MAYO CLINIC

Cancer and Cardiovascular Risk in Women With Hypertensive Disorders of Pregnancy Carrying a Common IGF1R Variant

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Abstract

Objective: To evaluate the impact of insulin-like growth factor 1 receptor variant rs2016347 on the risk for breast and nonbreast cancers and cardiovascular disease in women with a history of hypertensive disorders of pregnancy (HDP).

Patients and Methods: This retrospective cohort study included all parous women in the UK Biobank with prior rs2016347 genotyping (N=204,155), with enrollment taking place from March 2006 to July 2010. History of HDP was self-reported, and outcomes included breast and all nonbreast cancers, hospital diagnoses of hypertension and cardiovascular disease, and direct blood pressure measurements.

Results: Women with previous HDP had a higher risk for future hypertension and cardiovascular diagnoses, increased blood pressures, and lower risk for breast cancer compared with women without HDP, consistent with prior studies. Hazard ratios for all nonbreast cancers were unchanged. However, when taking genotype into account, HDP-positive women carrying at least 1 thymine (T) allele of rs2016347 had a lower risk for nonbreast cancer (hazard ratio, 0.59; 95% CI, 0.37 to 0.92; P=.02) and lower systolic blood pressure (−2.08±0.98 mm Hg; P=.03) compared with women with the guanine/guanine (GG) genotype with positive evidence of interaction (HDP:T allele) for both outcomes; P=.04 and P=.03, respectively.

Conclusion: Women who experience HDP and carry a T allele of rs2016347 have 41% lower risk for developing nonbreast cancer and a lower systolic blood pressure of 2.08 mm Hg when compared with those with the GG genotype, suggesting a possible role of the insulin-like growth factor 1 axis for both cardiovascular and cancer risk in women with HDP.

 ■ Mayo Clin Proc. 2020;95(12):2684-2696

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Hypertensive disorders of pregnancy (HDPs) include gestational hypertension (HTN) and preeclampsia and currently complicate up to 10% of all pregnancies. In addition to being one of the major causes of maternal and fetal mortality, these conditions are known to be associated with major changes in the risk for future disease for the mother. It is now well established that women with a history of HDPs have an increased risk for cardiovascular disease (CVD) and related mortality, including approximately 2 to 2.5 times the risk for ischemic heart disease, congestive heart failure, and stroke, and 3 to 4 times the risk for HTN.[1-4]

Studies dating back decades have reported a decreased risk for breast cancer as well, and although results have not always been consistent, most larger cohort studies have reported a decrease in risk of 10% to 20%.[5-9] The risk for all nonbreast cancers combined appears largely unchanged. However, some studies have reported differences in certain cancer types, with 2 reporting a decreased risk for lung/respiratory cancers and others reporting an increased risk for endometrial cancer, suggesting that the

nonbreast cancer impact of HDP may vary by organ or cell type.[10-12] Although HDP-associated cancer and CVD risks may be either competing or additive, the hazard ratio (HR) for all-cause mortality in women with HDP is 1.65 compared with women without HDP,[13] reflecting its major impact on future health.

Hypertensive disorders of pregnancy have been associated with changes in hormone levels, alterations in the balance of angiogenic/antiangiogenic factors, vascular dysfunction, and variations in growth factors, including lower levels of insulin-like growth factor 1 (IGF1), all of which have been hypothesized to play a role in the modified maternal risk for future disease.[14] With regard to HDPs and future cancer risk, our prior population studies[15-17] have called specific attention to the role of the IGF1 axis by demonstrating that breast cancer protection after HDP appears to be significantly increased in women inheriting the thymine (T) allele of rs2016347, a common but functionally blunted single-nucleotide polymorphism (SNP) of the IGF1 receptor (IGF1R). Most recently, we have demonstrated that this breast cancer protection may be due to more complete mammary gland involution, a process known to be regulated by the IGF1 axis.[18]

Because dysregulation and overactivation of the IGF1 axis have been implicated in the development and/or progression of many other malignancies besides breast cancer,[19-21] and given that the degree of functional blunting of the IGF1R variant rs2016347 across normal tissues varies considerably (some showing much greater and others lesser effects than seen in the breast),[22] it remains to be determined whether HDP in combination with the T allele of rs2016347 protects from malignancies other than breast cancer. Moreover, the IGF1 axis plays a major role in normal organ growth and development. In particular, there have been many reports of its impact on the developing cardiovascular system and its proclivity toward CVD.

Although specific IGF1R variants have been linked to the future risk for developing HTN,[23] in general, the IGF1 axis appears to exert a complex and frequently opposite effect on specific CVD risks relative to its tumor-promoting affect. For example, whereas higher IGF1 levels have been associated with lower blood pressure and have been linked to reduced atherosclerotic plaques (by exerting anti-inflammatory and antioxidative effects), reduced IGF1R expression seemingly accelerates atherosclerosis and loss of cardiac function with aging.[24-26] Thus, to address the question of potentially competing lifespan effects from a systemwide change in the IGF1 axis as induced by HDPs, it is important to assess both CVD and cancer risks in a given HDP population genotyped for the IGF1R SNP rs2016347.

