Cigarette Smoking and Breast Cancer Risk in Hispanic and Non-Hispanic White Women: The Breast Cancer Health Disparities Study

Avonne E. Connor, PhD, MPH,^{1,*} Kathy B. Baumgartner, PhD,² Richard N. Baumgartner, PhD,² Christina M. Pinkston, MS,² Stephanie D. Boone, PhD,² Esther M. John, PhD,^{3,4} Gabriela Torres-Mejía, MD,⁵ Lisa M. Hines, ScD,⁶ Anna R. Giuliano, PhD,⁷ Roger K. Wolff, PhD,⁸ and Martha L. Slattery, PhD⁸

Abstract

Objective: Few epidemiological studies have included Hispanics with the evaluation of the effects of cigarette smoking and breast cancer. We examined the relationship between cigarette smoking, ethnicity, and breast cancer risk using data from the Breast Cancer Health Disparities Study (BCHDS).

Materials and Methods: The BCHDS is a consortium of three population-based case-control studies, including U.S. non-Hispanic whites (NHWs) (1,525 cases; 1,593 controls), U.S. Hispanics/Native Americans (1,265 cases; 1,495 controls), and Mexican women (990 cases; 1,049 controls). Multivariable logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Breast cancer risk was elevated among Mexican former smokers (OR 1.43, 95% CI 1.04–1.96) and among those who smoked ≥ 31 years (OR 1.95, 95% CI 1.13–3.35), compared to never smokers. In addition, Mexican former smokers with a history of alcohol consumption had increased breast cancer risk (OR 2.30, 95% CI 1.01–5.21). Among NHW premenopausal women, breast cancer risk was increased for smoking ≥ 20 cigarettes per day (OR 1.61, 95% CI 1.07–2.41).

Conclusion: Our findings suggest the possibility of ethnic differences with the associations between cigarette smoking and breast cancer risk.

Introduction

CIGARETTE SMOKING HAS been implicated as a risk factor for at least 15 types of cancer,^{1,2} with the most consistent findings reported for lung cancer.³ Many of these cancers, including cancers of the uterine cervix, colon, stomach, and pancreas,⁴ are not directly associated with inhalation pathways, warranting the study of systemic effects of smoking exposure.³ Cigarette smoke contains over 7,000 chemicals, 69 of which are considered to be carcinogenic,⁴ with 20 confirmed to be mammary carcinogens.⁵ Human studies in-

dicate that tobacco chemicals can reach mammary tissue,^{6,7} with cigarette smoke metabolites detected in the breast fluid of smokers.^{8,9}

The association between smoking and breast cancer risk has been evaluated extensively in epidemiological studies, as summarized in the 50th Anniversary of the Surgeon General's Report on the Health Consequences of Smoking, with an emerging consensus for a weak positive association.¹⁰ Discrepant results have been attributed to variation in exposure assessment methods and control of confounding by body size, alcohol consumption, and passive smoke exposure.^{11,12}

¹Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

²Department of Epidemiology and Population Health, James Graham Brown Cancer Center, School of Public Health & Information Sciences, University of Louisville, Louisville, Kentucky.

³Cancer Prevention Institute of California, Fremont, California.

⁴Division of Epidemiology, Department of Health Research and Policy, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California.

⁵Instituto Nacional de Salud Pública, Centro de Investigación en Salud Poblacional, Cuernavaca, Morelos, México.

⁶Department of Biology, University of Colorado at Colorado Springs, Colorado Springs, Colorado.

⁷H. Lee Moffit Cancer Center & Research Institute, Tampa, Florida.

⁸Department of Internal Medicine, University of Utah, Salt Lake City, Utah.

*Current affiliation.

Smoking may also increase risk of breast cancer in women who initiated smoking during adolescence^{13,14} or before their first pregnancy^{15,16} before differentiation of breast tissue. Few studies have examined the association with smoking among racial/ethnic groups, and data are particularly sparse for Hispanic women.^{17,18}

In a recent study, a joint association of smoking and obesity with breast cancer risk has emerged,¹⁹ but racial/ethnic differences in this potential interaction have not been explored. The relationship between alcohol consumption and risk of breast cancer has been examined in a few studies that included Hispanic women.^{20–22} While some results have shown that recent alcohol consumption increases breast cancer risk,²³ the combined effects of smoking and alcohol with breast cancer are yet to be fully illuminated. It is biologically plausible that obesity and alcohol consumption may modify the susceptibility of breast tissues to tobacco carcinogens.²⁴ Menopause, which involves a myriad of metabolic changes associated with decreased endogenous estrogens, may further alter these joint associations.¹⁹

We examined the relationship between cigarette smoking and breast cancer risk in non-Hispanic white (NHW), U.S. Hispanic/Native American (NA), and Mexican women included in the Breast Cancer Health Disparities Study (BCHDS). We also examined associations between smoking and ethnicity by menopausal status, alcohol consumption, and several anthropometric measures of obesity, including body mass index (BMI), waist circumference (WC), and waist-hip ratio (WHR).

