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Pregnancy-related Characteristics and Breast Cancer Risk

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Abstract

Breast tissues undergo extensive physiologic changes during pregnancy, which may affect breast carcinogenesis. Gestational hypertension, pre-eclampsia/eclampsia, gestational diabetes, pregnancy weight gain, and nausea and vomiting (N&V) during pregnancy may be indicative of altered hormonal and metabolic profiles and could impact breast cancer risk. Here, we examined associations between these characteristics of a woman's pregnancy and her subsequent breast cancer risk. Participants were parous women that were recruited to a population-based case-control study (Western New York Exposures and Breast Cancer Study). Cases (n=960), aged 35-79 years, had incident, primary, histologically-confirmed breast cancer. Controls (n=1,852) were randomly selected from Motor Vehicle records (<65 years) or Medicare rolls (≥65 years). Women were queried on their lifetime pregnancy experiences. Multivariable-adjusted logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI). N&V during pregnancy was inversely associated with breast cancer risk. Relative to those who never experienced N&V, ever experiencing N&V was associated with decreased risk (OR 0.69, 95% CI: 0.56-0.84) as were increased N&V severity (P-trend<0.001), longer duration (P-trend<0.01), and larger proportion of affected pregnancies (P-trend<0.0001) among women with ≥3 pregnancies. Associations were stronger for more recent pregnancies (<5y). Findings did not differ by menopausal status or breast cancer subtype including estrogen receptor and HER2 expression status. Other pregnancy characteristics examined were not associated with risk. We observed strong inverse associations between pregnancy N&V and breast cancer risk. Replication of these findings and exploration of underlying mechanisms could provide important insight into breast cancer etiology and prevention.

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Conflict of interest statement
The authors declare no competing financial interests

Keywords

gestational hypertension; gestational diabetes; nausea; pre-eclampsia; pregnancy weight gain; vomiting

Introduction

Considerable evidence implicates reproductive factors in breast carcinogenesis [1-7]. It has long been recognized that parity and age at first pregnancy affect breast cancer risk [8] and that there is a transient increase in breast cancer risk following pregnancy [9]. There is increasing evidence that factors related to involution of the ducts in the breast in the period following a pregnancy account for the transient increase, at least in part [10-12]. There is less known about whether characteristics of the pregnancy itself also affect risk both in the short-term and in the longer term. Breast ductules undergo rapid changes with cellular and anatomical alterations, and differentiation, associated with substantial increases in steroid hormone exposures [13, 14]. Pregnancy characteristics may provide accessible proxy measures for changes in hormones during pregnancy, and may also be useful to characterize hormonal profiles that persist following pregnancy [15]. Exploration of associations between these characteristics and breast cancer risk has the potential to provide insight into breast carcinogenesis.

While studies of reproductive factors (e.g., age at first birth) are numerous, relatively few epidemiologic studies have examined the associations between characteristics during pregnancy, including pregnancy-induced hypertension, preeclampsia or eclampsia, gestational diabetes, pregnancy weight gain, or pregnancy-related nausea and vomiting (N&V) [15]. Findings from these studies are largely inconsistent. Differences between studies may be explained, in part, by differences in the molecular portraits of breast cancer under study; there is accumulating evidence that differences in etiology exist by breast cancer subtype [16]. Time since last pregnancy may also play a role in explaining these differences. To our knowledge, only one other study [17] has examined the association between pregnancy-related characteristics and breast cancer risk by time since last pregnancy, and none have examined associations with breast cancer by tumor molecular characteristics.

We report here results from our investigation into the associations between several pregnancy-related characteristics during pregnancy and breast cancer risk in a large, population-based case-control study of women living in western New York State. We examined associations for breast cancer overall, by menopausal status and time since pregnancy, as well as by breast cancer molecular subtypes defined by estrogen receptor (ER) and progesterone receptor (PR) and by human epidermal growth factor (HER)-2 receptor status.

Methods

The Western New York Exposures and Breast Cancer Study

Data utilized in this analysis were collected as part of a population-based case-control study of breast cancer, the Western New York Exposures and Breast Cancer (WEB) Study, which has been described in detail elsewhere [18, 19]. Briefly, women were eligible to participate if they were between the ages of 35 and 79 years, resided in Erie or Niagara counties, had no history of cancer other than non-melanoma skin cancer, and spoke English. Breast cancer cases were women with incident, primary, histologically-confirmed breast cancer who were diagnosed between 1996 and 2001. Nurse case-finders who visited pathology departments of

area hospitals identified potential cases. Patients' physicians were contacted to verify the diagnosis and to obtain permission to contact the cases. Once permission was granted, cases were interviewed within one year of diagnosis, with most cases being interviewed within 6 months (median 5.4 months). Controls were frequency matched to cases on age and race at a 2 to 1 ratio; those <65 years of age were randomly selected from the drivers' license list from the New York State Department of Motor Vehicles, while those ≥65 years of age were selected from the Health Care Financing Administration rolls. Seventy-two percent of eligible cases (n=1,170) and 63% of eligible controls (n=2,115) were interviewed.

