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Prenatal Factors and Infant Feeding in Relation to Risk of Benign Breast Disease in Young Women

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Abstract

Purpose—Benign breast disease (BBD) is a well-established risk factor for breast cancer, but little work has considered a girl's early life and her risk for BBD in adulthood. We investigated factors, from pre-conception through infant feeding practices, in relation to subsequent BBD risk in young women.

Methods—The Growing Up Today Study (GUTS) includes 9032 females, born 1980–1987, who completed questionnaires annually from 1996 through 2001, then 2003, 2005, 2007, 2010, 2013. In 1996, their mothers provided each participant's birth weight and length, gestational age, biological father's height, and infant feeding factors (e.g. breast fed, type of formula). In 1999, their mothers reported maternal pre-pregnancy weight and weight gain during index pregnancy. Beginning in 2005, daughters (18yr+) reported whether they had ever been diagnosed with biopsy-confirmed BBD (n=142 cases, through 2013). Logistic regression estimated associations between early life factors and biopsy-confirmed BBD.

Results—Girls whose mother's BMI prior to pregnancy was 20–25kg/m² were at lower risk of BBD as young women (OR=0.66, p=0.04, vs maternal pre-pregnancy BMI<20). Girls whose mothers gained 20+ pounds (vs <20 pounds) during pregnancy were at lower risk (among full-term singleton births: OR=0.48, p=0.007, if mother gained 20–35 pounds). However, neither birth weight nor BMI at birth were associated with subsequent BBD risk. We found no evidence that infant feeding practices were linked to BBD.

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Ethical Approval

All procedures were in accordance with the ethical standards of Harvard University and Brigham & Women's Hospital, and with the 1964 Helsinki declaration.

Informed Consent

Informed consent was obtained from all individual participants included in this study.

Conflict of Interest

The authors declare that they have no conflict of interest.

Conclusion—A healthy maternal BMI before pregnancy and sufficient weight gain during pregnancy may produce daughters at lower risk for BBD as young women. Further examination of these findings is needed.

Keywords

birth weight; maternal pre-pregnancy BMI; gestational weight gain; breast fed; soy formula; BBD

Introduction

Substantial evidence implicates the period in life before a woman's initial pregnancy, when mammary gland cells are undergoing rapid proliferation, as a critical time for exposures that may increase her lifetime risk for breast cancer [1]. Some childhood and adolescent exposures are more important than adult exposures in breast cancer development [2–5], so prevention efforts must begin early [6]. Animal studies have shown that perinatal factors, including maternal diet during pregnancy when differentiation of offspring mammary glands is ongoing, can impact breast cancer risk in the female offspring [7] as well as in the mother [8].

An impressive body of literature links high birth weight to increased risk of premenopausal breast cancer [9]. Elevated breast cancer risk has also been noted with higher birth length and parental age, while decreased risk was seen with maternal pre-eclampsia, eclampsia, and twin membership [10]. Maternal pre-pregnancy weight and gestational weight gain were not associated with breast cancer in daughters [11]. A review article, acknowledging inconsistencies in the literature, concluded there is increased breast cancer risk for females of lower gestational age (pre-term), yet with greater birth weight and length [12].

Because benign breast disease (BBD) is a well-established risk factor for breast cancer [13], the investigation of exposures in girls and their subsequent development of BBD may provide insight into the etiology of breast cancer and present possible new strategies for prevention. A previous investigation of fetal and infant factors found no associations between proliferative BBD in premenopausal women and their own birth weight or with having been breast fed [14]. In that study, nurses (then aged 27–44) self-reported their own birth weights and whether, and for how long, they had been breastfed as infants.

Here we investigate, using data reported by mothers as soon as 9 years after the birth of their daughters, a series of factors from pre-conception through infant feeding practices in relation to the daughters' subsequent risk for BBD as young women. The daughters in our cohort were born between 1980 and 1987, and disease follow-up is ongoing.

Materials and Methods

Study Population

The Growing Up Today Study (GUTS; founding PI, Dr. Colditz) includes 9032 girls from all 50 states who are daughters of Nurses' Health Study II (NHSII) participants [15]. The study, approved by Institutional Review Boards at Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital, is described elsewhere [16]. Mothers provided informed

consent, and their 9–15 yr old daughters assented by completing baseline questionnaires. The cohort returned questionnaires annually (by mail or Internet) from 1996 through 2001, then in 2003, 2005, 2007, 2010 and 2013. The response rate to one or more follow-ups after baseline has been 97%. Over 81% returned at least one of the 2005 through 2013 surveys inquiring about BBD. At baseline, participants reported their race/ethnic group by marking all (of six) options that applied to them; most are white/non-Hispanic (95%).

