Prenatal and Perinatal Correlates of Adult Mammographic Breast Density

James R. Cerhan,[1] Thomas A. Sellers,[3] Carol A. Janney,[1] V. Shane Pankratz,[1] Kathy R. Brandt,[2] and Celine M. Vachon[1]

Departments of [1]Health Sciences Research and [2]Radiology, Mayo Clinic College of Medicine, Rochester, Minnesota and [3]Division of Cancer Prevention and Control, H. Lee Moffitt Cancer and Research Institute, Tampa, Florida

Abstract

Background: **Adult mammographic percent density is one of the strongest known risk factors for breast cancer. *In utero* exposure to high levels of endogenous estrogens (or other pregnancy hormones) has been hypothesized to increase breast cancer risk in later life. We examined the hypothesis that those factors associated with higher levels of estrogen during pregnancy or shortly after birth are associated with higher mammographic breast density in adulthood.**

Methods: **We analyzed data on 1,893 women from 360 families in the Minnesota Breast Cancer Family Study who had screening mammograms, risk factor data, over age 40, and no history of breast cancer. Prenatal and perinatal risk factor data were ascertained using a mailed questionnaire. Mammographic percent density and dense area were estimated from the mediolateral oblique view using Cumulus, a computer-assisted thresholding program. Linear mixed effects models incorporating familial correlation were used to assess the association of risk factors with percent density, adjusting for age, weight, and other breast cancer risk factors, all at time of mammography.**

Results: **The mean age at mammography was 60.4 years (range, 40-91 years), and 76% were postmenopausal. Among postmenopausal women, there was a positive association of birthweight with percent density (P trend <0.01), with an adjusted mean percent density of 17.1% for <2.95 kg versus 21.0% for ≥3.75 kg. There were suggestive positive associations with gestational age (mean percent density of 16.7% for preterm birth, 20.2% for term birth, and 23.0% for late birth; P trend = 0.07), maternal eclampsia/preeclampsia (mean percent density of 19.9% for no and 14.6% for yes; P = 0.16), and being breast-fed as an infant (mean percent density of 18.2% for never and 20.0% for ever; P = 0.08). There was no association of percent density with maternal age, birth order, maternal use of alcohol or cigarettes, or neonatal jaundice. Except for being breast-fed, these associations showed similar but attenuated trends among premenopausal women, although none were statistically significant. The results for dense area paralleled the percent density results. The associations of gestational age and being breast-fed as an infant with percent density attenuated when included in the same model as birthweight.**

Conclusions: **Birthweight was positively associated with mammographic breast density and dense area among postmenopausal women and more weakly among premenopausal women, suggesting that it may be a marker of this early life exposure. These results offer some support to the hypothesis that pregnancy estrogens or other pregnancy changes may play a role in breast cancer etiology, and suggest that these factors may act in part through long-term effects on breast density.** (Cancer Epidemiol Biomarkers Prev 2005;14(6):1502–8)

Introduction

Trichopoulos (1) hypothesized that breast cancer might originate from *in utero* exposure to elevated concentrations of estrogens, and empirical tests of this hypothesis have taken the form of evaluating factors thought to be reasonable surrogates of low or high estrogen concentration during pregnancy or shortly after birth as breast cancer risk factors. For example, greater birthweight and neonatal jaundice, both surrogates of higher estrogen exposure to the fetus/newborn (2, 3), may be positively associated with breast cancer risk, although these findings have not been universal (4-6). Women whose mothers had preeclampsia/eclampsia, a surrogate of decreased estrogen exposure (7), may have a decreased risk of breast cancer (8). There is also some evidence that other prenatal or perinatal factors (which may be surrogates for estrogen levels) may also be associated with breast cancer risk, but data are only available from a limited number of studies and are somewhat conflicting (4-6).

Whether defined by the parenchymal pattern or percent mammographic density, the radiographic appearance of the breast has been shown to be a major risk factor for breast cancer (9-11). Many breast cancer risk factors have been shown to be risk factors for higher mammographic density, although the strength and consistency of these associations have varied (10, 11). However, only two studies have evaluated prenatal or perinatal factors with mammographic features (12, 13). We hypothesized that those factors associated with higher levels of estrogen during pregnancy or shortly after birth (i.e., neonatal jaundice) would be associated with higher levels of mammographic breast density in adulthood.

Materials and Methods

Study Population. The baseline enrollment (14) and first follow-up (15) for this study population have been previously described. Briefly, breast cancer probands seen at the Tumor Clinic of the University of Minnesota Hospital between 1944 and 1952 (n = 544) were enrolled into a family study. From 1990 to 1996, 426 families were updated, and each proband's first and second degree female relatives and spouses of male relatives were contacted, and extensive risk factor data were collected by telephone interview on 6,194 women.

Received 10/18/04; revised 2/28/05; accepted 3/21/05.