The present study used the UK Biobank with its more than 500,000 participants and extensive phenotypic and genetic data to test 2 hypotheses: 1) women with a history of HDP who also carry a T allele of IGF1R SNP rs2016347 have a reduced risk for malignancies other than breast cancer, and 2) the risk for future CVD in women with a history of HDPs is modified by the rs2016347 genotype. This study may provide new insights into a mechanistic link underlying these 2 seemingly disparate yet most common life-threatening chronic diseases facing women today.

PATIENTS AND METHODS

Study Design

The current retrospective cohort study was performed in the UK Biobank, a large longitudinal study population including 272,974 women recruited from across the United Kingdom in 2006 to 2010 with a median age in 2019 of 68 years and age range of 49 to 82 years. The study collected extensive phenotypic and genetic information, including data from questionnaires; physical measurements such as height, weight, and blood pressure readings; blood sampling with genotyping and extensive SNP imputation; and longitudinal health outcomes including cancer as *International Classification of Diseases, Tenth Revision*

(*ICD-10*) coded diagnoses from the cancer registry and hospital inpatient diagnostic codes.[27,28] Covariates including age, ethnicity, smoking history, body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared), parity, age at first birth, age of menarche, alcohol intake, exercise frequency, and family history of cancer were available.

Informed consent was obtained from all UK Biobank participants. Ethical procedures and study approval was provided by the UK Biobank Ethics Committee, REC approval number 11/NW/0382.

Study Population

This study included only parous women, which resulted in the exclusion of 52,872 participants from the UK Biobank's cohort of 272,974 women. In addition, 3.2% (7067 of 220,102) female participants did not have genomic data, 8856 were excluded because their imputed genotype call probability did not reach our probability threshold of 0.95, and 24 participants recently withdrew from the study, leaving a total study population of 204,155.

Upon study entry, participants were asked health-related questions using a computer touchscreen, and those who reported additional serious medical conditions then underwent a verbal interview. There were 1896 participants who reported an HDP, and this included both gestational HTN and preeclampsia, with no distinction made by the recording staff. The comparison group consisted of 202,259 parous women who did not self-report HDPs.

The UK Biobank collected blood specimens from all participants at the time of entry into the study. Initially, 9.9% (49,950 of 502,505) of all study participants were genotyped using the Applied Biosystems UK BiLEVE Axiom Array by Affymetrix (807,411 markers), and after this, an additional 87.2% (438,427 of 502,505) of participants were genotyped using the closely related Applied Biosystems UK Biobank Axiom Array (825,927 markers). The 2 arrays share 95% of their marker content. Specimens then underwent imputation using the Haplotype Reference Consortium and UK10K haplotype resource for efficient imputation resulting in an increase to about 96 million variants, including our SNP of interest, rs2016347. The observed allele frequencies for rs2016347 were consistent with Hardy-Weinberg equilibrium, $P=.26$, with a T-allele frequency of 0.503, whereas that for guanine (G) was 0.497.

Specific cancer outcomes from the cancer registry were determined by *ICD-10* coding. Breast cancer cases (n=65) were identified by *ICD-10* code C50 for invasive cases, and the category of "all nonbreast cancers" included all other invasive cancers from C00 to C97, excluding only nonmelanoma skin cancers (C44). There were a total of 83 nonbreast cancers in women with HDPs, and these included 16 colon/rectal, 10 uterus, 10 lymphoma, 8 ovary, 6 melanoma, 5 lung, 4 cervix, 4 kidney, and 3 each of hematopoietic, thyroid, and connective/soft tissue malignancies.

Cardiovascular outcomes of interest included direct measurements of systolic and diastolic blood pressures recorded using an Omron automated device at the time of study entry. Two measurements were taken a few minutes apart, and the average of these 2 readings was used in our study. Hospital inpatient diagnoses of ischemic heart disease, myocardial infarction, or stroke by *ICD-10* codes I20 to I25 and I63 to I66, whether either as a primary or secondary diagnosis, are collectively referred to as "hospital diagnoses of CVD." An additional outcome of "hospital diagnoses of HTN" includes women who had a primary or secondary hospital inpatient diagnosis of primary HTN, which consisted of *ICD-10* code I10.

Statistical Analyses

Many of the variables of interest had missing values; within the adjustment set, these included BMI, age at menarche, and age at first birth. Because the number missing was low for BMI (0.32%) and age at menarche (2.78%), analyses were run using only participants with complete information for these variables. Age at first birth was not

reported for 34,603 of 204,155 parous women (16.95%) and was multiply imputed through predictive mean matching. The multiply imputed data sets were used to analyze the cancer outcomes only. For our SNP of interest, rs2016347, genotype had already been imputed by the UK Biobank and only predicted genotypes with a probability greater than 0.95 were included in the analyses.

