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Mothers' pre-pregnancy BMI and weight gain during pregnancy and risk of breast cancer in daughters

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Abstract

Previous studies have established that higher birthweight is associated with increased risk of breast cancer. However, the mechanisms underlying this association remain unclear. We explored whether maternal pregnancy weight gain and pre-pregnancy body mass index (BMI), which influence birthweight, are associated with risk of breast cancer in offspring. The Nurses' Mothers case-control study of breast cancer was nested in the Nurses' Health Study I and II cohorts. Mothers of 814 nurses with and 1809 nurses without breast cancer completed questionnaires with information on pre-pregnancy height and weight, pregnancy weight gain, and other aspects of their pregnancies with the nurse daughters. We calculated odds ratios for breast cancer using conditional logistic regression. Mean pregnancy weight gain was 23 pounds, and average pre-pregnancy BMI was 21 kg/m^2. Mothers' weight gain during pregnancy was not associated with the daughters' risk of breast cancer. Compared to women whose mothers gained 20–29 pounds, women whose mothers gained less than 10 pounds had a relative risk of 0.92 (95% confidence interval [CI]: 0.62–1.36), adjusting for the age of the nurses. Women whose mothers gained 40 or more pounds had a relative risk of 0.82 (95% CI: 0.55–1.23). Mothers' pre-pregnancy BMI was not associated with the daughters' risk of breast cancer. Women whose mothers had a pre-pregnancy BMI of 30 or more had a relative risk of 0.77 (95% CI: 0.34–1.74) compared to those with BMI less than 20. Additional adjustment for prenatal factors or for nurses' characteristics later in life had no effect on the results. The association between birthweight and breast cancer risk is likely due to factors independent of mothers' weight gain during pregnancy or pre-pregnancy BMI. Because BMIs and pregnancy weight gains were lower in this population than today, we cannot rule out associations for very high pre-pregnancy BMIs or pregnancy weight gains.

Keywords

pregnancy; body mass index; weight gain; mothers; in utero exposures; breast cancer

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Introduction

Previous studies have established that high birthweight is associated with increased risk of breast cancer later in life.[1] However, the mechanisms underlying this association remain unclear. Birth weight has been hypothesized to be a marker of intrauterine exposure to estrogen or other hormones, growth factors such as insulin, insulin-like growth factors 1 and 2 (IGF-1, IGF-2), and epigenetic variation.[2]

A high birthweight may result from a high pregnancy weight gain and/or a high pre-pregnancy body mass index (BMI).[3–9] In addition, high pregnancy weight gain may be associated with higher levels of estrogens [10] and progesterone [11, 12] and lower levels of sex hormone-binding globulin (SHBG) [13], though other studies have not observed these associations [14]. Higher pre-pregnancy BMI has been associated with lower levels of estriol [12] and SHBG [15], and with higher insulin and lower insulin-like growth factor binding protein 1 (IGFBP1) [16]. Thus pregnancy weight gain and/or pre-pregnancy BMI could be associated with daughters' risk of breast cancer later in life, andbirthweight may be an intermediate variable.

The possible association between pregnancy weight gain and pre-pregnancy BMI and daughters' risk of breast cancer is particularly important given increases in BMIs, pregnancy weight gains, and pregnancy weight gain recommendations in recent decades. [17] We studied the association between higher pregnancy weight gain and higher pre-pregnancy BMI and risk of breast cancer in daughters using unique data from a case-control study of breast cancer nested in the Nurses' Health Study and Nurses' Health Study II cohorts, in which the nurses' mothers provided information about their pregnancies.

Methods

Study population

The Nurses' Mothers case-control study of breast cancer was nested in two prospective cohort studies, the Nurses' Health Study (NHS I) and the Nurses' Health Study II (NHS II). [18] The NHS I cohort was established in 1976 when 121,700 nurses born between 1921 and 1945 completed a mailed questionnaire on lifestyle and health. The NHS II cohort was established in 1989 when 116,680 nurses born between 1946 and 1965 completed a mailed questionnaire. Both cohorts have been followed with questionnaires every two years to collect information on breast cancer, other diseases, and lifestyle factors.

