Gestational Hypertensive Disorders and Maternal Breast Cancer Risk in a Nationwide Cohort of 40,720 Parous Women

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Background: Preeclampsia and gestational hypertension are hypothesized to be associated with reduced maternal breast cancer risk, but the epidemiologic evidence is inconclusive. Our objective was to examine associations between gestational hypertensive disorders and breast cancer in a nationwide cohort of women with a family history of breast cancer.

Methods: Women ages 35–74 years who had a sister previously diagnosed with breast cancer, but had never had breast cancer themselves, were enrolled in the Sister Study from 2003 to 2009 (N = 50,884). At enrollment, participants reported diagnoses of eclampsia, preeclampsia, or gestational hypertension in each pregnancy. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between history of a gestational hypertensive disorder and incident invasive breast cancer or ductal carcinoma in situ among 40,720 parous women. We used age as the time scale and adjusted for birth cohort, race–ethnicity, and reproductive, socioeconomic, and behavioral factors. We examined effect measure modification by risk factors for gestational hypertensive disease and breast cancer and assessed possible etiologic heterogeneity across tumor characteristics.

Results: The prevalence of gestational hypertensive disease was 12%. During follow-up (mean = 10.9 years), 3,198 eligible women self-reported a breast cancer diagnosis. History of a gestational hypertensive disorder was not associated with breast cancer risk (HR = 1.0; 95% CI = 0.90, 1.1). We did not observe clear evidence of effect measure modification or etiologic heterogeneity.

Conclusions: History of a gestational hypertensive disorder was not associated with breast cancer risk in a cohort of women with a first-degree family history of breast cancer.

Key words: Breast cancer; Eclampsia; Gestational hypertension; Preeclampsia

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Gestational hypertensive disorders affect approximately 6%–7% of US pregnancies.[1–4] These disorders include gestational hypertension (new-onset high blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic after 20 weeks gestation), preeclampsia (hypertension plus proteinuria or other features of maternal organ dysfunction), and eclampsia (preeclampsia plus seizures with no other known cause).[5] Gestational hypertensive disorders are associated with adverse maternal and perinatal outcomes[6] and long-term increased risks of maternal cardiovascular diseases,[7] but are hypothesized to reduce maternal breast cancer risk, potentially through hormonal or anti-angiogenic pathways.[8]

The epidemiologic evidence for this hypothesis is inconsistent. Almost 30 years ago, Polednak and Janerich[9] reported a reduced risk of breast cancer in women with a history of preeclampsia in a small case–control study. This association was replicated in several case–control studies,[10–13] while others observed a null[14] or positive[15] association. Longitudinal studies using registry linkages[16–27] or prospective cohort data[23,28–32] also yielded conflicting findings. While there was heterogeneity between studies, a recent meta-analysis observed a decreased risk of breast cancer associated with preeclampsia (risk ratio = 0.88; 95% confidence interval [CI] = 0.83, 0.93) based on high-quality cohort studies (assessed using the Newcastle-Ottawa Scale).[33] Prior meta-analyses were inconclusive and did not indicate overall reductions in breast cancer risk associated with preeclampsia or gestational hypertension.[34–36] Age at birth,[12,13] time since birth,[11,13,21,24,37] parity,[19,24] offspring sex,[12,13,18,19,24,29,38,39] preterm delivery,[12,18,19] race–ethnicity,[22,32]

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De-identified data is available upon request (for more information, see https://sisterstudy.niehs.nih.gov/English/data-requests.htm). The data sharing policy was developed to protect the privacy of participants and is consistent with informed consent documents. Analysis code is available upon request.

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menopausal status,[12,15,29,37] tumor invasiveness,[28,29] and tumor subtype[29,37] have been examined as potential modifiers, but the association has not consistently differed by any of these factors.

We hypothesized that conflicting findings across studies may reflect differences in the distribution of factors that modify the association between gestational hypertensive disorders and breast cancer risk. We took advantage of rich covariate data collected in the Sister Study to examine associations of gestational hypertensive disorders with incident breast cancer and to explore associations within strata of potential modifiers, including demographic, reproductive, and breast cancer characteristics.

METHODS

Study Population

From 2003 to 2009, 50,884 women enrolled in the Sister Study (for more details, see Sandler et al[40]). Women were eligible if they lived in a US state or Puerto Rico, were between the ages of 35–74 years, and had a sister previously diagnosed with breast cancer but had never had breast cancer themselves.

Women provided information on demographics, lifestyle factors, and reproductive, medical, and family cancer history in baseline telephone interviews and self-administered questionnaires. Women are followed prospectively with annual health updates and more comprehensive questionnaires every 2–3 years. Approximately 85% of the cohort completed the most recent follow-up activity. Follow-up questionnaires asked about postenrollment pregnancies but did not obtain related information on complications such as hypertensive disorders. Less than 1% of women reported a birth after enrollment. This analysis utilized Sister Study Data Release 9.1, including follow-up data up to 30 September 2019.

Participants provided written informed consent. The institutional review board of the National Institutes of Health approved the study.

Incident Breast Cancer

Women self-reported breast cancer diagnoses during follow-up. We requested permission to obtain medical records, including pathology reports, for cancer confirmation. Medical records have been obtained for >80% of women who self-reported breast cancer. Agreement between self-reports and medical records has been high (positive predictive value >99%),[41] so we used self-reports when medical records were not available. Our primary outcome was incident breast cancer (invasive or ductal carcinoma in situ [DCIS]).

