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Article

Disparities in Cardiovascular Disease Risk Among Hispanic Breast Cancer Survivors in a Population-Based Cohort

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Abstract

Background: Breast cancer is the leading cause of cancer death among Hispanic women. The aim of our study was to estimate cardiovascular disease (CVD) risk among Hispanic and non-Hispanic White (NHW) breast cancer survivors compared with their respective general population cohorts. **Methods:** Cohorts of 17 469 breast cancer survivors (1774 Hispanic and 15 695 NHW) in the Utah Cancer Registry diagnosed between 1997 and 2016, and 65 866 women (6209 Hispanic and 59 657 NHW) from the general population in the Utah Population Database were identified. Cox proportional hazards models were used to estimate hazard ratios (HRs) for CVD. **Results:** The risk of diseases of the circulatory system was higher in Hispanic than NHW breast cancer survivors 1-5 years after cancer diagnosis, in comparison with their respective general population cohorts ($HR_{Hispanic} = 1.94$, 99% confidence interval [CI] = 1.49 to 2.53; $H_{NHW} = 1.38$, 99% CI = 1.33 to 1.43; 2-sided $P_{heterogeneity} = .01$, respectively). Increased risks were observed for both Hispanic and NHW breast cancer survivors for diseases of the heart and the veins and lymphatics, compared with the general population cohorts. More than 5 years after cancer diagnosis, elevated risk of diseases of the veins and lymphatics persisted in both ethnicities. The CVD risk due to chemotherapy and hormone therapy was higher in Hispanic than NHW breast cancer survivors but did not differ for distant stage, higher baseline comorbidities, or baseline smoking. **Conclusions:** We observed a risk difference for diseases of the circulatory system between Hispanic and NHW breast cancer survivors compared with their respective general population cohorts but only within the first 5 years of cancer diagnosis.

By 2030, it is estimated that there will be 5 million breast cancer survivors in the United States (1). The Hispanic population is one of the fastest growing ethnic groups in the United States (2). Breast cancer is the most common cancer and a leading cause of cancer death among Hispanic women, accounting for 29% of cancer cases and 16% of cancer deaths (3). From 2005 to 2014, the breast cancer incidence rates increased by 0.3% per year among Hispanic women but were stable among non-Hispanic White (NHW) women. The 5-year relative survival rate of breast cancer was lower in Hispanic women than in NHW women with breast cancer (87.7% vs 91.4%) in 2010-2016 (4).

Hispanic women with breast cancer were more likely to be diagnosed at younger ages, with advanced cancer stages and grades, larger tumor size, and triple-negative subtype, compared with NHW women with breast cancer (2,5). These clinical factors were associated with more aggressive cancer with poorer prognosis (6). Hispanic women with breast cancer also reported more baseline comorbidities, which was associated with reduced overall breast cancer survival (7).

Approximately 42.6% of Hispanic and 43.4% NHW women had prevalent cardiovascular disease (CVD) between 2013 and 2016. CVD and breast cancer were leading causes of mortality in women and have shared risk factors (8). Hispanic women had

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higher prevalences of multiple risk factors, including poor diet, physical inactivity, obesity, and diabetes, compared with the NHW women (9). For different Hispanic origins, Puerto Rican women had the highest prevalence of obesity (51.4%) and smoking (31.7%), and Mexican and Puerto Rican women had the highest prevalence of diabetes (19%) (10).

Several population-based studies investigated the CVD risk or mortality among breast cancer survivors (11-16) but did not focus on the Hispanic population. To our knowledge, there has been no study investigating the disparity in CVD risk among Hispanic breast cancer survivors. The aim of our study was to estimate the CVD risk for Hispanic breast cancer survivors compared with a general population cohort and to compare to the corresponding risk estimates for NHW women. The secondary aim of our study was to assess risk factors for CVD among Hispanic and NHW breast cancer survivors.

Methods

Study Population

Initial cohorts of 2471 Hispanic and 21 673 NHW breast cancer survivors were identified in the Utah Cancer Registry. Eligibility criteria were women 18 years or older diagnosed with an invasive first primary breast cancer (International Classification of Diseases [ICD]-O-3 codes: C50.0-C50.6, C50.8-C50.9) from 1997 to 2016 in Utah. A total of 697 Hispanic and 5978 NHW breast cancer survivors were excluded because of cancer in situ, missing cancer stage, and follow-up time of less than 1 year. Breast cancer survivors were matched on birth year and birth state with up to 5 women from the general population from the Utah Population Database. The Utah Population Database links data from the Utah Cancer Registry, Utah driver's licenses, vital records, electronic medical records (EMRs), and the Utah Department of Health statewide health-care facilities data. We obtained approval from the University of Utah's Resource for Genetic and Epidemiologic Research and the University of Utah Institutional Review Board.

Covariate Assessment

A modified Charlson comorbidity index (CCI) score was calculated at baseline, excluding cancer and CVDs to avoid double counting (17). We also identified baseline smoking by ICD-9 "tobacco use disorders," ICD-10 "nicotine dependence," and Current Procedural Terminology (CPT) codes "tobacco cessation counseling" based on the American Academy of Family Physicians coding guidelines (18). To validate the use of our databases, we previously investigated concordance between self-reported data and EMR with statewide data for smoking (221 patients with cancer). We had 94.4% concordance on smoking. Also, the percentage of Hispanic women identified as smokers was close to the expected numbers for the Utah population (11.4% vs 12.0%) (19).

Outcome Data

Outcome data were from the statewide ambulatory and inpatient data from the Utah Department of Health and EMR data from Intermountain Health Care and the University of Utah Health Sciences Center. These data sources included the uninsured. Utah is considered to have a minimal percentage of residents who seek health care out of the state (20). Additionally, approximately 2.9% of Utahns left the state in 2016, thus the out-migration rate is fairly low (21).

Outcome data included all available ICD-9 and ICD-10 diagnoses and dates. Follow-up time for incident cases of each outcome was calculated from the breast cancer survivor's cancer diagnosis to the date of CVD diagnosis or censored with the last date of follow-up or date of death. For the general population, the follow-up time was calculated from the index date, which was the cancer diagnosis date for the cancer patient to which they were matched. Individuals who did not have that outcome were censored at the date of last follow-up.