Benign Breast Disease

The 2005, 2007, 2010 and 2013 surveys inquired “Has a health care provider ever diagnosed you as having Benign Breast Disease?” and, if yes, whether it had been “Confirmed by breast biopsy”. A total of 7298 females (when aged 18–32yr) reported whether a health care provider ever, or never, diagnosed them with BBD (n=334 said yes), and if any diagnosis had been confirmed by breast biopsy (n=142). After excluding six girls whose mothers reported childhood cancer in their daughters, 6958 females who returned surveys during this period but never reported a BBD diagnosis provide the non-cases for these analyses.

Most BBD cases were likely diagnosed because participants (or their physicians) found a clinically palpable mass which was then biopsied, for participants were too young to be undergoing routine screening mammography. The most common type of BBD occurring in adolescents and young women is fibroadenoma, which accounts for nearly 70% of benign breast lesions; the remaining types are primarily cysts and fibrocystic changes [17]. A validation study conducted in NHSII women confirmed the accuracy of self-reports of biopsy-confirmed BBD [18].

Early Life Factors: Pre-Pregnancy through Infant-Feeding

In 1996 the mothers reported, for their daughters who were born during the previous decade, the birth weight (pounds and ounces), birth length (inches), gestational age (full term, 1–2 weeks early, 3–6 weeks early, or greater than 6 weeks early), and the height (feet and inches) of the biological father.

Mothers also answered a series of questions regarding infant feeding, including “Did you feed this child breastmilk or infant formula during the first 6 months of her life?” with response options “breastmilk only”, “more breastmilk than infant formula”, “both equally”, “more infant formula than breastmilk”, and “infant formula only”. The following question asked her child’s age when breastfeeding stopped (six categories from never breastfed to over nine months). Another question asked the type of infant formula most often used (cow’s milk-based, soybean-based, other: rice-based or elemental). Other questions concerned the ages (in months) when child began consuming infant formula, cow’s milk, and solid foods.

Our 1999 survey to the mothers asked “How much did you weigh before this pregnancy?” in pounds, “How much weight did you gain during this pregnancy”, in pounds, and “During this pregnancy, were you diagnosed with gestational diabetes” or “... high blood pressure (pregnancy-related)?”.

The mothers, as part of their participation in the Nurses' Health Study II, had reported their own birth dates, adult heights, breast cancer in themselves and in their sisters, personal diagnoses of benign breast disease, and their personal smoking and drinking history at various earlier periods in life (<15yr, 15–19yr, 20–24yr, etc) but not specifically during the index pregnancy.

Regarding the validity of our maternal-recalled early life exposures, a study conducted on 154 women, who recalled pregnancy-related events from thirty or more years before, compared their recollections to data collected at the time of their pregnancies [19]. Their recalls were very accurate for both their pre-pregnancy weight ($r=.86$) and the birth-weight of their infants ($r=.91$). Another validation study [20] compared maternal reports (3 decades later) of their infants' birth-weights with state birth records and found $r=0.85$. Maternal recalls, 4 to 12 years after delivery, of weight gain during pregnancy agreed moderately well ($r=0.63$) with medical-record reports [21]; analyses using recalled weight gain may provide attenuated associations, but those authors found no evidence that pre-pregnancy BMI or time since delivery modified associations with recalled weight gain [21]. The validity of maternal recall of breastfeeding is strongly supported ($r=0.95$) by a study that compared maternal recall, 8–9 years after childbirth, of breast feeding duration with prospectively collected data [22]. Because our early life data were recalled by mothers who were all nurses, we expect our data to have a high degree of validity.

Statistical Analyses

To assess potential for selection bias, we compared the early life factors of those participants who returned year 2005 or later surveys including BBD questions with those who did not.

The outcome for all analyses was biopsy-confirmed BBD. Logistic regression models, estimated using SAS [23], provided odds ratios (OR) and 95% confidence intervals (CI). Because the age of each GUTS participant was related to being diagnosed during our follow-up period, all models adjusted for each girl's age (to the month) at study initiation in 1996. A multivariable model further included together four key factors from pre-pregnancy through birth (maternal height, pre-pregnancy BMI, weight gain during pregnancy, and infant birth weight or birth BMI) for mutual adjustment; maternal height was included because taller mothers are themselves at higher risk for breast cancer, and they have newborns that are longer and weigh more. In addition, the multivariable model adjusted for family history of breast disease, multiple vs singleton birth, maternal age at childbirth, maternal smoking and drinking prior to pregnancy, and gestational age (these factors have previously been investigated in studies of breast cancer). Models of infant feeding factors included the same multivariable adjustment factors (family history, etc.).

Models were fit using continuous measures (birth weight in pounds and ounces), when possible, but models were also fit using 3-level categorical versions of each continuous exposure, to consider nonlinear associations. Infant feeding models used the categories appearing on survey questions. Tests for trend were performed by using the median exposure value, within each category, as a continuous variable (in separate age-adjusted models).

