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Hypertensive conditions of pregnancy, preterm birth, and premenopausal breast cancer risk: a premenopausal breast cancer collaborative group analysis

Hazel B. Nichols[1] · Melissa G. House[2] · Rina Yarosh[1] · Sara Mitra[3] · Mandy Goldberg[4] · Kimberly A. Bertrand[5] · A. Heather Eliassen[6,7] · Graham G. Giles[8,9,10] · Michael E. Jones[11] · Roger L. Milne[8,9,10] · Katie M. O'Brien[4] · Julie R. Palmer[5,12] · Sven Sandin[13,14,15] · Walter C. Willett[6,7,16] · Weiyao Yin[13,17] · Dale P. Sandler[4] · Anthony J. Swerdlow[11,18] · Minouk J. Schoemaker[11,19]

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Abstract

Purpose Women with preeclampsia are more likely to deliver preterm. Reports of inverse associations between preeclampsia and breast cancer risk, and positive associations between preterm birth and breast cancer risk are difficult to reconcile. We investigated the co-occurrence of preeclampsia/gestational hypertension with preterm birth and breast cancer risk using data from the Premenopausal Breast Cancer Collaborative Group.

Methods Across 6 cohorts, 3096 premenopausal breast cancers were diagnosed among 184,866 parous women. We estimated multivariable hazard ratios (HR) and 95% confidence intervals (CI) for premenopausal breast cancer risk using Cox proportional hazards regression.

Results Overall, preterm birth was not associated (HR 1.02, 95% CI 0.92, 1.14), and preeclampsia was inversely associated (HR 0.86, 95% CI 0.76, 0.99), with premenopausal breast cancer risk. In stratified analyses using data from 3 cohorts, preterm birth associations with breast cancer risk were modified by hypertensive conditions in first pregnancies (P-interaction = 0.09). Preterm birth was positively associated with premenopausal breast cancer in strata of women with preeclampsia or gestational hypertension (HR 1.52, 95% CI: 1.06, 2.18), but not among women with normotensive pregnancy (HR = 1.09, 95% CI: 0.93, 1.28). When stratified by preterm birth, the inverse association with preeclampsia was more apparent, but not statistically different (P-interaction = 0.2), among women who did not deliver preterm (HR = 0.82, 95% CI 0.68, 1.00) than those who did (HR = 1.07, 95% CI 0.73, 1.56).

Conclusion Findings support an overall inverse association of preeclampsia history with premenopausal breast cancer risk. Estimates for preterm birth and breast cancer may vary according to other conditions of pregnancy.

Keywords Epidemiology · Breast cancer · Cohort

Abbreviations

BP	Blood pressure
BWHS	Black Women's Health Study
CI	Confidence interval
ER	Estrogen receptor
GEN	Generations Study
HR	Hazard ratio
MCCS	Melbourne Collaborative Cohort Study
NHS2	Nurses' Health Study II
RR	Relative risk
SIS	Sister Study
SWLS	Swedish Women's Lifestyle and Health Study
UK	United Kingdom
USA	United States of America

Introduction

Women who experience preeclampsia or gestational hypertension are more likely to deliver preterm, but these conditions appear to act in opposite directions for future breast

Dale P. Sandler, Anthony J. Swerdlow and Minouk J. Schoemaker have contributed equally to this work.

✉ Hazel B. Nichols
Hazel.Nichols@unc.edu

Extended author information available on the last page of the article

cancer risk. Preeclampsia is typically defined as the onset of hypertension (systolic blood pressure (BP) ≥ 140 mm Hg or diastolic BP ≥ 90 mmHg) and proteinuria (defined as ≥ 300 mg per 24 h) during pregnancy after 20 weeks of gestation [1]. Preeclampsia occurs in roughly 3–9% of United States (U.S.) pregnancies [2, 3]. A 2021 meta-analysis estimated that women with a history of preeclampsia had an estimated 19% lower risk of premenopausal breast cancer (relative risk (RR) 0.81, 95% CI 0.75–0.87) [4]. Lower breast cancer risk after preeclampsia may be related to antiangiogenic profiles that inhibit tumor progression and metastasis [5], although this has not been observed in all studies [6, 7].

Conversely, shorter gestation (time between conception and birth) is a potential risk factor for breast cancer. The World Health Organization categorizes shorter gestation births as very preterm (28–32 weeks) and moderate/late preterm (32–37 weeks) relative to term (> 37 weeks) [8]. In the U.S., approximately 10% of pregnancies are delivered preterm, or before 37 weeks [9, 10]. In some cases, delivery may be induced preterm to prevent the progression of preeclampsia to eclampsia. To date, no meta-analyses have assessed the association between pregnancy duration and breast cancer risk. Several individual studies have reported an increased risk of breast cancer among mothers of preterm infants [11–13], with the strength of association inversely related to gestational age [14–16]. Other studies, however, have reported null results [5, 17–22] or an inverse association [23] between shorter gestation and breast cancer risk. Proposed pathways to account for increased susceptibility to breast carcinogenesis among women who deliver preterm include incomplete terminal differentiation of mammary gland tissue associated with shorter gestation combined with high hormone levels (e.g., estrogens, progesterone, IGF-I) during pregnancy [5, 9, 13, 24].