Grant support: Grant P01 CA82267.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: James R. Cerhan, Department of Health Sciences Research, Mayo Clinic College of Medicine, 200 First Street Southwest, Rochester, MN 55905. Phone: 507-538-0499; Fax: 507-266-2478. E-mail: cerhan.james@mayo.edu

In 2001, questionnaires were mailed to all female blood relatives and spouses of male blood relatives in the 426 pedigrees who completed the first follow-up survey. Nonresponders were contacted by telephone to complete priority questions and obtain consent to retrieve mammograms. Of the 6,194 eligible women from the first follow-up, 604 were deceased (9.8%), 654 were lost to follow-up (10.6%), 1,109 refused (17.9%), and 84 required a next of kin (1.4%) to complete the questionnaire. A total of 3,743 women completed the 2001 questionnaire, giving a response rate of 77.1% of those contacted and competent to complete a survey, and an overall participation rate of 60.4% of those who participated in the first follow-up. The 2001 questionnaire ascertained updated cancer information, new exposure data on early childhood and adolescence exposures, and authorization for release of mammograms. Authorization for mammogram retrieval was unavailable for 295 women and not attempted for 539 (because of few longitudinal mammograms available), leaving 1,893 available for study (69.4% of women providing authorization and 61.5% of the age-eligible women without breast cancer who responded to the follow-up 2 survey).

For this cross-sectional analysis, we excluded women with breast cancer and used the mammogram with the date closest to the date of the first follow-up (1990-1996), which was within 1 year for 39% of the women, and within 5 years for over 90% of the women. In a comparison of women with and without percent density estimates, there were no differences in education level, weight, age at menarche, adult alcohol use, birthweight, mother's age at first birth, eclampsia/preeclampsia and neonatal jaundice, and trivial differences in parity/age at first birth, birth order, gestational age, breast-fed as an infant, and maternal use of alcohol or tobacco during pregnancy. However, women with density measures were on average older (58 versus 53 years), had more longitudinal mammograms (another aim of the study), were more likely to be postmenopausal (76% versus 59%), and had ever used hormone replacement therapy (HRT; 47% versus 34%).

Estimation of Percent Density and Dense Area. Mammograms obtained on the 1,693 women from the 2001 follow-up were digitized on a Lumiscan 75 scanner with 12-bit grayscale depth. The pixel size was 0.130×0.130 mm^2 for both the 18×24 cm^2 and the 24×30 cm^2 films. Percent mammographic breast density (dense area divided by total area multiplied by 100) and absolute dense area (square centimeter) were estimated from the left mediolateral oblique view of the mammogram using Cumulus, a computer-assisted thresholding program (16). All images were read by a single trained technician with a high intrareader reliability ($r > 0.90$ for rereading of over 500 duplicate images randomly included throughout the readings).

Data Analysis. We modeled the association of prenatal and perinatal factors with density measures using linear mixed effects models. Tests for trends were computed by ordering the categorical variable and performing a Wald test with 1 degree of freedom. These models adjusted for potential intrafamilial correlation by accounting for degree of relationship using a random effect based on a familial kinship matrix (17). We used a four-stage approach to model building. First, we fit a simple model which adjusted for age at mammography, weight at the first follow-up, HRT use (never, former, current), and menopausal status, variables strongly associated with mammographic breast density in this study. This step in the modeling process eliminated 126 women with missing data (effective sample size, 1,767). Second, we fit a full model that included potential confounders: education, age at menarche, parity/age at first birth, oral contraceptive use, alcohol use, and smoking history (all coded as in Table 1). Further consideration of time between survey and mammogram, age at menopause, years since menopause, time since HRT start/stop, and HRT formulation (only available from a later survey) did not alter the results (data not reported). Third, we added a frailty score to account for familial breast cancer risk.[4] For each woman, a specific frailty score was obtained based on the degree of relationship (kinship) among the women in the family and the pattern of breast cancer in the pedigree. The median of the frailty scores was obtained and used as the cutpoint to classify each woman's frailty score as either high or low. Because the addition of this frailty score did not change the estimates derived by the first two models, they are not reported here. Fourth, we simultaneously modeled several prenatal and perinatal factors that were individually associated with percent density.

Adjusted means were calculated for each of the models using a smearing estimate (18). Means for the simple model were adjusted to reflect the following characteristics: a postmenopausal, 60-year-old woman, with a weight of 150 lbs, and no HRT use. Adjusted means reported from the full model reflect the additional characteristics of a woman having a high school education, being 13 years of age at menarche, having one to two births over age 20, and reporting no oral contraceptive use, no alcohol use, and never having smoked. In addition, separate models were built for pre- and postmenopausal women, with the premenopausal model adjusted means to the same reference values except for age, which was referenced to a 45-year-old woman.

Results

The mean age at mammography was 60.4 years (range, 40-91 years) and 76% of the women were postmenopausal. Table 1 provides descriptive characteristics of the sample with respect to traditional breast cancer risk factors. Of note, postmenopausal women, compared with premenopausal women, were more likely to have three or more births and to have used HRT, but they were less likely to have used oral contraceptives.

There was no association of percent density with maternal age, birth order, or maternal smoking or alcohol use during pregnancy, and these results were similar among pre- and postmenopausal women (Table 2).

There was a positive association of birthweight, modeled as a continuous variable, with percent density in both the simple ($P = 0.01$) and full ($P = 0.01$) models (Table 3). Similar associations were apparent when birthweight was divided into quartiles. In the full model, women with a birthweight of <2.95 kg had a mean density of 20.1% compared with 23.0% for women with a birthweight of ≥3.75 kg (P trend <0.01). This association was strongest among postmenopausal women (P trend <0.01), and a weaker and nonsignificant association was seen among premenopausal women (P trend = 0.19).

There was also a suggestive positive association of gestational age with percent density, with a younger gestational age associated with a lower percent density (P trend = 0.07). This association was also stronger among postmenopausal women (P trend = 0.07) than among premenopausal women (P trend = 0.25). Women whose mother had eclampsia/preeclampsia during their pregnancy had a lower percent density (17.7%) compared with women whose mother did not have this condition (21.5%), although this was not statistically significant ($P = 0.25$). Among postmenopausal women, there was also a

[4] Pankratz VS, de Andrade M, Therneau TM. The random effects Cox Proportional Hazards Model: general variance components methods for Time-to-Event Data, Genetic Epidemiology (in press).