For the current analysis, we restricted women to those who had at least one term pregnancy or live birth. Therefore we excluded 165 cases and 188 controls who were nulliparous, 41 cases and 65 controls who had an abortion or miscarriage, and 4 cases and 10 controls who were missing data on gravidity. Following these exclusions, a total of 960 cases and 1,852 controls that had given birth were available for analysis.

Written informed consent was obtained from all study participants. The study protocol was approved by the Institutional Review Boards of the University at Buffalo, Georgetown University Medical Center, The Ohio State University, and all participating hospitals.

Data collection

Self-administered questionnaires and in-person computer-assisted interviews were utilized to collect information on demographic, dietary, and anthropometric variables, and breast cancer risk factors, including information about reproductive history. Specifically, data on pregnancy history and menopause was collected via interview. Demographic, diet, and family history data were collected via self-administered questionnaire. Current body mass index (BMI, kg/m^2) was calculated from participants' measured height and weight for all women. BMI prior to first pregnancy was calculated from self-reported height and weight data. Participants were asked whether they had been diagnosed with gestational hypertension, eclampsia/preeclampsia/toxemia, and/or diabetes during at least one pregnancy. These three exposure variables were each classified as ever/never. Gestational hypertension and eclampsia/preeclampsia/toxemia were combined for analysis because gestational hypertension is regularly associated with incidence of pre-eclamptic conditions (as well as subsequent development of eclampsia and/or toxemia), and hypertension is typically used as a marker for diagnosis of preeclampsia.

Data regarding pregnancy weight gain and nausea and vomiting (N&V) were collected for each reported pregnancy across a woman's lifetime. Average weight gain during pregnancy was calculated by summing the overall reported amount of weight gained and dividing by the total number of pregnancies. If weight gain data were missing for a specific pregnancy, weight gain from the other pregnancies was used. For pregnancies in which women reported ever experiencing N&V, data regarding the severity and duration of N&V for each pregnancy were obtained. The severity of N&V was subjectively reported by the participant on a scale from 1 (minimal N&V) to 5 (extreme N&V). Duration of N&V was reported as lasting into the 1^{st}, 2^{nd}, or 3^{rd} trimester. We restricted analyses between the proportion of pregnancies in which N&V occurred and breast cancer risk to women who had ≥3 pregnancies.

Biological specimens

Paraffin-embedded breast cancer tumor blocks were available for 751 (78%) cases. ER and PR status was independently determined by a single pathologist using immunohistochemistry (IHC), as described by Allred et al. [20]. Briefly, positive hormone receptor status was assigned to tumors when the summed proportion score (ranging from 1

to 5) and staining intensity score (ranging from 1 to 3) was 3 or greater; a total score of 2 or less was labeled as negative. Similarly, HER2 expression for each sample was determined by a single pathologist using IHC. HER2 was scored using the guidelines of HerceptTest™. We classified tumors with scores 0-2+ (negative equivocal) as HER2-negative (HER2−) and tumors with a score of 3+ (strongly positive) as HER2-positive (HER2+).

For patients in whom ER status (n=179) or HER-2 status (n=84) could not be determined from tumor blocks (i.e., tumor tissue was unavailable or insufficient for staining purposes), these data were obtained from the participant's medical records. Agreement between both sources was good [21]. Data regarding ER and PR status were available for 864 (90.0%) and 876 (89.9%) of cases, respectively; HER-2 status was available for 617 (64.3%) cases.

Statistical analysis

All analyses were performed using SAS v9.2 (Cary, NC). Differences in continuous and categorical variables between cases and controls were determined using t-tests and chi-square tests, respectively. Age- and multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CI) for the association between pregnancy-related characteristics and breast cancer risk were calculated using unconditional logistic regression. Average pregnancy weight gain was categorized into quartiles, while average severity of N&V was categorized into never N&V and tertiles of severity based on their respective distributions among controls. Age at menopause was categorized as premenopausal, <45 years, 45-49 years, ≥50 years. Regression models were adjusted for age, education, history of benign breast disease, family history of breast cancer, age at first pregnancy, number of pregnancies, menopausal status and age at menopause. Other known breast cancer risk factors were assessed for confounding, including race, current or pre-pregnancy BMI, lifetime alcohol intake, energy intake, age at menarche, total months of breastfeeding, time since last pregnancy (among premenopausal women) and use of hormone replacement therapy (among postmenopausal women); however, these factors did not alter risk estimates and were not included in the final models.

We classified breast cancer cases into subtypes defined by ER and PR, and HER2. Associations between pregnancy-related characteristics and breast cancer characterized by subtype were performed using unordered polytomous logistic regression. *P*-values for trend (*P*-trend) were calculated by treating ordered categorical exposure variables as continuous in regression models. All statistical tests were two-sided, and a $P<0.05$ was considered statistically significant. Given the fixed sample size and alpha level, we had 90% power to detect an OR≤0.74 (≥1.35).

Given that first pregnancy represents a critical milestone that may have significant impact upon subsequent breast cancer risk, sub-analyses were performed to examine the effects of weight gain and N&V reported during first pregnancy.