Further analyses investigated effects using our categories of pre-pregnancy BMI cross-classified by weight gain during pregnancy, since heavier women are often advised to gain less weight. We repeated this exercise instead using categories from the 2009 Institute of Medicine (IOM) recommendations for weight gain during pregnancy, which vary by pre-pregnancy BMI [24]. The IOM advises the thinnest women (pre-pregnancy BMI <18.5 kg/m²) to gain from 28 to 40 pounds, the normal weight women (18.5–25kg/m²) to gain 25–35 pounds, for overweight women (25–30kg/m²) the recommendation is to gain 15–25 pounds, and for obese women (>30kg/m²) 11–20 pounds.

Results

Eighty-one percent of our females returned, from 2005 through 2013, at least one survey containing questions about BBD. Comparing early data of these participants with the 19% who returned none of those surveys, we found only very small differences with respect to the exposures evaluated in this study. For example, the included girls were slightly younger (by 5.8 weeks) than those not included, but their mothers were slightly older (by 3.6 months) when their daughter was born, and mothers of the included girls were more likely to have breast fed their daughters and for longer (by 12 days) (each age-adjusted $p < .05$). But the other factors (gestational age, maternal height, gestational weight gain, birth weight, birth BMI, maternal pre-pregnancy BMI, cow-milk-based vs other formula) were each similar for the included and missing females. These small differences are unlikely to present serious sources of bias.

Table 1 provides means or percents, within tertile of birth weight, of exposure variables and other important characteristics. As expected, heavier newborns were closer to full-term, they had mothers who were heavier prior to pregnancy, and their mothers gained more weight while pregnant. Surprisingly, the most biopsy-confirmed BBD cases (2.3%) were among girls in the lowest birth weight tertile. Regarding family history, the heaviest babies tended to have more mothers or maternal aunts with breast cancer (7.9%), but maternal BBD rates were similar across birth weight tertiles.

Table 2 summarizes results from our age-adjusted analyses, where for each early life factor (up through birth), we present the odds ratios of the middle and highest exposures relative to the lowest exposure group, along with the p for trend across the three categories. Those girls whose maternal BMI prior to pregnancy was between 20 and 25 kg/m² were at significantly lower risk of BBD as young women (age-adjusted OR=0.66, $p=0.04$), compared to girls with maternal BMI <20 [Table 2]. Maternal BMI prior to pregnancy was highly correlated ($r=0.87$) with BMI at the time of delivery, which was similarly associated with BBD [Table 2]. For those factors that are clearly impacted by pre-term deliveries or multiple births, estimates are further presented separately for full-term singleton births [Table 2]. Models of maternal weight gain during pregnancy suggest that very low weight gain may increase risk; girls whose mothers gained 20 or more pounds during pregnancy were at significantly lower risk for BBD compared to mothers who gained fewer than 20 pounds (among full-term singleton births, OR=0.48, $p=0.007$, if mother gained 20–35 pounds, and OR=0.47, $p=0.02$, if mother gained >35 pounds). Among full-term singleton births, neither birth weight (OR=0.93, $p=0.80$, for heaviest vs lightest) nor BMI at birth (OR=0.88, $p=0.61$, for highest

vs lowest) were associated with subsequent BBD risk [Table 2]. Instead analyzing each of the exposures in Table 2 as continuous measures (not shown), none were significant (all $p > 0.18$), but this is not unexpected given the categorical models generally indicated non-linear associations.

Girls from multiple births (OR=1.98, $p=0.14$, vs singleton births), from pre-term births (OR=1.09, $p=0.64$), from a pregnancy with toxemia/pre-eclampsia (OR=1.67, $p=0.15$), and those born in the spring (OR=1.36, $p=0.23$ vs summer birth) may be at higher risk of BBD, but these were not significant (Table 2). Neither gestational diabetes nor gestational high blood pressure was significantly associated with BBD risk (Table 2).

Multivariable-adjustment had little impact on the estimated risks. Table 3 presents results for the four key exposures in a single model, for mutual adjustment, along with other adjustment factors. The apparent protective effect of maternal pre-pregnancy BMI between 20 and 25 kg/m² was slightly attenuated (OR=0.70, $p=0.09$), but the association with pregnancy weight gain persisted (OR=.50, $p=0.01$ for middle vs bottom category of weight gain) [Table 3]. Birth weight continued to be non-significant, as was birth BMI (when included in the multivariable model in place of birth weight) [Table 3 footnote]. Further adjusting the model for participant's BMI at ages 10yr and 18yr had minimal impact, other than diminishing the estimated effect of maternal pre-pregnancy BMI (OR=0.78, $p=0.24$, for middle and OR=0.79, $p=0.46$, for highest, versus lowest, maternal pre-pregnancy BMI). Maternal pre-pregnancy BMI was significantly correlated with daughter's BMI at both age 10yr ($r=0.28$) and at 18yr ($r=0.35$), but far less correlated with daughter's BMI at birth ($r=0.09$).

