics* | Breast-fed | | | | |
|---|---|---|---|---|---|
| | No | Yes | ≤3 mo | 4–8 mo | 9+ mo |
| Person-years | 631,016 | 1,116,121 | 106,370 | 158,013 | 204,498 |
| Family history of endometrial cancer (%) | 2.8 | 3.4 | 2.5 | 3.3 | 3.9 |
| Birth cohort (%) | | | | | |
| 1913–1929 | 23.6 | 35.9 | 24.1 | 32.3 | 38.0 |
| 1930–1940 | 47.4 | 46.3 | 47.8 | 47.4 | 47.0 |
| 1941–1946 | 29.0 | 17.8 | 28.1 | 20.3 | 15.0 |
| Premature birth (%) | 6.8 | 3.3 | 4.1 | 3.5 | 3.4 |
| Parity | | | | | |
| Nulliparous (%) | 6.4 | 7.0 | 7.2 | 7.1 | 6.0 |
| Parous (mean parity) | 3.2 | 3.3 | 3.2 | 3.2 | 3.3 |
| Birth weight <5.5 lb (%) | 13.0 | 7.0 | 9.9 | 7.2 | 6.4 |
| First born (%) | 41.4 | 31.9 | 48.0 | 37.2 | 30.1 |
| Age at menarche (mean; y) | 12.4 | 12.5 | 12.3 | 12.5 | 12.5 |
| Height (mean; m) | 1.64 | 1.64 | 1.64 | 1.64 | 1.64 |
| BMI at age 18 y (mean; $kg/m^2$) | 21.3 | 21.3 | 21.1 | 21.3 | 21.5 |
| Current BMI (mean; $kg/m^2$) | 25.4 | 25.2 | 25.3 | 25.3 | 25.4 |
| Ever smoked (%) | 58.4 | 54.0 | 53.0 | 53.0 | 53.4 |
| Premenopausal (%) | 34.9 | 34.1 | 35.4 | 34.2 | 33.8 |

*Data were missing for 36.7% of total person-years of follow-up for family history, 3.1% for premature birth, 1.3% for parity, 16.5% for birth weight, 22.2% for birth order, 0.7% for age at menarche, 10.9% for BMI at age 18 y, 0.2% for current BMI, 0.8% for ever smoking status, and 1.9% for menopausal status. Person-years with missing data were included in the denominator when proportion of each factor across breast-fed exposure levels was calculated but were not included in the analysis for mean levels of continuous variables (parity among parous women, age at menarche, height, BMI at age 1 y, and current BMI).

**Table 2**

The association between being breast-fed and incidence of endometrial cancer among NHS women during follow-up from 1976 to 2004, and stratified analysis by menopausal status

| Being breast-fed | Person-years | No. cases | HR (95% CI) | | | |
|---|---|---|---|---|---|---|
| | | | Age-adjusted | Multivariate-adjusted I* | Multivariate-adjusted II † | Multivariate-adjusted III ‡ |
| Overall | | | | | | |
| No | 631,016 | 228 | 1.0 | 1.0 | 1.0 | 1.0 |
| Yes | 1,116,121 | 480 | 0.93 (0.79–1.10) | 0.94 (0.79–1.11) | 0.91 (0.77–1.08) | 0.91 (0.77–1.07) |
| ≤3 mo | 106,370 | 44 | 1.13 (0.81–1.57) | 1.11 (0.80–1.54) | 1.08 (0.78–1.51) | 1.09 (0.78–1.52) |
| 4–8 mo | 158,013 | 56 | 0.85 (0.63–1.15) | 0.84 (0.62–1.13) | 0.82 (0.60–1.11) | 0.80 (0.59–1.09) |
| 9+ mo | 204,498 | 99 | 1.03 (0.80–1.32) | 1.02 (0.79–1.31) | 1.02 (0.79–1.32) | 0.99 (0.77–1.29) |
| *P* for trend | | | 0.93 | 0.88 | 0.92 | 0.73 |
| Premenopausal | | | | | | |
| No | 277,869 | 49 | 1.0 | 1.0 | 1.0 | 1.0 |
| Yes | 339,038 | 50 | 0.70 (0.46–1.07) | 0.67 (0.43–1.04) | 0.65 (0.42–1.02) | 0.66 (0.42–1.03) |
| ≤3 mo | 46,949 | 5 | 0.65 (0.25–1.67) | 0.60 (0.23–1.55) | 0.65 (0.25–1.71) | 0.63 (0.23–1.70) |
| 4–8 mo | 54,245 | 4 | 0.34 (0.12–0.99) | 0.37 (0.13–1.07) | 0.37 (0.13–1.07) | 0.36 (0.12–1.05) |
| 9+ mo | 56,034 | 11 | 0.81 (0.38–1.75) | 0.75 (0.34–1.66) | 0.70 (0.31–1.58) | 0.70 (0.31–1.59) |
| *P* for trend | | | 0.34 | 0.27 | 0.22 | 0.21 |
| Postmenopausal | | | | | | |
| No | 301,683 | 174 | 1.0 | 1.0 | 1.0 | 1.0 |
| Yes | 692,678 | 427 | 1.01 (0.84–1.21) | 1.02 (0.85–1.23) | 0.99 (0.82–1.19) | 0.98 (0.81–1.18) |
| ≤3 mo | 51,309 | 39 | 1.31 (0.92–1.87) | 1.29 (0.91–1.84) | 1.25 (0.87–1.78) | 1.26 (0.88–1.81) |
| 4–8 mo | 91,394 | 52 | 0.96 (0.70–1.31) | 0.94 (0.69–1.30) | 0.92 (0.67–1.27) | 0.91 (0.66–1.25) |
| 9+ mo | 132,496 | 87 | 1.09 (0.84–1.43) | 1.09 (0.83–1.43) | 1.10 (0.83–1.45) | 1.06 (0.81–1.40) |
| *P* for trend | | | 0.70 | 0.73 | 0.68 | 0.87 |

*HR and 95% CI were adjusted for age, premature birth, birth order, birth weight, and family history of endometrial cancer.

†HR and 95% CI were adjusted for age, premature birth, birth order, birth weight, family history of endometrial cancer, age at menarche, oral contraceptive use, parity, age at first birth, age at last birth, physical activity, cigarette smoking, and tamoxifen use, menopausal status, age at menopause, and postmenopausal hormone use. Menopause status was not adjusted for in the analysis stratified by menopausal status. Age at menopause and postmenopausal hormone use were not adjusted for in the analysis restricted to premenopausal women.

‡HR and 95% CI were adjusted for age, premature birth, birth order, birth weight, family history of endometrial cancer, age at menarche, oral contraceptive use, parity, age at first birth, age at last birth, physical activity, cigarette smoking, tamoxifen use, menopausal status, age at menopause, postmenopausal hormone use, BMI, BMI at age 18 y, and somatotype at ages 5 and 10 y. Menopause status was not adjusted for in the analysis stratified by menopausal status. Age at menopause and postmenopausal hormone use were not adjusted for in the analysis restricted to premenopausal women.