We hypothesized *a priori* that the associations between pregnancy-related characteristics and breast cancer risk may be modified by BMI prior to first pregnancy, menopausal status, and time since last pregnancy. We performed stratified analyses for time since last pregnancy, classified as <5y, 5-10y, and >10y. Breast cancers diagnosed <5y since last pregnancy were considered to be pregnancy-associated (PABC). Because the last pregnancy occurred >10y before diagnosis or time of interview for the majority of postmenopausal women, we restricted the analysis to premenopausal women. *P*-values for interaction (*P*-interaction) were calculated by including a cross-product term for the exposure and the potential effect-modifier in multivariable models.

Results

Descriptive characteristics of breast cancer cases and controls, stratified by menopausal status, are shown in Table 1. The study population was predominantly Caucasian (91.3%) and generally well-educated. As expected, cases were more likely than controls to have a history of benign breast disease or a family history of breast cancer, with slightly greater proportions among pre-menopausal women. Pre- and post-menopausal women with breast cancer were less likely to have a history of N&V during pregnancy than controls.

Age- and multivariable-adjusted associations between pregnancy-related characteristics and overall breast cancer risk are shown in Table 2. Ever having experienced pregnancy-related N&V was associated with a 31% reduction in breast cancer risk (adjusted OR 0.69, 95% CI: 0.56-0.84). Relative to never N&V, the highest category of N&V severity (OR 0.64, 95% CI: 0.50-0.81), longest duration (OR 0.66, 95% CI: 0.52-0.84), and N&V for more than 75% of pregnancies (OR 0.62, 95% CI: 0.50-0.78) were inversely associated with breast cancer risk. There was a significant linear trend for all three measures of N&V. In examination of characteristics of N&V limited to those experiencing N&V however, the trend was not significant for severity and duration, but was for proportion of pregnancies ($P<0.001$). Because treatment for breast cancer could influence patients' recollection of N&V severity during pregnancy, we examined the association between N&V and breast cancer stratified on chemotherapy and radiation. Ever N&V did not differ by chemotherapy status (Yes: OR 0.63, 95% CI: 0.47-0.83; No: OR 0.73, 95% CI: 0.57-0.93; p-difference=0.77) or radiation therapy status (Yes: OR 0.62, 95% CI: 0.48-0.80; No: OR 0.77, 95% CI: 0.59-1.00; p-difference=0.15; data not shown). The remaining pregnancy-related characteristics: hypertension or preeclampsia, gestational diabetes, or greater weight gain during pregnancy were not associated with breast cancer risk. There were no differences in the associations between any pregnancy-related characteristic stratified on BMI prior to first pregnancy (data not shown). In addition, there were no differences in the associations for pregnancy weight gain or N&V when restricted to women's' 1st pregnancy (data not shown).

Associations between pregnancy-related characteristics and breast cancer stratified on menopausal status are shown in Table 3. The inverse associations observed for N&V, including N&V severity, duration, and proportion of affected pregnancies, were generally stronger for premenopausal women; however P-values for interaction did not achieve statistical significance. There were no differences between associations for pre- and post-menopausal breast cancer for the remaining pregnancy characteristics.

In an analysis restricted to premenopausal women, we stratified participants further into those who had a pregnancy <5y, 5-10y, and >10y prior to the index date to determine whether N&V was differentially associated with PABC (Table 4). For women with more recent pregnancies, ever N&V was more strongly associated with risk of PABC (OR 0.22, 95% CI: 0.07-0.70) than for those whose pregnancy was more than 10 years previously (OR 0.62, 95% CI: 0.37-1.04), although confidence intervals were wide and overlapped. The highest categories of severity, duration, and proportion of pregnancies affected by N&V were also more strongly associated with PABC than non-PABC (Table 4). Because proportion of affected pregnancies was restricted to women who had ≥3 pregnancies, there were few numbers in table cells. N&V was not associated with breast cancer among premenopausal women who had a pregnancy 5-10y prior.

Lastly, we examined the association between ever N&V and breast cancer characterized by ER and HER2 status (Table 5). Ever N&V was associated with similar reductions in both ER+ (OR 0.67, 95% CI: 0.53-0.85) and ER- tumors (OR 0.69, 95% CI: 0.50-0.95). Findings by PR status were similar (data not shown). The reduction in risk was statistically significant

for HER2-tumors but not HER2+ tumors; however there were few HER2+ cases. The remaining pregnancy characteristics did not differ by ER, PR, or HER2 status (data not shown).

Discussion

In this population-based case-control study of women living in Western New York, pregnancy-related N&V was associated with statistically significant reductions in breast cancer risk. There were no clear differences in the association by menopausal status or by breast cancer subtype; however, there was evidence that N&V during pregnancy may be more strongly associated with a reduction in the risk of pregnancy-associated breast cancers. The other pregnancy-related characteristics that were examined (pregnancy related hypertension-preeclampsia, weight gain, and gestational diabetes) were not associated with breast cancer risk. We did not find evidence that associations differed by breast cancer subtype.