Table 1. Descriptive characteristics (means ±SD; percent distribution) of the study sample

Variable	All women (n = 1,893)	Menopausal status at time of mammography	
		Premenopausal (n = 451)	Postmenopausal (n = 1,442)
Mammographic breast density (10th, 90th percentile)	22.8 ± 14.7 (5.1, 42.5)	31.3 ± 15.3 (12.4, 50.9)	20.2 ± 13.5 (4.3, 39.4)
Age at mammogram (y)	60.4 ± 11.1	47.7 ± 4.6	64.4 ± 9.4
Weight at follow-up 1 (lbs)	157.3 ± 35.5	157.9 ± 35.9	157.2 ± 31.4
Age at menarche (y)	12.9 ± 1.5	12.7 ± 1.5	12.9 ± 1.6
Birthweight (kg)	3.35 ± 0.73	3.31 ± 0.60	3.36 ± 0.78
Missing birthweight	47%	28%	53%
Relationship to proband			
Blood relative	61%	67%	59%
Marry-in	39%	33%	41%
Some college or college graduate	47%	60%	43%
Number of live births, age at first live birth			
Nulliparous	9%	12%	7%
1-2, ≤20 y	6%	9%	5%
1-2, >20 y	23%	34%	20%
3+, ≤20 y	22%	17%	24%
3+, >20 y	33%	22%	36%
Missing	7%	6%	7%
Oral contraceptive use			
Never	44%	12%	54%
Former	55%	84%	46%
Current	1%	4%	<1%
Missing	<1%	0%	<1%
Hormone therapy use at follow-up 1			
Never	53%	80%	44%
Former	17%	11%	19%
Current	30%	9%	37%
Missing	<1%	<1%	<1%
Alcohol use at follow-up 1			
Never	14%	8%	16%
Monthly	63%	64%	62%
Weekly or Daily	23%	28%	21%
Missing	<1%	<1%	<1%
Smoking status at follow-up 1			
Never	56%	52%	57%
Former	29%	28%	30%
Current	15%	20%	14%
Missing	<1%	0%	<1%

suggestive inverse association, although this was not statistically significant (P = 0.16). There was no association among premenopausal women.

There were weak positive associations of jaundice after birth with percent density overall and among pre- and postmenopausal women, although none of the differences approached statistical significance. Overall, if a woman was breast-fed as an infant, there was no significant association with percent density (P = 0.52). However, there was a suggestive association among postmenopausal women (P = 0.08), such that there was a higher density among women who were breast-fed in the full model (20.0% versus 18.2%); the pattern, however, was opposite among premenopausal women.

We also evaluated the association of all of these factors with dense area, and the results strongly paralleled the results seen for percent density (data not shown).

We next evaluated whether the association of birthweight with percent density among postmenopausal women was influenced by other early life factors. When we included birthweight and gestational age in the same full model, the association with gestational age was eliminated (P trend = 0.25), whereas the association with birthweight was unchanged (P trend <0.01). Similarly, when birthweight and having been breast-fed as an infant were included in the same model, the suggestive association with being breast-fed attenuated (P trend = 0.14), whereas the association with birthweight was unchanged (P trend <0.01). There was no evidence that birth order or preeclampsia/eclampsia confounded the association of birthweight with percent density (P trends for birthweight were both <0.01). Finally, we evaluated birthweight and adult height in the same model; the association for birthweight was only slightly attenuated (P trend = 0.04).

Discussion

Our major finding was that birthweight was positively associated with adult mammographic percent density and dense area, particularly among postmenopausal women. These associations did not seem to be confounded by traditional breast cancer risk factors or other early life factors. Among postmenopausal women, gestational age was also positively associated with percent density, but this association was eliminated after adjustment for birthweight. Strengths of this study include the use of a defined, community-based study population. There were detailed risk factor data collected over the life span and around the time of mammography, and the statistical approach included careful adjustment for these potential confounders. Percent mammographic density was estimated using a semiautomated method assessed by a single trained reader with excellent intrareader reliability. Mammographic percent density has been shown to have a genetic influence (19, 20), and our family-based design permitted adjustment for this effect.

There are also limitations. All of the exposures evaluated here were self-reported and there was no attempt at validation. Validity of self-reported early life characteristics, including birthweight (21-24), gestational age (22), being breast-fed as an infant (21), and maternal smoking (22), has

been shown to be reasonably high and of sufficient accuracy for epidemiologic studies. One study found that being younger at time of interview and the eldest in the family was an important predictor of reporting an accurate birthweight (24). However, adjustment for these factors did not alter our results. We also had a large amount of missing data for many of these variables, with the most extreme being birthweight, where 47% of women in the sample did not know their birthweight. Whereas this is a large amount of missing data, other studies of similarly aged women have reported between 20% and 72% of the participants were unable to self-report their birthweight (23-27). In our study, women with missing birthweight had mean percent density similar to the overall mean of women with birthweight data after accounting for multiple other factors (Table 3). Thus, we have no clear evidence that missing data has introduced a large and systematic bias.

