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Breast cancer risk associations with birth order and maternal age according to breast-feeding status in infancy

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Abstract

Background—Early life risk factors for breast cancer have been investigated in relation to hormonal, nutritional, infectious, and/or genetic hypotheses. Recently, studies of potential health effects associated with exposure to environmental contaminants in breastmilk have been considered.

Methods—We analyzed data from a population-based case-control study of female Wisconsin residents. Cases (N=2,016) had an incident diagnosis of invasive breast cancer in 2002−2006 reported to the statewide tumor registry. Controls (N=1,960) of similar ages were randomly selected from driver's license lists. Risk factor information was collected during structured telephone interviews. Odds ratios (ORs) and 95% confidence intervals (CI) were estimated from multivariable logistic regression.

Results—In multivariable models, maternal age and birth order were not associated with breast cancer risk in the full study population. The odds ratio for breast cancer risk associated with having been breastfed in infancy was 0.83 (95% CI 0.72−0.96). In analyses restricted to breastfed women, maternal age associations with breast cancer were null (p-value=0.2). Increasing maternal age was negatively associated with breast cancer risk among women who were not breastfed; the odds ratio for breast cancer associated with each 5-year increase in maternal age was 0.90 (95% CI 0.82−1.00). Higher birth order was inversely associated with breast cancer risk among breastfed women (OR=0.58; 95% CI 0.39−0.86 for women with ≥3 older siblings compared to first-born women) but not among non-breastfed women (OR=1.13; 95% CI 0.81−1.57).

Conclusion—These findings suggest that early life risk factor associations for breast cancer may differ according to breastfeeding status in infancy.

The detection of widespread contamination of human breastmilk with environmental pollutants has raised concerns regarding potential adverse health effects.[1, 2] A number of exogenous chemicals in breastmilk exhibit carcinogenic or xenoestrogenic activity, including polychlorinated biphenyls (PCBs), chlorinated dioxins, chlorinated furans, polybrominated diphenylethers (PBDEs), polycyclic aromatic hydrocarbons (PAHs), dichlorodiphenyltrichloroethane (DDT) and other pesticides.[3-6]

Due to the persistence and accumulation of these chemicals in the human body, maternal age is an important predictor of contaminant levels in breastmilk.[7] Many of these contaminants are

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poorly metabolized, leaving breastfeeding as the primary means of excretion.[2, 8] Parity has been inversely associated with breastmilk contaminant levels; first-born infants generally consume higher levels of contaminants relative to later siblings.[7, 9, 10]

Breastmilk consumption has been associated with greater levels of PCBs and related organochlorines in adipose tissue samples from children age 1–2 years.[11] Studies among adults have hypothesized that organochlorine levels in adipose tissue may be related to increased breast cancer risk [12, 13], although evidence is currently insufficient to support an association.[14] It is unknown whether exposure to contaminants in breastmilk has the potential to increase cancer risk in adulthood.

Despite a wealth of epidemiologic research, evidence has been conflicting with modest or null associations with adult breast cancer risk reported for breastmilk consumption in infancy, birth order, and maternal age as primary exposures.[15-55] With this background, we explored whether maternal age and birth order associations for breast cancer risk varied according to exposure to breastmilk in infancy. We hypothesized that, due to lesser exposure to environmental contaminants in breastmilk, increasing birth order and younger maternal age would be associated with decreased adult breast cancer risk only among women who were breastfed in infancy. We investigated this relation in a population-based case-control study of women in Wisconsin, USA.

Materials and methods

Selection of Cases

Female residents of Wisconsin age 20–69 years with an incident diagnosis of invasive breast cancer in 2002–2006 reported to the state-mandated cancer registry, a listed telephone number, and self-reported driver's license were eligible for participation. Telephone interviews were conducted according to institutionally approved protocols from May 2004-November 2006. Of 2,633 eligible breast cancer cases, 55 (2.1%) were deceased, 93 (3.5%) could not be located and 469 (17.8%) refused participation. Therefore, 2,016 (76.6%) women were interviewed.

Selection of Controls

Controls were randomly selected from the community within 5-year age strata to yield an age distribution similar to the cases using lists of licensed drivers from the Wisconsin Department of Transportation. Inclusion criteria required no personal history of breast cancer and a publicly available telephone number. Of the 2,781 potential controls, 7 (0.2%) were deceased, 140 (5.0%) could not be located, and 673 (24.2%) refused to participate. Interviews were obtained for 1,961 (70.5%) of these women. One interviewed control was considered unreliable by the interviewer. Hence, 1,960 controls were available for analysis.