In agreement with our findings, N&V occurs in about 70-80% of pregnancies [22]. It is thought to result from metabolic and hormonal factors, of both ovarian and placental origin [23]. However, there is no consensus on exactly which factor(s) may be causative. Several human studies have shown that N&V is associated with higher circulating levels of human chorionic gonadotropin (hCG) [24-27], while others have suggested that higher systemic concentrations of estradiol and progesterone may induce nausea [23, 28-30]; however associations are not consistent [22]. Serum hCG has been shown to have anti-cancer properties *in vitro* [31, 32] and *in vivo* [33], possibly due to differentiation of the terminal end buds in breast tissue [33]. There is also evidence from human studies that it may reduce the risk of breast cancer. Bernstein et al. [34], found that women who reported having received hCG injections for medical purposes were at decreased risk of breast cancer, particularly women with lower BMI. Consistent with this finding, Toniolo et al. [35], found that increased serum levels of hCG in pregnancy was inversely associated with subsequent breast cancer risk (tertile 3 vs. 1: OR 0.67, 95% CI: 0.46-0.99) in a recent nested case-control study of Swedish women.

The association between pregnancy-related N&V and maternal breast cancer risk has been examined in one cohort [36] and one population-based case-control study [17]. In a population-based case-control study of women under 45 years of age, Troisi et al. [17] found that ever having experienced pregnancy-associated N&V was associated with a statistically non-significant 9% reduction in breast cancer risk (OR 0.91, 95% CI: 0.77-1.10). The authors reported a borderline 13% reduction in risk for women with N&V during their first pregnancy (OR 0.87, 95% CI: 0.72-1.0) [17]. They also reported that the strongest reduction in risk was for women who experienced N&V in the first and second trimesters (OR 0.65, 95% CI: 0.47-0.91). In contrast to our findings, there were no differences when the analysis was stratified by time since last pregnancy (<5y and ≥5y) [17]. In the California Teachers Study investigating a large, prospective cohort of postmenopausal women, authors reported no association between breast cancer risk and ever vs. never N&V (RR=0.92, 95% CI: 0.84-1.02) or increasing number of pregnancies during which N&V occurred (*P*-trend=0.25) [36]. We found linear reductions in breast cancer risk associated with increasing severity and proportion of pregnancies affected by N&V; no prior study has examined these characteristics, to our knowledge.

There are two additional case-control studies, which have examined more extreme N&V, one limited to women reporting pharmacologic treatment of N&V [37] and the other to those with a clinical diagnosis of hyperemesis gravidarum [24]. Although there is some overlap in risk factors, N&V and hyperemesis gravidarum are different clinical entities [22].

In the former study, treatment for N&V was associated with a two-fold increase in breast cancer risk (OR 2.03, 95% CI: 1.05-3.92)[37]. It is unclear, however, if these findings are reflective of the treatment or the underlying indication. In the latter study, a clinical diagnosis of hyperemesis gravidarum was not associated with breast cancer risk (OR 1.05, 95% CI: 0.86-1.27)[24].

Women diagnosed with pre-eclampsia during pregnancy tend to have higher circulating levels of androgens [38] and lower concentrations of insulin-like growth factors (IGF) compared to women with normal pregnancy [39]. Several cohort studies have reported on the association between pregnancy-induced hypertension/preeclampsia and breast cancer risk [36, 40-46]. In a recent review, Nechuta et al. [15] concluded that pregnancy-induced hypertension/preeclampsia was associated with a 20-30% reduction in breast cancer risk. We did observe a reduction in premenopausal breast cancer of similar magnitude to that reported by Nechuta et al. [15]; however the confidence interval included the null.

There is evidence that type II diabetes is associated with a 10-20% excess risk of breast cancer [47]. By analogy, gestational diabetes, whose pathophysiological mechanisms include activation of the insulin and IGF-1 pathways as well as altered regulation of endogenous hormone pathways, may also predispose women to breast cancer [47]. In addition to the current study, authors of two population-based case-control studies [17, 48] and three registry-based cohort studies [49-51] have examined the association between gestational diabetes and maternal breast cancer risk. Among these, findings have been mixed. Our finding of no association is similar to findings in the population-based case-control study of women <45y conducted by Troisi et al. [17], and the prospective analysis from the Jerusalem Perinatal Study by Sella et al. [51]. Others have reported positive [49, 50] and inverse [48] associations with breast cancer risk. It is not clear what explains the differences in the findings.

The association between pregnancy weight gain and breast cancer is poorly understood and few have examined this association [38, 52-54]. Consistent with our findings, two population-based case-control studies [38, 54] and one nested case-control study [52], reported no association with overall breast cancer risk. In a small retrospective cohort of Finnish women including 123 cases, Kinnunen et al. [53], reported a statistically significant increase in breast cancer risk among women who gained >15kg (33lbs.) vs. 11-15kg (24-33lbs.) during pregnancy (OR 1.62, 95% CI: 1.03-2.53); however, when the highest category of weight gain (>15kg) was compared to the lowest (<11kg), there was no increase in risk. We further observed no differences in the association by menopausal status. Two studies were performed exclusively in premenopausal women [38, 54]. In the other two studies, no differences were reported by menopausal status [52, 53].