Clinical Classification Software

The Clinical Classification Software was used to categorize ICD-9 into 4 levels and ICD-10 into 2 levels of specificity (22). Level 1 (diseases of the circulatory system) and level 2 (5 CVDs) are broader and contain multiple CVD conditions, thus we did not exclude prevalent CVD diagnosis and adjusted on prevalent diagnosis for incident events of the same disease. Level 3 (26 CVDs) and level 4 (40 CVDs) are more specific conditions, thus we excluded prevalent CVD diagnosis to capture the incident CVD risk. The general equivalence mappings were used to examine the consistency between the ICD-9 and ICD-10 for CVD in our dataset (Supplementary Methods; Supplementary Table 1-4, available online). The 2010 US census data were used to investigate Hispanic origins in Utah (Supplementary Methods; Supplementary Table 5, available online).

Statistical Analysis

The χ^2 tests were used to compare baseline characteristics between the breast cancer survivor and the general population cohort. Cox proportional hazards models were used to calculate hazard ratios (HRs) for CVD 1-5 years and more than 5 years after the index date. Cox proportional hazards were adjusted for birth year and birth state, race, baseline body mass index (BMI), baseline modified CCI (17), and baseline smoking.

Cox proportional hazards models were also used to investigate CVD risk factors among breast cancer survivors. The proportional hazards assumption was checked for each model using a test for nonzero slope of the Schoenfeld residuals vs time. Models that were in violation of the proportional hazards assumption were then tested with flexible parametric survival models. The hazard ratios between Hispanic and NHW groups were compared using the test of heterogeneity with Cochran Q statistic (23).

Baseline BMI values at least 1 year prior to index date were calculated from the driver's license records. For individuals missing BMI, values were imputed using a linear regression model including race, age at cancer diagnosis, and baseline CCI as covariates. Models were run with and without the imputed values to assure that the inferences did not change because of the imputation of BMI.

For baseline smoking and CCI, we considered an individual who did not have the specified codes as nonsmoker or no comorbidities. The missing data for race were excluded from the analysis (0.06% for Hispanic breast cancer survivors and 2.14% for Hispanic women from the general population; Supplementary Methods, available online), and we categorized race as "White" and "Other" for the adjustment among Hispanic women.

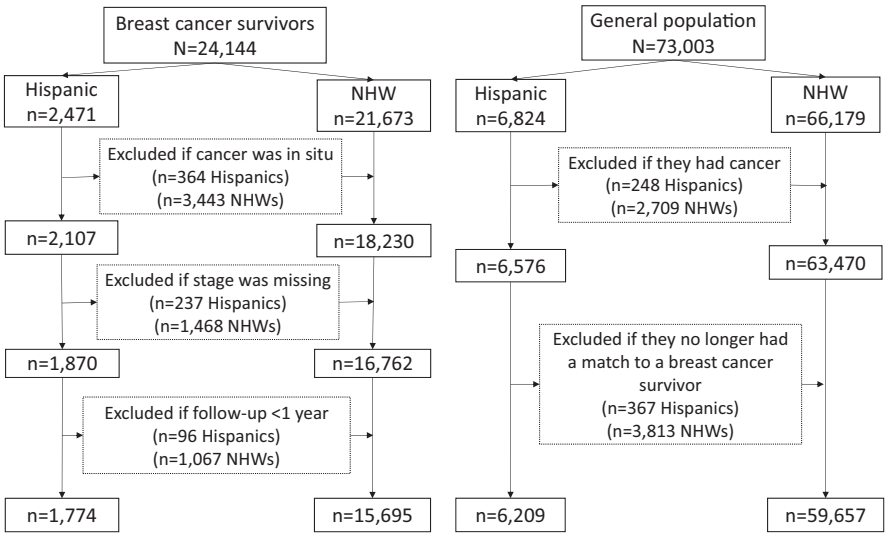

Figure 1. Study exclusion criteria for breast cancer survivors and general population cohorts, stratified by ethnicity. We identified a cohort of 24 144 breast cancer survivors (2471 Hispanic and 21 673 non-Hispanic White [NHW]) and 73 003 age-matched general population without cancer (6824 Hispanic and 66 179 NHW) in the dataset. We excluded breast cancer survivors if cancer was in situ, cancer stage was missing, or if follow-up time was less than 1 year. We also excluded women from the general population if they were diagnosed with cancer or if they did not match to a breast cancer survivor. The final sample size for data analysis was 17 469 breast cancer survivors (1774 Hispanic and 15 695 NHW survivors) and 65 866 women from the general population (6209 Hispanic and 59 657 NHW women).

We used SAS 9.4 (SAS Institute, Inc, Cary, NC) to analyze data. All statistical tests were 2-sided, and a *P* value of less than .01 was considered statistically significant for risks of CVD and a *P* value of less than .05 for CVD risk factors.

Results

A total of 17 469 breast cancer survivors (1774 Hispanic and 15 695 NHW) and 65 866 women from the general population (6209 Hispanic and 59 657 NHW) was included in the analysis (Figure 1). Both Hispanic and NHW breast cancer survivors had higher education levels, lower baseline CCI, and lower proportions of baseline smoking and family history of CVD compared with their respective general population cohorts (Table 1). Compared with NHW survivors, Hispanic breast cancer survivors were younger and more likely to be diagnosed with advanced stage, high tumor grade, and triple-negative subtype (Table 2). Hispanic breast cancer survivors were more likely to receive chemotherapy compared with NHW survivors.

An increased risk of diseases of the circulatory system was higher in Hispanic breast cancer survivors than NHW breast cancer survivors, in comparison with their respective general population cohorts ($HR_{Hispanic}$ = 1.94, 99% confidence interval [CI] = 1.49 to 2.53; HR_{NHW} = 1.38, 99% CI = 1.33 to 1.43; $P_{heterogeneity}$ = .01) (Table 3). The elevated risks of diseases of the heart and the veins and lymphatics were observed among Hispanic and NHW breast cancer survivors compared with their respective general population cohorts, without risk heterogeneities. More than 5 years after cancer diagnosis, elevated risk of diseases of the veins and lymphatics persisted, without risk heterogeneity between the 2 ethnicities (Table 4).

We did not observe increased risks of hypertension and cerebrovascular disease in breast cancer survivors compared with the general population cohort. For diseases of arteries, only small, elevated risks were observed among NHW breast cancer survivors compared with the general population cohort (Tables 3 and 4).

