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Genetic ancestry is not associated with breast cancer recurrence or survival in U.S. Latina women enrolled in the Kaiser Permanente Pathways Study

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Abstract

Background—The U.S. Hispanic/Latino population is heterogeneous both socio-culturally and by the proportion of European, Indigenous American and African ancestry of the regions from which individuals originate. A previous study reported that genetic ancestry was associated with breast cancer survival among Latinas, independent of socio-demographic and tumor characteristics, suggesting that a genetic factor associated with ancestry may affect breast cancer survival.

Methods—We evaluated the association of genetic ancestry with breast cancer outcomes among 506 Latina women with invasive breast cancer in the Pathways Study, a cohort study within Kaiser Permanente, an integrated health care delivery system. Proportional hazards models were used to assess the effect of ancestry on breast cancer recurrence (53 events), breast cancer-specific mortality (31 events) and all-cause mortality (54 events), with a mean follow-up time of 6 years.

Results—Indigenous American ancestry was not associated with breast cancer recurrence (HR=1.00 per 10% increase, 95% CI: 0.86, 1.16), breast cancer mortality (HR=0.95, 95% CI: 0.77, 1.17), or all-cause mortality (HR=0.93, 95% CI: 0.80, 1.08). Adjustment for socio-demographic variables, tumor characteristics and treatment did not alter the associations.

Conclusions—Our results suggest that previously reported differences in breast cancer survival by genetic ancestry may be overcome by improving healthcare access and/or quality.

Impact—Improving healthcare access and quality may reduce breast cancer disparities among US Latinas.

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Introduction

A previous study tested the association between genetic ancestry and breast cancer mortality in US Hispanic/Latina women from the San Francisco Bay Area Breast Cancer Study (SFBCS) and found an increased mortality hazard among Latina women with higher Indigenous American ancestry (1). This finding could be explained by the correlation between ancestry and germline genetic factors associated with mortality, comorbidities, or socioeconomic/sociocultural factors such as access and quality of healthcare that were not controlled for appropriately in the study. We tested the effect of Indigenous American ancestry on breast cancer outcomes among Latina women with breast cancer in a setting where women have uniform access to healthcare.

Methods

The Pathways Study is a prospective cohort of women with breast cancer recruited from Kaiser Permanente Northern California (KPNC) between 2006 and 2013, and is described elsewhere (2). Women who self-reported as Latina (n=565) were eligible for this analysis. Thirty-seven women (6.5%) with no available ancestry data, and 22 women with high Asian ancestry (>70%) were excluded from the analysis to improve comparability to the SFBCS study. The final sample included 506 women. Genetic ancestry was estimated using a panel of 118 ancestry informative markers (AIMs) previously validated in Latin American samples (3) and the program ADMIXTURE version 1.22 (4).

Covariate data were obtained from baseline questionnaires and tumor characteristics and treatment were ascertained through KPNC medical records and tumor registry data. Outcome data on breast cancer recurrence, breast cancer-specific mortality, all-cause mortality, and disease-free survival were obtained through routine mail and/or phone contact and monthly searches of KPNC electronic medical records. Outcomes were confirmed by medical record review and the KPNC mortality file.

We used Cox proportional hazards models to evaluate the association between Indigenous American ancestry and outcomes. Follow-up time was calculated from the date of diagnosis to the date of event or last follow-up. Indigenous American ancestry was modeled as a continuous variable and coefficients scaled to reflect a 10% increase in ancestry. All analyses were two-sided and conducted in Stata 13.1 (5).

The study was approved by the Institutional Review Board of Kaiser Permanente Northern California. Informed consent was obtained from all individual participants included in the study.

Results

Ancestry estimates were predominantly Indigenous American and European, with smaller proportions of African ancestry. Indigenous American ancestry was higher among women who were less educated, lower SES, and had BMI ≥25 kg/m^2, in concordance with the patterns observed in the Latinas from the SFBCS study (1). There were no differences in ancestry by tumor characteristics or treatment modality (Table 1).