This study has several limitations that should be considered in the interpretation of our results. Foremost, pregnancy-related characteristics were self-reported and subject to error. Nevertheless, self-reported pregnancy complications have been shown to be reliable [55]; however data on the reliability of self-reported pregnancy characteristics, rather than severe complications [56], is sparse. As pregnancy-related characteristics were not expressed to participants as hypotheses under investigation, misclassification of exposure data is likely to be predominantly non-differential. We note that associations between established risk factors and breast cancer risk are observed in this study in similar direction and magnitude, which argues against a blanket recall bias. The significant associations we observed for N&V would not be explained by such error. Another possible limitation is that the reliability of recalled pregnancy complications may decrease over time [55]. Given that we observed significant reductions in breast cancer risk in both recent (<5y) and more distant (>10y) pregnancies, this error may have been minimal in our study. It is possible that recall of N&V

in particular may be influenced by or compared against that of breast cancer treatment amongst cases. In a sensitivity analysis, however, we observed no differences in associations after stratifying cases on chemotherapy or radiation treatment.

We were additionally limited by exposure data on pregnancy-induced hypertension and gestational diabetes. Whereas women were queried on N&V and weight gain for each individual pregnancy, women were queried regarding an ever diagnosis for hypertension/preeclampsia and gestational diabetes for any pregnancy.

Lastly, our classification of breast cancer subtypes based on ER, PR, and HER2 is a surrogate for a more comprehensive nomenclature determine by tumor marker expression [57]. Therefore the subtypes defined in this study may be misclassified. Because fluorescence *in situ* hybridization was not performed to validate tumors with an equivocal (i.e., 2+) HER2 score, and the agreement between IHC and medical records was good but not excellent [21], misclassification of HER2 status is possible. Further, our power for these analyses was limited; grouping of cases by subtypes meant that the number of participants for some of the groups was small.

Despite these limitations, this study has several strengths. This study is the first, to our knowledge, to examine the association between the severity and duration of N&V and breast cancer risk, and the first to examine the association between several pregnancy-related characteristics and risk of breast cancer characterized by ER, PR, and HER2 subtype. This study is also among the first to examine associations for several characteristics by menopausal status and by time since last pregnancy. An additional strength of this study is our comprehensive measurement of weight gain and N&V across a woman's entire reproductive history.

In summary, in this population-based study of women living in western New York State, we found that nausea and vomiting during pregnancy were inversely associated with breast cancer risk. Associations were stronger among women whose last pregnancies were fewer than five years prior to diagnosis. We observed no differences by breast cancer histopathological subtype. Understanding of the mechanism underlying the finding of decreased risk with pregnancy-related N&V could provide insight into breast carcinogenesis and prevention.

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Table 1

Characteristics of parous breast cancer cases and controls, stratified by menopausal status.

	Premenopausal		Postmenopausal	
Characteristic	**Cases n=267**	**Controls n=512**	**Cases n=693**	**Controls n=1,340**
	Mean (SD)		Mean (SD)	
Age, y	44.8 (4.6)	44.2 (4.6)	63.3 (8.3)	63.6 (8.7)
Education, y	13.8 (2.3)	14.1 (2.2)	13.1 (2.5)	12.9 (2.3)[a]
Current BMI, (kg/m^2)	27.3 (7.1)	27.3 (6.7)	29.1 (6.1)	28.6 (6.2)
Age at menarche, y	12.6 (1.5)	12.6 (1.6)	12.6 (1.6)	12.7 (1.7)[a]
Age at 1st pregnancy, y	24.0 (4.8)	24.8 (4.7)[a]	23.5 (4.5)	23.2 (4.2)
Age at menopause, y			48.3 (5.6)	47.6 (6.2)[a]
	N (%)		N (%)	
Race				
White	245 (91.8)	487 (95.1)	641 (92.5)	1,193 (89.0)[a]
Non-white	22 (8.2)	25 (4.9)	52 (7.5)	147 (11.0)
Family history of breast cancer				
No	188 (79.3)	443 (90.6)[d]	516 (79.8)	1,058 (86.0)[c]
Yes	49 (20.7)	46 (9.4)	131 (20.3)	172 (14.0)
Benign Breast Disease				
No	162 (61.8)	396 (78.0)[d]	446 (65.8)	1,033 (78.0)[d]
Yes	100 (38.2)	112 (22.1)	232 (34.2)	291 (22.0)
Number of pregnancies				
1-2	122 (45.7)	226 (44.1)	211 (30.5)	338 (25.2)[b]
3-5	135 (50.6)	261 (51.0)	390 (56.3)	749 (55.9)
≥6	10 (3.8)	25 (4.9)	92 (13.3)	253 (18.9)
Hypertension-preeclampsia				
Never	242 (90.6)	450 (87.9)	609 (87.9)	1,166 (87.0)
Ever	25 (9.4)	62 (12.1)	84 (12.1)	174 (13.0)
Gestational Diabetes				
Never	254 (95.1)	474 (92.9)	678 (97.8)	1,308 (97.8)
Ever	13 (4.9)	36 (7.1)	15 (2.2)	30 (2.2)
Pregnancy weight gain, lbs				
<20.0	32 (12.1)	68 (13.4)	145 (21.0)	285 (21.4)
20.0 to 27.4	67 (25.3)	135 (26.5)	207 (30.0)	425 (31.9)
27.5 to 36.4	78 (29.4)	150 (29.5)	175 (25.4)	329 (24.7)
≥36.5	88 (33.2)	156 (30.7)	163 (23.6)	294 (22.1)
Nausea and vomiting				
Never	62 (23.2)	85 (16.6)[a]	168 (24.2)	254 (19.0)[b]