We investigated the co-occurrence of preeclampsia/gestational hypertension and preterm birth in relation to premenopausal breast cancer risk, overall and by estrogen receptor-defined subtypes, using data from the Premenopausal Breast Cancer Collaborative Group within the U.S. National Cancer Institute (NCI) Cohort Consortium.

Materials and methods

The Premenopausal Breast Cancer Collaborative Group was established to facilitate analysis of prospectively collected data to investigate risk factors for breast cancer among premenopausal women as previously described [25]. For this analysis, six cohorts were identified that had collected relevant information on pregnancy duration or hypertensive conditions of pregnancy (Table 1). Five cohorts contributed individual-level data and were pooled by the investigative team at the National Institute of Environmental Health Sciences. A sixth cohort, the Swedish Women's Lifestyle and Health Study [26], is reported separately and contributed aggregated results on gestational hypertension and preeclampsia for meta-analysis due to privacy regulations in the European Union. All studies were approved by the relevant institutional review boards.

Participating studies contributed data from women aged 55 and younger who enrolled in each cohort, did not have a breast cancer diagnosis at enrollment, and were followed by direct contact or linkage with cancer registries [26–31]. Contributed information included ages at enrollment and follow-up, menopausal status, breast cancer diagnosis and tumor characteristics, reproductive history and medical conditions, demographic factors, lifestyle characteristics, and family history of breast cancer at enrollment and each questionnaire round, as available. Data harmonization and quality control for the pooled data were performed by the study-coordinating centers in North Carolina (USA) and London (UK); statistical analysis was completed in North Carolina and Sweden.

Table 1 Characteristics of eligible studies from within the premenopausal breast cancer collaborative group

Cohort	Study location	Enrollment period	Age at enrollment	Premenopausal women < 55 years [a]	Premenopausal breast cancers < 55 years [a]
Black Women's Health Study	USA	1995	20–52	30,923	575
Generations Study	UK	2003–2012	19–54	40,438	465
Melbourne Collaborative Cohort Study	Australia	1990–1994	34–54	6,051	50
Nurses' Health Study II	USA	1989	24–44	68,559	1390
Sister Study	USA	2003–2009	35–54	12,135	348
Women's Lifestyle and Health Study	Sweden	1991–1992	29–49	26,760	268
Total				184,866	3096

[a]Premenopausal parous woman with non-missing age at first birth, education, smoking in young adulthood, and body mass index in young adulthood

Participating cohorts included the Black Women's Health Study (BWHS) (USA [31]), the Generations Study (GEN) (United Kingdom [27]), the Melbourne Collaborative Cohort Study (MCCS)(Australia [32]), the Nurses' Health Study II (NHS2)(USA [29]), the Sister Study (SIS)(USA [30]) and the Swedish Women's Lifestyle and Health Study (SWLS) (Sweden [26]). Figure 1 displays exclusions for the pooled data from the 5 cohorts analyzed centrally. Of 275,872 participants in the pooled data, analysis was restricted to women who had at least one birth prior to enrollment or during follow-up (N = 190,976). We then excluded women who had already reached menopause (N = 27,313). Of the remaining 163,663 women, 5557 (3.4%) were excluded due to missing information on required covariates (body mass index (BMI) in young adulthood, education, age of first birth, smoking status in young adulthood), leaving an analytic sample of 158,106 women in pooled analyses of individual-level data (Fig. 1). Of the 34,402 women enrolled in the Swedish Women's Lifestyle and Health Study, analysis was restricted to those who were parous (excluded N = 3534), premenopausal (N = 1952), had not emigrated out of Sweden (N = 553), had no history of breast cancer (N = 115) and were not missing covariate data (N = 1488). The final Swedish analytic sample included 26,760 women.

The primary exposures for this analysis were gestational weeks at delivery for each pregnancy (available in 4 cohorts [27–30]), ever having a preterm birth (< 37 weeks in any pregnancy, available in 5 cohorts[27–31]) or very preterm birth (< 32 weeks in any pregnancy, available in 4 cohorts[27–30]), ever experiencing gestational hypertension (available in 3 cohorts [29–31]) or preeclampsia (available in 4 cohorts [27, 29–31]), and the cross-classification of preterm birth (in any pregnancy) and hypertension during pregnancy (gestational hypertension or preeclampsia in any pregnancy)(defined for 4 cohorts [27, 29–31]). Pregnancy conditions were self-reported in all studies.

Preterm birth, gestational hypertension and preeclampsia were analyzed as time-varying exposures for women who contributed one or more births during follow-up. However, most of the person-time (74%) was contributed by participants who had completed childbearing prior to enrollment, where preterm birth, gestational hypertension, and preeclampsia status were fixed at study entry. Data from women who reported multiple pregnancies of variable lengths was harmonized according to the shortest gestation pregnancy to date through the end of follow-up to account for the lack of pregnancy-specific data in some studies. Women who reported separate pregnancies that were either short duration or characterized by hypertensive conditions were harmonized as having both short duration and hypertensive conditions in primary analyses because this information was not available per pregnancy in some cohorts, but instead reported for any pregnancy. In sensitivity analyses, we restricted to cohorts with pregnancy-specific information in order to ensure that both conditions occurred in the same pregnancy.