For CVD risk factors among breast cancer survivors 1-5 years after cancer diagnosis, cancer treatment was a risk factor among Hispanic and NHW survivors (Table 5). Hispanic breast cancer survivors had a higher risk of diseases of the heart because of chemotherapy and a higher risk of diseases of the veins and lymphatics because of hormone therapy, compared with NHW survivors. In addition, distant cancer stage, high baseline CCI, and baseline smoking were risk factors for Hispanic and NHW breast cancer survivors, but the risk did not differ between the 2 groups. The CVD risk factors also did not differ between the 2 ethnicities more than 5 years follow-up (Supplementary Table 6, available online).

Competing risk analysis was conducted because death was a competing risk for CVD. We observed that both Hispanic and NHW women with breast cancer had higher risks of diseases of the circulatory system and of the heart and veins and lymphatics 1-5 years follow-up, compared with women from the respective general population cohorts (Table 6).

Hispanic women with breast cancer who had CVD diagnosis had a similar risk of death compared with NHW women (HR = 1.04, 95% CI = 0.86 to 1.07) (Figure 2). Among women with breast cancer who were older than 66 years, the CVD death (12.4%) was slightly more common than breast cancer death (11.8%).

Discussion

This is the first study to examine CVD risk comprehensively for Hispanic breast cancer survivors in a large population-based cohort. Hispanic and NHW breast cancer survivors had increased risks of diseases of the circulatory system and diseases of the heart and the veins and lymphatics 1-5 years after cancer diagnosis, compared with their respective general population cohorts. In particular, compared with NHW survivors, Hispanic breast cancer survivors had a higher risk of diseases of the circulatory system 1-5 year follow-up than the general population cohort. More than 5 years after cancer diagnosis, an increased risk of diseases of the veins and lymphatics was also observed

Table 1. Characteristics among breast cancer survivor and general population cohorts, for Hispanic and non-Hispanic White women

Characteristics	Hispanic			Non-Hispanic White		
	Breast cancer survivors, No. (%) (n = 1774)	General population, No. (%) (n = 6209)	P[a]	Breast cancer survivors, No. (%) (n = 15 695)	General population, No. (%) (n = 59 657)	P[a]
Median age (IQR), y	54 (45-65)	54 (45-65)		60 (50-70)	61 (50-71)	
Follow-up, y						
1-5	670 (37.8)	1998 (32.2)	<.001	5607 (35.7)	18 485 (31.0)	<.001
>5-10	562 (31.7)	1921 (30.9)		4784 (30.5)	18 587 (31.1)	
>10-15	319 (18.0)	1320 (21.3)		3134 (20.0)	12 749 (21.4)	
>15	223 (12.6)	970 (15.6)		2170 (13.8)	9836 (16.5)	
Education						
<High school	344 (19.4)	1469 (23.7)	<.001	2183 (13.9)	7918 (13.3)	<.001
High school	635 (35.8)	2205 (35.5)		5059 (32.2)	19 633 (32.9)	
Some college	469 (26.4)	1584 (25.5)		4805 (30.6)	18 701 (31.4)	
College degree	192 (10.8)	572 (9.2)		2170 (13.8)	8445 (14.2)	
Post-college	134 (7.6)	379 (6.1)		1478 (9.4)	4960 (8.3)	
Baseline BMI, kg/m^2						
<18.5	54 (3.0)	207 (3.3)	.76	482 (3.1)	1869 (3.1)	.41
18.5-24.9	785 (44.2)	2745 (44.2)		7273 (46.3)	27 910 (46.8)	
25-29.9	519 (29.3)	1754 (28.2)		4610 (29.4)	17 582 (29.5)	
≥30	416 (23.4)	1503 (24.2)		3330 (21.2))	12 296 (20.6)	
Baseline CCI[b]						
0	1175 (66.2)	3792 (61.1)	<.001	10 330 (65.8)	38 961 (65.3)	<.001
1	368 (20.7)	1386 (22.3)		3402 (21.7)	12 567 (21.1)	
≥2	231 (13.0)	1031 (16.6)		1963 (12.5)	8129 (13.6)	
Baseline smoking						
No	1607 (90.6)	5498 (88.6)	.02	14 813 (94.4)	55 992 (93.9)	.01
Yes	167 (9.4)	711 (11.4)		882 (5.6)	3665 (6.1)	
Family history of breast cancer[c]						
No	1360 (76.7)	4835 (77.9)	.28	8473 (54.0)	32 689 (54.8)	.07
Yes	414 (23.3)	1374 (22.1)		7222 (46.0)	26 968 (45.2)	
Family history of cardiovascular disease[c]						
No	1036 (58.4)	2883 (46.4)	<.001	5353 (34.1)	15 842 (26.6)	<.001
Yes	738 (41.6)	3326 (53.6)		10 342 (65.9)	43 815 (73.4)	

[a]Two-sided χ^2 test. BMI = body mass index; CCI = Charlson comorbidity index; IQR = interquartile range.
[b]A modified Charlson comorbidity index score was calculated excluding cancer and cardiovascular outcomes (myocardial infarction, heart failure, peripheral vascular disease, and cerebrovascular accident or transient ischemic disease) to avoid double counting.
[c]First-, second-, and third-degrees family histories were included.

in Hispanic and NHW breast cancer survivors compared with their respective general population cohorts. The CVD risk due to cancer treatment was higher in Hispanic breast cancer survivors than in NHW breast cancer survivors. The other CVD risk factors, including distant cancer stage, higher CCI, and baseline smoking, did not differ between the 2 ethnicities.

We observed that Hispanic breast cancer survivors were more likely to be younger, be diagnosed with regional or distant stage, have poorly differentiated tumors, have the triple-negative subtype and receive chemotherapy than NHW breast cancer survivors, which was consistent with previous findings (24-26). These clinical factors were associated with more aggressive cancer (6) and subsequent aggressive treatment. A Surveillance, Epidemiology, and End Results (SEER) program study with 11 cancer registries (including Utah) reported that among breast cancer survivors with diverse Hispanic origins, Mexicans and Puerto Ricans were 20%-50% less likely to receive recommended treatment, and Central and South Americans received similar treatment, compared with NHW survivors (27). The difference in receipt of treatment might be because of socioeconomic status, acculturation, and/or the patient–physician relationship (27). Previous studies have also shown that breast cancer survivors had higher socioeconomic status than the general population (28,29), thus breast cancer survivors may have lower baseline comorbidity levels, lower smoking, and less family history of CVD.