Examining maternal pre-pregnancy BMI and gestational weight gain jointly [Table 4], daughters at greatest risk (for BBD as young women) had maternal pre-pregnancy BMI <20 kg/m² and gestational weight gain below 20 pounds (OR=2.71, $p=0.03$) or maternal pre-pregnancy BMI >25 kg/m² and gestational weight gain below 20 pounds (OR=2.76, $p=0.02$). The thinnest women before pregnancy (BMI <20 kg/m²) who gained 20–35 pounds during this pregnancy also had daughters at significantly higher risk for BBD (OR=1.80, $p=0.02$; Table 4). Alternatively utilizing the Institute of Medicine's recommended weight gain categories during pregnancy [24], that are specific to maternal pre-pregnancy BMI, we observed no significant associations with BBD risk (not shown; interaction also not significant). Aside from using different gestational weight gain categories, the IOM pre-pregnancy BMI groups differ from ours as well, with IOM placing nearly 80% of our mothers in their normal weight group, whereas our normal weight group includes only 61% of the mothers.

We observed no evidence that infant feeding practices (breast feeding, type of formula, ages beginning solid food, formula or cow's milk) were linked to BBD [Table 5]. During the first six months of life, infants fed only formula compared to only breast milk had OR=0.81 ($p=0.49$; age-adjusted). Among breast-fed daughters, maternal mastitis/breast infection during lactation was not associated with BBD (OR=1.16, $p=0.68$; not shown). Infants consuming soy-based formula rather than cow-based formula had OR=0.88 ($p=0.58$) [Table 5]. Multivariable-adjustment had little impact on estimated associations [Table 5], and

further adjusting these models for BMI later in childhood (ages 10 and 18yr) negligibly impacted our estimates.

Discussion

To our knowledge, this is the first investigation of factors from very early life (pre-pregnancy through infant feeding), with data reported by mothers when their daughters were still children, and their daughters' later risk for BBD as young women. The hypothesis that breast cancer may originate *in utero* [25] has been supported by animal studies of gestational diet and breast cancer in offspring [26]. Based upon previously published studies of early life and breast cancer risk in humans, we had expected high birth weight (which may reflect a high estrogenic environment *in utero*) and lack of breast feeding to be associated with higher risk for BBD, but we found neither. Instead, daughters were at higher risk if their mother's BMI prior to pregnancy was below 20kg/m² or if gestational weight gain was below 20 pounds. In addition to investigating an intermediate disease outcome (BBD) rather than the final outcome (breast cancer), our cohort was born more recently than women in studies of breast cancer risk.

However, our findings are consistent with the only previous BBD investigation of fetal and infant factors [14]; that study, in which women aged 27yr and older self-reported their own early life exposures, found no associations between proliferative BBD in premenopausal women and their own birth weight or with having been breast fed. For birth weight, the multivariable-adjusted risks for lightest (<5.5 pounds) to heaviest (≥8.5 pounds) babies were 1.10, 0.95, 1.00 (ref) and 0.96 (all *p*>.05). For duration of having been breast fed, the estimated risks for 0 months (1.00, referent) to ≥9 months were 1.02, 0.78 and 1.04 (all *p*>.05). Interestingly, in spite of no association between BBD and birth weight, they did find a strong inverse association with childhood body fatness at age 5yr (most overweight compared to most lean RR=0.71 (0.53–0.96)). Consistent with our findings, they found no significant risks due to prematurity or multiple births [14].

The inability to find any link between BBD and birth weight or breast feeding is puzzling. One earlier study found that higher birth-weight predicted greater risk of obesity in adolescence [27], while conflicting evidence was found regarding the association between having been breast-fed and adolescent overweight or obesity [28,29]. Being heavier in childhood and adolescence is associated with lower risk for BBD [30]. Other research (using mothers who in year 2001 recalled information regarding their own pregnancies from 1946 to 1964) found a positive association between pre-pregnancy BMI and obesity in their daughters at age 18yr, and a U-shape association between gestational weight gain and obesity in daughters [31]. We further adjusted our models for participant's BMI at ages 10yrs and 18yrs, which had little effect on our estimated associations.

Mechanisms for the association we observed between gestational weight gain and risk of BBD are unclear, but studies by others may provide some insight. Among pregnant Swedish women, there was a significant association between progesterone level and gestational weight gain [32]. In a cross-sectional investigation of maternal and cord blood, mother's weight gain during pregnancy was associated with methylation (of IGF2 gene) patterns in

maternal blood [33]. These maternal patterns of methylation were associated with folate, B12 and methylation in cord blood [33]. A recent study reported a link between age at menarche and some of the factors we studied (birth weight, maternal age, soy formula, pregnancy related diabetes and hypertension) [34]; however, in our cohort [30] and others [14, 35], age at menarche was not associated with benign breast disease, and there was no effect of age at menarche on breast cancer risk among women with BBD [36].

Inconsistencies in the literature may reflect different pathways to disease.