The mean follow-up time was 5.7 years (SD: 2.3 years) for disease-free survival and 6.05 years (SD: 2.1 years) for mortality outcomes. Indigenous American ancestry was not associated with breast cancer recurrence (HR=1.00 per 10% increase, 95% CI: 0.86, 1.16), breast cancer mortality (0.95; 0.77, 1.17), all-cause mortality (0.93; 0.80, 1.08), or disease-free survival (0.96; 0.85, 1.08). Adjustment for socio-demographics, tumor characteristics and treatment did not alter the associations (Table 2), nor did analyses fitting ancestry as a non-linear term.

Discussion

We found that, among Latina breast cancer patients enrolled at KPNC, Indigenous American ancestry was not associated with breast cancer outcomes.

Our findings are inconsistent with the Fejerman (2013) study in the SFBCS (1), and suggest no disparities in outcomes between highly Indigenous Latinas and those with greater European ancestry among women with uniform access to care. This finding suggests that if germline genetic factors associated with Indigenous ancestry predict poorer outcomes, this effect may be reversed among women with access to care. However, this conclusion should be taken with caution, as other socioeconomic factors correlated with access to care in Kaiser may explain the lack of observed disparities.

One limitation to the study is that the average follow-up in Pathways was 6 years compared to 9 years in the SFBCS study. However, a re-analysis of the data in the SFBCS study at 6 years of follow-up found similar, though slightly attenuated effects, compared to 9 years of follow-up (HR=1.80, p=0.137 vs. HR=1.75, p=0.014 for 6 vs. 9 years). While our study focused on assessing disparities in shorter-term outcomes, it is possible that long-term disparities may emerge with differential adherence to treatment or other sociocultural factors. We had only 40–70% power (α=5%) to detect a hazard ratio of 1.57 per 25% increase in ancestry (1.2 per 10% increase). However, with a 15% type I error rate (63–82% power), our p-values were much higher than p=0.15, with point estimates very close to 1, suggesting that our findings are unlikely to be due to inadequate power.

The major strength of our study is the use of data from KPNC, which eliminates the challenge of adequate control for the complex concept of access and quality of healthcare (6, 7). However, the generalizeability of our results may be limited to women who have access to clinical care.

To conclude, genetic ancestry was not associated with breast cancer outcomes among Latina breast cancer patients enrolled at KPNC.

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Table 1

Associations between genetic ancestry and demographic and clinical characteristics of Latinas in the Kaiser Permanente Northern California Pathways Study (n=506).

		Indigenous Ancestry		European Ancestry	
	N (%)	**Median (IQR)**	**P***	**Median (IQR)**	**P***
Age at Diagnosis					
<40 Years	40 (7.9)	39.8 (23.9)	<0.0001	51.4 (22.1)	0.0002
40–50 Years	138 (27.3)	38.2 (23.9)		52.9 (23.4)	
50–60 Years	157 (31.0)	31.2 (25.6)		57.1 (25.3)	
≥60 Years	171 (33.8)	28.9 (30.1)		59.1 (32.4)	
Body Mass Index					
<25 kg/m2	136 (27.8)	30.1 (27.4)	0.02	59.7 (30.4)	0.01
25–29.9 kg/m2	157 (32.0)	36.2 (22.1)		52.6 (23.3)	
30–34.9 kg/m2	105 (21.4)	32.5 (20.1)		55.8 (23.1)	
≥35 kg/m2	92 (18.8)	34.4 (30.4)		57.3 (25.0)	
Education Level					
High School	171 (33.9)	38.4 (22.1)	<0.0001	51.3 (22.4)	<0.0001
Some College	200 (39.6)	31.3 (24.8)		57.7 (22.2)	
College Graduate	77 (15.3)	31.1 (26.0)		56.9 (29.4)	
Post-Graduate Degree	57 (11.3)	13.8 (30.2)		77.9 (28.7)	
Household Income					
<$25,000	60 (11.9)	37.5 (20.5)	<0.0001	53.4 (24.6)	<0.0001
$25000–49,999	104 (20.6)	33.5 (25.0)		56.5 (22.6)	
$50,000–89,999	165 (32.6)	30.0 (28.1)		59.0 (28.7)	
>$90,000	92 (18.2)	28.0 (31.2)		62.8 (34.3)	
Not disclosed	85 (16.8)	38.3 (20.4)		50.2 (20.9)	
AJCC Stage					
Stage I or II	433 (86.3)	32.3 (25.3)	0.45	56.9 (24.9)	0.56
Stage III or IV	69 (13.7)	35.2 (26.1)		56.1 (24.8)	
Estrogen Receptor (ER) Positive					
No	94 (18.7)	31.0 (22.9)	0.13	59.2 (24.0)	0.21