Reproductive History, Including Gestational Hypertensive Disorders, at Baseline

Women reported the outcome and duration of each pregnancy, and their ages at the start and end of each. For all pregnancies lasting at least 20 weeks, participants were asked if they had (1) preeclampsia or toxemia; (2) eclampsia; and/or (3) pregnancy-related high blood pressure or borderline high blood pressure. We categorized women as having a history of a gestational hypertensive disorder if they reported that they had preeclampsia, eclampsia, or pregnancy-related high blood pressure in at least one pregnancy. Women who reported borderline pregnancy-related high blood pressure only were not considered to have had a gestational hypertensive disorder. We also examined women with preeclampsia or eclampsia separately from women with gestational hypertension only. We examined age at first diagnosis (<25 years or ≥25 years), age at most recent diagnosis (<30 years or ≥30 years), and time between most recent diagnosis and enrollment (<20 years or ≥20 years) among women with a gestational hypertensive disorder, compared with the referent group with no gestational hypertensive disease. We examined the number of pregnancies with a gestational hypertensive disorder (≥2, 1, or none). We also separately examined a diagnosis of a gestational hypertensive disorder in the first and the most recent pregnancy. Primiparous women are at an increased risk of developing preeclampsia,[42] and the first full-term pregnancy has a greater impact on breast cell differentiation than subsequent pregnancies.[43] Women who experience preeclampsia in the first pregnancy may choose not to have a subsequent pregnancy; analyses of first births only minimize the potential impact of selective fertility. We examined the most recent pregnancy since breast cancer risk varies by time since birth.[44]

Covariates

We categorized participants' birth years in approximate 10-year intervals (1928–1939, 1940–1949, 1950–1959, and 1960–1974). We asked women to self-identify their race as American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, and/or White. Women reported if they considered their ethnicity to be Hispanic or Latina. When adjusting associations of gestational hypertensive disorders with incident breast cancer for race–ethnicity, we categorized women as non-Hispanic White, non-Hispanic African American/Black, Hispanic/Latina, and other race–ethnicity, which included women who identified as non-Hispanic and either Asian/Pacific Islander, American Indian/Alaskan native, or with no specified race, due to the very low numbers of women in these groups. Women reported their highest level of education completed at baseline, which we categorized as high school equivalent or less, some college, associate or technical degree, and bachelor's degree or higher. We categorized parity (total number of live or still births) as 1, 2, 3, and ≥4 and age at first birth as <20, 20–24, 25–29, and ≥30 years. We categorized women as ever smokers before first pregnancy based on their reports of age when they first started smoking (at least one cigarette per month for a year or longer) and age at first birth. We categorized age at menarche as <12, 12–13, and ≥14 years. We included weight relative to peers in the teens (lighter, same, heavier) and average hours of physical activity per week in

childhood/teens (<1 hour/week, 1 to <7 hours/week, and ≥7 hours/week) as proxy measures of prepregnancy body size since we did not collect data on prepregnancy weight. We considered body mass index (BMI) calculated using self-reported weight in the 30s (<25, 25–29.9, or ≥30 kg/m^2) as an alternate proxy for prepregnancy BMI.

Analytic Sample

From the study population of 50,884 women, we excluded three women who withdrew their data, 94 women diagnosed with breast cancer before, at the same age as, or at unknown timing relative to the completion of all baseline study components and five women with uncertain breast cancer diagnoses (eFigure 1; http://links.lww.com/EDE/B939). We excluded 291 women without prospective follow-up data. We additionally excluded 9,136 nulliparous women and 35 women missing parity data. Last, we excluded women with missing data on covariates (N = 377) or gestational hypertensive disorders (N = 223). The final analytic sample included 40,720 parous women.

Statistical Analysis

We examined the distributions of participant characteristics by history of a gestational hypertensive disorder. We used Cox proportional hazards regression with age as the time scale to estimate hazard ratios (HRs) and 95% CIs for the associations between gestational hypertensive disorders and incident breast cancer. Women accrued person–time from age at enrollment until age at breast cancer diagnosis, last follow-up, loss to follow-up, or death. We tested for violations of the proportional hazard assumption using Wald tests of exposure-by-time interaction terms. There were some violations of the proportionality assumption in secondary analyses (noted in table footnotes). We examined age-adjusted and multivariable-adjusted models, with the latter including race–ethnicity, birth cohort, education, parity, age at first birth, smoking before pregnancy, relative weight in the teens, and physical activity in adolescence.

In sensitivity analyses, we considered women with a history of borderline gestational hypertension only as exposed. We conducted analyses excluding women who reported a diagnosis of chronic hypertension before first pregnancy, women who reported a diagnosis of diabetes before first pregnancy, or women with any multiple gestation pregnancy. We alternatively adjusted for BMI in the 30s instead of relative weight and physical activity in the teens.

We considered effect measure modification by time-varying menopausal status and tested for statistical heterogeneity using the Wald test. We calculated effect estimates and tested for statistical heterogeneity by estrogen receptor (ER) status and invasiveness using fully adjusted joint Cox models stratified by type.[45] For ER status, we included invasive and ductal carcinoma in situ (DCIS) cases and censored women with the alternative subtype or missing subtype information at age at diagnosis. For models examining invasive and DCIS disease separately, women with the alternate type or missing invasiveness information were censored at age at diagnosis.

We stratified adjusted models by race–ethnicity, participants' birth cohort, prenatal exposure to a gestational hypertensive disorder, familial risk of breast cancer, relative weight in the teens, parity, age at first birth, time since most recent birth, and history of gestational diabetes, and tested for statistical heterogeneity using the Wald test. For analyses by race–ethnicity, we only included women who identified as non-Hispanic White, non-Hispanic African American/Black, and Hispanic/Latina due to small numbers in other groups. Women who reported a diagnosis of gestational diabetes in at least one pregnancy were considered to have a history of gestational diabetes. We considered women who reported at baseline that their mother had pregnancy-related high blood pressure, preeclampsia, or eclampsia during their own gestation as having prenatal exposure to a gestational hypertensive disorder. We conducted post hoc analyses among women exposed in utero examining preeclampsia or eclampsia separately from gestational hypertension only. We assessed familial risk using the lifetime risk (from birth to age 80) of developing breast cancer estimated by the family history-based Breast Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) risk prediction model, version 5.[46] While this version can account for a polygenic risk score and nongenetic risk factors, these were not included as input variables. We dichotomized the score using a cutoff of 20% to define high familial risk, a threshold used in clinical guidelines.[47] We excluded women who reported at enrollment that they were adopted (n = 162) and women with insufficient data to estimate a BOADICEA score (n = 355) from familial risk analyses.