We estimated multivariable hazard ratios (HR) and 95% confidence intervals (CI) for premenopausal breast cancer risk using Cox proportional hazards regression, with age as the primary time scale and stratified by cohort. Person-time accrued from age at cohort entry (if parous) or age at which first birth was reported (if nulliparous at cohort entry) until last follow-up, age 55, age at menopause, or breast cancer diagnosis, whichever occurred first. Postmenopausal breast

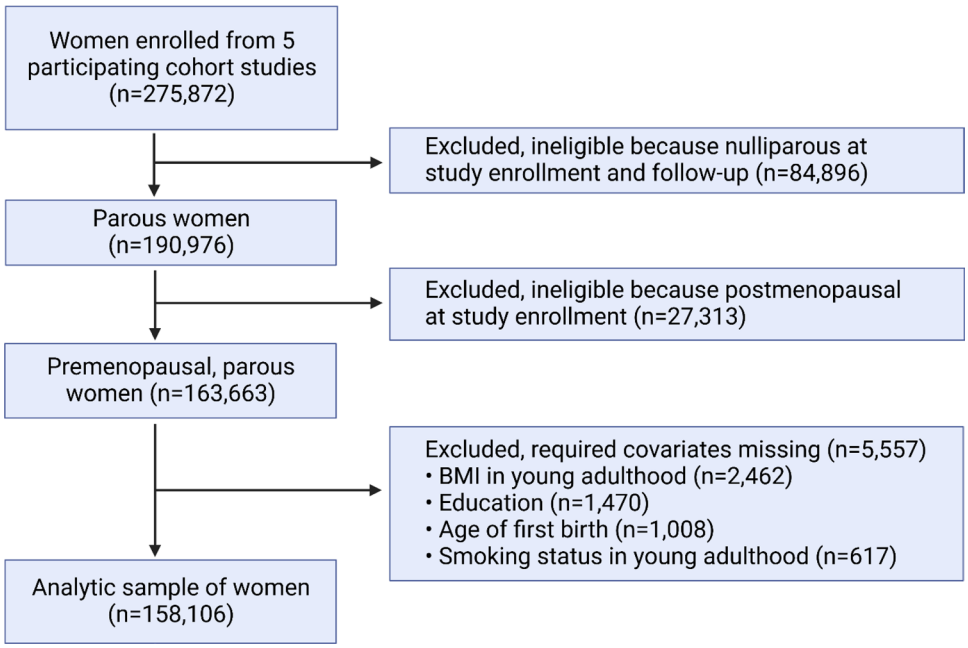

Fig. 1 Inclusion criteria for participating studies in the premenopausal breast cancer collaborative group with individual-level data available for pooled analyses of pregnancy complications and premenopausal breast cancer risk

cancers were not analyzed based on the data structure for the Premenopausal Breast Cancer Collaborative group [25]. We identified the following potential confounders for multivariable adjustment using a directed acyclic graph [33]: age at first birth (< 19, 19–22, 23–25, 26–29, 30–35, ≥ 36), education (high school or less, some college, college degree), smoking in young adulthood (none, any; start age < = 20 in BWHS, GEN, MCCS, NHS2 or < 20 in SIS and SWLH) and BMI in young adulthood (< 18.5 kg/m^2, 18.5–24.9, 25–29.9, ≥ 30; age 18 in MCCS, NHS2, BWHS, and SWLH, age 20 in GEN, age 30–39 in SIS). We used cross-product interaction terms and the Wald test [34] to evaluate potential statistical interactions between hypertensive conditions of pregnancy and preterm birth. Proportional hazards assumptions were assessed by visual inspection of plots of Schoenfeld residuals [35] and were not violated.

To assess heterogeneity between study cohorts in the pooled data, study-specific estimates were generated to obtain a pooled estimate across studies using a random-effects model, which weights HR estimates by the inverse of the study-specific variance [36–38]. No statistically significant heterogeneity between studies for the primary exposure or covariates was indicated by the Cochran Q test or I^2 statistic (all $P \geq 0.2$) [39–41]. We examined risk for invasive disease (stage I-IV) breast cancer by censoring at an in situ (stage 0) diagnosis. We performed sensitivity analyses restricting to women who reported only ever having one birth (primiparous women) to minimize potential bias associated with selective fertility after the first birth. To combine gestational hypertension and preeclampsia results from the Swedish Women's Lifestyle and Health with the pooled data from the other cohorts, we used DerSimonian-Laird estimators for random effects models in meta-analysis [40]. Thresholds for statistical significance were set at $P < 0.05$ overall, and $P < 0.1$ for tests of interaction, both two-sided, and were not adjusted for multiple comparisons. SAS software Version 9.4 was used for analyses.

Results

In the individual-level pooled data, 2,828 premenopausal breast cancers were diagnosed during 1,627,375 person-years of observation (mean = 10.3 years, median = 10.0 years, IQR: 8.5). An additional 268 premenopausal breast cancers were diagnosed during 239,703 person-years of follow-up from the Swedish Women's Lifestyle and Health Cohort. The distribution of participant characteristics by breast cancer diagnoses and person-years for the pooled data is shown in Supplementary Table 1. The majority of the pooled sample had two or more births (77.6%) and had a first birth at ages 23 and older (77.4% vs. < 23 years). By the end of follow-up, 60.9% of person-time contributed by participants reflected study participation ≥ 10 years from most recent birth. Approximately, a third of person-time was from women who reported smoking in young adulthood (29.5%) and three quarters was from participants in the 18.5–24.9 m/kg^2 BMI range in young adulthood (75.7%) or who had a college education (74.7%). By the end of follow-up, 18.5% of the sample reported having a family history of breast cancer. Reported menopausal age varied between 46 and 54 (10th and 90th percentiles) with a median of 50 years.