Cox proportional hazards regressions with attained age as the time scale were used to calculate HRs and 95% CIs for the analyses of breast cancers and all nonbreast cancers. To detect incident cancers with respect to HDPs, women entered the risk set after their first birth. Breast cancer models comparing HDP-positive (HDP+) with HDP-negative (HDP−) women were adjusted for participant birth year, ethnicity, BMI, smoking status, age at first birth, and family history of breast cancer in a first-degree relative at the time of study entry. Models examining the association of HDP with all nonbreast cancers were adjusted for participant birth year, BMI, smoking status, ethnicity, and age at first birth. Data for family history for nonbreast cancers were limited and not adequate for use. Violations of the proportional hazards assumption were assessed using model-based techniques as recommended for large sample sizes.[29]

Specific dates for later-life diagnoses of CVD and HTN were not available because these outcomes were based on inclusion in hospital discharge data. This did not permit time-to-event analysis, and logistic regression models were used to calculate odds ratios (ORs) and 95% CIs for the analyses of CVD and HTN. Associations of these outcomes with HDPs were adjusted for age at entry into the study, BMI, and smoking status at time of study. Linear regressions were used to estimate average additive changes and 95% CIs in systolic and diastolic blood pressure readings associated with HDP status. These models adjusted for age at entry into the study, BMI, smoking status at time of study, and current use of blood pressure medication.

TABLE 1. Characteristics of Study Participants by HDP Status[a,b]

Characteristic	HDP+ (n=1896)	HDP− (n=202,259)	*P*
Age at entry (y), mean ± SD	52.93±8.31	54.89±7.86	<.001
Ethnicity, no. (%)			
White	1835 (96.8)	192,738 (95.3)	<.001
Indian/Pakistani	7 (0.4)	2,600 (1.3)	
Black	13 (0.7)	1,442 (0.7)	
Mixed	16 (0.8)	1,981 (1.0)	
Other	19 (1.0)	2,997 (1.5)	
Smoking history, no. (%)			<.001
Never	1264 (66.7)	118,839 (58.8)	
Previous/current	626 (33.0)	82,620 (40.8)	
BMI (kg/m^2), mean ± SD	28.18±5.57	27.11±5.06	<.001
Education, no. (%)			.11
College/university	399 (21.0)	45,755 (22.6)	
Parity, mean ± SD	2.20±0.84	2.21±0.83	.59
Age at first birth (y), mean ± SD	26.07±4.96	25.29±4.76	<.001
Family history of breast cancer, no. (%)	204 (10.8)	22,778 (11.3)	.51
Alcohol intake (d/wk), no. (%)			<.001
<1	726 (38.3)	75,597 (37.4)	
1-4	931 (49.1)	94,736 (46.8)	
≥5	237 (12.5)	31,783 (15.7)	
Exercise (d/wk), no. (%)			.26
0-1	371 (19.6)	38,054 (18.8)	
2-4	765 (40.3)	79,086 (39.1)	
≥5	723 (38.1)	80,256 (39.7)	
rs2016347 (genotype), no. (%)			.84
GG	460 (24.3)	50,084 (24.8)	
GT	946 (49.9)	100,873 (49.9)	
TT	490 (25.8)	51,302 (25.4)	

[a]BMI = body mass index; G = guanine; HDP(+/−) = hypertensive disorder of pregnancy (positive/negative); T = thymine.
[b]Percentages may not total 100% due to missing values.

All analyses were carried out using R, version 3.6.1 Action of the Toes (The R Project for Statistical Computing).[30] The "mice" package was used for multiple imputation.[31] Regressions relied on the "survival" and "stats" packages.[32,33] Likelihood ratio tests made use of the "lmtest" package.[34] Plots were made with "ggplot2."[35] All code needed to recreate this analysis is available at https://github.com/sdufault15/breast-cancer.

Genetic Model Selection

To optimize statistical power and limit multiple testing issues related to the numerous

Outcome	HDP+, no. (%)	HDP−, no. (%)	MoA (95% CI)[a]	P
All nonbreast cancers	83 (4.3)	9975 (4.9)	1.00 (0.80-1.24)	.97
Breast cancer	65 (3.4)	9933 (4.8)	0.74 (0.58-0.95)	.02
Hospital CVD diagnosis	127 (6.6)	10,803 (5.3)	1.46 (1.21-1.76)	<.001
Hospital HTN diagnosis	478 (24.9)	34,725 (16.9)	1.87 (1.67-2.09)	<.001
Systolic blood pressure>140	1820 (50.8)	191,332 (37.4)	7.48 (6.68-8.28)	<.001
Diastolic blood pressure>90	1820 (28.2)	191,332 (16.3)	3.48 (3.05-3.91)	<.001