In analyses limited to the first or the most recent birth, we stratified by type of gestation (single or multiple), gestational length (preterm defined as <37 complete weeks gestation), and offspring sex. We restricted analyses of offspring sex and gestational length to singleton gestations. We also stratified by age at birth and time since birth.

We used robust variance estimates to account for within-family clustering. We conducted all analyses using SAS 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Approximately 12% of eligible, parous women reported a gestational hypertensive disorder in at least one pregnancy. Women with gestational hypertensive disorders were slightly younger at baseline and at first birth, and a higher proportion identified as non-Hispanic African American/Black, had ≥4 births, were heavier than their peers in adolescence, had a history of gestational diabetes, and reported that their mother had a gestational hypertensive disorder during their own gestation (Table 1).

Over an average of 10.9 years of follow-up, 3,198 women self-reported a breast cancer diagnosis. History of

TABLE 1. Participant Characteristics by History of a Gestational Hypertensive Disorder in 40,720 Parous Women Enrolled in the Sister Study Cohort

Characteristic	History of a Gestational Hypertensive Disorder: Yes, N = 4,841, n (%)	History of a Gestational Hypertensive Disorder: No, N = 35,879, n (%)
Age at baseline, years, mean (SD)	55.0 (9.1)	56.2 (9.0)
BOADICEA lifetime risk score, percent, mean (SD)	19.3 (5.4)	19.2 (5.2)
Birth cohort		
1928–1939	561 (12)	4,741 (13)
1940–1949	1,391 (29)	12,203 (34)
1950–1959	1,887 (39)	12,838 (36)
1960–1974	1,002 (21)	6,097 (17)
Race–ethnicity		
Non-Hispanic White	3,833 (79)	30,261 (84)
Non-Hispanic African American/Black	549 (11)	2,953 (8)
Hispanic/Latina	310 (6)	1,727 (5)
Non-Hispanic Asian, Native Hawaiian or other Pacific Islander	16 (<1)	240 (<1)
Non-Hispanic American Indian or Alaskan native	16 (<1)	68 (<1)
Non-Hispanic race not specified	117 (2)	630 (2)
Education at baseline		
High school equivalent or less	890 (18)	5,955 (17)
Some college, associate or technical degree	1,876 (39)	12,648 (35)
Bachelor's degree or higher	2,075 (43)	17,276 (48)
Parity (number of births[a])		
1	786 (16)	6,393 (18)
2	2,064 (43)	16,247 (45)
3	1,233 (25)	8,769 (24)
≥4	758 (16)	4,470 (13)
Age at first birth[a], years		
<20	924 (19)	5,636 (16)
20–24	1,859 (38)	13,697 (38)
25–29	1,214 (25)	10,118 (28)
≥30	844 (17)	6,428 (18)
Ever smoked before first birth		
Yes	1,781 (37)	13,599 (38)
No	3,060 (63)	22,280 (62)
Weight relative to peers in teens		
Lighter	1,568 (32)	12,895 (36)
Same	2,192 (45)	17,091 (48)
Heavier	1,081 (22)	5,893 (16)
Hours of physical activity per week in childhood/teens[b]		
<1 hour/week	3,104 (64)	24,575 (68)
1 to <7 hours/week	1,512 (31)	10,216 (28)
≥7 hours/week	225 (5)	1,088 (3)
Age at menarche, years		
<12 years	1,217 (25)	7,039 (20)
12–13 years	2,600 (54)	20,186 (56)
≥14 years	1,024 (21)	8,654 (24)
History of gestational diabetes		
Yes	416 (9)	1,292 (4)
No	4,388 (91)	34,536 (96)
Missing	37	51
Prenatal exposure to a maternal gestational hypertensive disorder		
Yes	341 (10)	1,020 (4)
No	2,994 (90)	25,922 (96)
Missing	1,506	8,937

Column percentages are displayed. Percentages may not add up to 100 due to rounding.
[a]Includes live and still births.
[b]Average hours of physical activity per week over ages 5–19 years.

a gestational hypertensive disorder was not associated with breast cancer risk (multivariable-adjusted HR = 1.0; 95% CI = 0.90, 1.1) (Table 2). Neither preeclampsia or eclampsia (HR = 1.0; 95% CI = 0.88, 1.1) nor gestational hypertension (HR = 1.0; 95% CI = 0.83, 1.2) was associated with breast cancer risk. Analyses considering age at first or most recent diagnosis, time since most recent diagnosis, or gestational hypertensive disease in the first or most recent birth similarly yielded null results. Having two or more pregnancies complicated with a gestational hypertensive disorder was not associated with risk (HR = 0.95; 95% CI = 0.74, 1.2).

Results were similarly null in sensitivity analyses including women with borderline gestational hypertension in the exposed group or excluding women with preexisting hypertension before pregnancy, nongestational diabetes before pregnancy, or women with a multifetal gestation (eTable 1; http://links.lww.com/EDE/B939). Associations were similar when we controlled for BMI in the 30s instead of relative weight and physical activity in the teens.