Table 2 provides estimates for associations between pregnancy conditions and premenopausal breast cancer overall; restricted to invasive breast cancer; according to ER status (regardless of invasiveness), and in sensitivity analyses restricted to primiparous women. Overall, we did not observe an association with premenopausal breast cancer risk for ever having a preterm (HR 1.02, 95% CI 0.92–1.14) or very preterm (HR 1.08, 95% CI 0.86–1.36) birth, compared with having only full-term births. These associations did not vary meaningfully in strata defined by invasive disease, ER status, or for primiparous women (Table 2); estimates similarly had overlapping confidence intervals within strata defined by recency of the last birth (± 15 years, Supplementary Table 2) or BMI in young adulthood (± 25 kg/m^2, Supplementary Table 3). While not statistically significant, the HRs associated having at least one child born at 24- < 32 weeks compared to having only pregnancies of 40–41 weeks were greater than 1 for overall premenopausal breast cancer and all examined subgroups (Table 2).

For overall premenopausal breast cancer risk, the HR for gestational hypertension was 0.88 (95% CI 0.75–1.04) and the HR for preeclampsia was 0.86 (95% CI 0.75–0.99) in the pooled analyses of individual-level data. Estimates were largely consistent across strata defined by invasive disease, ER status, and for primiparous women. For example, preeclampsia was associated with a 22% lower risk of premenopausal invasive breast cancer (HR 0.78, 95% CI 0.65–0.93, Table 2). When the pooled individual-level data were combined with estimates from the Swedish Women's Lifestyle and Health Cohort, the summary estimates were HR 0.89 (95% CI 0.77–1.03) for gestational hypertension and HR 0.86 (95% CI 0.76–0.99) for preeclampsia in relation to premenopausal breast cancer risk overall.

In the 4 studies with information on both conditions, we analyzed the co-occurrence of preterm birth and hypertensive conditions compared to experiencing neither (Table 3, Fig. 2). Among the 360,350 person-years contributed by participants who experienced preterm birth, gestational hypertension, or preeclampsia, 44,457 person-years (12%) were contributed by women who had ever experienced a preterm birth and a hypertensive condition in any pregnancy. Compared to not having either pregnancy complication, preterm birth was not associated with premenopausal breast cancer risk with or without having a hypertensive condition

Table 2 Hazard ratios (HR) and 95% confidence intervals (CI) for premenopausal breast cancer risk before age 55 according to pregnancy characteristics among parous women in the pooled sample

Pregnancy characteristics	Total breast cancer		Invasive breast cancer		Estrogen Receptor (ER) + breast cancer		ER- breast cancer		Breast cancer among primiparous women	
	N	HR (95% CI) [d]	*N*	HR (95% CI) [d]	*N*	HR (95% CI) [d]	*N*	HR (95% CI) [d]	*N*	HR (95% CI) [d]
Gestational weeks[a]	2235	1.00 (0.98, 1.01)	1338	1.00 (0.98, 1.01)	1,466	1.00 (0.98, 1.01)	321	0.99 (0.96, 1.02)	419	0.99 (0.96, 1.02)
Missing, N	18		7		12		1		4	
Gestational weeks[a]										
24- < 32 weeks	75	1.08 (0.85, 1.36)	48	1.17 (0.87, 1.56)	48	1.07 (0.80, 1.44)	14	1.32 (0.76, 2.27)	12	1.27 (0.71, 2.28)
32- < 37 weeks	229	1.04 (0.90, 1.19)	131	1.01 (0.84, 1.22)	152	1.06 (0.89, 1.26)	30	0.88 (0.60, 1.30)	43	1.03 (0.74, 1.42)
37- < 40 weeks	626	0.98 (0.89, 1.08)	381	1.02 (0.90, 1.16)	415	0.99 (0.87, 1.11)	84	0.85 (0.65, 1.10)	82	0.92 (0.71, 1.18)
40- < 42 weeks	1207	1	714	1	785	1	185	1	241	1
42 + weeks	98	0.97 (0.79, 1.20)	64	1.10 (0.85, 1.42)	66	0.99 (0.77, 1.27)	8	0.52 (0.25, 1.05)	41	0.95 (0.68, 1.32)
Missing	18		7		12		1		4	
Preterm birth (< 37 weeks)										
No	2307	1	1411	1	1451	1	373	1	526	1
Yes	396	1.02 (0.92, 1.14)	244	1.02 (0.89, 1.17)	247	1.04 (0.91, 1.19)	68	1.02 (0.79, 1.32)	77	0.96 (0.76, 1.22)
Missing	125		72		57		33		52	
Very preterm birth[a] (< 32 weeks)										
No	2156	1	1289	1	1415	1	306	1	407	1
Yes	75	1.08 (0.86, 1.36)	48	1.15 (0.86, 1.54)	48	1.07 (0.80, 1.43)	14	1.43 (0.83, 2.44)	12	1.30 (0.73, 2.31)
Missing	22		8		15		2		4	
Gestational hypertension[b]										
No	2102	1	1317	1	1276	1	345	1	495	1
Yes	162	0.88 (0.75, 1.04)	99	0.85 (0.69, 1.05)	98	0.90 (0.73, 1.10)	31	0.96 (0.66, 1.39)	41	0.88 (0.64, 1.22)
Missing	49		28		22		12		28	
Preeclampsia[c]										
No	2541	1	1562	1	1578	1	409	1	590	1
Yes	226	0.86 (0.75, 0.99)	125	0.78 (0.65, 0.93)	142	0.89 (0.74, 1.05)	42	0.93 (0.67, 1.28)	54	0.85 (0.64, 1.13)
Missing	11		9		6		5		6	