The longitudinal design of this investigation comprises its major strength, as exposure variables were reported by mothers (in 1996 and 1999), as soon as 9 years after childbirth, which is far earlier than many other studies utilizing recalled pregnancy/infant data, and long before the reporting of our disease outcome BBD (beginning in 2005), in our large cohort of girls from all over the US. Any misclassification due to errors in reporting early life factors is likely non-differential relative to subsequent BBD, but may attenuate estimated associations between these factors and later BBD. Though all models controlled for participant's age, and other potential confounders were included in multivariable-adjusted models, some residual and unmeasured confounding may remain. We cannot exclude the possibility of incomplete adjustment, or confounding through variables not considered, but little is known about early life risk factors for BBD. Though an earlier study suggested that women who smoked during pregnancy had daughters at increased risk for BBD [37], we do not have data on smoking during pregnancy; however, we were still able to adjust for smoking and drinking in age periods prior to the index pregnancy. The most serious limitation is our small number of BBD cases, particularly within the cells of our cross-classified model in Table 4. Because our participants are all daughters of nurses, this reduces confounding by socioeconomic and other unmeasured factors, while enhancing the accuracy of the data. Although our cohort is not representative of US females, the comparison of risks within our cohort should still be valid and generalizable [38]. However, the racial/ethnic makeup of our cohort (95% white/non-Hispanic) hinders race/ethnic group-specific analyses and generalization to these other races/ethnicities.

In conclusion, we assessed the relationship between biopsy-confirmed BBD in young women and their exposures from very early life, a period thought to be critical for the development of breast cancer and other adult diseases. Based upon pregnancies occurring in the 1980's, we found evidence that a healthy maternal BMI before pregnancy and sufficient weight gain during pregnancy may produce daughters at lower risk for BBD as young women. Because our number of cases was relatively small, and because some exposures may have longer latency periods, continued follow-up of this cohort will be critical to re-assess these results as new cases of BBD, and eventually cases of breast cancer, are diagnosed. These findings regard a single health outcome (BBD in the daughter) that may be associated with gestational weight gain, while many other health outcomes (in both the daughter and her mother) need to be considered to determine optimal gestational weight gain.

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Factors related to the fetal environment and infant diet in 7100 females in the Growing Up Today Study (142 BBD cases and 6958 non-cases), according to tertile of birth weight. Girls were born between 1980 and 1987, and cases of BBD reported from 2005 through 2013. Shown are Mean (SD) or % within each tertile of birthweight.

Table 1

Range	Tertile of Birth Weight			
	T1	T2	T3	
	< 7.15 pounds	7.15 to 8.0 pounds	> 8.0 pounds	
N =	2371	2412	2317	
Mother's pre-preg wt (lbs)	128.8 (21.7)	131.7 (20.8)	138.7 (23.9)	
Mother's Height (inches)	64.4 (2.5)	64.8 (2.5)	65.6 (2.5)	
Mother's pre-preg BMI (kg/m ²)	21.8 (3.4)	22.1 (3.2)	22.7 (3.7)	
Pregnancy weight gain (lbs)	29.2 (11.0)	30.7 (11.0)	33.9 (11.6)	
Mothers BMI at end of pregnancy	26.8 (3.8)	27.3 (3.7)	28.3 (4.0)	
Mother's alcohol before pregnancy (drinks/day)	0.4 (0.7)	0.4 (0.6)	0.4 (0.7)	
Mother's smoking before pregnancy (cigs/day)	4.2 (8.4)	3.8 (8.0)	3.8 (8.3)	
Father's height (inches)	70.5 (2.7)	70.8 (2.8)	71.3 (2.8)	
Term (weeks gestation)	38.5 (1.7)	39.4 (1.0)	39.6 (0.8)	
Mom's age at delivery (yr)	29.3 (3.6)	29.4 (3.6)	29.5 (3.4)	
Infant's Birth wt (lbs)	6.3 (0.8)	7.6 (0.2)	8.7 (0.6)	
Infant's Birth length (inches)	19.3 (1.2)	20.2 (0.9)	20.8 (1.0)	
Infant's BMI at birth (kg/m ²)	12.0 (1.5)	13.2 (1.2)	14.2 (1.4)	
Infant from Multiple birth (%)	5.1%	0.4%	0.04%	
Pre-term (<40 wks) Birth (%)	54.8%	30.1%	17.8%	
Gestational Diabetes (%)	2.5%	2.2%	4.1%	
Gestational High Blood Pressure (%)	9.4%	5.6%	6.0%	
Pre-eclampsia/toxemia	7.4%	3.2%	4.0%	
Race (white-NH %)	93%	95%	97%	
Season of Birth				
Summer	26%	26%	25%	
Fall	24%	25%	24%	