An elevated risk of diseases of the circulatory system was observed in Hispanic and NHW breast cancer survivors compared with their respective general population cohorts, with a higher risk in Hispanic women. The Women's Health Initiative (WHI) study reported that 6.5% of Hispanic and 7.9% of NHW postmenopausal breast cancer survivors developed CVDs (coronary heart disease, angina, heart failure, peripheral arterial disease, and stroke), but the ethnicity was not associated with CVD risk (14). However, the study included 93 Hispanic breast cancer survivors and might have been underpowered to detect the CVD risk. In our study, we included 1063 postmenopausal Hispanic breast cancer survivors and estimated that 7.5% Hispanic and 8.9% NHW survivors had incident CVDs listed in the WHI study, which was similar to the WHI finding.

An elevated risk of diseases of the veins and lymphatics was also observed in Hispanic and NHW breast cancer survivors compared with their respective general population cohorts, without a risk difference between the 2 ethnicities. A population-based study in California reported that a 2-year cumulative incidence of venous thromboembolism (VTE) was 1.1%

Table 2. Clinical characteristics among Hispanic and non-Hispanic White (NHW) breast cancer survivors

Characteristics	Hispanic survivors No. (%)	NHW survivors No. (%)	P[a]
Age at cancer diagnosis, y			
18-40	231 (13.0)	1173 (7.5)	<.001
41-50	480 (27.1)	2826 (18.0)	
51-60	431 (24.3)	3847 (24.5)	
61-70	354 (20.0)	3869 (24.6)	
71-101	278 (15.6)	3980 (25.4)	
Baseline BMI, kg/m^2			
<18.5	54 (3.0)	482 (3.1)	.16
18.5-24.9	785 (44.2)	7273 (46.3)	
25-29.9	519 (29.3)	4610 (29.4)	
≥30	416 (23.4)	3330 (21.2)	
Cancer stage			
Localized	1036 (58.4)	9696 (61.8)	.02
Regional	674 (38.0)	5446 (34.7)	
Distant	64 (3.6)	553 (3.5)	
Grade			
Grade I (well differentiated)	338 (19.0)	3349 (21.3)	<.001
Grade II (moderately differentiated)	706 (39.8)	6772 (43.2)	
Grade III (poorly differentiated)	626 (35.3)	4749 (30.3)	
Missing	104 (5.8)	829 (5.2)	
Histology			
Ductal	1315 (74.1)	11 484 (73.2)	.008
Lobular	305 (17.2)	2941 (18.7)	
Mucinous	33 (1.9)	374 (2.4)	
Medullary	19 (1.1)	76 (0.5)	
Papillary	7 (0.4)	41 (0.2)	
Missing	95 (5.3)	779 (5.0)	
Laterality			
Right	804 (45.3)	7769 (49.5)	.004
Left	970 (54.7)	7910 (50.5)	
Missing	0 (0)	16 (0.1)	
Initial treatment			
No treatment	18 (1.0)	164 (1.1)	.001
Surgery ± radiation	548 (30.9)	5385 (34.3)	
Surgery ± radiation + chemo	437 (24.6)	3462 (22.1)	
Surgery ± radiation + hormone	348 (19.6)	3382 (21.6)	
Surgery ± radiation + chemo + hormone	335 (18.9)	2658 (16.9)	
Other treatment[b]	83 (4.7)	591 (3.8)	
Missing	5 (0.3)	53 (0.3)	
Radiation			
No	792 (44.6)	6903 (44.0)	.61
Yes	977 (55.1)	8739 (55.7)	
Missing	5 (0.3)	53 (0.3)	
Chemotherapy			
No	929 (52.4)	9104 (58.0)	<.001
Yes	840 (47.3)	6538 (41.7)	
Missing	5 (0.3)	53 (0.3)	
Hormone therapy			
No	1058 (59.6)	9313 (59.3)	.83
Yes	711 (40.1)	6329 (40.4)	
Missing	5 (0.3)	53 (0.3)	
Hormone receptor-negative subtype			
No	1366 (77.0)	12 416 (79.1)	.09
Yes	311 (17.5)	2522 (16.1)	
Missing	97 (5.5)	53 (0.3)	
HER2-positive subtype[c,d]			
No	677 (82.6)	5011 (84.5)	.17
Yes	143 (17.4)	924 (15.5)	
Triple-negative subtype[c,d] (since 2010)			
No	717 (87.4)	5385 (90.7)	.005
Yes	98 (12.0)	532 (9.0)	
Missing	5 (0.6)	18 (0.3)	

[a]Two-sided χ^2 test. BMI = body mass index; chemo = chemotherapy.
[b]Other treatment included all other combinations of treatment.
[c]HER2 status was collected after 2010.
[d]n = 820 for Hispanic and n = 5935 for NHW since 2010.

Table 3. The risks of cardiovascular disease at 1-5 years follow-up among Hispanic and non-Hispanic White breast cancer survivors in comparison with general population cohorts of women[a]