The association of gestational hypertensive disease with premenopausal breast cancer risk was inverse but imprecise (HR = 0.85; 95% CI = 0.64, 1.1), while there was no association with postmenopausal cancer (HR = 1.0; 95% CI = 0.92, 1.2) (Table 3). The inverse association for premenopausal cancer was further from the null if the most recent diagnosis of gestational hypertensive disease

TABLE 2. Associations Between History of a Gestational Hypertensive Disorder and Incident Breast Cancer (Invasive or DCIS) in 40,720 Parous Women Enrolled in the Sister Study

Exposure Construct	Person-years	N Noncases	N cases	Age-adjusted HR (95% CI)	Multivariable-adjusted[a] HR (95% CI)
History of a gestational hypertensive disorder[b]					
Any	51,688	4,479	362	0.99 (0.89, 1.1)	1.0 (0.90, 1.1)
None	391,034	33,043	2,836	1 (Reference)	1 (Reference)
History of eclampsia or preeclampsia or gestational hypertension[c]					
Any eclampsia or preeclampsia	37,146	3,201	261	0.99 (0.87, 1.1)	1.0 (0.88, 1.1)
Any gestational hypertension without eclampsia or preeclampsia	14,314	1,258	100	1.0 (0.82, 1.2)	1.0 (0.83, 1.2)
None	391,034	33,043	2,836	1 (Reference)	1 (Reference)
Age at first diagnosis of a gestational hypertensive disorder[b,d]					
<25 years old	22,624	1,987	158	0.95 (0.81, 1.1)	0.99 (0.84, 1.2)
≥25 years old	29,063	2,491	204	1.0 (0.89, 1.2)	1.0 (0.88, 1.2)
No gestational hypertensive disorder	391,034	33,043	2,836	1 (Reference)	1 (Reference)
Age at most recent diagnosis of a gestational hypertensive disorder[b]					
<30 years old	34,117	2,961	243	0.99 (0.87, 1.1)	1.0 (0.90, 1.2)
≥30 years old	17,571	1,518	119	0.99 (0.83, 1.2)	0.96 (0.79, 1.2)
No gestational hypertensive disorder	391,034	33,043	2,836	1 (Reference)	1 (Reference)
Time since most recent diagnosis of a gestational hypertensive disorder[b,e]					
<20 years	14,063	1,214	87	1.0 (0.84, 1.3)	1.0 (0.81, 1.3)
≥20 years	37,625	3,265	275	0.97 (0.86, 1.1)	1.0 (0.88, 1.1)
No gestational hypertensive disorder	391,034	33,043	2,836	1 (Reference)	1 (Reference)
Number of pregnancies with a gestational hypertensive disorder[b]					
2 or more	9,445	842	62	0.93 (0.72, 1.2)	0.95 (0.74, 1.2)
1	42,243	3,637	300	1.0 (0.89, 1.1)	1.0 (0.90, 1.1)
0	391,034	33,043	2,836	1 (Reference)	1 (Reference)
History of a gestational hypertensive disorder in first pregnancy resulting in live or still birth[b,f]					
Any	36,247	3,120	255	1.0 (0.88, 1.1)	1.0 (0.89, 1.2)
None	406,279	34,384	2,943	1 (Reference)	1 (Reference)
History of a gestational hypertensive disorder in most recent pregnancy resulting in live or still birth[b,g]					
Any	27,390	2,401	192	1.0 (0.87, 1.2)	1.0 (0.86, 1.2)
None	415,172	35,108	3,004	1 (Reference)	1 (Reference)

[a]Multivariable model is adjusted for birth cohort (1928–1939, 1940–1949, 1950–1959, 1960–1974), race–ethnicity (non-Hispanic White, non-Hispanic African American/Black, Hispanic/Latina, other race–ethnicity), parity (1, 2, 3, ≥4), age at first birth (<20, 20–24, 25–29, ≥30), participant's education at baseline (high school equivalent or less, some college, college degree or more), relative weight in the teens (lighter than peers, same as peers, heavier than peers), average hours per week of physical activity in childhood/teens (<1, 1 to <7, ≥7), age at menarche (<12, 12–13, ≥14 years), and ever smoked before first birth (yes, no).

[b]History of a gestational hypertensive disorder includes a report of eclampsia, preeclampsia, and/or gestational hypertension in at least one pregnancy.

[c]Excludes 21 women where type of gestational hypertensive disorder could not be determined.

[d]Excludes one woman missing age at first diagnosis of gestational hypertensive disorder.

[e]Proportional hazards assumption violated ($P = 0.03$).

[f]Multivariable model does not include parity. Excludes 18 women missing history of gestational hypertension in first birth.

[g]Excludes 15 women missing history of gestational hypertension in most recent birth.

TABLE 3. Associations Between History of a Gestational Hypertensive Disorder and Incident Breast Cancer (Invasive or DCIS) by Menopausal Status at Diagnosis in 40,720 Parous Women Enrolled in the Sister Study