Range	Terile of Birth Weight			
	T1	T2	T3	
	< 7.15 pounds	7.15 to 8.0 pounds	> 8.0 pounds	
N =	2371	2412	2317	
Winter	24%	22%	23%	
Spring	26%	26%	28%	
Infant Feeding				
This Daughter Ever Breast-fed (%)	85.9%	90.2%	90.0%	
Maternal mastitis/infection (among breast-fed)	7.6%	7.6%	7.3%	
Breast vs Bottle (Formula) (first 6 months of life)				
only breast	29.0%	34.3%	34.0%	
more breast	30.0%	31.1%	32.8%	
both equally	7.0%	6.8%	6.3%	
more formula	19.6%	17.7%	16.6%	
only formula	14.3%	10.1%	10.3%	
Age when stop BF (months)	6.5 (3.4)	6.7 (3.3)	6.8 (3.3)	
Age begin Formula (months)	2.7 (2.7)	3.0 (2.7)	3.0 (2.7)	
Type of Formula				
Cow-based	63.0%	63.1%	63.8%	
Soybean-based	21.4%	17.9%	17.7%	
Other-based	0.8%	0.7%	0.8%	
Never fed formula	14.8%	18.2%	17.7%	
Age begin Cow's Milk (months)	11.6 (2.0)	11.6 (2.0)	11.5 (2.1)	
Age begin Solid Food (months)	5.2 (2.0)	5.1 (1.9)	5.0 (2.0)	
Family History of Breast Disease:				
In Mother or Maternal Aunt: Breast Cancer	6.1%	7.4%	7.9%	
In Mother: BBD	18.4%	18.8%	18.3%	
Infant's Disease Outcome as a Young Woman				
Biopsy-confirmed BBD ^a	2.3%	1.7%	2.0%	

^aBenign breast disease in participant, reported from 2005 through 2013.

Risk for biopsy-confirmed BBD in 7100 young women related to prenatal factors and birth outcomes. All single exposure models adjust for girl's age when cohort was founded. Exposure categories^a are (as close as possible to) bottom 25%, middle 50%, and top 25%.

Table 2

Factors	Never Reported	Biopsy-Confirmed	Three Category Exposure ^a Models (Age-adjusted)			P _{trend}
	BBD (n=6958)	BBD cases (n=142)	Middle vs Lowest	High vs Lowest		
	Mean (SD) or %	Mean (SD) or %	OR (95%CI)	OR (95%CI)		
Mother's pre-preg wt (lbs)	133.0 (22.5)	132.7 (25.1)	0.89 (0.58,1.37)	0.74 (0.43,1.26)	0.27	
Mother's Height (in)	64.9 (2.6)	65.1 (2.3)	1.44 (0.89,2.34)	1.26 (0.68,2.32)	0.45	
Mothers pre-preg BMI (kg/m ²)	22.2 (3.4)	21.9 (3.8)	0.66* (0.44,0.98)	0.62 (0.34,1.13)	0.13	
Mothers BMI at end of pregnancy	27.4 (3.9)	26.9 (4.0)	0.63* (0.41,0.96)	0.78 (0.48,1.25)	0.43	
Mothers BMI at end of pregnancy ^b	27.5 (3.8)	27.3 (4.3)	0.50** (0.30,0.81)	0.87 (0.52,1.47)	0.41	
Pregnancy weight gain (lbs)	31.3 (11.4)	30.8 (12.5)	0.51** (0.31,0.84)	0.53* (0.30,0.94)	0.14	
Pregnancy weight gain (lbs) ^b	31.7 (11.0)	31.1 (12.8)	0.48** (0.28,0.82)	0.47* (0.25,0.89)	0.11	
Father's height (in)	70.9 (2.8)	70.8 (2.9)	0.81 (0.53,1.24)	0.92 (0.54,1.57)	0.74	
Term (weeks)	39.2 (1.3)	39.1 (1.3)	0.94 (0.46,1.89)	0.87 (0.45,1.69)	0.61	
Mom's age at delivery (yr)	29.4 (3.5)	29.4 (3.7)	0.86 (0.49,1.50)	1.08 (0.61,1.90)	0.41	
Birth weight (lbs)	7.55 (1.14)	7.50 (1.18)	0.98 (0.62,1.56)	0.86 (0.48,1.53)	0.59	
Birth weight (lbs) ^b	7.86 (0.96)	7.90 (0.95)	0.93 (0.60,1.51)	0.93 (0.51,1.69)	0.68	
Birth length (in)	20.1 (1.2)	20.1 (1.3)	1.13 (0.72,1.77)	1.10 (0.72,1.68)	0.69	
Birth length (in) ^b	20.4 (1.1)	20.4 (1.0)	1.10 (0.67,1.81)	0.94 (0.60,1.50)	0.49	
Birth BMI (kg/m ²)	13.1 (1.6)	12.9 (1.7)	0.91 (0.60,1.37)	0.72 (0.44,1.18)	0.20	
Birth BMI (kg/m ²) ^b	13.3 (1.5)	13.4 (1.6)	0.77 (0.49,1.23)	0.88 (0.53,1.45)	0.22	
Infant from Multiple Birth	1.8%	3.5%	1.98 (0.80,4.92)			
Pre-term (<40wks) birth	34%	36%	1.09 (0.77,1.54)			
Gestational Diabetes (%)	2.9%	3.6%	1.29 (0.52,3.18)			
Gestational High BP (%)	7.0%	8.0%	1.14 (0.61,2.13)			
Toxemia/pre-eclampsia	4.8%	7.9%	1.67 (0.84,3.33)			
Race (white-NH %)	94.8%	93.7%	0.80 (0.40,1.59)			
Season of Birth (spring vs summer)			1.36 (0.86,2.16)			