	Premenopausal		Postmenopausal	
Characteristic	**Cases n=267**	**Controls n=512**	**Cases n=693**	**Controls n=1,340**
Ever	205 (76.8)	427 (83.4)	525 (75.8)	1,086 (81.0)

P-value for case-control differences in continuous and categorical variables calculated from t-tests and χ^2 tests, respectively.

[a] $P < 0.05$;

[b] $P < 0.01$;

[c] $P < 0.001$;

[d] $P < 0.0001$;

Table 2

Associations between pregnancv-related characteristics and breast cancer risk.

Pregnancy-related Characteristic	Cases, *n*=960 N (%)	Controls, *n*=1,852 N (%)	Age-adjusted OR (95% CI)	Multivariable-adjusted OR (95% CI)[1]
Hypertension-preeclampsia				
Never	851 (88.7)	1,616 (87.3)	1.00 reference	1.00 reference
Ever	109 (11.4)	236 (12.7)	0.88 (0.69-1.12)	0.94 (0.73-1.21)
Gestational Diabetes				
Never	932 (97.1)	1,782 (96.4)	1.00 reference	1.00 reference
Ever	28 (2.9)	66 (3.6)	0.81 (0.52-1.27)	0.79 (0.48-1.30)
Pregnancy weight gain, lbs				
<20.0	177 (18.5)	353 (19.2)	1.00 reference	1.00 reference
20.0 to 27.4	274 (28.7)	560 (30.4)	0.98 (0.77-1.23)	0.92 (0.72-1.17)
27.5 to 36.4	253 (26.5)	479 (26.0)	1.05 (0.83-1.34)	0.97 (0.76-1.25)
≥36.5	251 (26.3)	450 (24.4)	1.11 (0.88-1.41)	1.07 (0.83-1.37)
			P-trend = 0.26	*P*-trend = 0.45
Nausea and vomiting				
Never	230 (24.0)	339 (18.3)	1.00 reference	1.00 reference
Ever	730 (76.0)	1,513 (81.7)	0.71 (0.59-0.86)	0.69 (0.56-0.84)
Severity of nausea and vomiting[2]				
Never	230 (24.0)	339 (18.3)	1.00 reference	1.00 reference
>0 to <1.0	266 (27.7)	511 (27.6)	0.77 (0.61-.0.96)	0.75 (0.59-0.96)
1.1 to 2.9	229 (23.9)	498 (26.9)	0.68 (0.54-0.85)	0.67 (0.53-0.86)
≥3.0	235 (24.5)	504 (27.2)	0.69 (0.55-0.86)	0.64 (0.50-0.81)
			P-trend < 0.001	*P*-trend < 0.001
Duration of nausea and vomiting				
Never	230 (24.0)	339 (18.3)	1.00 reference	1.00 reference
1st trimester	507 (52.8)	1,002 (54.1)	0.75 (0.61-0.91)	0.70 (0.57-0.87)
2nd-3rd trimesters	223 (23.2)	511 (27.6)	0.64 (0.51-0.81)	0.66 (0.52-0.84)
			P-trend < 0.001	*P*-trend < 0.01
Proportion of pregnancies with nausea and vomiting, %[3]				
Never	134 (21.8)	206 (16.0)	1.00 reference	1.00 reference
>0 to 49	132 (21.1)	240 (18.6)	0.84 (0.62-1.14)	0.89 (0.64-1.23)
50 to 75	136 (21.7)	284 (22.1)	0.72 (0.53-0.98)	0.68 (0.49-0.94)
>75	225 (35.9)	558 (43.3)	0.62 (0.47-0.81)	0.61 (0.46-0.81)
			P-trend < 0.001	*P*-trend < 0.001

[1]Adjusted for age, education, history of benign breast disease, family history of breast cancer, age at first pregnancy, number of pregnancies, menopausal status and age at menopause (among postmenopausal women)

[2]Arbitrary units from subjective scale of severity ranging from 1 (minimal nausea) to 5 (severe nausea)

[3]Restricted to women who had ≥3 pregnancies

Table 3

Associations between pregnancy-related exposures and breast cancer risk, stratified on menopausal status.