	Premenopausal		Postmenopausal		
		Multivariable-adjusted[a]		Multivariable-adjusted[a]	
Exposure Construct	**N Cases**	**HR (95% CI)**	**N Cases**	**HR (95% CI)**	***P* for Heterogeneity**
History of a gestational hypertensive disorder[b,c]					0.18
Any	56	0.85 (0.64, 1.1)	306	1.0 (0.92, 1.2)	
None	447	1 (Reference)	2,389	1 (Reference)	
History of eclampsia or preeclampsia or gestational hypertension[d]					0.28
Any eclampsia or preeclampsia	41	0.91 (0.66, 1.3)	220	1.0 (0.89, 1.2)	
Any gestational hypertension without eclampsia or preeclampsia	15	0.72 (0.43, 1.2)	85	1.1 (0.88, 1.4)	
None	447	1 (Reference)	2,389	1 (Reference)	
Age at first diagnosis of a gestational hypertensive disorder[b,e]					0.28
<25 years old	12	0.66 (0.37, 1.2)	146	1.0 (0.87, 1.2)	
≥25 years old	44	0.92 (0.67, 1.3)	160	1.0 (0.88, 1.2)	
No gestational hypertensive disorder	447	1 (Reference)	2,389	1 (Reference)	
Age at most recent diagnosis of a gestational hypertensive disorder					0.29
<30 years old	28	0.77 (0.52, 1.1)	215	1.1 (0.93, 1.2)	
≥30 years old	28	0.94 (0.63, 1.4)	91	0.97 (0.78, 1.2)	
No gestational hypertensive disorder	447	1 (Reference)	2,389	1 (Reference)	
Time since most recent diagnosis of a gestational hypertensive disorder[b]					0.10
<20 years	45	0.98 (0.72, 1.3)	42	1.0 (0.75, 1.4)	
≥20 years	11	0.54 (0.29, 0.98)	264	1.0 (0.91, 1.2)	
No gestational hypertensive disorder	447	1 (Reference)	2,389	1 (Reference)	
Number of pregnancies with a gestational hypertensive disorder[b]					0.36
2 or more	8	0.69 (0.34, 1.4)	54	1.0 (0.77, 1.3)	
1	48	0.88 (0.65, 1.2)	252	1.0 (0.91, 1.2)	
0	447	1 (Reference)	2,389	1 (Reference)	
History of gestational hypertensive disorder in first pregnancy resulting in live or still birth[b,f]					0.06
Any	38	0.76 (0.54, 1.1)	217	1.1 (0.93, 1.2)	
None	465	1 (Reference)	2,478	1 (Reference)	
History of gestational hypertensive disorder in most recent pregnancy resulting in live or still birth[b,g]					0.43
Any	33	0.88 (0.62, 1.3)	159	1.0 (0.87, 1.2)	
None	470	1 (Reference)	2,534	1 (Reference)	

[a]Multivariable model is adjusted for birth cohort (1928–1939, 1940–1949, 1950–1959, 1960–1974), race–ethnicity (non-Hispanic White, non-Hispanic African American/Black, Hispanic/Latina, other race–ethnicity), parity (1, 2, 3, ≥4), age at first birth (<20, 20–24, 25–29, ≥30), participant's education at baseline (high school equivalent or less, some college, college degree or more), relative weight in the teens (lighter than peers, same as peers, heavier than peers), average hours per week of physical activity in childhood/teens (<1, 1 to <7, ≥7), age at menarche (<12, 12–13, ≥14 years), and ever smoked before first birth (yes, no).
[b]History of a gestational hypertensive disorder includes a report of eclampsia, preeclampsia, and/or gestational hypertension in at least one pregnancy.
[c]Proportionality assumption violated in strata of premenopausal women ($P = 0.04$).
[d]Excludes 21 women where type of gestational hypertensive disorder could not be determined.
[e]Excludes one woman missing age at first diagnosis of gestational hypertensive disorder.
[f]Multivariable model does not include parity. Excludes 18 women missing history of gestational hypertension in first birth.
[g]Excludes 15 women missing history of gestational hypertension in most recent birth.

was ≥20 years before baseline (HR = 0.54; 95% CI = 0.29, 0.98), but this estimate was based on 11 exposed cases. The association of gestational hypertensive disease with ER− cancer was also inverse (HR = 0.88; 95% CI = 0.64, 1.2) but included only 42 exposed ER− cases. Gestational hypertensive disease was not associated with the risk of ER+ cancers (HR = 1.0; 95% CI = 0.90, 1.2) (eTable 2; http://links.lww.com/EDE/B939). Associations were null in analyses stratified by tumor invasiveness (eTable 3; http://links.lww.com/EDE/B939).

We observed some differences in the association of gestational hypertensive disease and breast cancer risk in stratified analyses, although there were no clear patterns (Figure 1). For example, while the association appeared to differ by age at first birth, there was not a linear trend. We observed inverse associations among women ages <20 years or ≥30 years at