	Never Reported		Biopsy-Confirmed		Three Category Exposure ^a Models (Age-adjusted)		P _{trend}
	BBD (n=6958)		BBD cases (n=142)		Middle vs Lowest	High vs Lowest	
	Mean (SD) or %		Mean (SD) or %		OR (95%CI)	OR (95%CI)	
Spring	26.9%		31.7%				
Summer	25.8%		21.8%				
Fall	24.2%		25.3%				
Winter	23.1%		21.1%				

* p<0.05
** p<0.01

^aCutpoints between exposure categories: Mother's pre-pregnancy weight <120 and >140 pounds; Mother's height <63 and >67 inches; Mother's pre-pregnancy BMI <20.0 and ≥25.0 kg/m²; Mother's BMI at time of delivery 24.89 kg/m² (25%ile) and 29.23 kg/m² (75%ile); Father's height <69 and >73 inches; Weight gain during pregnancy <20 and >35 pounds; Term 37wks and 40wks; Maternal age at childbirth 25 and >30yrs; Birth weight 6.5 and 8.5 pounds; Birth length 19 and 21 inches; BMI at birth <12 and ≥14 kg/m².

^bFor relevant factors (maternal weight gain, birth weight, etc) estimates are shown for full-term singleton births.

Multivariable-adjusted^a risk for biopsy-confirmed BBD in young women related to prenatal factors and birth outcomes. The four factors shown here are included together in one model.

Table 3

Factors	Three Category ^b Exposures Model			
	Lowest	Middle vs Lowest	High vs Lowest	
	(referent)	OR (95%CI)	OR (95%CI)	
Mother's Height (in)				
Number of Cases (%)	20 (1.5%)	100 (2.2%)	22 (1.9%)	
Multivariable-adjusted OR (95%CI)	1.00	1.45 (0.89,2.38)	1.25 (0.66,2.34)	
Mothers pre-preg BMI (kg/m²)				
Number of Cases (%)	40 (2.8%)	66 (1.8%)	15 (1.7%)	
Multivariable-adjusted OR (95%CI)	1.00	0.70* (0.47,1.05)	0.61 (0.33,1.14)	
Pregnancy weight gain (lbs)				
Number of Cases (%)	20 (3.6%)	72 (1.9%)	31 (1.9%)	
Multivariable-adjusted OR (95%CI)	1.00	0.50** (0.30,0.84)	0.52** (0.28,0.94)	
Birth Weight (lbs)^c				
Number of Cases (%)	23 (2.1%)	93 (2.0%)	24 (1.8%)	
Multivariable-adjusted OR (95%CI)	1.00	1.03 (0.60,1.75)	0.97 (0.50,1.90)	

* p<0.10
** p<0.05

^aThe multivariable-adjusted model includes all four factors shown above, in the model simultaneously, along with girl's age when cohort was founded, family history of breast cancer and BBD, mother's age at childbirth, single/multiple birth, weeks gestation, and maternal smoking and drinking in years prior to this pregnancy.

^bCutpoints between exposure categories: Mother's height 62 and 68 inches; Mother's pre-pregnancy BMI <20.0 and 25.0 kg/m²; Weight gain during pregnancy <20 and >35 pounds; BMI at birth <12 and 14 kg/m².

^cFitting above multivariable-adjusted model with Birth BMI (kg/m²), in place of Birth Weight, provided similar results: Middle vs lowest BMI OR=0.95 (0.62,1.46), and Highest vs lowest BMI OR=0.80 (0.48,1.34).

Multivariable-adjusted model^a of pre-pregnancy BMI by weight gain during pregnancy, and risk for biopsy-confirmed BBD. The referent group includes girls in the middle cell (maternal pre-pregnancy BMI was within 20–25kg/m² and gestational weight gain between 20 and 35 pounds).

