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Childbearing Recency and Modifiers of Premenopausal Breast Cancer Risk

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Abstract

The purpose of this study was to examine the risk of premenopausal breast cancer for women in relation to childbearing recency, and whether this association differs by breastfeeding history and/or the amount of weight gained during pregnancy. This analysis was based on data from a population-based case-control study comprised of 1,706 incident cases of invasive breast cancer and 1,756 population controls from Wisconsin, New Hampshire, and Massachusetts. In a telephone interview conducted from 1996 to 2001, information was gathered on established breast cancer risk factors, as well as reproductive history, including amount of weight gained during the last full-term pregnancy, and whether or not the child was breast-fed. Unconditional logistic regression was used to estimate odds ratios (ORs) and Wald 95% confidence intervals (CIs) for the risk of breast cancer. When compared to nulliparous women, women that had given birth within the past 5 years prior to breast cancer diagnosis in the cases or a comparable period in controls had a non-significant 35% increased risk of invasive breast cancer (OR=1.35; 95% CI: 0.90–2.04) adjusting for age and known breast cancer risk factors (p trend = 0.14). We did not find a significant interaction with breast-feeding (p for interaction = 0.30) or pregnancy weight gain (p for interaction = 0.09).

Keywords

breast neoplasms; epidemiology; pregnancy; breast feeding; weight gain

INTRODUCTION

First full-term pregnancy achieved before the age of 35 is associated with a reduced lifetime risk of developing breast cancer in women.[1] However, this protection does not occur immediately and women are initially at higher risk for breast cancer after giving birth,[2] especially older first-time mothers.[3] This transient increase in breast cancer lasts for at least 10 years for younger first-time mothers (< 25 years) and up to 30 years for older first-time

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mothers (> 30 years).[4;5] Excessive weight gain during pregnancy has been reported to increase breast cancer risk,[6;7] and the mechanism may be due to alterations in estrogens or other sex steroids, insulin, insulin-like growth factor 1 (IGF-1), and adipokines.[8–15] Conversely, breast-feeding has been shown to reduce breast cancer risk overall,[16] but may contribute to the observed increase in breast cancer following pregnancy due to potential tumor-promoting effects of elevated prolactin levels seen in pregnancy and lactation.[17] To examine if pregnancy weight gain or breast-feeding influences premenopausal breast cancer risk following childbirth, we examined data collected in a large breast cancer case-control study.

SUBJECTS AND METHODS

The case-control study has been described in detail in previous reports.[18] In brief, cases were women with a first primary invasive breast cancer diagnosis identified from population-based cancer registries in Wisconsin, Massachusetts, and New Hampshire (1996–2001) according to protocols approved by institutional review boards at each site. Women eligible for the study resided in Wisconsin, Massachusetts (excluding metropolitan Boston), or New Hampshire, were age 20–69 years at diagnosis, had a listed telephone number, and were verified by self-report to have a driver's license. Approximately 80% of eligible case women were successfully interviewed. Within each state, controls, frequency matched to cases within 5-year age strata, were randomly selected from lists of licensed drivers. To be eligible as a control, a woman must have had a listed telephone number, no personal history of breast cancer and be a licensed driver. Approximately 76% of eligible controls were successfully interviewed. A total of 3,464 pre-menopausal women (1,706 cases and 1,758 controls) under 50 years of age at the reference date were eligible for the present analysis. For cases, the reference date was the date of diagnoses. For controls, the reference date corresponded to a date approximately 1 year before the interview to reflect the average times between diagnosis and interview for the cases.

Information on reproductive history was ascertained in a structured telephone interview. Women were asked to report the dates, length, and outcome of each pregnancy. For each live birth, women were asked if the child was breast-fed, and for how long. Women under the age of 50 were also asked to report the number of pounds they had gained during the final or most recent live birth. The interview also elicited information on known and suspected breast cancer risk factors.

Unconditional logistic regression was used to estimate odds ratios (ORs) and Wald 95% confidence intervals (CIs) for recency of childbearing and interactions with weight gain and lactation in reference to the most recent birth. All models included terms for referent age (in 5 year categories), state of residence (Wisconsin, Massachusetts or New Hampshire), total parity, and age at first birth. Models also included potential confounding breast cancer risk factors shown in Table 1 associated with breast cancer in these data including education, first degree family history of breast cancer, recent pre-diagnosis body mass index, history of screening mammography in the five years before the reference age, and history of benign breast disease. Tests for linear trend were performed by including ordinal variables in multivariate logistic regression models that also included terms for age, state of residence, and all other covariates. Among the 1,706 cases and 1,758 controls eligible for the analysis, data on total parity or age at first birth were missing for 2 controls. After excluding these women, a total of 1,706 cases and 1,756 controls were included in the present analysis.