Data Collection

In structured telephone interviews, study participants self-reported whether they were breastfed in infancy, how old their mother was when they were born, the number of children their mother gave birth to, and their birth order among siblings (including any deceased or half-siblings). The 35-minute interview also elicited information on reproductive history, physical activity, alcohol consumption, height and weight, oral contraceptive and postmenopausal hormone use, personal and family medical history, and demographic factors.

Statistical analysis

For each case, a reference date was defined as the registry-supplied date of invasive breast cancer diagnosis. For comparability, control subjects interviewed contemporaneously with cases were assigned an individual reference date, based on the normal distribution of days from diagnosis to interview in the cases already interviewed. Only exposures that occurred prior to the assigned reference date were included in analyses.

Odds ratios (OR) and 95% confidence intervals (CI) for breast cancer were produced using multivariable logistic regression models. Variables that were associated with breast cancer risk ($p \leq 0.05$) in preliminarily age-adjusted models were included in multivariable models. All final models included the following covariates: age, birth order, age at menarche, age at first birth, parity, menopausal status, age at menopause, postmenopausal hormone use, family history of breast cancer in a mother or sister, height, weight at age 20, weight gain since age 20 and mammography screening. When evaluating the effect of birth order or maternal age, both variables were included in the fully adjusted model. Effect modification was evaluated by including cross-product interaction terms in logistic models. The analyses described above were performed using SAS version 9.1 software (SAS Institute, Inc., Cary, NC).

Reliability substudy

The standardized questionnaire used in this study was also utilized in two other case-control studies conducted in 1992−1995 and 1997−2001[37, 40]. In these previous investigations, sequential samples of study participants were reinterviewed to evaluate the reliability of the questionnaire. Intraclass correlation coefficients (ICC) and 95% confidence intervals were estimated for continuous questionnaire items and Cohen's kappa (κ) was used with categorical variables.[56] For the breastmilk exposure status question, κ=0.88 (95% CI 0.79, 0.97) among controls and κ=0.96 (95% CI 0.90, 1.00) among. The ICC was 0.88 (95% CI 0.86, 0.90) for maternal age at the study participant's birth among control women. Reproducibility information for the maternal age question was not available for case participants.

Results

Table 1 presents odds ratios for breast cancer associations with established risk factors. Odds ratios decreased according to older age at menarche and increasing parity, and increased with later age at first birth, later age at menopause, use of postmenopausal hormones containing estrogen plus progestin, family history of breast cancer, greater weight gain since age 20, and frequent mammographic examinations.

Table 2 displays odds ratios for breast cancer according to early life factors. In multivariable-adjusted models, breast cancer associations with maternal age (OR=0.99 per 5-year increase; 95% CI 0.93−1.05) and birth order (OR=0.98 per 1-sibling increase; 95% CI 0.94−1.03) were null.

In our study sample, 634 (31%) cases and 681 (35%) control women self-reported being breastfed in infancy. After multivariable adjustment, the odds ratio for breast cancer associated with exposure to breastmilk in infancy was 0.83 (95% CI 0.72−0.96) compared to women who were not breastfed (Table 2). In analyses restricted to first-born women (N=557 cases; 514 controls), breastmilk exposure in infancy was not associated with breast cancer risk in age- or multivariable-adjusted models (OR=1.00; 95% CI: 0.77, 1.31 and OR=0.97; 95% CI: 0.74, 1.29, respectively).

According to our *a priori* hypotheses, we performed birth order and maternal age analyses stratified according to whether the participant was breastfed in infancy (Table 3). In multivariable models, we observed a reduced odds ratio of breast cancer associated with older maternal age among women who were not breastfed (OR=0.90 per 5-year increase; 95% CI 0.82−1.00). Compared to women with mothers age 20−24 years, women with mothers age 35 years or older had an odds ratio of 0.64 for breast cancer (95% CI 0.45−0.92). Maternal age did not appear related to breast cancer risk among women who reported being breastfed in infancy (OR=1.09 per 5-year increase; 95% CI 0.96–1.23). In the interaction test for breastmilk exposure by maternal age (continuous), p=0.20 (χ^2=1.65, 1 degree of freedom).