Clinical Classification Software disease level for cardiovascular disease	Hispanic			Non-Hispanic White			
	Breast cancer survivors N (%)	General population N (%)	HR (99% CI)	Breast cancer survivors N (%)	General population N (%)	HR (99% CI)	$P_{heterogeneity}$
7 Diseases of the circulatory system[b]	1079 (60.8)	2793 (47.9)	1.94 (1.49 to 2.53)	10 403 (66.3)	31 782 (53.3)	1.38 (1.33 to 1.43)	.01
7.1 Hypertension[b]	635 (35.8)	2074 (33.4)	1.07 (0.75 to 1.52)	6414 (40.9)	21 979 (36.8)	1.03 (0.98 to 1.08)	.08
7.2 Diseases of the heart[b]	638 (36.0)	1738 (28.0)	1.58 (1.13 to 2.22)	6074 (38.7)	18 748 (31.4)	1.27 (1.21 to 1.32)	.21
7.2.1 Heart valve disorders	69 (4.4)	204 (3.6)	0.83 (0.18 to 3.87)	704 (5.2)	2357 (4.4)	1.20 (1.07 to 1.36)	.64
7.2.1.1 Chronic rheumatic disease of the heart valves	42 (2.5)	86 (1.4)	1.72 (0.37 to 8.01)	330 (2.2)	980 (1.7)	1.35 (1.13 to 1.61)	.81
7.2.1.2 Nonrheumatic mitral valve disorders	42 (2.5)	101 (1.7)	0.71 (0.06 to 8.16)	385 (2.6)	1258 (2.2)	1.26 (1.07 to 1.49)	.44
7.2.2 Peri-, endo-, myocarditis, and cardiomyopathy	44 (2.6)	65 (1.1)	6.94 (0.89 to 54.13)	292 (1.9)	752 (1.3)	1.57 (1.29 to 1.90)	.16
7.2.2.1 Cardiomyopathy	24 (1.4)	45 (0.7)	4.19 (0.13 to 138.88)	177 (1.1)	510 (0.9)	1.37 (1.07 to 1.75)	.18
7.2.5 Nonspecific chest pain	138 (10.4)	334 (7.1)	1.27 (0.60 to 2.68)	1280 (10.8)	3626 (7.8)	1.48 (1.35 to 1.63)	.24
7.2.6 Pulmonary heart disease	49 (2.9)	171 (2.9)	1.56 (0.54 to 4.48)	495 (3.3)	1574 (2.8)	1.21 (1.05 to 1.40)	.81
7.2.9 Cardiac dysrhythmias	115 (7.7)	346 (6.6)	1.13 (0.56 to 2.31)	1088 (8.8)	3967 (8.1)	1.17 (1.06 to 1.29)	.92
7.3 Cerebrovascular disease[b]	99 (5.6)	329 (5.3)	1.61 (0.70 to 3.69)	1010 (6.4)	4005 (6.7)	1.00 (0.91 to 1.11)	.26
7.4 Diseases of arteries, arterioles, and capillaries[b]	355 (20.0)	993 (16.0)	1.50 (0.97 to 2.31)	3368 (21.5)	10 478 (17.6)	1.21 (1.14 to 1.28)	.34
7.4.1 Peripheral and visceral atherosclerosis	38 (2.2)	135 (2.3)	0.20 (0.02 to 1.62)	452 (3.0)	1393 (2.4)	1.31 (1.12 to 1.53)	.10
7.4.4.1 Hypotension	59 (3.5)	150 (2.5)	1.44 (0.47 to 4.43)	485 (3.2)	1546 (2.7)	1.26 (1.09 to 1.46)	.82
7.5 Diseases of veins and lymphatics[b]	426 (24.0)	853 (13.7)	2.75 (1.82 to 4.18)	4150 (26.4)	8953 (15.0)	1.87 (1.77 to 1.98)	.07
7.5.1 Phlebitis, thrombophlebitis, and thromboembolism	51 (3.1)	110 (1.9)	2.76 (0.71 to 10.70)	577 (4.1)	1436 (2.6)	1.70 (1.48 to 1.96)	.62
7.5.3 Hemorrhoids	114 (7.6)	320 (6.1)	1.93 (0.95 to 3.95)	1068 (8.2)	3155 (6.3)	1.39 (1.26 to 1.54)	.37

[a]Hazard ratios are adjusted for matched variables, baseline comorbidities, body mass index, baseline smoking, and race. CI = confidence interval; endo = endocarditis; HR = hazard ratio; peri = pericarditis.

[b]Hazard ratio is further adjusted for prevalent diagnoses of the disease. The following outcomes were evaluated, but no elevated risks were observed for both populations: essential hypertension, hypertension with complications and secondary hypertension, hypertensive heart and/or renal disease, other hypertensive complications, chronic rheumatic disease of the heart valves, nonrheumatic aortic valve disorders, other heart valve disorders, acute myocardial infarction, coronary atherosclerosis and other heart disease, angina pectoris, unstable angina, other acute and subacute forms of ischemic heart disease, coronary atherosclerosis, other forms of chronic heart disease, conduction disorders, atrioventricular block, bundle branch block, anomalous atrioventricular excitation, other conduction disorders, paroxysmal supraventricular tachycardia, paroxysmal ventricular tachycardia, atrial fibrillation, atrial flutter, premature beats, sinoatrial node dysfunction, cardiac arrest and ventricular fibrillation, congestive heart failure, and heart failure.

Table 4. The risks of cardiovascular disease more than 5 years follow-up among Hispanic and non-Hispanic White breast cancer survivors in comparison with general population cohorts of women[a]

Clinical Classification Software disease levels for cardiovascular disease	Hispanic			Non-Hispanic White			$P_{heterogeneity}$
	Breast cancer survivors No. (%)	General population No. (%)	HR (99% CI)	Breast cancer survivors No. (%)	General population No. (%)	HR (99% CI)	
7 Diseases of the circulatory system[b]	788 (71.4)	2816 (66.9)	0.99 (0.71 to 1.37)	7653 (75.9)	29 022 (70.5)	1.10 (1.05 to 1.15)	.53
7.1 Hypertension[b]	546 (49.5)	2124 (50.4)	0.75 (0.49 to 1.13)	5396 (53.5)	21 462 (52.1)	0.97 (0.92 to 1.02)	.23
7.2 Diseases of the heart[b]	536 (48.6)	1887 (44.8)	1.10 (0.74 to 1.62)	5287 (52.4)	19 524 (47.4)	1.08 (1.03 to 1.14)	.93
7.2.1 Heart valve disorders	69 (7.5)	265 (7.0)	2.02 (0.83 to 4.93)	811 (9.7)	2909 (8.0)	1.18 (1.04 to 1.33)	.24
7.2.1.1 Chronic rheumatic disease of the heart valves	41 (3.9)	124 (3.0)	2.50 (0.67 to 9.35)	455 (4.8)	1516 (3.8)	1.30 (1.10 to 1.52)	.37
7.2.1.2 Nonrheumatic mitral valve disorders	40 (3.9)	132 (3.3)	2.25 (0.65 to 7.84)	450 (4.9)	1594 (4.1)	1.18 (1.01 to 1.38)	.61
7.2.2 Peri-, endo-, myocarditis, and cardiomyopathy	40 (3.8)	101 (2.5)	1.59 (0.41 to 6.14)	377 (3.9)	994 (2.5)	1.67 (1.39 to 2.00)	.95
7.2.2.1 Cardiomyopathy	26 (2.4)	77 (1.9)	1.49 (0.36 to 6.10)	242 (2.5)	677 (1.7)	1.54 (1.23 to 1.93)	.96
7.2.5 Nonspecific chest pain	96 (13.1)	385 (12.6)	0.75 (0.30 to 1.88)	989 (14.4)	3670 (12.3)	1.28 (1.15 to 1.44)	.23
7.2.6 Pulmonary heart disease	59 (5.8)	208 (5.2)	1.22 (0.43 to 3.43)	613 (6.6)	2277 (5.9)	1.14 (0.99 to 1.31)	.89
7.2.9 Cardiac dysrhythmias	114 (13.0)	436 (12.8)	1.44 (0.66 to 3.16)	1134 (15.3)	4517 (14.1)	1.12 (1.01 to 1.24)	.45
7.3 Cerebrovascular disease[b]	123 (11.1)	487 (11.6)	1.02 (0.45 to 2.34)	1293 (12.8)	5320 (12.9)	0.97 (0.88 to 1.07)	.91
7.4 Diseases of arteries, arterioles, and capillaries[b]	348 (31.5)	1334 (31.7)	1.06 (0.67 to 1.67)	3723 (36.9)	14 094 (34.2)	1.08 (1.02 to 1.14)	.94
7.4.1 Peripheral and visceral atherosclerosis	41 (3.9)	172 (4.3)	1.44 (0.34 to 6.11)	529 (5.6)	1939 (5.0)	1.19 (1.02 to 1.37)	.79
7.4.4.1 Hypotension	59 (5.7)	197 (5.0)	4.66 (1.14 to 19.09)	541 (5.7)	2135 (5.5)	1.08 (0.93 to 1.24)	.04
7.5 Diseases of veins and lymphatics[b]	340 (30.8)	996 (23.7)	1.65 (1.03 to 2.65)	3368 (33.4)	10 811 (26.3)	1.27 (1.20 to 1.35)	.28
7.5.1 Phlebitis, thrombophlebitis, and Thromboembolism	58 (5.8)	154 (3.9)	1.61 (0.51 to 5.09)	454 (5.2)	1686 (4.5)	1.23 (1.05 to 1.44)	.65
7.5.3 Hemorrhoids	68 (8.0)	308 (9.2)	0.78 (0.30 to 2.02)	807 (10.7)	3326 (10.2)	1.15 (1.02 to 1.29)	.43