For the case-control study of early life factors and breast cancer risk we identified all NHS I and II participants who were diagnosed with breast cancer and whose mother was not known to be deceased between 1991 and 1998. Nurses were asked about new diagnoses of breast cancer during the previous two years on each biennial questionnaire. Women reporting a diagnosis were contacted for confirmation of the diagnosis and for permission to obtain medical records for further information, including estrogen and progesterone receptor (ER/PR) status of the cancer. For each case we matched two controls with the same birth year who were free of breast cancer at the time of the case's diagnosis. We wrote to the identified nurses to ask if their mothers were alive and if so, for permission to contact the mother. Mothers who had died, had dementia, or were otherwise incapable of responding to a questionnaire were excluded from this study. Of the 3550 mothers who were sent questionnaires and who had not died in the meantime or were otherwise incapacitated and were not able to take part in the study, 3037 (86%) completed and returned the Mothers' Questionnaire. The 14% of mothers who did not return the Mothers' Questionnaire included mothers who died since their nurse daughter gave permission to contact them and provided their contact information, mothers who were otherwise incapacitated and non-responders.

We excluded 42 cases (4.5%) and 94 controls (4.5%) whose mothers did not provide their daughters' year of birth or provided an incorrect year of birth on the questionnaire, as we could not be sure that the reported pregnancy data referred to the daughter participating in the Nurses' Health Study. We also excluded twin births (n=48) and premature births (n=232). This left 814 cases and 1807 controls in the study population

Assessment of mothers' pregnancy weight gain and pre-pregnancy BMI

Mothers were asked how much weight they had gained during their pregnancy with the nurse daughter, selecting from six categories: <10 pounds, 10–14 lbs, 15–19 lbs, 20–29 lbs, 30–40 lbs, more than 40 lbs, or don't remember. 151 cases' mothers and 394 controls' mothers either left the question blank or chose "don't remember". Therefore, 663 (81%) cases and 1413 (78%) controls were included in the weight gain analysis.

Mothers also reported their pre-pregnancy height and weight, from which we calculated BMI as kilograms/meters^2; 101 cases' mothers and 251 controls' mothers did not report either their height or weight. Therefore, 713 (88%) cases and 1556 (86%) controls were included in the pre-pregnancy BMI analysis.

Covariate information

Information on mothers' prenatal care, alcohol and tobacco use during pregnancy, pregnancy complications, and daughters' birthweight was collected from the mothers on the Mothers' Questionnaire. Additional covariate information was taken from the regular cohort questionnaires filled out by the nurses, including family history of breast cancer, age at menarche, adult height and weight, and reproductive characteristics.

Statistical analysis

Because cases and controls were matched before the mothers' participation in the study was known, matching was incomplete for many participants. Therefore, we pursued a risk set analysis using conditional logistic regression models conditioning on the matching factors, year of birth and cohort, rather than on the original matched case-control sets.

We used these models to estimate odds ratios of breast cancer for each category of pregnancy weight gain compared to the reference category of 20–29 pounds, which was the most common weight gain group. Our basic models were adjusted for nurses' year of birth and cohort. Covariate-adjusted model 1 was additionally adjusted for family history of breast cancer in mother or sister (yes/no, as reported by nurse) and maternal smoking during pregnancy (no, yes <25 cigarettes/day, yes ≥25 cigarettes/day). Covariate-adjusted model 2 was additionally adjusted for several characteristics of the nurses during later life: age at menarche (<12, 12, 13, ≥14 years), BMI at age 18 (<20, 20-<22.5, 22.5-<25, ≥25 kg/m^2), and adult height (quartiles).

We chose not to adjust for birthweight because it may be an intermediate between our exposures, pregnancy weight gain and pre-pregnancy BMI, and the daughters' risk of breast cancer; however, additional adjustment for birthweight did not affect our results. We also considered the following factors as possible covariates: mothers' age at birth, mothers' pre-pregnancy BMI (in the weight gain models), prenatal care, alcohol use in pregnancy, pregnancy complications (high blood pressure, proteinuria, gestational diabetes, pre-eclampsia, and eclampsia), and nurses' parity. None of these variables affected our results, and they were not included in the final models.

In addition to overall breast cancer risk, we looked at cases diagnosed before and after the age of 50 as a proxy for menopausal status, as risk factors for breast cancer, including

birthweight, may vary by menopausal status. We also looked separately at estrogen receptor (ER) positive and negative cases, because risk factors may vary by ER status.