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		Indigenous Ancestry		European Ancestry	
	N (%)	Median (IQR)	P*	Median (IQR)	P*
Yes	408 (81.3)	33.0 (27.0)		56.4 (25.8)	
HER-2 Positive					
No	404 (84.3)	32.4 (26.5)	0.72	56.2 (25.7)	0.56
Yes	75 (15.7)	31.7 (26.5)		59.0 (22.9)	
Triple-Negative					
No	439 (86.8)	32.6 (26.5)	0.16	56.6 (25.6)	0.35
Yes	67 (13.2)	33.3 (32.2)		57.6 (26.7)	
Chemotherapy					
No	229 (45.9)	32.2 (24.6)	0.53	56.3 (25.3)	0.73
Yes	270 (54.1)	33.2 (26.8)		57.5 (25.2)	
Hormonal Therapy					
No	138 (27.4)	31.7 (23.5)	0.35	57.6 (24.2)	0.46
Yes	366 (72.6)	33.0 (27.0)		56.4 (26.0)	
Radiotherapy					
No	283 (56.4)	33.1 (27.3)	0.30	56.7 (25.4)	0.36
Yes	219 (43.6)	32.3 (24.8)		57.0 (25.9)	
Surgery					
No Surgery	5 (1.0)	25.8 (32.3)	0.72	55.6 (34.6)	0.70
Lumpectomy	291 (58.0)	33.1 (25.7)		57.0 (26.4)	
Simple or Radical Mastectomy	206 (41.0)	31.7 (26.4)		56.7 (24.0)	

* p-values obtained by fitting univariable regression models for type of ancestry on each characteristic;

IQR, Interquartile Range

Table 2

Hazards ratios for the effect of Indigenous American ancestry on primary and secondary outcomes.

	Breast Cancer Recurrence		Breast Cancer-Specific Mortality		All-Cause Mortality		Disease Free Survival	
	Crude HR (95% CI)	**Adjusted HR ¥ (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR ¥ (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR ¥ (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR ¥ (95% CI)**
Indigenous American Ancestry *	1.00 (0.86, 1.16)	0.98 (0.84, 1.15)	0.95 (0.77, 1.17)	0.97 (0.78, 1.19)	0.93 (0.80, 1.08)	0.98 (0.83, 1.14)	0.96 (0.85, 1.08)	0.98 (0.87, 1.10)
Age at Diagnosis		0.99 (0.96, 1.00)		1.00 (0.98, 1.03)		1.02 (1.00, 1.04)		1.01 (1.00, 1.03)
AJCC Stage								
Stage I–II		ref		ref		ref		ref
Stage III–IV		4.01 (2.3, 7.1)		7.35 (3.60, 15.0)		4.61 (2.65, 8.03)		3.65 (2.31, 5.76)
Hormonal Therapy								
No		ref		ref		ref		ref
Yes		0.56 (0.32, 0.97)		0.49 (0.24, 1.00)		0.39 (0.23, 0.66)		0.57 (0.37, 0.88)

* Per 10% increase in ancestry

¥ Adjusted for age at diagnosis (years), AJCC stage and hormonal therapy.

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