[a]Hazard ratios are adjusted for matched variables, baseline comorbidities, body mass index, and baseline smoking. CI = confidence interval; HR = hazard ratio.

[b]Hazard ratio is further adjusted for prevalent diagnoses of the disease. The following outcomes were evaluated, but no elevated risks were observed for both populations: acute cerebrovascular disease; intracranial hemorrhage; occlusion of cerebral arteries; acute but ill; defined cerebrovascular accident; occlusion or stenosis of precerebral arteries; other and ill; defined cerebrovascular disease; transient cerebral ischemia; late effects of cerebrovascular disease; atherosclerosis of arteries of extremities; peripheral vascular disease unspecified; aortic, peripheral, and visceral artery aneurysms; abdominal aortic aneurysm without rupture; other aneurysm; aortic and peripheral arterial embolism or thrombosis; arterial embolism and thrombosis of lower extremity artery; and varicose veins of lower extremity.

Table 5. Potential risk factors for diseases of heart and veins and lymphatics among Hispanic and non-Hispanic White breast cancer survivors at 1-5 year of follow-up

	Diseases of the heart		Diseases of veins and lymphatics	
Risk factors	Hispanic HR (95% CI)	NHW HR (95% CI)	Hispanic HR (95% CI)	NHW HR (95% CI)
Treatment[a]				
Surgery ± radiation	1.00	1.00	1.00	1.00
Surgery ± radiation + chemo	1.43 (1.13 to 1.81)[i]	1.08 (1.00 to 1.17)[i]	1.63 (1.22 to 2.19)	1.37 (1.25 to 1.50)
Surgery ± radiation + hormone	1.20 (0.96 to 1.49)	1.12 (1.05 to 1.20)	1.79 (1.34 to 2.39)[i]	1.16 (1.06 to 1.26)[i]
Surgery ± radiation + chemo + hormone	1.25 (0.97 to 1.61)	1.23 (1.13 to 1.33)	1.87 (1.37 to 2.56)	1.51 (1.37 to 1.66)
Chemotherapy[a]				
No	1.00	1.00	1.00	1.00
Yes	1.27 (1.06 to 1.52)	1.13 (1.06 to 1.20)	1.40 (1.12 to 1.74)	1.38 (1.28 to 1.48)
Hormone therapy[a]				
No	1.00	1.00	1.00	1.00
Yes	1.04 (0.89 to 1.22)	1.12 (1.06 to 1.18)	1.42 (1.17 to 1.72)[i]	1.13 (1.06 to 1.20)[i]
Radiation therapy[a]				
No	1.00	1.00	1.00	1.00
Yes	0.99 (0.85 to 1.16)	0.97 (0.92 to 1.02)	1.11 (0.91 to 1.35)	1.12 (1.05 to 1.20)
Cancer stage[b]				
Localized	1.00	1.00	1.00	1.00
Regional	1.06 (0.91 to 1.26)	1.26 (1.17 to 1.30)	1.60 (1.33 to 1.97)	1.58 (1.48 to 1.68)
Distant	2.82 (1.90 to 3.82)	2.01 (1.73 to 2.23)	2.75 (1.63 to 4.02)	1.71 (1.46 to 2.03)
Baseline smoking[c]				
No	1.00	1.00	1.00	1.00
Yes	1.59 (1.25 to 2.02)	1.35 (1.22 to 1.49)	1.41 (1.05 to 1.91)	1.16 (1.02 to 1.33)
Family history of cardiovascular disease				
No	1.00	1.00	1.00	1.00
Yes	1.10 (0.94 to 1.29)	1.09 (1.04 to 1.15)	1.11 (0.92 to 1.35)	1.07 (1.01 to 1.14)
Family history of breast cancer				
No	1.00	1.00	1.00	1.00
Yes	1.11 (0.93 to 1.33)	1.11 (1.06 to 1.17)	1.15 (0.93 to 1.43)	1.03 (0.97 to 1.10)
Age at cancer diagnosis[d]				
18-40	1.00	1.00	1.00	1.00
41-50	1.06 (0.80 to 1.48)	0.93 (0.82 to 1.05)	1.20 (0.85 to 1.69)	1.03 (0.90 to 1.17)
51-60	1.25 (0.92 to 1.94)	0.99 (0.94 to 1.20)	1.42 (0.99 to 2.05)	1.07 (0.94 to 1.22)
61-70	1.33 (0.97 to 1.82)	1.28 (1.14 to 1.44)	1.25 (0.87 to 1.78)	1.07 (0.94 to 1.22)
71-101	2.25 (1.64 to 3.07)	2.02 (1.80 to 2.27)	1.14 (0.77 to 1.69)	0.94 (0.83 to 1.08)
Menopausal status[e]				
Premenopause	1.00	1.00	1.00	1.00
Postmenopause	1.45 (1.21 to 1.72)	1.49 (1.40 to 1.60)	1.14 (0.94 to 1.39)	1.00 (0.93 to 1.07)
Baseline BMI, kg/m^2 [f]				
<18.5	1.05 (0.68 to 1.61)	1.02 (0.88 to 1.17)	1.61 (1.05 to 2.47)	1.11 (0.94 to 1.31)
18.5-24.9	1.00	1.00	1.00	1.00
25-29.9	1.00 (0.83 to 1.20)	1.01 (0.95 to 1.08)	0.96 (0.76 to 1.21)	1.02 (0.95 to 1.10)
≥30	0.96 (0.79 to 1.18)	1.25 (1.17 to 1.33)	0.92 (0.72 to 1.17)	1.19 (1.10 to 1.29)
Baseline CCI score[g]				
0	1.00	1.00	1.00	1.00
1	1.44 (1.19 to 1.75)	1.66 (1.56 to 1.76)	1.64 (0.60 to 4.43)	1.38 (1.28 to 1.49)
≥2	2.30 (1.85 to 2.85)	2.53 (2.36 to 2.71)	1.83 (1.39 to 2.41)	1.71 (1.56 to 1.87)
Grade[b]				
Grade I	1.00	1.00	1.00	1.00
Grade II	1.15 (0.92 to 1.43)	1.12 (1.05 to 1.20)	1.20 (0.92 to 1.58)	1.20 (1.10 to 1.30)
Grade III	1.24 (0.98 to 1.58)	1.28 (1.19 to 1.37)	1.26 (0.95 to 1.67)	1.28 (1.17 to 1.40)
Laterality[b]				
Right	1.00	1.00	1.00	1.00
Left	1.04 (0.88 to 1.21)	1.02 (0.97 to 1.08)	1.05 (0.86 to 1.26)	1.10 (0.95 to 1.08)
Hormone receptor negative subtype[b]				
No	1.00	1.00	1.00	1.00
Yes	1.26 (1.03 to 1.53)	1.07 (1.00 to 1.15)	0.98 (0.76 to 1.26)	1.00 (0.92 to 1.09)
HER2-positive subtype[b,h]				
No	1.00	1.00	1.00	1.00
Yes	1.44 (1.09 to 1.90)	1.49 (1.35 to 1.66)	0.85 (0.58 to 1.24)	1.23 (1.08 to 1.40)
Triple-negative subtype[b,h]				
No	1.00	1.00	1.00	1.00
Yes	0.93 (0.65 to 1.34)	0.90 (0.78 to 1.04)	1.24 (0.82 to 1.86)	1.01 (0.84 to 1.20)