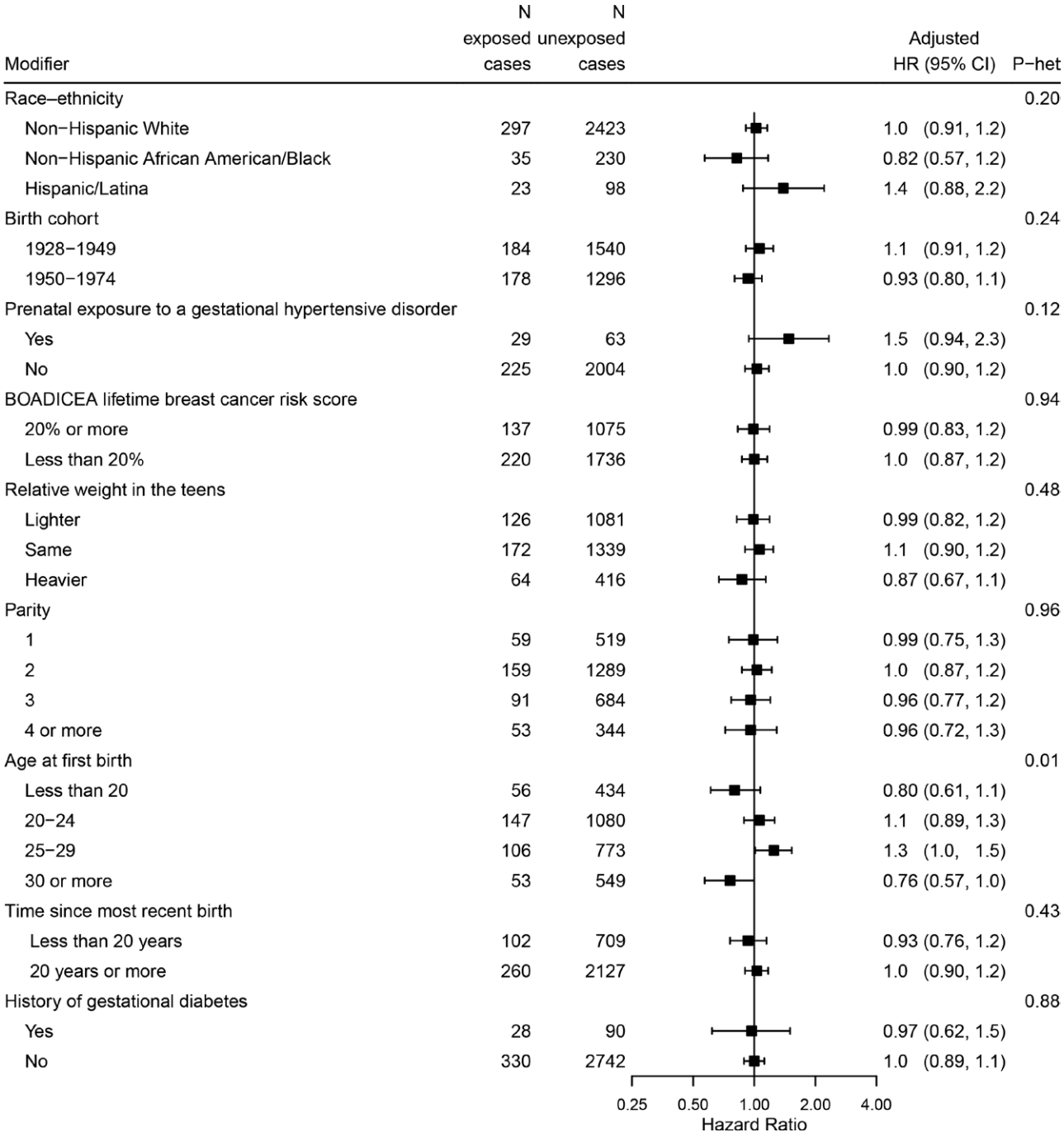

FIGURE 1. Association between history of a gestational hypertensive disorder and incident breast cancer stratified by potential modifiers in 40,720 parous women enrolled in the Sister Study. Any gestational hypertensive disorder includes a diagnosis of eclampsia, preeclampsia, or gestational hypertension in at least one pregnancy. Estimates are adjusted for birth cohort, race–ethnicity, parity, age at first birth, education at baseline, relative weight in the teens, average hours of physical activity in childhood/teens, age at menarche, and ever smoked before first birth. *P* for heterogeneity from a Wald test of an interaction term(s) between history of a gestational hypertensive disorder and the potential modifier of interest.

first birth and a positive association among women ages 25–29 years. While there was no association of gestational hypertensive disease and breast cancer risk in most subgroups, we observed positive associations among Hispanic/Latina women (HR = 1.4; 95% CI = 0.88, 2.2) and women who were exposed in utero to gestational hypertensive disease (HR = 1.5; 95% CI = 0.94, 2.3). Among women exposed in utero, an increased risk of breast cancer was seen in women who themselves had

preeclampsia or eclampsia (HR = 1.7; 95% CI = 1.0, 2.7) but not gestational hypertension (HR = 1.1; 95% CI = 0.44, 2.5).

In analyses limited to the first (Figure 2) or most recent birth (eFigure 2; http://links.lww.com/EDE/B939), there were no observed associations between gestational hypertensive disease and breast cancer risk across strata of type of gestation, gestational length, or offspring sex. While we again observed differences by age at first birth, associations were consistently null across categories of age or time since the most recent birth.

DISCUSSION

We examined associations of gestational hypertensive disorders with incident breast cancer in a nationwide cohort of women with a first-degree family history of breast cancer. Contrary to the hypothesis that gestational hypertensive disorders reduce the risk of maternal breast cancer, we did not observe associations of history of a gestational hypertensive disorder with incident breast cancer in this large, prospective study. We did not observe clear differences across strata of breast cancer characteristics or other risk factors that would explain our overall null finding. The generally null findings across subgroups do not support our hypothesis that inconsistencies across prior epidemiologic studies may be explained by differences in the distribution of factors that modify the association of gestational hypertensive disorders with breast cancer risk.