RESULTS

The characteristics of the cases and controls included in the analysis are presented in Table 1. Compared to controls, cases had similar education, had lower parity, were older at the time of first birth, were more likely to have a family history of breast cancer, had a lower BMI, were

less likely to have a mammogram in the previous 5 years, and were more likely to have benign breast disease.

The association between breast-feeding, weight gain during pregnancy, and recency with respect to the final or most recent birth and breast cancer risk is shown in Table 2. Recent childbearing was associated with a non-significant increased risk of breast cancer: when compared to nulliparous women, women that had given birth within 5 years of the referent date had a non-significant 35% increased risk of invasive breast cancer (OR=1.35; 95% CI: 0.90–2.04) adjusting for age and all covariates, with no evidence of a trend with more proximal childbearing (p trend = 0.14). Neither breast-feeding nor relative weight gain in pregnancy was significantly associated with breast cancer risk.

We examined whether breast-feeding or pregnancy weight gain associated with the last or most recent live birth modified the association between recent childbearing and breast cancer risk (Table 3). Among women who did not breast-feed, the risk of breast cancer was non-significantly elevated among women that recently gave birth (≤5 years) (OR=1.64; 95% CI: 0.97–2.78) when compared to nulliparous women. The excess risk associated with recent childbearing (≤5 years) was reduced in women that breast-fed for any duration during the last pregnancy (OR=1.24; 95% CI: 0.80–1.91). There was no evidence for interaction between recency of childbirth (ordinal variable) and any breast-feeding among parous women (p for interaction = 0.30). For pregnancy weight gain, the elevated risk associated with recent childbirth appeared to be higher in women with a lower percent body weight gain relative to the last recorded body weight: the odds ratio was 1.39 (95%CI: 0.80–2.42) for a weight gain of < 24% and 1.21 (95% CI: 0.70–2.09) for a weight gain of ≥ 24% during the most recent pregnancy, , adjusting for age and all covariates (p for interaction = 0.09). Results were similar for absolute weight gain (results not shown).

DISCUSSION

To our knowledge, this is the first study to consider whether pregnancy-associated factors have a modifying influence on the transient excess risk of breast cancer following childbirth. In line with previous studies (ORs 1.1–1.3),[2–4] we observed a modest increase in breast cancer risk associated with childbearing recency, though results in our analysis did not attain statistical significance. The transient increase in breast cancer after childbearing is often attributed to a promotional influence of pregnancy estrogens; however, as pregnancy-associated breast cancers are often estrogen receptor-negative,[19] other mechanisms may be more plausible.[20] Elevated levels of prolactin during pregnancy and breast-feeding may contribute to the observed increase in breast cancer following pregnancy.[17] However, lactation has been found to reduce breast cancer risk overall,[16] possibly by promoting terminal differentiation of breast tissue, and/or suppressing ovulation and lowering breast estrogen levels.[21;22] In this analysis, we examined whether lactation has any net benefit or untoward influence on premenopausal breast cancer risk following childbirth and found, if anything, a slight attenuation in the risk associated with childbearing recency among women who breastfed, though the test for interaction was non-significant. Greater weight gain during pregnancy may influence breast cancer risk secondary to alterations in estrogens or other sex steroids, insulin, IGF-1, and adipokines, but data has been conflicting.[8–15] The present analysis suggests that pregnancy-associated breast cancer risk is not significantly altered by weight gain during the most recent live birth consistent with prior findings,[23] although there was a suggestion that premenopausal breast cancer risk was lower among mothers who gained the most weight during pregnancy.

The strengths of this study include its large size and population-based design. Limitations included potential selection bias if cases and controls participated in the study differentially based on pregnancy-associated risk factors. Error in recall of lactation history and pregnancy

weight gain would have attenuated all associations, though studies suggest that past weight is reported with reasonable validity.[24;25] In addition, the analysis was restricted to younger women (under age 50) and focused on the most recent live-birth. Also, we did not attempt to specifically evaluate pregnancy-associated breast cancer which is defined as cancer diagnosed during pregnancy or within 1 year of delivery. It is unclear whether or not the pathophysiology of these cancers is different from that of all other premenopausal breast cancers. Despite the large overall size of the study, relatively few women in the present analysis were of child-bearing age, and therefore power in the study to evaluate recency main effects and interactions was less than optimal. In summary, we found no compelling evidence that pregnancy weight gain or breast-feeding following the final or most recent pregnancy modifies the association of childbearing recency with breast cancer risk in premenopausal women.