[a]Hazard ratios were adjusted for race, age at diagnosis, education, cancer stage, subtypes, baseline CCI, BMI, and baseline smoking. BMI = body mass index; CCI = Charlson comorbidity index; Chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; NHW = non-Hispanic White.

[b]Hazard ratios were adjusted for race, age at diagnosis, baseline CCI, BMI, and baseline smoking.

[c]Hazard ratios were adjusted for race and education.

[d]Hazard ratios were adjusted for race, baseline CCI, BMI, education, and baseline smoking.

[e]Hazard ratios were adjusted for race, baseline CCI, BMI, and baseline smoking.

[f]Hazard ratios were adjusted for race, age at diagnosis, education, and baseline smoking.

[g]Hazard ratios were adjusted for race, age at diagnosis, education, baseline BMI, and baseline smoking.

[h]HER2 subtype was collected after 2010.

[i]$P_{heterogeneity} < .05$.

Table 6. Competing risk analysis of CVD risk at 1-5 years follow-up for Hispanic and non-Hispanic White breast cancer survivors compared with their general population cohort

Cardiovascular disease	Hispanic HR (99% CI)	Non-Hispanic White HR (99% CI)	$P_{heterogeneity}$
Diseases of the circulatory system	1.30 (1.16 to 1.46)	1.24 (1.20 to 1.29)	.56
Diseases of the heart	1.21 (1.04 to 1.41)	1.18 (1.12 to 1.24)	.70
Diseases of arteries, arterioles, and capillaries	1.21 (0.99 to 1.47)	1.18 (1.10 to 1.26)	.75
Diseases of veins and lymphatics	1.82 (1.52 to 2.18)	1.75 (1.65 to 1.85)	.82

[a]CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio.

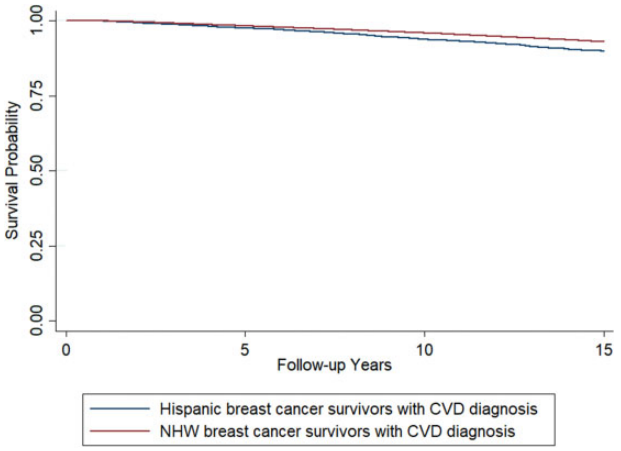

Figure 2. Survival plot among women with breast cancer who had cardiovascular disease (CVD) diagnosis. **Blue line** shows the survival probability for Hispanic breast cancer survivors with CVD diagnosis. **Red line** shows the survival probability for non-Hispanic breast cancer survivors with CVD diagnosis. The figure was adjusted for cancer treatment, cancer stage, age at cancer diagnosis, baseline body mass index, Charlson comorbidity index, and baseline smoking. NHW = non-Hispanic White.

and 1.3% for Hispanic and NHW breast cancer survivors, respectively (30). The 2-year VTE cumulative incidence in our study was 0.7% and 1.0% for Hispanic and NHW breast cancer survivors, respectively, which was slightly lower than the California study, possibly because we started the follow-up 1 year after index date. Furthermore, VTEs during cancer treatment were not likely to be included, although the cancer treatment period could extend beyond the first year for some patients. VTE is a serious complication among breast cancer survivors with a high economic burden, regardless of ethnicity (31).