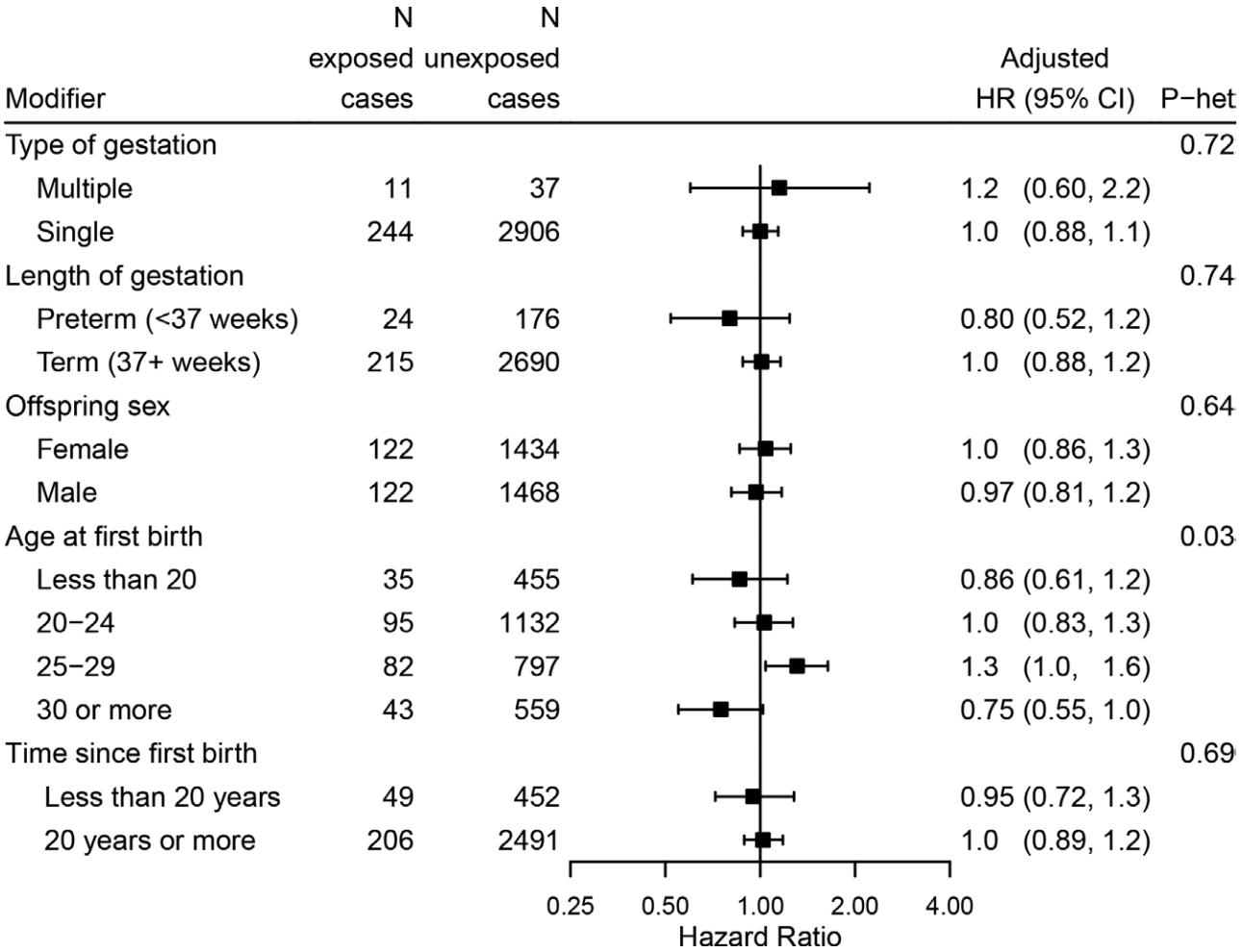

FIGURE 2. Associations between history of a gestational hypertensive disorder in first birth and incident breast cancer stratified by birth characteristics in 40,702 parous women in the Sister Study. Exposure of a diagnosis of eclampsia, preeclampsia, or gestational hypertension and potential modifying factors were assessed in the first pregnancy resulting in a live or still birth. Estimates are adjusted for birth cohort, race–ethnicity, age at first birth, education at baseline, relative weight in the teens, average hours of physical activity in childhood/teens, age at menarche, and ever smoked before first birth. *P* for heterogeneity from a Wald test of an interaction term(s) between history of a gestational hypertensive disorder in first birth and the potential modifier of interest. Analyses of length of gestation and offspring sex were restricted to singleton births. Five-hundred sixty-two women missing length of gestation and 23 women missing offspring sex were excluded from relevant analyses. Proportional hazards assumption was violated for strata of ≥20 years since first birth ($P = 0.04$).

Pregnancy has a complex relationship with breast cancer risk. Driven by changes to the endocrine milieu and tissue microenvironment, breast cells undergo rapid proliferation and differentiation during pregnancy, followed by postpartum involution.[43,48] The breast is more vulnerable to carcinogenesis during this period,[48,49] and women have an increased risk of breast cancer for >20 years after childbirth.[44] However, after completion of a full-term pregnancy, lactation induces terminal differentiation of breast cells,[43,48] and childbirth is associated with a long-term reduction in breast cancer risk.[50] Associations between pregnancy conditions and breast cancer risk may provide insight into biologic mechanisms that affect susceptibility to carcinogenesis.[8,51] Hormonal, immune, and anti-angiogenic pathways have been proposed to explain the reduction in maternal breast cancer risk associated with gestational hypertensive disease observed in prior studies.[38,52–54]

We did not identify subgroups with a clear reduction in breast cancer risk associated with gestational hypertensive disease in stratified analyses, except possibly women who were 30 years or older at first birth. There was a consistent signal across exposure constructs of a possible modest decrease in premenopausal breast cancer risk associated with gestational hypertensive disease, but estimates were imprecise. Several early studies that observed a reduction in breast cancer risk associated with gestational hypertensive disease were limited to young-onset cancers,[9–11,13] and an inverse association was observed only for premenopausal cancer in the Generations Study.[29] However, other studies have observed similar associations across age or menopausal status at diagnosis,[17,18,24] and one study observed a greater reduction in risk associated with postmenopausal cancer.[12] Consistent with the Generations Study,[29] we observed a modest reduction in ER− cancer associated with gestational hypertensive disease, but confidence intervals were wide. We had limited power to detect statistical differences by menopausal and ER status given the relatively small number of exposed premenopausal and ER− cases.

We did not observe any differences by parity or time since birth. Among women with a first birth at ≥30 years, we observed an inverse association of gestational hypertensive disease with breast cancer risk. However, the lack of consistent trend with increasing age at first birth suggests that the differences we observed could be due to chance. While a prior study observed a greater reduction in breast cancer risk associated with preeclampsia among women >30 years of age at first birth compared with younger women,[13] others observed inverse associations across categories of age at birth.[12,19]

Birth characteristics have been hypothesized to modify the association between gestational hypertensive disease and breast cancer risk. Vatten et al.[39] reported a greater risk reduction associated with preeclampsia in women carrying a son, particularly for pregnancies ending in preterm delivery. This difference by offspring sex was also observed by Troisi et al.,[38] although only in women >30 years at birth. Subsequent studies have not observed sex differences.[12,18,19,24,29,32] We did not observe any associations between gestational hypertensive disease and breast cancer risk across strata of offspring sex, timing of delivery, or type of gestation.