The design of the study allowed us to compare differences in adult and early life risk factors between women who did and did not provide a mammogram. These were generally small and suggest that our sample was representative of an older, more frequently screened population. The mammograms were taken as a part of routine clinical practice from hundreds of different facilities over time, raising concerns about variability in acquisition variables and film quality on density estimation. However, most of the mammograms were taken in the late 1980s and early 1990s, when film technology and more rigorous accreditation standards were in place. Furthermore, the variability introduced across radiologic practices would be expected to be independent of birth characteristics and mammographic density, and thus would most likely attenuate associations to the null. Finally, although the study is generalizable to white women of European descent, generalizability to other racial/ethnic groups is unknown.

To our knowledge, this is the first study to evaluate percent mammographic density and dense area with prenatal and perinatal factors. The only other studies to evaluate these associations (12, 13) used the subjective Wolfe classification, which is a categorical measure based on both percent density and parenchymal pattern (prominent ducts and dysplasia; ref. 28). Current evidence suggests that percent density is a better predictor of future breast cancer risk than the Wolfe pattern (9, 29, 30).

The positive association of birthweight with mammographic breast density in this study is in agreement with a study of 370 Swedish women, ages 40 to 79 years, with no history of breast cancer, where there was a weak but suggestive positive association of birthweight with the high-risk (i.e., P2/DY) Wolfe pattern [odds ratio, 1.39; 95% confidence interval (95% CI), 0.56-3.47, for >4.0 versus 2.5-2.9 kg; P trend = 0.53; ref. 12]. In a study of 1,298 British women, age 53 years, there was also a weak and not statistically significant association of birthweight with higher risk Wolfe pattern (odds ratio, 1.03; 95% CI, 0.92-1.15, for each SD increment in birthweight; ref. 13). Birthweight may be less strongly associated with the Wolfe classification because there are four discrete categories rather than a continuous measure of percent density or dense area. Of other pregnancy characteristics previously evaluated (12), birth length was weakly associated with the high-risk parenchymal pattern, whereas placental weight was strongly related to this pattern; we did not have data on these factors.

Table 2. Association of prenatal factors with percent density for all women and by menopausal status at time of mammography, Minnesota Breast Cancer Family Study

Prenatal factor	All women			Premenopausal			Postmenopausal		
			Full model			Full model			Full model
	n	Adj mean*	Adj mean† (95% CI)	n	Adj mean*	Adj mean† (95% CI)	n	Adj mean*	Adj mean† (95% CI)
Maternal age									
<19	96	19.6	20.8 (19.1-22.5)	26	33.2	32.5 (28.8-36.2)	70	18.5	18.9 (17.1-20.6)
20-24	381	19.8	20.6 (19.8-21.4)	82	32.2	31.8 (30.1-33.4)	299	19.0	19.0 (18.0-19.9)
25-29	371	21.5	22.2 (21.4-23.1)	96	34.8	33.6 (32.0-35.3)	275	20.6	20.5 (19.5-21.5)
30-34	350	19.9	20.7 (19.8-21.6)	85	33.2	31.9 (29.9-33.8)	265	18.9	19.0 (18.0-19.9)
35+	352	20.9	21.6 (20.7-22.5)	99	34.5	33.8 (32.0-35.5)	253	19.7	19.7 (18.7-20.7)
P trend		0.24	0.42		0.49	0.65		0.37	0.49
Don't know	87	19.2	20.7 (18.8-22.6)	8	25.9	26.2 (18.7-33.8)	79	18.8	19.4 (17.4-21.4)
Missing	130	19.8	20.5 (19.1-21.9)	26	32.6	31.8 (29.3-34.3)	104	19.1	18.9 (17.3-20.5)
Birth order									
1st child	430	20.2	21.1 (20.3-21.9)	96	33.0	32.5 (30.8-34.2)	334	19.4	19.3 (18.4-20.2)
2nd child	336	20.8	21.3 (20.4-22.3)	93	36.5	35.8 (34.1-37.5)	243	18.8	18.7 (17.6-19.7)
3rd child	264	20.8	21.5 (20.4-22.5)	65	34.1	33.3 (31.4-35.2)	199	19.8	19.8 (18.6-21.0)
4th child	197	21.0	22.0 (20.9-23.1)	50	32.4	32.4 (30.1-34.8)	147	20.6	20.6 (19.4-21.9)
5th+ child	409	19.8	20.7 (19.9-21.6)	90	31.8	32.3 (30.5-34.2)	319	19.1	19.2 (18.3-20.1)
P trend		0.80	0.91		0.20	0.39		0.54	0.39
Don't know	131	19.7	20.7 (19.2-22.1)	28	31.4	30.9 (27.8-34.1)	103	19.4	19.4 (17.7-21.0)
Mother smoked during pregnancy									
No	1,376	20.5	21.3 (20.8-21.7)	279	33.3	32.6 (31.6-33.6)	1,097	19.6	19.5 (19.1-20.0)
Yes	157	20.0	20.9 (19.4-22.3)	80	33.9	33.2 (31.4-35.0)	77	17.8	17.6 (15.5-19.8)
P		0.67	0.74		0.64	0.68		0.26	0.23
Don't know	107	19.4	20.3 (18.4-22.2)	35	34.0	32.4 (28.5-36.4)	72	18.1	18.2 (16.1-20.3)
Missing	127	19.9	20.7 (19.3-22.2)	28	32.7	31.7 (29.4-34.0)	99	19.3	19.2 (17.6-20.8)
Mother drank alcohol during pregnancy									
No	1,223	20.4	21.2 (20.7-21.6)	239	33.0	32.6 (31.6-33.6)	984	19.5	19.4 (18.9-19.9)
Yes	108	20.7	21.4 (19.7-23.2)	57	33.6	33.1 (30.9-35.2)	51	20.0	20.0 (17.4-22.6)
P		0.97	1.0		0.89	0.85		0.72	0.68
Don't know	312	20.3	21.1 (20.1-22.1)	99	34.7	33.5 (31.5-35.5)	213	18.8	18.5 (17.3-19.7)
Missing	124	19.9	20.7 (19.2-22.2)	27	32.7	31.8 (29.4-34.3)	97	19.4	19.1 (17.4-20.7)