On the whole, we observed fewer elevated risks of CVDs among Hispanic breast cancer survivors than NHW survivors in comparison with their general population cohorts. This may be because of the small numbers of Hispanic breast cancer survivors who had the specific CVD diagnoses. In addition, CVD diagnosis may have been overlooked among Hispanic breast cancer survivors because of cultural barriers (8). Hispanic women with breast cancer might be overcome by the cancer diagnosis and have paid less attention to other disease symptoms. Another possible explanation is that Hispanic breast cancer survivors may not have completed treatments because of less access to health care, resulting in fewer CVD late effects.

Hispanic breast cancer survivors had higher risks of diseases of the heart because of chemotherapy, and diseases of the veins and lymphatics because of hormone therapy, compared with NHW breast cancer survivors. Previous studies have indicated that chemotherapeutic agents were associated with diseases of the heart (32). Heart damage may occur during or after drug administration, with progressive symptoms from pericarditis-myocarditis to heart failure (33). Hormone therapy was associated with diseases of the veins and lymphatics (32,34-37). The wide range of CVDs was probably driven by different biological mechanisms. Hypotension might be seen if a patient had dehydration from nausea or diarrhea or in conjunction with infection, cardiomyopathy, arrhythmia, and other non-CVD conditions (38,39). Cardiomyopathy has many hypothesized mechanisms with anthracyclines: myocyte cell death, reactive oxygen species generation, apoptosis, and DNA damage (32,40). Trastuzumab could also induce cardiomyopathy by ErbB2 inhibition in cardiomyocytes (41). Chest pain is the most common cardiac side effect from 5-fluorouracil and capecitabine, possibly because of thrombosis or coronary arterial vasospasm, by interrupting DNA and RNA synthesis (42). Paclitaxel can also induce chest pain by interrupting the mitotic cycle progression or apoptosis (43). However, previous studies did not differentiate the CVD late effects by ethnicity. Genetic susceptibility studies on disparities in late effects among Hispanic population are also lacking (44,45).

The competing risk analysis showed consistent results for CVDs, although no risk difference was observed for circulatory system diseases. The competing risk analysis may require more statistical power to detect the risk difference (46), or it is possible that there is no difference between the 2 ethnicity groups.

We observed that the CVD death (12.4%) surpassed breast cancer death (11.8%) among women with breast cancer who were older than 66 years. A SEER-Medicare study indicated that among breast cancer survivors older than 66 years, CVD was the leading cause of death (15.9%), followed by breast cancer death (15.1%) (47). Another study reported CVD death in elderly women surpassed the combined causes of death from lung cancer, breast cancer, colon cancer, and endometrial cancer (48).

This is the first study to investigate a comprehensive range of CVD risks among Hispanic breast cancer survivors. Our population-based study had a large sample size of Hispanic women, although for some specific CVDs, it may have been underpowered to detect the risks. The data in this study incorporated medical records from the state's 2 largest health-care providers as well as statewide ambulatory surgery and inpatient data, which provided comprehensive medical data for a large number of individuals. Approximately 97.0% of Hispanic women with breast cancer and 93.9% of Hispanic women from the general population had records in these data sources. In addition, we had a long follow-up for individuals, up to 23 years with a mean follow-up of 9.6 years. In contrast to cancer

survivor studies that rely on self-reports of disease diagnoses, our study is less susceptible to survival bias and recall bias.

A possible limitation of the study is that some individuals might have undiagnosed CVDs. Our study may miss less severe diagnoses, but most CVDs are fairly severe and could be possibly captured during each clinic or hospital visit. Furthermore, there might be surveillance bias because cancer survivors are more likely to receive screening and examinations during the treatment and follow-up than the general population. Although surveillance bias is a general limitation for our study, we are concerned about undiagnosed CVD and less interaction with the health-care system for the Hispanic population (24). We also had less statistical power for Hispanic breast cancer survivors. Thus, although we only identified an increased risk of diseases of the veins and lymphatics more than 5 years after cancer diagnosis, we believe these diseases need to be studied further. Because risk differences were not identified in the first follow-up period, we would expect similar risk levels in the later follow-up period.

Another limitation of the study is that BMI was derived from the self-reported data in the driver's license. However, a study reported that BMI from the driver's license had a high concordance with BMI from the clinical records (94.4% for BMI $\geq 35\,kg/m^2$) (49). In addition, baseline smoking is likely underreported because we relied on ICD and Current Procedural Terminology (CPT) codes to identify them. However, our concordance rate with self-reported smoking was high, and the proportion of Hispanic smokers identified was very close to what we expected. In addition, baseline smoking misclassification would be expected to be nondifferential between breast cancer survivors and the general population cohorts because smoking history was identified before the index date (cancer diagnosis date for cancer patients), and we used the EMR and health-care facilities data to identify them. Moreover, the specific treatment information, such as drug name, duration, frequency, and dosage, was limited in our database. We also lacked information about breast cancer recurrence and the subsequent treatment. In the future, we hope to obtain more detailed cancer treatment information and recurrence data.

In conclusion, we observed a disparity in the diseases of the circulatory system risk among Hispanic breast cancer survivors but similar levels of risk for other CVDs. The CVD risk due to cancer treatment was higher in Hispanic than NHW breast cancer survivors. Future multicenter population-based studies are needed to investigate dose-specific outcomes for a larger Hispanic population, as well as for Hispanic groups from different origins. Genetic susceptibility studies of late effects across ethnicities may contribute to better understanding the biological mechanisms of late effects for breast cancer survivors.

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Author contributions: QH: conceptualization and design, formal data analysis, original draft. CPC: data analysis, review and editing. KR, JS, VD, KS, MN, and AF: data acquisition and method development. LHG, CP, JBS, DG, NLH, IL: critical revision of the manuscript. MH: funding acquisition, conceptualization, overall supervision.

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Data Availability

The data that support the findings of this study are available upon request with appropriate approval from the UPDB oversight committee, the Resource for Genetic and Epidemiologic Research (RGE), and IRB approval.

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