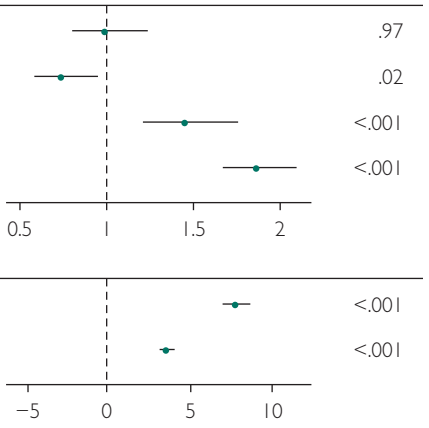

FIGURE 1. Outcome by hypertensive disorder of pregnancy (HDP) exposure, with number and percent of each outcome, systolic blood pressure outcome defined as greater than 140 mm Hg and diastolic blood pressure outcome defined as greater than 90 mm Hg. [a]Measures of association (MoA) for recessive genetic model. All nonbreast cancers: hazard ratio (HR) adjusted for birth year, ethnicity, smoking, and body mass index (BMI). Breast cancer: HR adjusted for birth year, ethnicity, age at first birth, parity, BMI, smoking, and family history of breast cancer. Hospital cardiovascular disease (CVD) and hypertension (HTN) diagnoses: odds ratios adjusted for age, BMI, and smoking. Systolic and diastolic blood pressure: difference in mean adjusted for age, BMI, smoking, and current use of blood pressure medication.

outcomes, covariate-adjusted models, and potential genetic models (eg, 6 outcomes × 4 adjusted models/outcome × 4 genetic models/adjusted model = 96 genetic models), we used strategies based on previously published studies of the association of rs2016347 with disease outcomes to select our primary genetic model. These studies demonstrated that the effect of the GT genotype tracked most closely to the TT genotype when assessing breast density[15] and breast cancer risk[16] in women with HDPs, and for pathologic response after neoadjuvant chemotherapy for breast cancer[36] and disease recurrence and survival in women with estrogen receptor−positive breast cancer treated with tamoxifen.[37] Hence our analytic approach focused on using the recessive model, which compares the GG genotype with the GT/TT genotypes combined. After all analyses were completed, we checked univariate models for outcomes with statistical significance and found that the recessive model demonstrated lower *P* values than the dominant and additive models, and likelihood ratio analysis failed to demonstrate a superior fit for the codominant over the recessive model. Therefore, only the recessive model results are provided.

RESULTS

Participant Characteristics

Characteristics of study participants are summarized in Table 1. Compared with women without HDPs, women with a history of HDP were 2 years younger, were more likely to be white, had higher BMI, were less likely to have smoked, and had a later age of first birth, but all differences were small in magnitude and controlled for in subsequent analyses. Obesity is a well-established risk factor for HDPs, and cigarette smoking has been previously associated with decreased risk for HDPs.[38] In looking at outcomes of interest in the entire study population, the overall unadjusted incidence rates for all nonbreast cancers was 4.93% (10,058 of 204,155); for breast cancer, 4.90% (9,998 of 204,155); for inpatient CVD diagnosis, 5.35% (10,930 of 204,155); and for inpatient HTN diagnosis, 17.24% (35,203 of 204,155). Mean

Mayo Clin Proc. ■ December 2020;95(12):2684-2696 ■ https://doi.org/10.1016/j.mayocp.2020.03.037
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TABLE 2. Association of IGF1R SNP rs2016347 Genotype With Study Outcomes[a]

Outcome[b] (n=total cases/readings)	rs2016347 Genotype[c] GG	GT	TT	P[d]	MoA (95% CI)[e]	P
All nonbreast cancers (n=9900)	5.06	4.75	4.85	.03	0.94 (0.90 to 0.98)	.01
Breast cancer (n=9830)	4.81	4.89	4.68	.20	1.00 (0.95 to 1.04)	.90
Hospital CVD diagnosis (n=10,758)	5.15	5.24	5.45	.09	1.03 (0.99 to 1.08)	.18
Hospital HTN diagnosis (n=34,604)	17.14	16.81	17.04	.22	0.98 (0.96 to 1.01)	.18
Systolic blood pressure (n=193,152)	135.85	135.92	135.85	.75	0.05 (−0.15 to 0.25)	.62
Diastolic blood pressure (n=193,155)	80.68	80.65	80.57	.46	-0.06 (−0.16 to 0.05)	.29

[a]CVD = cardiovascular disease; G = guanine; HTN = hypertension; IGF1R = insulin-like growth factor 1 receptor; MoA = measures of association; SNP = single-nucleotide polymorphism; T = thymine.

[b]All nonbreast cancer cases include all cancers except breast and nonmelanoma skin cancers; breast cancer cases include only invasive cancers; hospital cardiovascular diagnosis (CVD) and hospital hypertension diagnosis (HTN) cases are based on inpatient *International Classification of Diseases, Tenth Revision* diagnostic codes. Systolic and diastolic blood pressures are mean values in millimeters of Mercury on study entry.

[c]For nonbreast cancers, breast cancer, CVD, and HTN, values represent percent of each genotype with outcome; for systolic and diastolic blood pressures, values are mean pressures for each genotype.