*Means adjusted for age at mammography, weight at follow-up 1, HRT use, and menopausal status.
†Means and 95% CIs, additionally adjusted for education, age at menarche, parity and age at first birth, oral contraceptive use, alcohol use, current smoking status, and smoking history.

Table 3. Association of perinatal factors with percent density for all women and by menopausal status at time of mammography

	All women			Premenopausal women			Postmenopausal women		
			Full model			Full model			Full model
	n	Adj mean*	Adj mean† (95% CI)	*n*	Adj mean*	Adj mean† (95% CI)	*n*	Adj mean*	Adj mean† (95% CI)
Birthweight (kg)									
Continuous	940	17.6	19.4 (18.7-20.2)	299	32.1	32.1 (30.7-33.4)	641	15.6	16.5 (15.6-17.3)
P trend		0.01	0.01		0.43	0.53		<0.001	0.01
<2.95	206	19.4	20.1 (19.0-21.2)	63	34.6	33.4 (31.1-35.7)	143	17.1	17.1 (15.9-18.3)
2.95-3.37	262	20.1	21.0 (20.1-22.0)	98	32.0	31.4 (30.0-32.8)	164	19.8	19.8 (18.5-21.0)
3.38-3.74	248	22.0	22.9 (21.8-24.0)	76	36.2	35.4 (33.2-37.5)	172	20.2	20.2 (18.9-21.4)
3.75+	224	22.3	23.0 (21.8-24.1)	62	35.9	34.6 (32.6-36.6)	162	21.0	21.0 (19.7-22.3)
P trend		<0.01	<0.01		0.16	0.19		<0.01	<0.01
Don't know	827	19.8	20.6 (20.1-21.2)	123	31.0	30.4 (28.9-31.9)	704	19.3	19.3 (18.6-19.9)
Gestational age									
Preterm	62	18.5	19.2 (17.3-21.1)	21	32.8	30.5 (26.9-34.0)	41	16.3	16.7 (14.4-19.0)
Term	773	21.1	22.0 (21.4-22.6)	245	33.8	33.3 (32.2-34.4)	528	20.3	20.2 (19.5-21.0)
Postterm	27	23.1	23.7 (20.9-26.5)	11	33.9	34.7 (30.3-39.0)	16	23.3	23.0 (19.2-26.8)
P trend		0.07	0.07		0.68	0.25		0.04	0.07
Don't know	780	19.8	20.7 (20.1-21.3)	118	32.8	31.6 (29.9-33.2)	662	18.9	18.9 (18.3-19.5)
Missing	125	19.7	20.5 (19.1-22.0)	27	33.9	33.2 (30.9-35.6)	98	18.6	18.5 (16.8-20.1)
Eclampsia/preeclampsia									
No	1,029	20.7	21.5 (21.0-22.0)	291	33.5	32.7 (31.8-33.6)	738	19.9	19.9 (19.3-20.4)
Yes	18	18.8	17.7 (14.5-20.9)	5	36.1	35.5 (30.5-40.6)	13	17.0	14.6 (10.5-18.7)
P		0.63	0.25		0.69	0.61		0.49	0.16
Don't know	596	20.0	20.7 (19.9-21.4)	99	33.5	32.9 (30.8-34.9)	497	18.9	18.7 (18.0-19.5)
Missing	124	19.5	20.3 (18.9-21.8)	27	32.6	31.7 (29.2-34.1)	97	18.8	18.6 (17.0-20.2)
Jaundice									
No	1,035	20.3	21.2 (20.6-21.7)	263	33.5	32.6 (31.6-33.6)	772	19.3	19.4 (18.8-20.0)
Yes	29	23.4	23.7 (20.5-26.8)	8	37.4	33.1 (25.6-40.7)	21	22.1	21.6 (18.3-24.9)
P		0.17	0.27		0.40	0.89		0.28	0.39
Don't know	574	20.5	21.4 (20.7-22.1)	119	33.9	33.0 (31.4-34.5)	455	19.5	19.6 (18.8-20.4)
Missing	129	19.5	20.6 (19.1-22.0)	32	31.7	31.7 (29.2-34.2)	97	19.1	19.2 (17.5-20.9)
Breastfed as an infant									
No	352	20.2	20.9 (20.3-21.4)	158	33.8	33.1 (31.8-34.4)	194	18.5	18.2 (17.6-18.8)
Yes	911	20.8	21.7 (20.8-22.6)	155	32.6	31.9 (30.6-33.3)	756	19.9	20.0 (18.9-21.1)
P		0.69	0.52		0.29	0.31		0.16	0.08
Don't know	382	20.2	20.8 (19.9-21.6)	83	34.0	32.8 (30.8-34.8)	299	19.1	18.9 (17.9-19.8)
Missing	122	19.7	20.6 (19.1-22.0)	26	33.2	32.0 (29.6-34.4)	96	18.9	18.8 (17.1-20.4)

*Means adjusted for age at mammography, weight at follow-up 1, HRT use, and menopausal status.
†Means and 95% CIs, additionally adjusted for education, age at menarche, parity and age at first birth, oral contraceptive use, alcohol use, current smoking status and smoking history.