We observed an inverse association with increasing birth order among women who reported being breastfed in infancy, but not among women who were not breastfed. Among breastfed women, the odds ratio for breast cancer associated with each one child increase in birth order was 0.91 (95% CI 0.84–0.99). Women with three or more older siblings had 0.58 times the odds of breast cancer compared to first-born women (95% CI 0.39–0.86). For the interaction test for breastmilk exposure by birth order (first, second or third, fourth or higher), p=0.28 (χ^2=2.53, 2 degrees of freedom). We repeated the analyses in Tables 2 and 3 after excluding individuals with missing data on the variables of interest (maternal age, birth order, and breastfeeding status in infancy); odds ratios and 95% confidence intervals remained virtually unchanged.

Discussion

Our findings suggested null associations for maternal age and birth order in relation to adult breast cancer risk in the full study population. Breastmilk exposure in infancy was associated with a small decrease in the odds ratio for breast cancer overall. However, this relation was not observed among first-born women. Consistent with our initial hypotheses, higher birth order was associated with reduced breast cancer risk only among breastfed women. However, maternal age was related to an unexpected inverse association with breast cancer risk among women who were not breastfed. To our knowledge, no previous study has reported on potential interactions of birth order or maternal age with breastmilk exposure in determining adult breast cancer risk.

Previous reports have generally suggested a protective effect of younger maternal age in relation to adult breast cancer risk.[21, 25, 26, 28, 43, 46, 50] However, an approximately equal number of reports detected weak or statistically non-significant positive trends [24, 27, 33, 36, 52, 54] or found no association.[23, 29, 35, 37, 39, 41, 55] In 2005, Forman et al. recalculated previous findings to create a uniform reference group of maternal age 20–24.[53] Of 12 studies, only two detected a statistically significant increase in breast cancer risk among women with mothers older than 25 [43] or 35–39 years.[26]

Although many publications of the independent effects of birth order in relation to breast cancer risk have indicated null or statistically non-significant associations [17, 21, 24, 25, 29, 35, 36, 43, 47, 48, 50, 51, 54, 55], at least three studies have shown inverse associations between birth order and breast cancer risk, either overall, or among subgroups of premenopausal women [28, 32, 46]

Within the substantial literature of breastmilk consumption in infancy in relation to adult breast cancer risk, two reviews [42, 53] and a meta-analysis [57] suggest that women exposed to breastmilk as infants may have a 20–35% reduction in breast cancer risk. A third review concluded that while early viral etiology hypotheses[58] have clearly not been upheld, results regarding the association between breastmilk exposure and breast cancer risk have been largely inconsistent.[49]

A predominant explanation for potential decreases in breast cancer incidence according to high birth order and younger maternal age is variation in the *in utero* hormonal environment and the potential creation of a "fertile soil" for breast carcinogenesis in adult life [59]. Hormonal profiles differ according to parity with higher estrogen levels in first pregnancies.[60, 61] One early study also provided evidence of higher estrogen levels during pregnancy among women age 20–24 years old compared to both younger and older women.[62] However, a second, more recent study did not detect differences in estrogen levels during pregnancy according to maternal age.[63]

Another theory suggests that older maternal age results in a greater probability of genetic mutation and chromosomal aberrations; however, some controversy remains whether these effects are independent of paternal age.[64] In our study, information about paternal age was not collected during the telephone interview and was therefore unavailable for analysis.

Previous investigations of breastmilk exposure in infancy have highlighted differences relative to bottle-feeding in terms of nutrition, immunologic activity, and hormonal exposures. Other studies have indicated that environmental contaminant exposure is higher in breastfed infants compared to formula-fed infants. [65-69] Duration of breastfeeding has demonstrated a dose-response relation with PCB and DDT exposure in the infant.[11, 69-72] Information on duration of breastfeeding in infancy was not available in our study.

Other limitations of our study should be considered. Birth order and maternal age were evaluated as proxies for potential relative concentration of persistent organic pollutants in breastmilk. The study questionnaire did not explicitly ask whether a participant's older siblings were breastfed in infancy. Therefore, our interpretation of the potential interaction between birth order and breastfeeding status is dependent on the assumption that if a woman was breastfed in infancy, then her older siblings were breastfed as well.