Pregnancy-related Characteristic	Menopausal Status: Premenopausal Cases, *n*=267 N (%)	Premenopausal Controls, *n*=512 N (%)	Premenopausal Multivariable-adjusted OR (95% CI)[1]	Postmenopausal Cases, *n*=693 N (%)	Postmenopausal Controls, *n*=1,340 N (%)	Postmenopausal Multivariable-adjusted OR (95% CI)[1]	*P*-interaction
Hypertension-preeclampsia							
Never	242 (90.6)	450 (87.9)	1.00 reference	609 (87.9)	1,166 (87.0)	1.00 reference	0.40
Ever	25 (9.4)	62 (12.1)	0.78 (0.46-1.33)	84 (12.1)	174 (13.0)	1.00 (0.75-1.34)	
Gestational Diabetes							
Never	254 (95.1)	474 (92.9)	1.00 reference	678 (97.8)	1,308 (97.8)	1.00 reference	0.28
Ever	13 (4.9)	36 (7.1)	0.60 (0.29-1.27)	15 (2.2)	30 (2.2)	1.03 (0.52-2.05)	
Weight gain, lbs							
<20.0	32 (12.1)	68 (13.4)	1.00 reference	145 (21.0)	285 (21.4)	1.00 reference	0.38
20.0 to 27.4	67 (25.3)	135 (26.5)	0.93 (0.53-1.62)	207 (30.0)	425 (31.9)	0.92 (0.70-1.21)	
27.5 to 36.4	78 (29.4)	150 (29.5)	1.13 (0.66-1.96)	175 (25.4)	329 (24.7)	0.96 (0.72-1.28)	
≥36.5	88 (33.2)	156 (30.7)	1.30 (0.76-2.24)	163 (23.6)	294 (22.1)	1.03 (0.77-1.39)	
			P-trend = 0.15			*P*-trend = 0.73	
Nausea and vomiting							
Never	62 (23.2)	85 (16.6)	1.00 reference	168 (24.2)	254 (19.0)	1.00 reference	0.36
Ever	205 (76.8)	427 (83.4)	0.57 (0.38-0.85)	525 (75.8)	1,086 (81.0)	0.73 (0.58-0.93)	
Severity of nausea and vomiting[2]							
Never	62 (23.2)	85 (16.6)	1.00 reference	168 (24.2)	254 (19.0)	1.00 reference	0.38
>0 to ≤1.0	75 (28.1)	144 (28.1)	0.60 (0.37-0.96)	191 (27.6)	367 (27.4)	0.81 (0.61-1.07)	
1.1 to 2.9	65 (24.3)	129 (25.2)	0.65 (0.40-1.04)	164 (23.7)	369 (27.5)	0.68 (0.51-0.90)	
≥3.0	65 (24.3)	154 (30.1)	0.48 (0.30-0.77)	170 (24.5)	350 (26.1)	0.71 (0.54-0.95)	
			P-trend < 0.01			*P*-trend = 0.01	
Duration of nausea and vomiting							
Never	62 (23.2)	85 (16.6)	1.00 reference	168 (24.2)	254 (19.0)	1.00 reference	0.29
1st trimester	149 (55.8)	283 (55.3)	0.60 (0.39-0.91)	358 (51.7)	719 (53.7)	0.74 (0.58-0.94)	
2nd-3rd trimesters	56 (21.0)	144 (28.1)	0.51 (0.31-0.83)	167 (24.1)	367 (27.4)	0.73 (0.55-0.97)	

Pregnancy-related Characteristic	Menopausal Status: Premenopausal Cases, *n*=267 N (%)	Premenopausal Controls, *n*=512 N (%)	Premenopausal Multivariable-adjusted OR (95% CI)[1]	Postmenopausal Cases, *n*=693 N (%)	Postmenopausal Controls, *n*=1,340 N (%)	Postmenopausal Multivariable-adjusted OR (95% CI)[1]	*P*-interaction
			P-trend < 0.01			*P*-trend = 0.03	
Proportion of pregnancies with nausea and vomiting, %[3]							0.74
Never	26 (17.9)	35 (12.2)	1.00 reference	108 (22.4)	171 (17.1)	1.00 reference	
>0 to 49	26 (17.9)	48 (16.8)	0.66 (0.31-1.39)	106 (22.0)	192 (19.2)	0.95 (0.66-1.37)	
50 to 75	43 (29.7)	98 (34.3)	0.47 (0.24-0.92)	93 (19.3)	186 (18.6)	0.77 (0.53-1.11)	
>75	50 (34.5)	105 (36.7)	0.49 (0.26-0.94)	175 (36.3)	453 (45.2)	0.63 (0.46-0.86)	
			P-trend = 0.03			*P*-trend < 0.01	

[1]Adjusted for age, education, history of benign breast disease, family history of breast cancer, age at first pregnancy, number of pregnancies, menopausal status and age at menopause (among postmenopausal women)

[2]Arbitrary units from subjective scale of severity ranging from 1 (minimal nausea) to 5 (severe nausea)

[3]Restricted to women who had ≥3 pregnancies

Table 4

Associations between pregnancy-related nausea and vomiting and breast cancer risk among premenopausal women, stratified on time since last pregnancy.