[d]*P* values are for χ^2 independence between genotype and outcome.

[e]MoA are for recessive genetic model with *P* values for hazard ratios for nonbreast and breast cancers, odds ratios for hospital CVD and HTN, and differences in mean blood pressures for systolic and diastolic blood pressures.

systolic blood pressure was 135.88 mm Hg, and mean diastolic blood pressure was 80.63 mm Hg.

Risks for Later-Life Cancer and CVD in HDP+ Women

Women with a history of HDP had no change in the risk for developing all nonbreast cancers as a group (adjusted HR, 1.00; 95% CI, 0.80 to 1.24; *P*=.97) when not considering the impact of genotype. However, they had lower risk for developing breast cancer (adjusted HR, 0.74; 95% CI, 0.58 to 0.95; *P*=.02). Their odds of having a later-life hospital diagnosis of CVD or HTN were increased (adjusted OR, 1.46; 95% CI, 1.21 to 1.76; *P*<.001; and OR, 1.87; 95% CI, 1.67 to 2.09; *P*<.001, respectively) when compared with HDP− participants. They also had higher mean systolic and diastolic blood pressures at study baseline, demonstrating an increased mean systolic blood pressure of 7.48±0.80 mm Hg and an increased diastolic mean blood pressure of 3.48±0.43 mm Hg; *P*<.001 for both). These findings are summarized in Figure 1, which includes total numbers and unadjusted incident rates for each outcome.

Association of IGF1R rs2016347 Genotype With Study Outcomes

The association of genotype with each study outcome is provided in Table 2. The distribution of genotypes was not significantly different for any outcome with the exception of all nonbreast cancers, for which the χ^2 for independence of genotypes and outcome was significant at *P*=.03. The HR for all nonbreast cancers for the recessive genetic model was 0.94; 95% CI, 0.90 to 0.98; *P*=.01.

Results of Analyses Stratified by HDP Status for rs2016347 Genotype

Despite showing no change in risk for nonbreast cancers when not taking genotype into account, stratified analyses by HDP status revealed a significant impact of genotype for those carrying at least 1 T allele (recessive model); adjusted HR, 0.59; 95% CI, 0.37 to 0.92; *P*=.02 among women who are HDP+ compared with adjusted HR, 0.94; 95% CI, 0.90 to 0.99; *P*=.01 for participants who are HDP−. The *P* value for the HDP+:T allele interaction term was significant at *P*=.04 (Figure 2).

Analyses for breast cancer stratified by HDP status revealed no impact of genotype on risk; HR, 1.16; 95% CI, 0.64 to 2.09;