Birthweight has been positively associated with pre- and postmenopausal breast cancer risk in the majority of studies reported to date, although findings are strongest and most consistent for premenopausal breast cancer (4-6). Greater birth length has been weakly but positively associated with breast cancer risk (8, 31-33), whereas gestational age, a strong correlate of birthweight, has shown no association with breast cancer risk in most (25, 26, 34, 35) but not all (32, 36) studies. The biological mechanisms linking birthweight to both mammographic breast density and breast cancer risk in adulthood are not known. The strongest evidence implicates estrogens, which play a role in both breast cancer (37) and breast density (38, 39), although the latter association is not consistent (40) and progestins are also likely involved (41, 42). There is a positive association of maternal endogenous estrogen levels with birthweight (2, 43-45), although fetal levels may differ (44, 46, 47). Experimental data from animal models support a role for prenatal estrogen levels influencing mammary gland structure and function (48, 49) and the development of breast tumors (50). Epidemiologic data are more limited, but the strongest support for the prenatal estrogen hypothesis is that exposure to diethylstilbestrol during pregnancy seems to increase breast cancer risk among daughters (22, 36, 51, 52).

Besides estrogens, other aspects of the hormonal milieu correlated with birthweight may be relevant. Progesterone and sex hormone binding globulin (37, 40, 45), prolactin (40, 45, 53), and testosterone and dehydroepiandrosterone (37, 44, 46) could link birthweight, mammographic density, and breast cancer risk, but data remain limited. Insulin-like growth factor I has also been positively associated with birthweight (47, 54), mammographic density (40, 55), and breast cancer risk (56), but only among premenopausal women.

The prenatal factors evaluated in our study (i.e., maternal age, birth order, maternal smoking or alcohol use during pregnancy) were not associated with mammographic breast density. Maternal parity was weakly and positively associated with high-risk parenchymal pattern in one study (odds ratio, 1.24; 95% CI, 0.74-2.07), whereas maternal age was not associated with risk (12). Although these factors have been associated with altered maternal estrogen levels (2, 44, 57-59), they have not shown any consistent association with breast cancer risk (4-6).

We found slightly higher percent density among postmenopausal women whose mother had eclampsia/preeclampsia, but this was not statistically significant and the association was in the opposite direction of the association observed among premenopausal women. However, we had limited power to assess this association. A single other study reported no association of maternal eclampsia/preeclampsia with high-risk parenchymal pattern (12). Maternal eclampsia/preeclampsia, which is associated with lower levels of estrogen (7), has been inversely associated with breast cancer risk in most (3, 36, 60) but not all (34) studies, although only one of these studies achieved statistically significance (3). Larger studies with a

sufficient number of women whose mothers had eclampsia/preeclampsia will be needed to fully address this hypothesis.

Of the perinatal factors evaluated, neonatal jaundice was associated with a small and not statistically significant higher percent density. Neonatal jaundice may be associated with both higher estrogen levels in neonates as well as later breast cancer risk, although this has been reported in only a single study (3). After adjustment for birthweight, we found no association of being breast-fed as an infant and breast density; no previous study has evaluated this association. Being breast-fed as an infant has shown no association (36, 61) or an inverse association (62-64) with breast cancer risk.

In conclusion, birthweight was positively associated with mammographic breast density and dense area among postmenopausal women and more weakly among premenopausal women. These differences were small and of unknown clinical significance, but we were still able to detect these differences during the postmenopausal years. These data suggest that mammographic density may be a marker of the biological effect of birthweight. In addition, these results offer some support to the hypothesis that pregnancy estrogens or other pregnancy changes may play a role in breast cancer etiology, and suggest that these factors may act in part through long-term effects on breast density.

Acknowledgments

We thank Fang-Fang Wu for estimation of percent density, Erin Carlson and Zach Fredericksen for assistance in data analysis, and Mary Jo Eversman and Jessica Curry for assistance in manuscript preparation.