	Time since last pregnancy									*p*-interaction
	< 5years			5-10 years			> 10years			
Pregnancy-related Characteristic	**Cases, *n*=36 N (%)**	**Controls, n=60 N (%)**	**Multivariable-adjusted OR (95% CI)[2]**	**Cases, *n*=44 N (%)**	**Controls, *n*=95 N (%)**	**Multivariable-adjusted OR (95% CI)[2]**	**Cases, *n*=176 N (%)**	**Controls, *n*=329 N (%)**	**Multivariable-adjusted OR (95% CI)[2]**	
Nausea and vomiting										
Never	12 (33.3)	8 (13.3)	1.00 reference	8 (18.2)	18 (19.0)	1.00 reference	38 (21.6)	55 (16.7)	1.00 reference	0.14
Ever	24 (66.7)	52 (86.7)	0.22 (0.07-0.70)	36 (81.8)	77 (81.1)	1.11 (0.39-3.13)	138 (78.4)	274 (83.3)	0.62 (0.37-1.04)	
Severity of nausea and vomiting[3]										
Never	12 (33.3)	8 (13.3)	1.00 reference	8 (18.2)	18 (19.0)	1.00 reference	38 (21.6)	55 (16.7)	1.00 reference	0.08
>0 to ≥1.0	14 (38.9)	16 (26.7)	0.36 (0.09-1.44)	7 (15.9)	30 (31.6)	0.62 (0.18-2.19)	49 (27.8)	88 (26.8)	0.69 (0.38-1.26)	
>1.0	10 (27.8)	36 (60.0)	0.16 (0.04-0.58)	29 (65.9)	47 (49.5)	1.48 (0.50-4.40)	89 (50.6)	186 (56.5)	0.59 (0.35-1.02)	
			P-trend < 0.01			*P*-trend = 0.26			*P*-trend = 0.06	
Duration of nausea and vomiting										
Never	12 (33.3)	8 (13.3)	1.00 reference	8 (18.2)	18 (19.0)	1.00 reference	38 (21.6)	55 (16.7)	1.00 reference	0.06
1st trimester	21 (58.3)	32 (53.3)	0.29 (0.09-1.00)	22 (50.0)	47 (49.5)	1.35 (0.41-4.46)	101 (57.4)	188 (57.1)	0.65 (0.38-1.11)	
2^{nd}-3^{rd} trimesters	3 (8.3)	20 (33.3)	0.11 (0.02-0.54)	14 (31.8)	30 (31.6)	1.09 (0.96-1.24)	37 (21.0)	86 (26.1)	0.56 (0.30-1.05)	
			P-trend < 0.01			*P*-trend = 0.58			*P*-trend = 0.08	
Proportion of pregnancies, %[4]										
Never	7 (30.4)	5 (11.4)	1.00 reference	3 (11.1)	8 (12.7)	1.00 reference	14 (15.7)	20 (12.2)	1.00 reference	0.01
>0 to 49	7 (30.4)	5 (11.4)	0.87 (0.12-6.31)	5 (18.5)	15 (23.8)	1.21 (0.17-8.48)	13 (14.6)	26 (15.9)	0.66 (0.23-1.85)	
50 to 75	7 (30.4)	14 (31.8)	0.13 (0.02-0.91)	11 (40.7)	23 (36.5)	1.65 (0.30-8.98)	23 (25.8)	55 (33.5)	0.46 (0.18-1.13)	
>75	2 (8.7)	20 (45.5)	0.05 (<0.01-0.38)	8 (29.6)	17 (27.0)	0.80 (0.14-4.63)	39 (43.8)	63 (38.4)	0.70 (0.30-1.66)	
			P-trend < 0.01			*P*-trend = 0.80			*P*-trend = 0.53	

[1] Excludes 5-10 year category

[2]Adjusted for age, education, history of benign breast disease, family history of breast cancer, age at first pregnancy, number of pregnancies, menopausal status and age at menopause (among postmenopausal women)

[3]Arbitrary units from subjective scale of severity ranging from 1 (minimal nausea) to 5 (severe nausea)

[4]Restricted to women who had ≥3 pregnancies

Table 5

Association between pregnancy-related nausea and vomiting and risk of breast cancer defined by histonathological subtype.

	Nausea and vomiting, OR (95% CI)[1,2]	
Histopathological subtype	**Never**	**Ever**
Sex hormone receptor status		
ER+	1.00 reference	0.67 (0.53-0.85)
n cases	150	456
ER−	1.00 reference	0.69 (0.50-0.95)
n cases	64	206
HER2 status		
HER2+	1.00 reference	0.86 (0.42-1.76)
n cases	11	46
HER2−	1.00 reference	0.68 (0.54-0.87)
n cases	137	423

[1] Adjusted for age, education, history of benign breast disease, family history of breast cancer, age at first pregnancy, number of pregnancies, menopausal status and age at menopause (among postmenopausal women)

[2] All case comparisons versus controls: never N&V, n=339; ever N&V, n=1,513