Materials and Methods

The BCHDS includes data from three population-based case-control studies: the 4-Corners Breast Cancer Study (4-CBCS), the San Francisco Bay Area Breast Cancer Study (SFBCS), and the Mexico Breast Cancer Study (MBCS).²⁵ The three studies collected information on risk factors for breast cancer by in-person interview and took measurements of weight, height, and waist and hip circumferences using standard protocols.^{26–28} All participants signed informed written consent, and the study was approved by the Institutional Review Board for Human Subjects at each institution. The methods have been previously described.²⁹ The analysis included cases and controls with complete data on smoking.

The 4-CBCS included NHW and Hispanic/NA women aged 25–70 years residing in Arizona, Colorado, New Mexico, and Utah at the time of diagnosis (cases) or selection into the study (controls). Only 2.5% of the total study population for the 4-CBCS was NA, therefore, respondents who reported being NA precluded separate analysis for this group, and these women were included with Hispanics for all of the 4-CBCS analyses.²⁶ Cases newly diagnosed with *in situ* or invasive breast cancer between October 1999 and May 2004 were identified through the state-wide cancer registries.²⁶ Controls were selected from the target populations of cases and were frequency matched to cases on ethnicity and 5-year age distribution. A total of 3,761 cases were contacted and 2,556 completed the in-person interview, including 873 Hispanics/NA (63%) and 1,683 NHWs (71%). Of 6,152 controls contacted, 2,605 completed the interview, including 936 (36%) Hispanics/NA and 1,669 (47%) NHWs. The present analysis included 2,320 cases

(795 Hispanic/NA and 1,525 NHW) and 2,511 controls (918 Hispanic/NA and 1,593 NHW).

The SFBCS included Hispanic, African American, and NHW women between the ages of 35 and 79 years from the San Francisco Bay Area.^{30,31} A total of 17,537 cases newly diagnosed with invasive breast cancer between April 1995 and April 2002 were identified through the Greater Bay Area Cancer Registry; controls were selected by random digit dialing and frequency matched based on race/ethnicity and 5-year age distribution of cases. Self-reported race/ethnicity and eligibility for several studies were assessed by a telephone screening interview, with participation rates of 89% among 15,573 cases contacted (alive, valid address, no physician refusal) and 92% among 3,547 controls contacted. Women eligible for an in-person interview included all Hispanic cases diagnosed from 1995 to 2002, all African American cases diagnosed from 1995 to 1999, and a sample of NHW cases diagnosed from 1995 to 1999. NHW women were randomly sampled at 10% due to their large number of diagnoses. Interview data were attained for 1,715 cases, including 1,119 (89% response among eligibles) Hispanics and 596 (86%) NHWs, and 2,108 controls, including 1,462 (88%) Hispanics and 646 (83%) NHWs. Information on smoking histories was collected only for Hispanic cases diagnosed from 1999 to 2002 and their matched controls; 470 cases and 577 controls were included in the present analysis.

The MBCS included women between 28 and 74 years of age, living in Monterrey, Veracruz, or Mexico City, for the past 5 years.³² Eligible cases in Mexico were women diagnosed with either a new histologically confirmed *in situ* or invasive breast cancer between January 2004 and December 2007 at 12 participating hospitals from three main healthcare systems; controls were randomly selected from the catchment area of the 12 participating hospitals using a probabilistic multistage design. A total of 1,000 cases and 1,074 controls were recruited. The response rate for cases was 95.5% for Mexico City, 94.4% for Monterrey, and 97.4% for Veracruz. The response rate for controls was 87.4% for Mexico City, 90.1% for Monterrey, and 97.6% for Veracruz. The present analysis included 990 cases and 1,049 controls.

Interview data were harmonized across the three studies.²⁵ Cigarette smoking measures for women who reported ever smoking 100 cigarettes or more, at least 1 cigarette per day for at least 6 months or more included the following: cigarette smoking status (never, former, current) at interview; duration (number of years smoked); number of cigarettes smoked per day regularly (at least 1 cigarette/day for 6 months or more); pack-years (duration × cigarettes/day); and age at smoking initiation.