References

1. Trichopoulos D. Does breast cancer originate *in utero*? Lancet 1990;335:939–40.
2. Kaijser M, Granath F, Jacobsen G, Cnattingius S, Ekbom A. Maternal pregnancy estriol levels in relation to anamnestic and fetal anthropometric data. Epidemiology 2000;11:315–9.
3. Ekbom A, Hsieh CC, Lipworth L, Adami HQ, Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst 1997;89:71–6.
4. Potischman N, Troisi R. In-utero and early life exposures in relation to risk of breast cancer. Cancer Causes Control 1999;10:561–73.
5. Shibata A, Minn AY. Perinatal sex hormones and risk of breast and prostate cancers in adulthood. Epidemiol Rev 2000;22:239–48.
6. Okasha M, McCarron P, Gunnell D, Davey Smith G. Exposures in childhood, adolescense and early adulthood and breast cancer risk: a systematic review of the literature. Breast Cancer Res Treat 2003;78:223–76.
7. Innes KE, Byers TE. Preeclampsia and breast cancer risk. Epidemiology 1999;10:722–32.
8. Ekbom A, Trichopoulos D, Adami HO, Hsieh CC, Lan SJ. Evidence of prenatal influences on breast cancer risk. Lancet 1992;340:1015–8.
9. Warner E, Lockwood G, Tritchler D, Boyd NF. The risk of breast cancer associated with mammographic parenchymal patterns: a meta-analysis of the published literature to examine the effect of method of classification. Cancer Detect Prev 1992;16:67–72.
10. Oza AM, Boyd NF. Mammographic parenchymal patterns: a marker of breast cancer risk. Epidemiol Rev 1993;15:196–208.
11. Boyd NF, Lockwood GA, Byng JW, Tritchler DL, Yaffe MJ. Mammographic densities and breast cancer risk. Cancer Epidemiol Biomarkers Prev 1998;7:1133–44.
12. Ekbom A, Thurfjell E, Hsieh C-C, Trichopoulos D, Adami H-O. Perinatal characteristics and adult mammographic patterns. Int J Cancer 1995;61:177–80.
13. McCormack V, dos Santos Silva I, De Stavola B, et al. Life-course body size and perimenopausal mammographic parenchymal patterns in the MRC 1946 British birth cohort. Br J Cancer 2003;89:852–9.
14. Sellers TA, Anderson VE, Potter JD, et al. Epidemiologic and genetic follow-up study of 544 Minnesota breast cancer families: design and methods. Genet Epidemiol 1995;12:417–29.
15. Sellers TA, King RA, Cerhan JR, et al. Fifty-year follow-up of cancer incidence in a historical cohort of Minnesota breast cancer families. Cancer Epidemiol Biomarkers Prev 1999;8:1051–7.
16. Byng JW, Yaffe MJ, Jong RA, et al. Analysis of mammographic density and breast cancer risk from digitized mammograms. Radiographics 1998;18:1587–98.
17. Amos CI. Robust variance-components approach for assessing genetic linkage in pedigrees. Am J Hum Genet 1994;54:535–43.
18. Duan N. Smearing estimate: a nonparametric retransformation method. J Am Stat Assoc 1983;78:605–10.
19. Pankow JS, Vachon CM, Kuni CC, et al. Genetic analysis of mammographic breast density in adult women: evidence of a gene effect. J Natl Cancer Inst 1997;89:549–56.
20. Vachon CM, King RA, Atwood LD, Kuni CC, Sellers TA. Preliminary sibpair linkage analysis of percent mammographic density. J Natl Cancer Inst 1999;91:1778–9.
21. Troy LM, Michels KB, Hunter DJ, et al. Self-reported birthweight and history of having been breastfed among younger women: an assessment of validity. Int J Epidemiol 1996;25:122–7.
22. Sanderson M, Williams MA, White E, et al. Validity and reliability of subject and mother reporting of perinatal factors. Am J Epidemiol 1998;147:136–40.
23. Andersson SW, Niklasson A, Lapidus S, Hallberg L, Bengtsson C, Hulthen L. Poor agreement between self-reported birth weight and birth weight from original records in adult women. Am J Epidemiol 2000;152:609–16.
24. Allen DS, Ellison GT, dos Santos Silva I, De Stavola BL, Fentiman IS. Determinants of the availability and accuracy of self-reported birth weight in middle-aged and elderly women. Am J Epidemiol 2002;155:379–84.
25. Michels KB, Trichopoulos D, Robins JM, et al. Birthweight as a factor for breast cancer. Lancet 1996;348:1542–6.
26. Sanderson M, Williams MA, Malone KE, et al. Perinatal factors and risk of breast cancer. Epidemiology 1996;7:34–7.
27. Titus-Ernstoff L, Eagen KM, Newcomb PA, et al. Early life factors in relation to breast cancer risk in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2002;11:207–10.
28. Wolfe JN. Breast patterns as an index of risk for developing breast cancer. AJR Am J Roentgenol 1976;126:1130–7.
29. Byrne C, Schairer C, Wolfe J, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 1995;87:1622–9.
30. Brisson J, Diorio C, Masse B. Wolfe's parenchymal pattern and percentage of the breast with mammographic densities: redundant or complementary classifications? Cancer Epidemiol Biomarkers Prev 2003;12:728–32.
31. Andersson SW, Bengtsson C, Hallberg L, et al. Cancer risk in Swedish women: the relation to size at birth. Br J Cancer 2001;84:1193–8.
32. Hubinette A, Lichtenstein P, Ekbom A, Cnattingius S. Birth characteristics and breast cancer risk: a study among like-sexed twins. Int J Cancer 2001;91:248–51.
33. Vatten LJ, Maehle BO, Lund Nilsen TI, et al. Birth weight as a predictor of breast cancer: a case-control study in Norway. Br J Cancer 2002;86:89–91.
34. Le Marchand L, Kolonel LN, Myers BC, Mi M-P. Birth characteristics of premenopausal women with breast cancer. Br J Cancer 1988;57:437–9.
35. Kaijser M, Akre O, Cnattingius S, Ekbom A. Preterm birth, birthweight, and subsequent risk of female breast cancer. Br J Cancer 2003;89:1664–6.
36. Sanderson M, Williams MA, Daling JR, et al. Maternal factors and breast cancer risk among young women. Paediatr Perinat Epidemiol 1998;12:397–407.
37. Bernstein L. Epidemiology of endocrine-related risk factors for breast cancer. J Mammary Gland Biol Neoplasia 2002;7:3–15.
38. Greendale GA, Reboussin BA, Slone S, Wasilauskas C, Pike MC, Ursin G. Postmenopausal hormone therapy and change in mammographic density. J Natl Cancer Inst 2003;95:30–7.
39. Brisson J, Brisson B, Cote G, Maunsell E, Berube S, Robert J. Tamoxifen and mammographic breast densities. Cancer Epidemiol Biomarkers Prev 2000;9:911–5.
40. Boyd NF, Stone J, Martin LJ, et al. The association of breast mitogens with mammographic densities. Br J Cancer 2002;87:876–82.
41. Ursin G, Palla SL, Reboussin BA, et al. Post-treatment change in serum estrone predicts mammographic percent density changes in women who received combination estrogen and progestin in the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. J Clin Oncol 2004;22:2842–8.
42. Conner P, Svane G, Azavedo E, et al. Mammographic breast density, hormones, and growth factors during continuous combined hormone therapy. Fertil Steril 2004;81:1617–23.
43. Wuu J, Hellerstein S, Lipworth L, et al. Correlates of pregnancy oestrogen, progesterone and sex hormone-binding globulin in the USA and China. Eur J Cancer Prev 2002;11:283–93.
44. Troisi R, Potischman N, Roberts J, et al. Associations of maternal and umbilical cord hormone concentrations with maternal, gestational and neonatal factors (United States). Cancer Causes Control 2003;14:347–55.
45. Mucci LA, Lagiou P, Tamimi RM, Hsieh CC, Adami HO, Trichopoulos D. Pregnancy estriol, estradiol, progesterone and prolactin in relation to birth weight and other birth size variables (United States). Cancer Causes Control 2003;14:311–8.
46. Simmons D, France JT, Keelan JA, Song L, Knox BS. Sex differences in umbilical cord serum levels of inhibin, testosterone, oestradiol, dehydroepiandrosterone sulphate, and sex hormone-binding globulin in human term neonates. Biol Neonate 1994;65:287–94.
47. Shibata A, Harris DT, Billings PR. Concentrations of estrogens and IGFs in umbilical cord blood plasma: a comparison among Caucasian, Hispanic, and Asian-American females. J Clin Endocrinol Metab 2002;87:810–5.
48. Hilakivi-Clarke L, Cho E, Clarke R. Maternal genistein exposure mimics the effects of estrogen on mammary gland development in female mouse offspring. Oncol Rep 1998;5:609–16.
49. Tomooka Y, Bern HA. Growth of mouse mammary glands after neonatal sex hormone treatment. J Natl Cancer Inst 1982;69:1347–52.