TABLE 4

Pre-pregnancy BMI (kg/m ²)	Maternal weight gain during pregnancy (pounds)			
	< 20 pounds	20–35 pounds	>35 pounds	
<20 kg/m ²	N cases (%)	6 (4.7%)	28 (2.9%)	6 (1.7%)
	OR (95%CI)	2.71* (1.11,6.61)	1.80* (1.09,2.97)	0.96 (0.40,2.31)
20–25 kg/m ²	N cases (%)	7 (2.8%)	38 (1.6%)	21 (2.1%)
	OR (95%CI)	1.74 (0.76,3.99)	1.00 (referent)	1.34 (0.77,2.31)
>25 kg/m ²	N cases (%)	7 (4.2%)	4 (0.8%)	4 (1.7%)
	OR (95%CI)	2.76* (1.20,6.33)	0.56 (0.20,1.57)	1.07 (0.37,3.09)

* p<0.05 (Referent is middle group on both factors)

^a Multivariable-adjusted model include girl's age when cohort was founded, family history of breast cancer and BBD, maternal height, mother's age at childbirth, maternal smoking and drinking in years prior to this pregnancy, gestational age, multiple or singleton birth, and girl's birth weight.

TABLE 5

Risk for biopsy-confirmed BBD in young women related to infant feeding factors.

Factors	Categorical Exposure Models					P-value for trend
	only breast	more breast	both equally	more formula	only formula	
Breast vs Formula (1st 6 mo)						
Number of cases (%)	46 (2.0%)	45 (2.1%)	10 (2.1%)	25 (2.0%)	13 (1.6%)	
Age-adjusted OR (95% CI)	1.00 (ref)	1.04(0.68,1.57)	1.08(0.54,2.15)	1.01(0.62,1.65)	0.81(0.43,1.50)	0.63
Multivar-adj OR (95% CI) ^a	1.00 (ref)	0.98(0.58,1.67)	1.03(0.47,2.24)	0.96(0.52,1.76)	0.80(0.39,1.64)	
Type of Formula						
Number cases (%)	Never 23 (2.0)	Cow-based 89 (2.1)	Soybean-based 23 (1.8)	Other-based 1 (1.9)		---
Age-adjusted OR (95% CI)	0.96(0.60,1.52)	1.00 (ref)	0.88(0.55,1.39)	0.91(0.13,6.68)		
Multivar-adj OR (95% CI) ^a	0.88(0.48,1.63)	1.00 (ref)	0.87(0.55,1.39)	1.01(0.14,7.43)		
Age begin Solid Food						
Number cases (%)	3 months 22 (1.8)	4–6 months 93 (2.1)	7–9 months 17 (1.6)	>9 months 6 (2.7)		0.86
Age-adjusted OR (95% CI)	1.11(0.58,2.10)	1.29(0.76,2.17)	1.00 (ref)	1.71(0.66,4.38)		
Multivar-adj OR (95% CI) ^a	1.21(0.62,2.37)	1.30(0.76,2.21)	1.00 (ref)	1.77(0.68,4.59)		
Duration of BF						
Number cases (%)	Never-<1mo 18 (1.6)	1–3 months 20 (2.0)	4–6 months 33 (2.4)	7–9 months 25 (2.4)	>9 months 42 (1.8)	
Age-adjusted OR (95% CI)	1.00 (ref)	1.27(0.67,2.41)	1.50(0.84,2.67)	1.48(0.80,2.74)	1.13(0.64,1.97)	0.86
Multivar-adj OR (95% CI) ^b	1.00 (ref)	1.19(0.56,2.54)	1.55(0.76,3.19)	1.38(0.64,3.00)	1.05(0.48,2.29)	
Age begin Formula						
Number cases (%)	<1 month 34 (1.8)	1–3 months 44 (2.3)	4–6 months 18 (1.7)	>6 months 17 (2.3)	Never 24 (2.1)	
Age-adjusted OR (95% CI)	1.08(0.61,1.92)	1.37(0.79,2.39)	1.00 (ref)	1.39(0.71,2.71)	1.22(0.66,2.26)	0.84
Multivar-adj OR (95% CI) ^b	1.30(0.65,2.58)	1.42(0.79,2.54)	1.00 (ref)	1.62(0.79,3.32)	1.45(0.71,2.95)	
Age begin Cow's Milk (not in formula)						
Number cases (%)	6 months 5 (2.1)	7–9 months 17 (2.3)	10–12 months 43 (2.1)	>12 months (includes Never) 74 (1.9)		0.61
Age-adjusted OR (95% CI)	1.08(0.43,2.69)	1.16(0.68,1.98)	1.07(0.73,1.56)	1.00 (ref)		
Multivar-adj OR (95% CI) ^b	1.11(0.43,2.86)	1.19(0.68,2.07)	1.09(0.74,1.61)	1.00 (ref)		

^aThe multivariable-adjusted model includes Breast vs Formula during first 6 months, type of formula, age began eating solid food, mother's age when daughter born, gestational age, girl's age when cohort founded, family history of breast cancer and BBD, multiple birth (singleton vs twins+), maternal smoking and maternal drinking in years prior to this pregnancy.

^bThe multivariable-adjusted model includes duration of breast feeding, age began drinking formula, age began drinking cow's milk, mother's age when girl born, gestational age, girl's age when cohort founded, family history of breast cancer and BBD, multiple birth (singleton vs twins+), maternal smoking and maternal drinking in years prior to this pregnancy.