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References

1. Trichopoulos D, Hsieh CC, MacMahon B, et al. Age at any birth and breast cancer risk. Int J Cancer 1983;31:701–704. [PubMed: 6862681]
2. Janerich DT, Hoff MB. Evidence for a crossover in breast cancer risk factors. Am J Epidemiol 1982;116:737–742. [PubMed: 6756128]
3. Lambe M, Hsieh C, Trichopoulos D, Ekbom A, Pavia M, Adami HO. Transient increase in the risk of breast cancer after giving birth. N Engl J Med 1994;331:5–9. [PubMed: 8202106]
4. Albrektsen G, Heuch I, Hansen S, Kvale G. Breast cancer risk by age at birth, time since birth and time intervals between births: exploring interaction effects. Br J Cancer 2005;92:167–175. [PubMed: 15597097]
5. Chie WC, Hsieh C, Newcomb PA, et al. Age at any full-term pregnancy and breast cancer risk. Am J Epidemiol 2000;151:715–722. [PubMed: 10752799]
6. de Assis S, Wang M, Goel S, Foxworth A, Helferich W, Hilakivi-Clarke L. Excessive weight gain during pregnancy increases carcinogen-induced mammary tumorigenesis in Sprague-Dawley and lean and obese Zucker rats. J Nutr 2006;136:998–1004. [PubMed: 16549464]
7. Kinnunen TI, Luoto R, Gissler M, Hemminki E, Hilakivi-Clarke L. Pregnancy weight gain and breast cancer risk. BMC Womens Health 2004;4:7. [PubMed: 15498103]
8. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–1638. [PubMed: 12711737]
9. Lawlor DA, Smith GD, Ebrahim S. Hyperinsulinaemia and increased risk of breast cancer: findings from the British Women's Heart and Health Study. Cancer Causes Control 2004;15:267–275. [PubMed: 15090721]
10. Muti P, Quattrin T, Grant BJ, et al. Fasting glucose is a risk factor for breast cancer: a prospective study. Cancer Epidemiol Biomarkers Prev 2002;11:1361–1368. [PubMed: 12433712]
11. Hankinson SE. Endogenous hormones and risk of breast cancer in postmenopausal women. Breast Dis 2005;24:3–15. [PubMed: 16917136]
12. Schernhammer ES, Holly JM, Hunter DJ, Pollak MN, Hankinson SE. Insulin-like growth factor-I, its binding proteins (IGFBP-1 and IGFBP-3), and growth hormone and breast cancer risk in The Nurses Health Study II. Endocr Relat Cancer 2006;13:583–592. [PubMed: 16728584]

13. Schernhammer ES, Holly JM, Pollak MN, Hankinson SE. Circulating levels of insulin-like growth factors, their binding proteins, and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2005;14:699–704. [PubMed: 15767352]
14. Rose DP, Komninou D, Stephenson GD. Obesity, adipocytokines, and insulin resistance in breast cancer. Obes Rev 2004;5:153–165. [PubMed: 15245384]
15. Hu X, Juneja SC, Maihle NJ, Cleary MP. Leptin–a growth factor in normal and malignant breast cells and for normal mammary gland development. J Natl Cancer Inst 2002;94:1704–1711. [PubMed: 12441326]
16. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet 2002;360:187–195. [PubMed: 12133652]
17. Bulbrook RD, Wang DY, Hayward JL, Kwa HG, Cleton F. Plasma prolactin levels and age in a female population: relation to breast cancer. Int J Cancer 1981;28:43–45. [PubMed: 7309281]
18. Sprague BL, Trentham-Dietz A, Newcomb PA, Titus-Ernstoff L, Hampton JM, Egan KM. Lifetime recreational and occupational physical activity and risk of in situ and invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2007;16:236–243. [PubMed: 17301255]
19. Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: a literature review. Arch Surg 2003;138:91–98. [PubMed: 12511159]
20. Schedin P. Pregnancy-associated breast cancer and metastasis. Nat Rev Cancer 2006;6:281–291. [PubMed: 16557280]
21. Enger SM, Ross RK, Paganini-Hill A, Bernstein L. Breastfeeding experience and breast cancer risk among postmenopausal women. Cancer Epidemiol Biomarkers Prev 1998;7:365–369. [PubMed: 9610784]
22. Ursin G, Bernstein L, Wang Y, et al. Reproductive factors and risk of breast carcinoma in a study of white and African-American women. Cancer 2004;101:353–362. [PubMed: 15241834]
23. Hilakivi-Clarke L, Luoto R, Huttunen T, Koskenvuo M. Pregnancy weight gain and premenopausal breast cancer risk. J Reprod Med 2005;50:811–816. [PubMed: 16419626]
24. Perry GS, Byers TE, Mokdad AH, Serdula MK, Williamson D. The validity of self-reports of past body weights by U.S. adults. Epidemiology 1995;6:61–66. [PubMed: 7888448]
25. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466–473. [PubMed: 2090285]