Confidence in our findings is strengthened by the high response rates, use of a standardized instrument with high reproducibility, and multivariable adjustment scheme. Self-reported exposure to breast-milk in infancy has been highly correlated with mother's reports (r=0.74).[73] Being breastfed in infancy may also be correlated with the decision to breastfeed as an adult, a behavior known to reduce breast cancer risk.[74] We additionally adjusted model estimates for duration of adult breastfeeding; odds ratios remained unchanged.

These findings suggest that maternal age and birth order associations with adult breast cancer risk may differ according to exposure to breastmilk in infancy.

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TABLE 1

Odds ratios and 95% confidence intervals for invasive breast cancer according to select characteristics, 2004–2006.

Characteristic	Cases (N=2,016) N	Cases %[*]	Controls (N=1,960) N	Controls %[*]	Age-adjusted OR (95% CI)
Age at menarche					
≤12	923	45.8	818	41.7	1
13	520	25.8	522	32.3	0.88 (0.76, 1.03)
14	281	13.9	293	18.1	0.85 (0.70, 1.02)
≥15	226	11.2	259	16.0	0.77 (0.63, 0.94)
Age at first birth[†]					
14–19	312	18.4	337	19.7	1
20–22	452	26.7	545	31.9	0.90 (0.74, 1.09)
23–25	344	20.3	374	21.9	0.99 (0.80, 1.22)
26–42	571	33.7	446	26.1	1.36 (1.12, 1.67)
Parity					
Nulliparous	302	15.0	238	12.1	1
1–2	947	47.0	848	43.3	0.88 (0.73, 1.07)
3–4	621	30.8	691	35.3	0.72 (0.59, 0.88)
≥5	125	6.2	171	8.7	0.60 (0.45, 0.80)
Age at menopause[‡]					
23–42	215	18.7	295	24.5	1
43–48	229	19.9	267	22.2	1.16 (0.91, 1.49)
49–51	277	24.1	251	20.8	1.52 (1.19, 1.95)
52–59	278	24.2	261	21.7	1.50 (1.17, 1.91)
Postmenopausal hormone use[‡]					
None	507	44.1	531	44.1	1
Estrogen only	239	20.8	311	25.8	0.81 (0.66, 0.99)
Estrogen plus progestin only	300	26.1	251	20.8	1.25 (1.02, 1.54)
Other/unknown	85	7.4	88	7.3	1.01 (0.73, 1.40)
Family history of breast cancer					
No	1,556	77.2	1,611	82.2	1
Yes	406	20.1	294	15.0	1.45 (1.23, 1.71)
Weight gain since age 20[§]					
Lost weight	106	5.3	110	5.6	1.10 (0.82, 1.49)
0–15 lbs.	536	26.6	556	28.4	1
16–30 lbs.	506	25.1	492	25.1	1.10 (0.92, 1.30)
31–50 lbs.	430	21.3	423	21.6	1.10 (0.91, 1.32)
>50 lbs.	433	21.5	373	19.0	1.24 (1.03, 1.50)
Mammographic examination within 5 years					
No	171	8.5	213	10.9	1
Yes	1,761	87.4	1,705	87.0	1.37 (1.10, 1.70)
<5 mammograms	508	25.2	580	29.6	1.15 (0.91, 1.46)
5 mammograms	1,043	51.7	1,015	51.8	1.43 (1.13, 1.80)
>5 mammograms	141	7.0	61	3.1	3.16 (2.19, 4.56)

[*] Due to missing values, some categories do not sum to 100%.

[†] Among parous women only (N=1,693 cases; 1,710 controls).

[‡] Among postmenopausal women only (N=1,149 cases; 1,205 controls).

[§] Odds ratios additionally adjusted for weight at age 20 (lbs.) and height (m).

TABLE 2

Odds ratios and 95% confidence intervals for invasive breast cancer according to early life factors, 2004–2006.