The most consistent evidence for a modest reduction in breast cancer risk associated with gestational hypertensive disorders come from studies in Scandinavia,[17–19,21,23,24] although two registry-based studies in Sweden did not observe an association.[16,27] Other Western European studies have predominantly observed inverse[25,31] or null associations,[26,29,30] although an Italian case–control study observed a positive association.[15] Preeclampsia was also associated with an increased risk of breast cancer in Israeli women.[32] The positive association was particularly pronounced in women of Israeli and Western Asian origin while essentially null in women of European origin. A recent study in Taiwan did not observe an association between gestational hypertensive disease and breast cancer risk, although the point estimate was in the direction of increased risk.[22] Our analyses stratified by race–ethnicity suggested a positive association between gestational hypertensive disease and breast cancer risk among Hispanic/Latina women. Differences in genetic susceptibility have been proposed as an explanation for differences across populations.[22,23,32] Gestational hypertensive disease has been found to interact with variants of insulin-like growth factor-1 receptor (IGF1R) and vascular endothelial growth factor (VEGF-A) genes, with reductions in breast cancer risk and lower breast density, a breast cancer risk factor,[55] observed only in women with specific allelic variants.[56,57] These gene–environment interactions suggest that differences in the prevalence of effect-modifying variants between populations could contribute to the differences observed in the epidemiologic literature.

Gestational hypertensive disease is a risk factor for chronic hypertension,[7] which has been positively associated with breast cancer risk.[58] Incidence and treatment of chronic hypertension could differ between populations and potentially contribute to inconsistencies in the literature, although the literature on antihypertensive medication use and breast cancer risk is inconsistent.[59] We previously observed no evidence of an association between antihypertensive medication use and breast cancer in our cohort.[60] The definitions of gestational hypertensive disorders have also changed over time and clinical guidelines and classification systems vary across countries,[61,62] which complicates comparisons across studies and may contribute to inconsistencies.[63]

Women in our cohort have at least one full- or half-sister with breast cancer and have approximately twice the risk of breast cancer than women without a first-degree family history.[64] Two studies examining sisters of women with breast cancer in Sweden suggest there may be an underlying familial or shared genetic risk component connecting preeclampsia and breast cancer.[21,23] In a registry-based nested case–control study of breast cancer before age 50 years, Hajiebrahimi et al.[21] observed an inverse association between preeclampsia

and breast cancer risk in crude and adjusted models using population controls. Using sister controls, they also observed an inverse association in crude analyses (odds ratio [OR] = 0.72; 95% CI = 0.58, 0.89), but this association changed direction after controlling for age at latest pregnancy, parity, educational level, and year of the birth (adjusted OR = 1.22; 95% CI = 0.92, 1.62). A study utilizing data from two cohorts found that sisters of breast cancer patients were less likely to develop preeclampsia compared to women without a sister with breast cancer and that women with a personal history of preeclampsia and women with a sister with preeclampsia both had lower percent mammographic density.[23] If there are shared genetic factors that contribute to gestational hypertensive disorders and breast cancer, that may explain the lack of association in our cohort of women with a first-degree family history. However, if this were the case, then we would expect to see a difference in the association between gestational hypertensive disease and breast cancer by extent of familial breast cancer risk, which we did not observe.

Like breast cancer, gestational hypertensive disorders have a familial component.[65] In utero exposure to a gestational hypertensive disorder has been linked to reduced breast cancer risk in daughters,[66] although this association has been inconsistent across studies.[67–73] We were interested in whether women who were both exposed in utero and had a pregnancy complicated by gestational hypertensive disease had an additional reduction in breast cancer risk. Contrary to that hypothesis, we found that preeclampsia/eclampsia was associated with an increase in breast cancer risk among women who were exposed in utero to a maternal gestational hypertensive disorder. Women with a maternal or sister history of chronic hypertension, preeclampsia or eclampsia are more likely to develop severe preeclampsia.[74] These differences could reflect a shared familial component that contributes to increased risks of preeclampsia and breast cancer. However, our results are based on a small number of exposed cases and could be due to chance. In the Generations Study, the association between preeclampsia and breast cancer risk did not vary among women with and without in utero exposure to preeclampsia.[29]

Study strengths include the large sample size and prospective design, which is expected to limit differential recall of gestational hypertensive disorders by breast cancer status. The size and diversity of our cohort enabled us to stratify by demographic, lifestyle, pregnancy, and breast cancer characteristics, although we acknowledge reduced precision in some strata. We were limited by our reliance on self-reported data on gestational hypertensive disorders. A systematic review of recall of gestational hypertensive disorders found that specificity of self-report was high (>90%), but sensitivity ranged from 73% to 87% for preeclampsia in prospective cohort studies and slightly lower for gestational hypertension,[75] which suggests a potential bias towards the null when using self-reports. However, bias due to imperfect sensitivity is likely small since the exposure is rare. The prevalence of gestational hypertensive disorders in our cohort (8%, considering first birth only) is slightly higher than US prevalence estimates based on administrative data (6%–7% of pregnancies),[1–4] which could reflect overreporting in our cohort. If this is the case, our findings may be biased towards the null. However, accuracy in administrative databases is variable[76,77] and underreporting of gestational hypertensive conditions could contribute to this difference. The overall prevalence in our cohort (12%, considering all births) was lower than in other prospective cohorts using self-reported data (~14% in the Nurses' Health Study II[78] and the Generations Study, which considered preeclampsia only[29]). We were unable to consider phenotypes of preeclampsia, which can vary in terms of severity and pathogenesis.[62]

Among parous women with a family history of breast cancer, history of a gestational hypertensive disorder was not associated with incident breast cancer. Given the conflicting results of epidemiologic studies and that the primary purpose of examining this association is to understand possible mechanisms of breast carcinogenesis, we recommend that future studies directly assess hormonal, anti-angiogenic, immune, or other hypothesized pathways during pregnancy in relation to breast cancer risk instead of using gestational hypertensive disease as a proxy.

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