[a]Unavailable for the Black Women's Health Study

[b]Unavailable for the Generations Study and the Melbourne Collaborative Cohort Study

[c]Unavailable for the Melbourne Collaborative Cohort Study

[d]Age as the time scale, adjusted for education, body mass index, smoking, and age at first birth

Table 3 Hazard ratios (HR) and 95% confidence intervals (CI) for premenopausal breast cancer risk before age 55 according to the co-occurrence of preterm birth and hypertensive conditions in the pooled sample

Pregnancy complications combined[a]	Total breast cancer		Invasive breast cancer		Estrogen Receptor (ER) + breast cancer		ER- breast cancer		Breast cancer among primiparous women	
	N	HR (95% CI) [b]	*N*	HR (95% CI) [b]	*N*	HR (95% CI) [b]	*N*	HR (95% CI) [b]	*N*	HR (95% CI) [b]
No preterm birth or hypertensive condition[c]	2056	1	1268	1	1294	1	323	1	472	1
Preterm birth, no hypertensive condition	300	0.99 (0.87, 1.11)	185	0.98 (0.84, 1.14)	194	1.04 (0.89, 1.21)	44	0.87 (0.63, 1.19)	55	0.91 (0.69, 1.20)
Hypertensive condition, no preterm birth	203	0.80 (0.69, 0.93)	114	0.73 (0.60, 0.88)	130	0.83 (0.69, 0.99)	32	0.76 (0.53, 1.10)	47	0.79 (0.58, 1.07)
Preterm birth and hypertensive condition	84	1.04 (0.84, 1.30)	48	0.95 (0.71, 1.27)	46	0.94 (0.70, 1.27)	19	1.34 (0.84, 2.13)	17	0.92 (0.57, 1.50)

[a] Unavailable for Melbourne Collaborative Cohort Study

[b] Age as the time scale, adjusted for education, body mass index, smoking, and age at first birth

[c] Any hypertensive condition includes gestational hypertension or preeclampsia

of pregnancy. Hypertensive conditions of pregnancy were generally inversely associated with premenopausal breast cancer risk when not accompanied by preterm birth (HR 0.80, 95% CI 0.69–0.93 overall; HR 0.73, 95% CI 0.60–0.88 for invasive disease; HR 0.83, 95% CI 0.69–0.99 for ER positive disease) compared to the reference group. Estimates were similar, but not statistically significant, for the association between hypertensive conditions and ER negative breast cancer and premenopausal breast cancer in primiparous women, with fewer events in these groups (Table 3). We did not observe an inverse association between hypertensive conditions and premenopausal in situ breast cancer risk, with or without preterm birth, compared to experiencing neither condition (Supplementary Table 4).

Study-specific estimates are shown in Fig. 2. Although the heterogeneity of estimates between cohorts was not statistically significant according to the Cochran Q test or I^2 statistic, the Sister Study cohort had HR estimates greater than 1 for pregnancies characterized by preterm birth (with and without hypertension in pregnancy). The Sister Study is unique in that all participants had a first-degree family history of breast cancer at enrollment. Therefore, we repeated analyses restricting person-time in the pooled data to participants with a family history of breast cancer to evaluate if findings were sensitive to this specification. The overall pattern of results was unchanged from the pooled analysis that did not account for family history (*data not shown*).

Using data from the three studies that had pregnancy-specific information, we conducted sensitivity analyses that required gestational hypertension/preeclampsia and preterm birth to occur in the same pregnancy and stratified analyses specific to a woman's first pregnancy (consistent with prior studies [42–44]). Results for sensitivity analyses of gestational hypertension/preeclampsia and preeclampsia that occurred in the same pregnancy showed the same pattern as seen in the larger number of studies that did not have pregnancy-specific information (*data not shown*). In analyses of a woman's first pregnancy, we did not see evidence of an association between preterm birth and premenopausal breast cancer risk in strata of women who did not have a hypertensive first pregnancy (Table 4). However, in strata of women who experienced gestational hypertension or preeclampsia in a first pregnancy, preterm birth was positively associated with premenopausal breast cancer risk (HR 1.52, 95% CI 1.06–2.18, P-interaction = 0.09). In analyses stratified according to preterm birth in a first pregnancy, inverse associations between hypertensive conditions of pregnancy and premenopausal breast cancer risk were apparent only among those with term births, although the P for interaction was not statistically significant. The HR for gestational hypertension was 0.76 (95% CI 0.58–0.98), and the HR for preeclampsia was 0.82 (95% CI 0.68–1.00), in relation to premenopausal breast cancer risk when preterm birth did not