Current weight gain recommendations for pregnancy are based on pre-pregnancy BMI, and the biological impact of different weight gains may vary by mothers' pre-pregnancy BMI, so we stratified the weight gain analysis by mothers' pre-pregnancy BMI (<21/≥21, the median BMI in the population, and <25/≥25, the cutoff for overweight). For the weight gain and pre-pregnancy BMI analyses we also stratified by nurses' birthweight (<7.4/≥7.4 lbs, the median, and <8/≥8 lbs), as the meaning of different pregnancy weight gains might depend on the size of the baby.

To test for a linear trend across categories of pregnancy weight gain, we created a continuous variable using the midpoint of each category (except for the lowest category, where we used 10 lbs, and the highest, where we used 40 lbs). To test for a linear trend across categories of pre-pregnancy BMI, we used BMI as a continuous variable in the models.

Results

Characteristics of the 814 breast cancer cases and 1807 controls are shown in Table 1. Mothers' average pregnancy weight gain and the distribution across weight gain categories were similar for cases and controls. Mean pregnancy weight gain was 23 pounds, and average pre-pregnancy BMI in the mothers was 21 kg/m^2. The mean year of birth of the nurses was 1942 for cases and 1940 for controls. Mothers of cases were slightly more likely to have smoked during the pregnancy. Cases were more likely to have a family history of breast cancer. Pregnancy weight gain and daughters' birthweight was positively related, with a Spearman correlation of 0.20 ($p<0.0001$). Average birthweight was 7.05 pounds in the < 10 lbs weight grain group and 7.94 in the 40+ lbs weight gain group. Mothers' pre-pregnancy BMI was weakly positively related to birthweight, with a Spearman correlation of 0.09 ($p=<0.0001$).

Mothers' weight gain during pregnancy was not associated with the daughters' risk of breast cancer (Table 2). Compared to women whose mothers gained 20–29 pounds, women whose mothers gained less than 10 pounds had a relative risk of 0.92 (95% CI: 0.62–1.36), adjusting for the age of the nurses. Women whose mothers gained 40 or more pounds had a relative risk of 0.82 (CI: 0.55–1.23). Further adjustment for family history of breast cancer and maternal smoking during pregnancy did not appreciably alter the results (covariate-adjusted model 1). Additional adjustment for several characteristics of the nurses – age at menarche, BMI at age 18, and adult height – also did not change the results (covariate-adjusted model 2). Excluding those whose mothers had pregnancy complications including high blood pressure, proteinuria, gestational diabetes, pre-eclampsia or eclampsia (n=97) had no effect on the results (data not shown). Excluding those whose mothers smoked (n=358) or drank alcohol (n=220) during the pregnancy also did not alter the results (data not shown).

We considered breast cancer cases separately by age at diagnosis as a proxy for premenopausal versus postmenopausal breast cancer (Table 3). The risk of being diagnosed with breast cancer before age 50 (n=458) did not vary according to maternal weight gain. The relative risk of early breast cancer was 0.95 (CI: 0.59–1.54) for women whose mothers gained less than ten pounds and 0.90 (CI: 0.57–1.42) for women whose mothers gained 40 or more pounds, compared to women whose mothers gained 20–29 pounds, adjusting for age of nurses, family history of breast cancer, and maternal smoking during pregnancy. The risk of being diagnosed with breast cancer at age 50 or older (n=205) also did not vary

according to maternal weight gain, with a relative risk of 0.93 (CI: 0.46–1.89) for less than ten pounds weight gain and a relative risk of 0.65 (0.28–1.49) for 40 or more pounds, compared to a weight gain of 20–29 pounds.

There was no association between maternal weight gain and risk of ER+ cancer (n=347) or ER-cancer (n=141) (Table 3). We also stratified by mothers' pre-pregnancy BMI and by nurses' birthweight and found no association between pregnancy weight gain and breast cancer risk in any subgroup (data not shown).