Characteristic	Cases (N=2,016) N	Cases %‡	Controls (N=1,960) N	Controls %‡	OR (95% CI)*	OR (95% CI)†
Maternal age§						
<20	142	7.0%	156	8.0%	0.81 (0.62, 1.04)	0.81 (0.62, 1.06)
20–24	595	29.5%	532	27.1%	1	1
25–29	524	26.0%	511	26.1%	0.92 (0.77, 1.09)	0.87 (0.73, 1.04)
30–34	344	17.1%	318	16.2%	0.97 (0.80, 1.18)	0.91 (0.73, 1.12)
≥35	299	14.8%	315	16.1%	0.85 (0.70, 1.03)	0.83 (0.66, 1.05)
5-year increase					1.00 (0.95, 1.05) p-value=0.9	0.99 (0.93, 1.05) p-value=0.7
Birth order§						
First-born	557	27.6%	514	26.2%	1	1
Second- or third-born	877	43.5%	833	42.5%	0.96 (0.83, 1.12)	0.99 (0.84, 1.17)
Fourth-born or higher	446	22.1%	491	25.1%	0.83 (0.69, 0.98)	0.88 (0.70, 1.10)
1-sibling increase					0.96 (0.93, 1.00) p-value=0.03	0.98 (0.94, 1.03) p-value=0.5
Breastfed in infancy						
No	1014	50.3%	920	46.9%	1	1
Yes	634	31.4%	681	34.7%	0.87 (0.76, 1.01)	0.83 (0.72, 0.96)
Unknown/missing	368	18.3%	359	18.3%		

*Odds ratios adjusted for age.

†Odds ratios adjusted for age, age at menarche, age at first birth, parity, menopausal status, age at menopause, postmenopausal hormone use, family history of breast cancer, height, weight at age 20, weight gain, mammography use, and whether breastfed in infancy.

‡Due to missing values, some categories do not sum to 100%.

§In multivariable models, birth order and maternal age are adjusted for simultaneously when evaluating the effect of either variable.

TABLE 3

Odds ratios and 95% confidence intervals for invasive breast cancer according to breastfeeding status in infancy, 2004–2006.

	Breastfed in infancy						Non-breastfed in infancy					
	Cases N=634		Controls N=681				Cases N=1,014		Controls N=920			
	N	%‡	N	%‡	OR (95% CI)*	OR (95% CI)†	N	%‡	N	%‡	OR (95% CI)*	OR (95% CI)†
Maternal age												
<20	38	6.0	51	7.5	0.84 (0.53, 1.33)	0.82 (0.50, 1.35)	82	8.1	80	8.7	0.79 (0.56, 1.13)	0.79 (0.54, 1.16)
20–24	181	28.5	204	30.0	1	1	311	30.7	241	26.2	1	1
25–29	176	27.8	183	26.9	1.08 (0.81, 1.44)	1.00 (0.73, 1.36)	269	26.5	254	27.6	0.82 (0.65, 1.04)	0.77 (0.60, 1.00)
30–34	115	18.1	104	15.3	1.25 (0.89, 1.74)	1.18 (0.81, 1.73)	175	17.3	164	17.8	0.83 (0.63, 1.09)	0.73 (0.54,1.00)
≥35	101	15.9	118	17.3	0.96 (0.69, 1.34)	1.04 (0.67, 1.60)	134	13.2	134	14.6	0.78 (0.58, 1.04)	0.64 (0.45, 0.92)
5-year increase§					1.04 (0.96, 1.14)	1.09 (0.96, 1.23)					0.96 (0.89, 1.03)	0.90 (0.82, 1.00)
					p-value=0.3	p-value=0.2					p-value=0.2	p-value=0.04
Birth order//												
First-born	195	30.8	183	26.9	1	1	272	26.8	249	27.1	1	1
Second- or third-born	255	40.2	268	39.4	0.90 (0.69, 1.17)	0.82 (0.61, 1.10)	429	42.3	386	42.0	0.99 (0.80, 1.23)	1.08 (0.85, 1.38)
Fourth-born or higher	140	22.1	186	27.3	0.71 (0.53, 0.96)	0.58 (0.39, 0.86)	204	20.1	193	23.3	0.94 (0.72, 1.21)	1.13 (0.81, 1.57)
1-sibling increase					0.95 (0.90, 1.00)	0.91 (0.84, 0.99)					0.97 (0.92, 1.02)	1.02 (0.95, 1.09)
					p-value=0.07	p-value=0.02					p-value=0.2	p-value=0.6

*Odds ratios adjusted for age.

†Odds ratios adjusted for age, birth order, maternal age, age at menarche, age at first birth, parity, menopausal status, age at menopause, postmenopausal hormone use, family history of breast cancer, height, weight at age 20, weight gain, and mammography use.

‡Due to missing values, some categories do not sum to 100%.

§For the test of interaction between breastfed in infancy and maternal age (continuous), χ^2=1.65, 1 df, p=0.20.

//For the test of interaction between breastfed in infancy and birth order (first, second or third, fourth or higher), χ^2=2.53, 2 df, p=0.28.