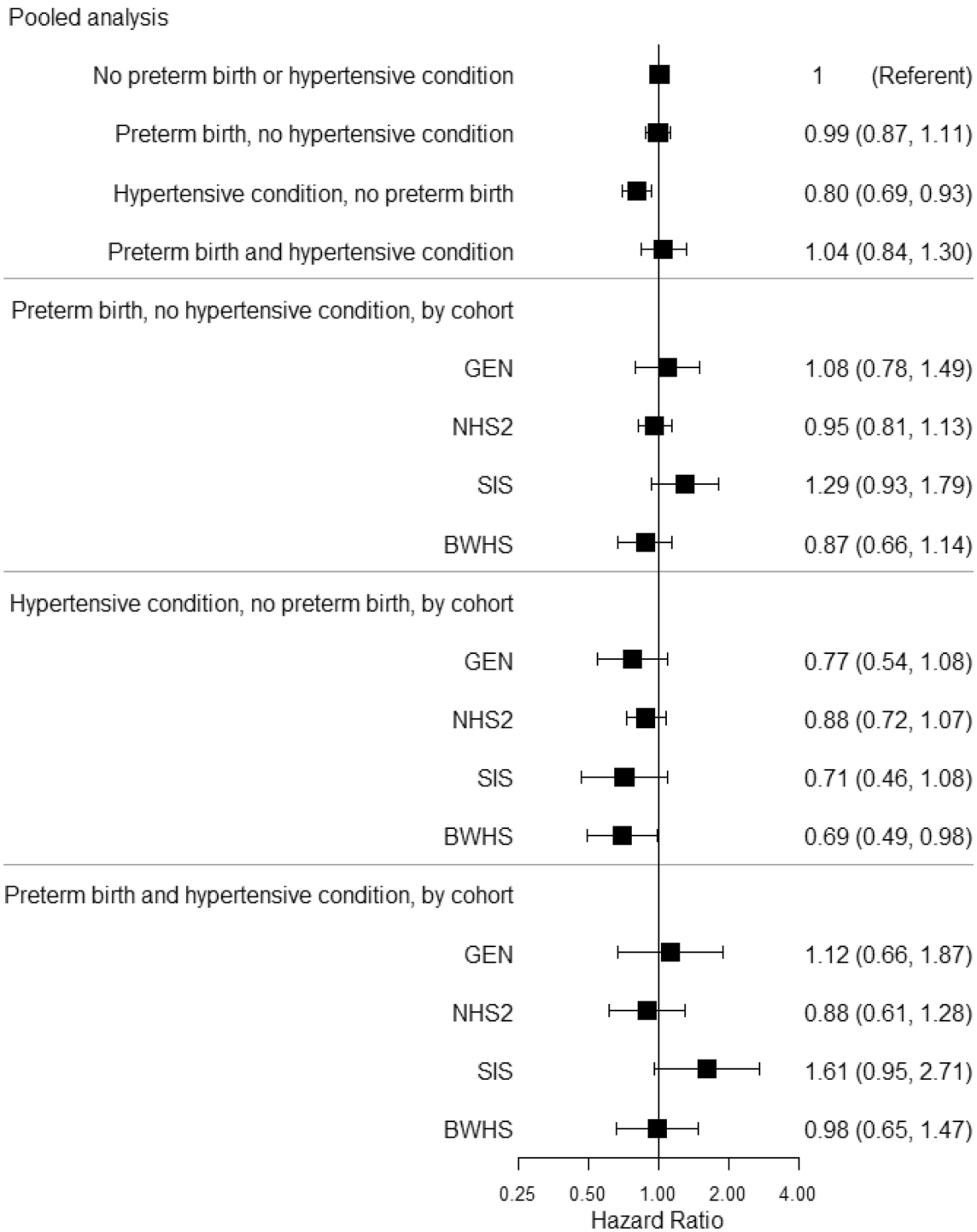

Fig. 2 Hazard ratios (HR) and 95% confidence intervals (CI) for preterm birth (<37 weeks) and hypertensive conditions of pregnancy in relation to premenopausal breast cancer risk. HRs are shown for the pooled analysis, and according to the individual study results in the Generations Study (GEN), Nurses' Health Study II (NHS2), Sister Study (SIS), and Black Women's Health Study (BWHS) cohorts

occur (Table 4). For first pregnancies with known infant sex, we did not observe meaningful variation in the overall estimates for preterm birth, gestational hypertension, or preeclampsia between male and female gestations (Supplementary Table 5).

Table 4 Hazard ratios (HR) and 95% confidence intervals (CI) for premenopausal breast cancer risk before age 55 stratified according to preeclampsia/ gestational hypertension and preterm birth in a first pregnancy

	PREECLAMPSIA/GESTATIONAL HYPERTENSION		NO HYPERTENSIVE CONDITION		*P* -interaction
	N	HR (95% CI) [c]	*N*	HR (95% CI) [c]	
Gestational weeks[a]	177	0.95 (0.91, 0.99)	2,001	0.99 (0.98, 1.01)	0.08
Gestational weeks[a]					
24- < 32 weeks	10	2.66 (1.36, 5.20)	33	1.01 (0.71, 1.43)	0.2
32- < 37 weeks	29	1.48 (0.95, 2.30)	130	1.11 (0.93, 1.33)	
37- < 40 weeks	50	1.22 (0.84, 1.76)	377	1.01 (0.90, 1.13)	
40- < 42 weeks	70	1	1238	1	
42 + weeks	18	1.24 (0.74, 2.09)	223	0.97 (0.84, 1.12)	
Preterm birth (< 37 weeks)					
No	138	1	1838	1	0.09
Yes	39	1.52 (1.06, 2.18)	163	1.09 (0.93, 1.28)	
	PRETERM BIRTH		NO PRETERM BIRTH		*P* -interaction
	N	HR (95% CI) [c]	*N*	HR (95% CI) [c]	
Gestational hypertension[b]					
No	142	1	1522	1	0.3
Yes	15	1.03 (0.60, 1.77)	59	0.76 (0.58, 0.98)	
Preeclampsia[a]					
No	169	1	1871	1	0.2
Yes	33	1.07 (0.73, 1.56)	105	0.82 (0.68, 1.00)	