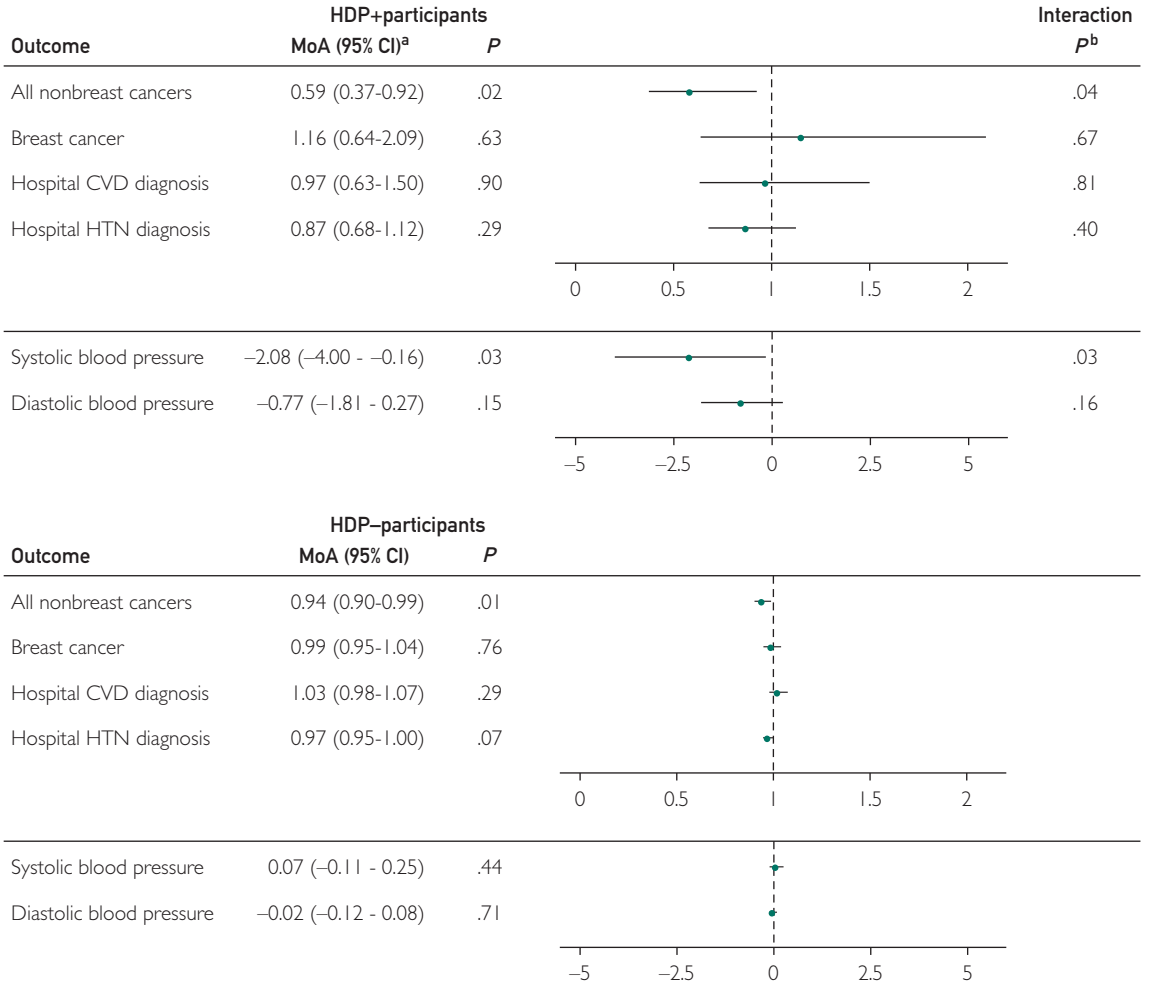

FIGURE 2. Association of outcomes for recessive genetic model of rs2016347 stratified by hypertensive disorder of pregnancy (HDP) status. [a]Measures of association (MoA): All nonbreast cancers: hazard ratio (HR) adjusted for birth year, ethnicity, smoking, and body mass index (BMI). Breast cancer: HR adjusted for birth year, age at first birth, parity, BMI, ethnicity, smoking, and family history of breast cancer. Hospital cardiovascular disease (CVD) and hypertension (HTN) diagnoses: odds ratios adjusted for age, BMI, and smoking. Systolic and diastolic blood pressure: change in mean adjusted for age, BMI, smoking, and current use of blood pressure medication. [b]Interaction term is HDP-positive (HDP+):T allele (thymine [T]T/guanine [G]T compared to GG genotype) of rs2016347.

P=.63 for HDP+ and HR, 0.99; 95% CI, 0.95 to 1.04; *P*=.76 for HDP− participants.

Results for hospital CVD and HTN diagnoses did not vary by genotype. In the HDP+ group, those carrying a T allele had an adjusted OR of 0.97; 95% CI, 0.63 to 1.50; *P*=.90 for hospital CVD compared with OR, 1.03; 95% CI, 0.98 to 1.07; *P*=.29 in the HDP− group, and for hospital HTN diagnosis, OR, 0.87; 95% CI, 0.68 to 1.12; *P*=.29 compared with OR, 0.97; 95% CI, 0.95 to 1.00; *P*=.07 in the HDP− group.

Although systolic and diastolic blood pressures were higher in the HDP+ group as a whole, the stratified analysis demonstrated that these increases were significantly diminished in those who are HDP+ and carry a T allele. Although mean systolic blood pressure did not change significantly by genotype in the HDP− group, +0.07±0.09 mm Hg; *P*=.44, in HDP+ participants, mean systolic blood pressure at study entry was lower in those with a T allele, −2.08±0.98 mm Hg; *P*=.03. The interaction term for HDP+:T

Mayo Clin Proc. ■ December 2020;95(12):2684-2696 ■ https://doi.org/10.1016/j.mayocp.2020.03.037
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allele was significant at $P=.03$. The diastolic blood pressure difference had a similar but attenuated pattern. There was no significant difference in the HDP− group, mean difference of −0.02±0.05 mm Hg, $P=.71$, whereas in the HDP+ group, mean diastolic blood pressure was −0.77±0.53 mm Hg; $P=.15$, with the interaction term for HDP+:T allele demonstrating $P=.16$.

DISCUSSION

This study demonstrated a favorable impact on the risk for future disease for women with a history of HDPs who carry a T allele of IGF1R SNP rs2016347. This risk reduction spans multiple systems and tissue types, with lower risk for developing nonbreast cancers and lower systolic blood pressure when compared with those carrying the GG genotype. These findings also support the hypothesis that the IGF1 axis plays a significant mechanistic role in determining the future health risks of women with HDPs in regard to 2 major chronic diseases, cancer and CVD.