Table 1

Selected Characteristics of Premenopausal Breast Cancer Cases and Controls: Collaborative Breast Cancer Study (1996–2001)

	Cases (n = 1,706)*		Controls (n = 1,756)*		P†
	No.	%	No.	%	
Education					
Less than high school	33	2.0	53	3.0	
High school graduate	570	33.7	539	30.7	
Some college	475	28.1	512	29.2	
College graduate	614	36.3	650	37.1	0.08
Parity					
Nulliparous	274	16.1	255	14.5	
1–2	996	58.4	943	53.7	
3–4	400	23.5	513	29.2	
≥5	36	2.1	45	2.6	0.001
Age at first birth‡					
<20 yrs	190	13.3	246	16.4	
20 – <25 yrs	462	32.3	557	37.1	
25 – <30 yrs	497	34.7	442	29.5	
≥30 yrs	283	19.8	256	17.1	0.0003
Family history of breast cancer					
No	1371	81.6	1555	89.8	
Yes	310	18.4	176	10.2	<.0001
Body mass index (kg/m^2)					
<25	971	58.5	930	54.6	
25 – <30	430	25.9	474	27.8	
≥30	259	15.6	300	17.6	0.07
Mammogram in the last 5 years					
No	477	28.2	427	24.4	
Yes	1213	71.8	1326	75.6	0.01
Benign breast disease					
No	1174	69.8	1355	78.0	
Yes	508	30.2	383	22.0	<.0001

	Cases (n = 1,706)*		Controls (n = 1,756)*		P†
	No.	%	No.	%	

*Unequal column totals reflect missing data.

†χ^2-test for differences between cases and controls.

‡Only includes parous women.

Table 2

Risk of breast cancer in relation to pregnancy-related factors: Collaborative Breast Cancer Study (1996–2001)

	Cases (N=1,706)	Controls (N=1,756)	OR*	95% CI
Recency of last birth				
Nulliparous	274	255	1.00	Ref
>10 years	952	1053	1.12	0.85–1.47
>5–10 years	275	272	1.22	0.85–1.73
≤5 years	205	176	1.35	0.90–2.02
p trend			0.14	
Breast-feeding duration†				
None	649	680	1.00	Ref
≤3 months	357	406	0.85	0.70–1.04
>3 months	426	415	1.10	0.91–1.34
p trend			0.39	
Weight Change‡				
<20%	416	418	1.00	Ref
20% – ≤29%	496	526	0.92	0.76–1.11
≥29%	417	463	0.87	0.72–1.07
p trend			0.18	

*Adjusted for age, state, parity, age at first birth, education, mammogram in last 5 years, family history, body-mass index, benign breast disease.

†Duration of breast-feeding the last-born child; parous women only.

‡Weight gain in final pregnancy relative to the most recent reported BMI; parous women only.

Table 3

Recency of breast cancer according to breast-feeding and pregnancy weight gain: Collaborative Breast Cancer Study (1996–2001)

	Any Breast-feeding				No Breast-feeding			
Recency of last birth	**Cases**	**Controls**	**OR***	**95% CI**	**Cases**	**Controls**	**OR***	**95% CI**
Nulliparous	274	255	1.00	Ref	-	-	-	-
>10 years	472	515	1.11	0.82–1.50	480	538	1.11	0.84–1.48
>5–10 years	170	175	1.18	0.80–1.74	105	97	1.25	0.83–1.90
≤5 years	141	133	1.24	0.80–1.91	64	43	1.64	0.97–2.78
p trend			0.32				0.12	
Interaction term p-value†				0.30				
	< 24% increase in weight‡				**≥ 24% increase in weight‡**			
Recency of last birth	**Cases**	**Controls**	**OR***	**95% CI**	**Cases**	**Controls**	**OR***	**95% CI**
Nulliparous	274	255	1.00	Ref	-	-	-	-
>10 years	431	484	1.09	0.81–1.47	452	494	1.10	0.82–1.48
>5–10 years	133	111	1.40	0.93–2.12	124	150	0.91	0.61–1.36
≤5 years	92	77	1.39	0.86–2.24	97	91	1.10	0.69–1.74
p trend			0.18				0.62	
Interaction term p-value†				0.09				

*Adjusted for age, state, parity, age at first birth, education, mammogram in last 5 years, family history, body-mass index, benign breast disease.

†Breastfeeding and weight gain according to years since most recent birth among parous women.

‡197 women with missing data for weight change.