Mothers' pre-pregnancy BMI was not associated with the daughters' risk of breast cancer (Table 4). Compared to women whose mothers had a pre-pregnancy BMI less than 20, women whose mothers had a pre-pregnancy BMI of 30 or more had a relative risk of 0.77 (0.34–1.74) adjusting for the age of the nurses. Additional adjustment for family history of breast cancer and maternal smoking during pregnancy (covariate-adjusted model 1) and nurses' age at menarche, BMI at age 18, and adult height (covariate-adjusted model 2) did not change the results.

Pre-pregnancy BMI was not associated with risk of ER+ cancer or ER- cancer or with cancer diagnosed before or after age 50. (Table 5) In stratified analyses, pre-pregnancy BMI was not associated with breast cancer risk within subgroups defined by birthweight (data not shown).

Discussion

In this study, we found no association between mothers' weight gain during pregnancy or mothers' pre-pregnancy BMI and daughters' subsequent risk of breast cancer. There were no associations with breast cancer risk in subtypes of cancer defined by age at diagnosis or ER status. Our data provided a unique opportunity to study these associations because data collected directly from the mothers was available in addition to data provided by the nurses themselves. This also allowed us to account both for other pregnancy-related factors and for factors from the nurses' adult lives.

One previous analysis examined these associations in two population-based case-control studies of premenopausal breast cancer in Washington state with similar results [19]. Compared to mothers who gained 15–24 pounds, women whose mothers gained 25–34 pounds had a statistically significant increased risk of breast cancer, with an odds ratio of 1.5 (95% CI: 1.1–2.0); however, there was no indication of increased risk for mothers who gained 35 or more pounds, and weight gain of less than 15 pounds was also not associated with risk. Given the lack of any dose-response and the number of possible risk factors examined in this study, the significantly increased risk in the 25–34 pounds group may well be due to chance. Mothers' pre-pregnancy BMI was also not associated with breast cancer risk. As in our study population, prepregnancy BMIs were low; the highest quartile of BMI was 22.6 kg/m^2 or greater.

Our results may not be generalizable to today's population, as both pregnancy weight gains and pre-pregnancy BMIs have increased over time. The nurses in this study were born between 1921 and 1964. In the first half of the 1900s, obstetricians recommended much more restricted weight gain during pregnancy than is recommended today [20]. In 1966, *Williams' Obstetrics*, an American textbook, recommended a gain of 15–20 pounds, or 25 pounds at most. Data collected in the 1940s and 1950s show an average pregnancy weight gain of 18–22 pounds, while data from the 1980s show an average of 30–35 pounds [20]. In 2005, approximately half of women gained 30 pounds or more during full-term pregnancies, with approximately 20% gaining more than 40 pounds [21]. This is in stark contrast to our study population, in which only 20% of the women gained 30 or more pounds, and 5%

gained 40 or more pounds. Thus we had limited ability to study weight gains at the upper limit of current recommendations and beyond. In addition, the median pre-pregnancy BMI of the mothers was 21, and only 9% of the mothers had pre-pregnancy BMIs of 25 or greater. Therefore, we had limited power to look at the effects of pregnancy weight gain for mothers who were overweight or obese.

The validity of mothers' recall of weight gain during pregnancy 40 to 60 years later has not been studied. However, several studies have found good agreement between data recorded during pregnancy and maternal recall of pregnancy-related factors after 30 to 50 years. Correlations were between 0.8 and 0.9 for daughter's birthweight [22–24], mother's height and pre-pregnancy weight, and smoking during pregnancy [24]. In addition, measuring weight at prenatal visits and limiting maternal weight gain to prevent pre-eclampsia and other complications was considered important during this time period, so mothers were likely aware of their weight gain during pregnancy [25]. Since mothers in our study would be unlikely to relate their pregnancy weight gain to their daughters' breast cancer status, any misclassification due to errors in reporting of pregnancy weight gain is likely non-differential relative to case status, and thus would be expected to attenuate any association between weight gain and breast cancer risk.

In conclusion, we found no association between pregnancy weight gain and pre-pregnancy BMI and risk of breast cancer in offspring. We had limited power to examine large pregnancy weight gains that are more common in recent years. However, our results suggest that the association between birthweight and breast cancer risk observed in this and other study populations are likely due to factors independent of mothers' weight gain during pregnancy or mothers' pre-pregnancy BMI, in spite of observed associations of pregnancy weight gain and pre-pregnancy BMI with both birthweight and maternal hormone levels. Thus the perinatal factors underlying the birthweight-breast cancer association remain to be elucidated.