Results here confirm previously reported associations of HDPs without genotype with increased risk for CVD, lower risk for breast cancer, and no change for nonbreast cancer risk.[1-11] Looking at genotype alone, rs2016347 was only associated with all nonbreast cancers, HR, 0.94; 95% CI, 0.90 to 0.98: $P=.01$, and although this decrease in risk was relatively small, it was statistically significant for the recessive model and has not been previously reported. Further studies are needed to validate this finding and facilitate the identification of associations with specific cancer sites, which could have significant clinical relevance. Supporting our hypothesis that the genotype of rs2016347 is a moderator (ie, effect modification) of HDP exposure, we observed that the risk for developing all nonbreast cancers was 41% lower in women with a history of HDPs if they carry a T allele as compared with those carrying the GG genotype. Limited numbers did not permit proper statistical analysis of specific organ cancers. However, a non−statistically significant lower HR for those carrying a T allele was seen in all cancer groups examined, including respiratory, gastrointestinal, melanoma, female genital, and blood/lymph cancers.

In addition, systolic blood pressure, although higher in women with HDP exposure, was diminished by 27.8% if they carried the T allele and diastolic blood pressure was decreased by 22.1%. There was evidence of interaction for both the lowered risk for all nonbreast cancers and the lower systolic blood pressure, demonstrating that the association for women with a history of HDPs carrying the T allele was greater than what would have been expected by the impact of each exposure alone.

The role of the IGF1 axis in tumor formation, patient survival, and response to treatment has been well documented, as has the critical role of its major receptor, IGF1R, in driving malignant transformation.[39,40] Perhaps most relevant to this study's findings are the lower IGF1 levels reported in women with a history of HDPs.[41-44] The possibility of a mechanistic interaction between the lower circulating IGF1 levels and expression of rs2016347, a functional IGF1R SNP located in its noncoding 3′ untranslated region, is suggested by in silico prediction of a new microRNA binding site within the rs2016347 T allele transcript.[45] The expected microRNA blunting of IGF1R messenger RNA expression levels for the T allele can be seen in multiple types of normal human tissues within the Genotype-Tissue Expression databases.[22] Although it is remotely conceivable that the observed lower risk for nonbreast cancer might be secondary to HDP-linked HTN, this seems unlikely because HTN and its treatments have nil to weak associations with cancer development in women, with the possible exception of renal cancer.[46-49]

The likelihood of a lasting organ effect by HDP exposure is supported in part by previous findings that pregnancy can produce durable epigenetic tissue changes mediated by gene methylation.[50] In particular, the IGF1 gene and various genes involved in IGF1 signaling are similarly downregulated, and animal models have

confirmed that in the mammary gland, giving birth induces long-lasting methylation and downregulation of IGF1R and downstream mediators.[51,52] Whereas the impact of giving birth and age of first birth in relation to nonbreast cancer risk is variable and perhaps most significant in hormonally responsive tissues,[53] there are many reports of associations of decreased risk related to parity and early childbirth in colorectal, lung, renal, bladder, and pancreatic cancers,[54-59] raising the possibility that systemwide epigenetic tissue changes may occur after a hypertensive pregnancy, and that these effects may be further enhanced to effectively decrease a woman's overall cancer risk in those carrying the functionally blunted IGF1R T allele variant of rs2016347.

To our knowledge, the impact of rs2016347 on nonbreast cancer has not been previously reported in women with HDPs. However, there have been studies describing its impact on cancer risk unrelated to HDPs. The T allele of rs2016347 has been associated with a better pathologic response to neoadjuvant chemotherapy, as well as less tumor progression and decreased mortality in patients with estrogen receptor−positive breast cancer treated with tamoxifen.[35,36] The T allele of rs2016347 was also shown to interact with an IGF1 polymorphism to decrease the risk for prostate cancer recurrence after radical prostatectomy.[60]

For breast cancer, women with HDPs had a 26% decrease in risk, which is at the high end but consistent with what has been demonstrated in other large cohorts.[8] Our study found no evidence of rs2016347 genotype modification of the discussed HDP+ protective effect, in contrast to our earlier California Teachers Study (CTS) findings.[17] The low number of HDP+ UK Biobank women developing invasive breast cancer (n=65) and the high rate of protection resulting from HDPs alone in this study may have limited statistical power to evaluate this association. Alternatively, this inconsistency could represent differences between the UK Biobank and CTS cohorts because the former enrolled a cross-section of women throughout the United Kingdom whereas the latter enrolled only California teachers, a known high-risk breast cancer group.

The relationship between the IGF axis and HTN and CVD is complex. Insulin-like growth factor 1 induces vasodilation and displays anti-inflammatory and plaque-stabilizing properties, yet it also drives cellular proliferation and has proatherogenic activities.[61] Many studies have shown a significant inverse association between blood pressure and IGF1 levels, suggesting that the lower IGF1 levels reported in HDPs might directly contribute to higher blood pressure. Lower IGF1 levels have also been associated with increased risk for metabolic syndrome and CVD.[62,63] Our finding of lower systolic blood pressure in women with HDPs carrying a T allele is mechanistically provocative, but longitudinal studies with longer follow-up are required. Although the impact on future risk for CVD varies with blood pressure level, a decrease in systolic blood pressure of 2.08 mm Hg would be expected to decrease lifetime risk for CVD by only 2% to 4%, and this study was not powered sufficiently to detect this degree of change in HDP+ women analyzed by genotype.[64,65]

It appears that women who have a predisposition for CVD are more likely to experience HDPs under the stress of pregnancy because the risk factors for HDPs are very similar to the risk factors for CVD and include obesity, higher initial blood pressure, increased waist size, insulin resistance, and lipid level abnormalities.[66,67] Furthermore, these risk factors seem to be present in both gestational HTN and preeclampsia.[68] It is certainly possible or even likely that the increased risk for future CVD is already largely predetermined in women who have a hypertensive pregnancy, but the impact on cancer risk, which is largely favorable, is a direct result of the events accompanying a hypertensive pregnancy.