Long-term alcohol consumption (defined as the average amount of alcohol consumption in grams over specific ages, *i.e.*, 15, 30, and 50) was also of interest as an effect modifier and as a confounder. For the present analysis, alcohol consumption was modeled as history of alcohol consumption versus none. BMI (kg/m^2) was calculated as self-reported weight during the referent year (or more distantly recalled weight if referent year weight was not available or measured weight if neither was available) divided by measured height squared. The referent year was defined as the calendar year before diagnosis for cases and selection into the study for controls. Other potentially confounding variables that were harmonized included parity (number of live births and

stillbirths), age at first live birth or stillbirth, self-reported ethnicity in the U.S. studies (all women in Mexico were considered Hispanic), highest level of education, family history of breast cancer in first-degree relatives, age at menarche, history of hormone therapy (HT) use, and physical activity in the referent year.

Women were classified as either premenopausal or postmenopausal based on self-reported responses to questions on menstrual history. Women who reported menstruation during the referent year were classified as premenopausal. The classification for postmenopausal women was established by using criteria provided by each individual study. If women were taking HT and still having periods and were at or above the 95th percentile of age for ethnicity of those who reported having a natural menopause among their study site, they were classified as postmenopausal. This age was 58 years for NHWs and 56 for Hispanics in the 4-CBCS, age 54 in the MBCS, and 56 for Hispanics in the SFBCS.

Descriptive statistics was calculated for all covariates and cigarette smoking measures, and *t*-tests and chi-square tests were used to compare ethnic groups (NHWs vs. Hispanics/ NAs vs. Mexicans). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariable logistic regression to estimate breast cancer risk associated with smoking exposures and to assess differences in risk by ethnicity. Cigarette smoking measures were categorized as follows: smoking status (former, current, never), pack-years (≤ 10 , 11–20, ≥ 21), duration in years (≤ 10 , 11–20, 21–30, ≥ 31), average number of cigarettes per day (< 10 , 10–19, ≥ 20), and age at smoking initiation (< 20 , ≥ 20 years). Smoking before first full-term pregnancy was calculated based on age at initiation and age at first full-term pregnancy. Covariates were included in multivariable models if the univariate *p*-values were ≤ 0.20 and if they altered the main effect for a measure of smoking by 10% or more.³³ Two-way interactions between smoking exposures with ethnicity were assessed using the likelihood ratio test to compare models with and without interaction terms. Final models included adjustment for age, study, ethnicity (when not stratified), history of alcohol consumption, menopausal status, parity, education, family history of breast cancer, and BMI at referent year; study is only included when modeling U.S. Hispanic/NA women. All data analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

A total of 7,917 breast cancer cases and controls were included in the analyses. There were significant ($p < 0.001$) differences between NHW, Hispanic/NA, and Mexican women with regard to smoking status, total pack-years, years of smoking, average number of cigarettes per day, and age at smoking initiation, with women from Mexico being less likely to smoke than women living in the United States. Cases from Mexico were less likely to report alcohol consumption (15.7%), compared to U.S. Hispanic/NA (31.7%) and NHW (50.9%) cases. However, cases from Mexico had higher measures of adiposity (Table 1), with significantly higher means for BMI, WHR, and WC than NHW and Hispanic/NA cases (Table 1).

Breast cancer risk was increased among Mexican women who were former smokers (OR 1.43, 95% CI 1.04–1.96), who

smoked for more than 30 years (OR 1.95, 95% CI 1.13–3.35), and smoked an average of 10–19 cigarettes per day (OR 2.07, 95% CI 1.04–4.10), compared to never smokers (Table 2). No significant associations were observed among NHW or Hispanic/NA women or among all women combined for any of the smoking variables.

In analyses stratified by menopausal status, among Mexican women, associations were limited to postmenopausal women, with positive associations found for former smokers (OR 1.65, 95% CI 1.09–2.50), smoking initiated before age 20 (OR 1.78, 95% CI 1.10–2.82), and smoking for more than 30 years (OR 2.13, 95% CI 1.18–3.86). Among NHW women, increased breast cancer risk was associated with smoking 20 cigarettes or more per day (OR 1.61, 95% CI 1.07–2.41) among premenopausal women (Table 3).

We also examined breast cancer risk between smoking and ethnicity by alcohol consumption. Among Mexican women, there was a significant positive association for those who were former smokers with a history of alcohol consumption (OR 2.30, 95% CI 1.01–5.21). No other significant estimates were observed with history of alcohol consumption; however, among U.S. Hispanic/NA women who initiated smoking before 20 years of age, we found a significant positive association among women without a history of alcohol consumption (OR 1.42, 95% CI 1.07–1.88). We also observed significant associations for increased breast cancer risk among women without a history of alcohol consumption from Mexico for the following smoking exposures: smoking an average of 10–20 cigarettes per day (OR 2.28, 95% CI 1.04–5.00) and among those who initiated smoking at 20 years or older (OR 1.33, 95% CI 1.01–1.76). Significant trends were not observed for either of these findings among Mexican women (Table 4).