[a]Available for the Nurses' Health Study II, Sister Study, and Generations Study

[b]Available for the Nurses' Health Study II and Sister Study

[c]Age as the time scale, adjusted for education, body mass index, smoking, and age at first birth

Discussion

This analysis leverages an existing collaboration, the Premenopausal Breast Cancer Collaborative Group, with an established infrastructure for investigation of exposures relevant to breast cancer incidence among reproductive-age women [45]. Hypertensive pregnancy conditions can result in a shorter gestational length, but few studies have jointly considered gestational hypertension and preterm birth in relation to breast cancer risk. Our results suggest that women who are diagnosed with hypertensive conditions experience lower premenopausal breast cancer risk compared to those without hypertensive conditions when the delivery is not preterm. Among women diagnosed with hypertensive conditions of pregnancy, subsequent preterm birth is associated with an increased risk of premenopausal breast cancer.

Our findings are consistent with a meta-analysis [4] of two cohorts (totaling more than 1.6 million women) in Norway [42, 43] and a third (> 778,000 women) in Denmark [44] that provided estimates for the association between preeclampsia and breast cancer risk stratified according to preterm birth. In analyses restricted to women who delivered at term, preeclampsia was associated with an HR of 0.79 (95% CI 0.75–0.84) for breast cancer risk [4]. However, in analyses restricted to women who delivered preterm, preeclampsia was not associated with breast cancer risk (HR 0.98, 95% CI 0.84–1.14) [4]. In an analysis of parous women in Norway, pregnancy duration (continuous weeks) was examined stratified by hypertensive conditions of pregnancy; pregnancy duration was not associated with breast cancer risk among women with a normotensive first pregnancy (HR 0.99, 95% CI 0.98–1.00) [43]. However, in those with preeclampsia or gestational hypertension, pregnancy duration was inversely related to overall breast cancer risk (HR 0.95, 95% CI 0.93–0.98) [43]. Our results mirrored these estimates,

although our analyses were specific to premenopausal breast cancer risk.

One potential explanation for these patterns may be related to the timing and origin of hypertensive conditions of pregnancy [43]. Earlier-detected preeclampsia (< 37 weeks) may be more related to placental dysfunction and reflect stronger anti-angiogenic profiles [46], while preeclampsia diagnosed closer to term may be more reflective of maternal metabolic factors such as overweight and obesity [47]. In our analyses, the magnitude of association appeared stronger in strata of women with an early adulthood BMI ≥ 25 kg/m^2. Although our primary analyses adjusted for early adulthood BMI, it is possible that the lower risk of breast cancer associated with hypertensive conditions at longer gestational lengths could reflect residual confounding from BMI, consistent with inverse associations between early adulthood BMI and premenopausal breast cancer risk in the Premenopausal Breast Cancer Collaborative Group [45]. The differential association with hypertensive conditions according to term and preterm delivery may provide clues concerning the genetic, hormonal, metabolic or immune factors that underlie shared associations with pregnancy outcomes and future breast cancer risk.

With the exception of the two analyses described above[4, 43], most previous studies have analyzed preterm birth and hypertensive conditions separately. A recent meta-analysis of preeclampsia and breast cancer risk reported an inverse association for premenopausal breast cancer (RR 0.81, 95% CI 0.75–0.87; 4 studies) [4]. The four studies included in the meta-analytic estimate were the Generations cohort (also included here), the prospective California Teachers Study, and two linkage studies of national data in Norway. To date, we are unaware of any available meta-analytic estimates for the association between gestational age and breast cancer risk. Among prospective studies, results for the association between gestational age and breast cancer risk are inconsistent. For example, in a Danish study, delivering at earlier gestational ages was positively associated with overall breast cancer risk [14], while a study of women in Israel, where preterm birth is more common (17% vs. 5%), earlier gestational age was negatively associated with breast cancer risk [22]. In the Danish investigation, after adjustment for age, calendar period, parity and age at first birth, the relative risk of breast cancer was 2.11 (95% CI 1.00–4.45) for deliveries < 29 weeks and 2.08 (95% CI 1.20–3.60) for 29–31 weeks compared with deliveries at term (40 weeks), with a statistically significant trend as gestational weeks increased (P-trend = 0.04) [14]. In contrast, in the Israeli study, women with a history of preterm birth had an estimated lower odds of overall breast cancer risk (HR 0.8, 95% CI 0.6–1.1) compared with those who delivered at term; statistical models adjusted for spontaneous versus induced labor, age, parity, diabetes mellitus, preeclampsia, and year of delivery [22].