50. Hilakivi-Clarke L, Clarke R, Onojafe I, Raygada M, Cho E, Lippman M. A maternal diet high in n-6 polyunsaturated fats alters mammary gland development, puberty onset, and breast cancer risk among female rat offspring. Proc Natl Acad Sci U S A 1997;94:9372–7.
51. Huckell C, Laskin J, Gelmon K. Premenopausal breast cancer after in-utero exposure to stilboestrol. Lancet 1996;348:331.
52. Palmer JR, Hatch EE, Rosenberg CL, et al. Risk of breast cancer in women exposed to diethylstilbestrol *in utero*: preliminary results (United States). Cancer Causes Control 2002;13:753–8.
53. Hankinson SE, Willett WC, Michaud DS, et al. Plasma prolactin levels and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst 1999;91:629–34.
54. Vatten LJ, Nilsen ST, Odegard RA, Romundstad PR, Austgulen R. Insulin-like growth factor I and leptin in umbilical cord plasma and infant birth size at term. Pediatrics 2002;109:1131–5.
55. Byrne C, Colditz G, Willett WC, Speizer FE, Pollak M, Hankinson SE. Plasma insulin-like growth factor (IGF) I, IGF-binding protein 3, and mammographic density. Cancer Res 2000;60:3744–8.
56. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. Nat Rev Cancer 2004;4:505–18.
57. Bernstein L, Depue RH, Ross RK, Judd HL, Pike MC, Henderson BE. Higher maternal levels of free estradiol in first compared to second pregnancy: early gestational differences. J Natl Cancer Inst 1986;76:1035–9.
58. Panagiotopoulou K, Katsouyanni K, Petridou E, Garas Y, Tzonou A, Trichopoulos D. Maternal age, parity, and pregnancy estrogens. Cancer Causes Control 1990;1:119–24.
59. Petridou E, Panagiotopoulou K, Katsouyanni K, Spanos E, Trichopoulos D. Tobacco smoking, pregnancy estrogens, and birth weight. Epidemiology 1990;1:247–50.
60. Innes K, Byers T, Schymura M. Birth characteristics and subsequent risk for breast cancer in very young women. Am J Epidemiol 2000;152:1121–8.
61. Michels KB, Trichopoulos D, Rosner BA, et al. Being breastfed in infancy and breast cancer incidence in adult life: results from the two nurses' health studies. Am J Epidemiol 2001;153:275–83.
62. Brinton LA, Hoover R, Fraumeni JF Jr. Reproductive factors in the aetiology of breast cancer. Br J Cancer 1983;47:757–62.
63. Freudenheim JL, Marshall JR, Graham S, et al. Exposure to breastmilk in infancy and the risk of breast cancer. Epidemiology 1994;5:324–31.
64. Weiss HA, Potischman NA, Brinton LA, et al. Prenatal and perinatal risk factors for breast cancer in young women. Epidemiology 1997;8:181–7.

Prenatal and Perinatal Correlates of Adult Mammographic Breast Density

James R. Cerhan, Thomas A. Sellers, Carol A. Janney, et al.

Cancer Epidemiol Biomarkers Prev 2005;14:1502-1508.