Using the large and well-documented UK Biobank provided this study with many strengths, including availability of a wide range of covariates, disease outcomes from

the cancer registry and from inpatient hospital diagnoses, and almost complete SNP data for study participants, including our main SNP of interest, rs2016347. The T allele frequency in this study was 50.3% (205,403 of 408,310), which is only slightly higher than the mean global frequency of 48.3% and slightly lower than the 51.0% seen in the CTS.[69] As with all studies, there is an issue of generalizability of the results, especially with white women comprising more than 95% (194.573 of 204,155) of study participants. However, the UK Biobank has been shown to have similar breast cancer rates to the general UK population and overall cancer and CVD rates are relatively similar between the United Kingdom and United States.[70-72]

A major limitation of this study was the relatively low number of women who self-reported HDPs. These 1896 women represented about 1% of parous women in the UK Biobank, while we would have expected this number to be much larger. This may have misclassified women with HDPs, resulting in their inclusion in the reference group. It is unlikely that women without HDPs were included in the HDP+ group, particularly given the characteristics (higher BMI and lower smoking rates) and increased risk for CVD and lower breast cancer risk consistent with previous studies. The inclusion of HDP cases in the reference group would be expected to bias our findings toward the null and thus would not diminish the statistically significant findings. The lower numbers of HDPs resulted in a correspondingly lower number of cases for the studied outcomes, affecting most notably the breast and all nonbreast cancer analyses.

The study was also limited in its ability to perform time-to-event analyses for future outcomes of HTN and CVD due to its reliance on hospital diagnoses, which may not accurately reflect time to initial diagnosis, and does not include participants who may have developed these outcomes without a hospital admission. However, logistic regression has been shown to closely approximate time-to-event analyses when the outcome is relatively uncommon, the duration of the outcome is long, and the magnitude of the association is not particularly strong,[73,74] yet the resulting ORs are not directly comparable to the HRs generated for nonbreast and breast cancers. In addition, using hospital diagnoses might be expected to disproportionately underestimate the cases of HTN and CVD in HDP+ participants due to their demonstrated higher mortality rates[13] and higher blood pressures at study entry, making them more likely to have developed HTN or CVD that was not captured in a hospital admission.

In addition, the UK Biobank data did not separate gestational HTN from preeclampsia, and combining the conditions could affect the genotypic findings because they may involve distinct pathways of pathogenesis. However, most studies have shown that the risks for CVD and cancer are relatively similar for preeclampsia and gestational HTN.[5,6,8,68,75]

CONCLUSION

Women who experience HDPs have 41% lower risk for developing nonbreast cancer and have lower later-life blood pressures if they inherit a T allele of the common functional IGF1R variant rs2016347. These novel findings add to a growing body of epidemiologic evidence pointing to a clinically significant exposure interaction between HDPs and rs2016347 (effect modification) and strongly implicate a mechanistic role for the IGF1 axis in driving both cardiovascular and cancer risk, particularly in women with a history of HDPs. Because nonbreast cancers afflict 30% of women in their lifetime, confirmation of this study's findings could lead to improved individualized cancer screening, as well as novel prevention strategies.

ACKNOWLEDGMENTS

This research has been conducted using the UK Biobank Resource, and Zero Breast Cancer provided valuable administrative assistance.

Abbreviations and Acronyms: **BMI** = body mass index; **CTS** = California Teachers Study; **CVD** = cardiovascular disease; **G** = guanine; **HDP(+/−)** = hypertensive disorder of pregnancy(-positive/negative); **HR** = hazard ratio; **HTN** = hypertension; ***ICD-10*** = *International Classification of Diseases, Tenth Revision*; **IGF1** = insulin-like growth factor 1; **IGF1R** = insulin-like growth factor 1 receptor; **MoA** = measure of association; **OR** = odds ratio; **SNP** = single-nucleotide polymorphism; **T** = thymine

Grant Support: This work was supported in part by the National Institutes of Health and National Cancer Institute (grant U24CA210990), and research and publication costs were supported by the Elizabeth MA Stevens donor funds provided to the Buck Institute for Research on Aging. The funding sources had no role in any aspect of the conception, design, implementation, analysis, or interpretation of this study and had no involvement in the decision to submit the article for publication.

Potential Competing Interests: The authors declare no competing interests regarding the analysis of the data or the publication of this report.

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