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Table 1

Characteristics of the study population by case status (means or percents)

	Controls	Cases
N	1807	814
% in NHS I	77%	66%
% in NHS II	23%	34%
Mothers' pregnancy weight gain[a]	23	23
% in each weight gain category[a]:		
Gained <10 lbs	4.9%	4.2%
Gained 10–14 lbs	15.7%	14.9%
Gained 15–19 lbs	22.8%	24.1%
Gained 20–29 lbs	36.4%	35.8%
Gained 30–40 lbs	14.7%	16.9%
Gained 40+ lbs	5.6%	4.1%
Mothers' pre-pregnancy BMI(kg/m^2)[a]	21.3	21.4
% in each BMI category[a]:		
BMI <20	31.2%	31.4%
20–22.4	42.8%	39.4%
22.5–24.9	18.8%	21.9%
25.0–29.9	6.0%	6.5%
BMI ≥ 30	1.2%	0.8%
Nurses' year of birth	1940	1942
Nurses' birthweight (lbs)	7.4	7.5
Mother smoked during pregnancy	13%	17%
Family history of breast cancer[b]	14%	22%
Nurses' age at menarche <12 years	24%	24%
Nurses' adult height (inches)	65	65
Nurses' BMI at age 18	21.3	20.8

[a] Excluding those with missing data for that question.

[b] Family history in mother or sister as reported by nurse.

Table 2

Odds ratios (and 95% confidence intervals) for breast cancer by category of maternal weight gain in pregnancy

Maternal weight gain in pregnancy	N cases/controls	Age-adjusted[a]	Covariate-adjusted 1[b]	Covariate-adjusted 2[c]
Wt gain <10 lbs	28/69	0.92 (0.62–1.36)	0.94 (0.63–1.40)	0.96(0.64–1.42)
Wt gain 10–14 lbs	99/222	1.03 (0.81–1.31)	1.04 (0.82–1.31)	1.03 (0.81–1.31)
Wt gain 15–19 lbs	160/322	1.05 (0.86–1.29)	1.04 (0.85–1.27)	1.05(0.85–1.28)
Wt gain 20–29 lbs	237/514	1.00 (ref)	1.00 (ref)	1.00 (ref)
Wt gain 30–40 lbs	112/207	1.11 (0.88–1.39)	1.12 (0.89–1.41)	1.14 (0.90–1.43)
Wt gain 40+ lbs	27/79	0.82 (0.55–1.23)	0.85 (0.57–1.26)	0.82 (0.55–1.23)
p-trend*		0.95	0.94	0.97

[a] Age-adjusted model adjusted for birth year of nurse and cohort.

[b] Covariate-adjusted 1 model additionally adjusted for family history of breast cancer in nurses' mother orsister (yes/no; as reported by nurse), maternal smoking during pregnancy (no, yes <25 cigs/day, yes >=25 cigs/day).

[c] Covariate-adjusted 2 model includes variables in covariate-adjusted 1 as well as Nurse's age at menarche (<12, 12, 13, 14+ years), Nurses' adult height (quartiles), and Nurse's BMI at age 18 (<20, 20-<22.5, 22.5-<25, >=25).

* p-trend from model using the midpoint of each weight gain category as a continuous variable.

Table 3

Odds ratios (and 95% confidence intervals) for breast cancer by category of maternal weight gain in pregnancy, according to age at diagnosis and ER status of the tumor