Our analysis of pooled data from the Premenopausal Breast Cancer Collaborative Group is among the first to report associations between hypertensive conditions, preterm birth and breast cancer risk according to estrogen receptor status. In a previous report from the Generations cohort, one of the studies contributing to the current analysis, the hazard ratio for overall breast cancer associated with very preterm delivery (26–31 weeks) was 1.30 (95% CI 0.85–1.99) compared with delivering at term (40–41 weeks)[19]. The overall association was similar for ER positive breast cancer and was null, but imprecise, for ER negative breast cancer (ER+: $HR_{26\text{-}31\ vs\ 40\text{–}41} = 1.31$, 95% CI 0.82–2.08, ER-: $HR_{26\text{-}31\ vs\ 40\text{–}41} = 0.97$, 95% CI 0.31–3.06). Associations appeared stronger for premenopausal breast cancer risk; a first pregnancy duration of 26–31 weeks was associated with an HR of 2.38 (95% CI 1.26–4.49) compared with durations of 40–41 weeks. Premenopausal breast cancer risk associations were not stratified according to ER status.

The association between gestational age and breast cancer risk may be inconsistent in part due to the diverse factors that contribute to preterm birth risk, including genetics, infections, diabetes, and local medical practices and policies, in addition to potential modifying effects of hypertensive conditions of pregnancy. The Premenopausal Breast Cancer Collaborative Group has previously reported a lack of association between gestational diabetes and premenopausal breast cancer risk [48]; however, comprehensive data on medical practices, infection status, or other potential risk factors for preterm birth were not available for analysis. Despite our ability to pool data from five large cohort studies, analyses of subgroups defined by estrogen receptor status, number of pregnancies, or multiple pregnancy conditions invariably face analytic challenges due to small sample size. Information on preeclampsia, gestational hypertension, and gestational age was self-reported and may be subject to misclassification. However, due the prospective nature of the outcome data collection, any misclassification due to self-report is likely to be non-differential according to breast cancer status. For some cohorts, we also lacked comprehensive information on the characteristics of each individual pregnancy. Sensitivity analyses among participating cohorts that had detailed information on individual pregnancies (as opposed to whether any reported pregnancy was preterm, for example) provided reassurance that estimates were similar when pooled across pregnancies to reflect the

shortest gestation pregnancy, ever experiencing gestational hypertension, or preeclampsia.

Our findings support an inverse association between gestational hypertension or preeclampsia and premenopausal breast cancer in the absence of preterm birth. While some evidence supports variation in antiangiogenic profiles that accompany preeclampsia that have potential to inhibit tumor progression and metastasis [5], whether these profiles are sustained years after pregnancy has not been demonstrated. More work is needed to uncover the mechanisms contributing to associations with preeclampsia, and to investigate the heterogeneous conditions that may give rise to preterm birth, to inform future breast cancer risk.

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Author contributions The work reported in the paper has been performed by the authors, unless clearly specified in the text. HBN, DPS, AJS, and MJS contributed to study conceptualization, methodology, and supervision. HBN and MH conducted the formal analysis. HBN drafted the original manuscript, which was critically reviewed and approved by all authors.

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Data availability The data that support the findings of this study are not publicly available due to privacy or ethical restrictions. Study data may be shared upon reasonable request to senior authors.

Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethical approval Individual study protocols were approved by the relevant institutional review boards and obtained informed consent from participants.

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Authors and Affiliations

Hazel B. Nichols[1] · Melissa G. House[2] · Rina Yarosh[1] · Sara Mitra[3] · Mandy Goldberg[4] · Kimberly A. Bertrand[5] · A. Heather Eliassen[6,7] · Graham G. Giles[8,9,10] · Michael E. Jones[11] · Roger L. Milne[8,9,10] · Katie M. O'Brien[4] · Julie R. Palmer[5,12] · Sven Sandin[13,14,15] · Walter C. Willett[6,7,16] · Weiyao Yin[13,17] · Dale P. Sandler[4] · Anthony J. Swerdlow[11,18] · Minouk J. Schoemaker[11,19]

1 Department of Epidemiology, Hazel B. Nichols, University of North Carolina at Chapel Hill Gillings School of Global Public Health, 2104F McGavran-Greenberg Hall, 135 Dauer Drive, Chapel Hill, Chapel Hill, NC 27599-7435, USA

2 Westat, USA

3 Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, USA

4 Epidemiology Branch, National Institute of Environmental Health Sciences, Durham, USA

5 Slone Epidemiology Center, Boston University, Boston, USA

6 Channing Division of Network Medicine, Department of Medicine Brigham and Women's Hospital and Harvard Medical School, Boston, USA

7 Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, USA

8 Cancer Epidemiology Division Cancer Council Victoria, Melbourne, Australia

9 Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, Melbourne, Australia

10 Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Melbourne, Australia

11 Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK

12 Boston University Chobanian & Avedisian School of Medicine, Boston University, Boston, USA

13 Department of Medical Epidemiology and Biostatistics Karolinska Institutet, Solna, Sweden

14 Department of Psychiatry Icahn School of Medicine at Mount Sinai, New York, USA

15 Seaver Autism Center for Research and Treatment at Mount Sinai Icahn School of Medicine at Mount Sinai, New York, USA

16 Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, USA

17 Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu, China

18 Division of Breast Cancer Research, The Institute of Cancer Research, London, UK

19 Real World Solutions IQVIA, Amsterdam, The Netherlands