Maternal weight gain in pregnancy	Age at diagnosis				ER status of tumor			
	Cases <50 years		Cases ≥ 50 years		ER+ Cases		ER- Cases	
Wt gain <10 lbs	19/69	0.95 (0.59–1.54)	9/69	0.93 (0.46–1.89)	15/69	0.95(0.55–1.63)	8/69	1.23 (0.57–2.63)
Wt gain 10–14 lbs	54/222	0.93 (0.69–1.27)	45/222	1.22 (0.83–1.80)	56/222	1.13 (0.82–1.56)	20/222	1.06 (0.62–1.79)
Wt gain 15–19 lbs	113/322	1.05 (0.83–1.34)	47/324	1.09 (0.75–1.61)	83/322	1.08 (0.81–1.43)	30/324	0.95 (0.60–1.51)
Wt gain 20–29 lbs	173/514	1.00 (ref)	64/514	1.00 (ref)	120/514	1.00 (ref)	50/514	1.00 (ref)
Wt gain 30–40 lbs	78/207	1.11 (0.85–1.45)	34/207	1.22 (0.80–1.86)	54/207	1.11(0.80–1.53)	29/207	1.54 (0.97–2.45)
Wt gain 40+ lbs	21/79	0.90 (0.57–1.42)	6/79	0.65 (0.28–1.49)	19/79	1.09 (0.66–1.78)	4/79	0.59 (0.21–1.65)
p-trend*		0.69		0.56		0.99		0.56

Odds ratios are adjusted for birth year of nurse, cohort, family history of breast cancer in nurses' mother or sister (yes/no; as reported by nurse), maternal smoking during pregnancy (no, yes <25 cigs/day, yes >=25 cigs/day).

*p-trend from model using the midpoint of each weight gain category as a continuous variable.

Table 4

Odds ratios (and 95% confidence intervals) for breast cancer by category of maternal pre-pregnancy BMI

	N cases/controls	Mean BMI	Age-adjusted[a]	Covariate-adjusted 1[b]	Covariate- adjusted 2[c]
BMI <20	224/486	18.7	1.00	1.00	1.00
BMI 20 -<22.5	281/666	21.2	0.93 (0.78–1.11)	0.93 (0.78–1.10)	0.95 (0.79–1.13)
BMI 22.5 -<25	156/292	23.5	1.10 (0.89–1.35)	1.09 (0.89–1.34)	1.13 (0.92–1.40)
BMI 25 -<30	46/94	26.5	1.03 (0.75–1.42)	1.06 (0.77–1.46)	1.12 (0.81–1.55)
BMI ≥ 30	6/18	31.9	0.77 (0.34–1.74)	0.72 (0.32–1.64)	0.76 (0.34–1.73)
p-trend*			0.71	0.71	0.48

[a] Age-adjusted model adjusted for birth year of nurse and cohort.

[b] Covariate-adjusted 1 model additionally adjusted for family history of breast cancer in nurses' mother or sister (yes/no; as reported by nurse), maternal smoking during pregnancy (no, yes <25 cigs/day, yes >=25 cigs/day).

[c] Covariate-adjusted 2 model includes variables in covariate-adjusted 1 as well as Nurse's age at menarche (<12, 12, 13, 14+ years), Nurses' adult height (quartiles), and Nurse's BMI at age 18 (<20, 20-<22.5, 22.5-<25, >=25).

* p-trend based on model with BMI as a continuous variable.

Table 5

Odds ratios (and 95% confidence intervals) for breast cancer by category of pre-pregnancy BMI, according to age at diagnosis and ER status of the tumor

Pre-pregnancy BMI	Age at diagnosis				ER status of tumor			
	Cases <50 years		Cases ≥ 50 years		ER+ Cases		ER- Cases	
BMI <20	149/486	1.00 (ref)	75/486	1.00 (ref)	111/486	1.00 (ref)	52/486	1.00 (ref)
BMI 20 -<22.5	191/666	0.93 (0.75–1.15)	90/666	0.90 (0.66–1.22)	164/666	1.06 (0.84–1.36)	44/666	0.60 (0.40–0.90)
BMI 22.5 -<25	102/292	1.09 (0.85–1.41)	54/292	1.10 (0.77–1.56)	82/292	1.18 (0.88–1.57)	28/292	0.84 (0.52–1.34)
BMI ≥ 25	32/112	0.94 (0.64–1.39)	20/112	1.15 (0.70–1.89)	26/112	1.01(0.66–1.56)	13/112	0.95 (0.51–1.77)
p-trend*		0.92		0.51		0.60		0.75

Odds ratios are adjusted for birth year of nurse, cohort, family history of breast cancer in nurses' mother or sister (yes/no; as reported by nurse), maternal smoking during pregnancy (no, yes <25 cigs/day, yes >=25 cigs/day).

*p-trend is the p-value from model using the midpoint of each weight gain category as a continuous variable.