When we stratified the analyses by body size, breast cancer risk was increased among Mexican women who were obese (BMI ≥ 30 kg/m²) and who smoked for more than 30 years (OR 2.30, 95% CI 1.02–5.21). There was also an increased risk of breast cancer in Mexican women who smoked for more than 30 years with a WC > 88.9 cm (OR 2.04, 95% CI 1.12–3.73). Mexican women with a WHR > 0.85 had an increased risk for breast cancer if they smoked for more than 20 pack-years (OR 2.67, 95% CI 1.01–7.01) or for more than 30 years (OR 1.88, 95% CI: 1.06–3.35). No other significant associations were observed between smoking and breast cancer risk by body size measures (data not shown).

Discussion

In this breast cancer case-control analysis, we examined the association between cigarette smoking and breast cancer risk. Overall, an association was observed primarily among women from Mexico. Risk of breast cancer was increased significantly for smoking status, duration of smoking, and cigarettes per day in women from Mexico. Accordingly, there were significant interactions between smoking status and duration of smoking and ethnicity. Postmenopausal women from Mexico who were former smokers or who smoked for more than 30 years had an increased risk for breast cancer. Finally, former smoking was positively associated with breast cancer risk among Mexican women who reported alcohol consumption.

TABLE 1. CHARACTERISTICS OF STUDY POPULATION, STRATIFIED BY ETHNICITY AND CASE-CONTROL STATUS,
THE BREAST CANCER HEALTH DISPARITIES STUDY (N=7,917)

	U.S. <i>NHWs</i> (n = 3,118)				U.S. <i>Hispanics/NAs</i> (n = 2,760)				Mexico (n = 2,039)			
	Case		Control		Case		Control		Case		Control	
	n	%	n	%	n	%	n	%	n	%	n	%
Total subjects	1,525		1,593		1,265		1,495		990		1,049	
Study site												
4-CBCS	1,525		1,593		795	62.9	918	61.4	—		—	
Mexico	—		—		—		—		990		1,049	
SFBCS	—		—		470	37.2	577	38.6	—		—	
Age (years)												
<40	99	6.5	116	7.3	135	10.7	163	10.9	110	11.1	126	12.0
40–49	433	28.4	419	26.3	413	32.7	434	29.0	327	33.0	381	36.3
50–59	453	29.7	411	25.8	352	27.8	402	26.9	317	32.0	325	31.0
60–69	354	23.2	367	23.0	253	20.0	316	21.1	202	20.4	213	20.3
≥70	186	12.2	280	17.6	112	8.9	180	12.0	34	3.4	4	0.4
Education												
<High school	64	4.2	72	4.5	420	33.7	559	38.2	809	81.8	944	90.0
High school graduate/GED	308	20.2	342	21.5	328	26.3	354	24.2	84	8.5	60	5.7
Some college or more	1,152	75.6	1,178	74.0	499	40.0	549	37.6	96	9.7	45	4.3
Menopausal status												
Premenopausal	538	35.4	492	30.9	506	41.2	542	37.4	403	40.7	452	43.1
Postmenopausal	984	64.6	1,101	69.1	723	58.8	907	62.6	587	59.9	597	56.9
History of alcohol consumption												
None	740	49.1	832	53.1	855	68.4	1,037	70.3	832	84.3	957	91.2
Yes	767	50.9	736	46.9	396	31.7	439	29.7	155	15.7	92	8.8
BMI (kg/m ²)												
Premenopausal												
<25	313	58.5	269	54.8	170	33.9	141	26.2	96	24.2	70	15.7
25–29.9	129	24.1	129	26.3	150	29.9	184	34.1	180	45.5	193	43.3
≥30	93	17.4	93	18.9	182	36.3	214	39.7	120	30.3	183	41.0
Postmenopausal BMI												
<25	413	42.1	455	41.6	173	24.1	177	19.6	90	15.7	72	12.2
25–29.9	314	32.0	320	29.3	267	37.1	330	36.6	239	41.7	211	35.6
≥30	254	25.9	318	29.1	279	38.8	395	43.8	244	42.6	309	52.2
WHR												
≤0.85	1,146	76.4	1,165	74.9	705	57.0	836	57.0	218	22.7	182	17.7
>0.85	355	24.7	390	25.1	531	43.0	630	43.0	741	77.3	846	82.3
WC (cm)												
≤88.9	937	62.4	965	62.1	599	48.5	689	47.0	261	27.2	199	19.3
>88.9	564	37.6	590	37.9	637	51.5	777	53.0	700	72.8	830	80.7

(continued)

TABLE 1. (CONTINUED)

	U.S. NHWs (n = 3,118)				U.S. Hispanics/NAAs (n = 2,760)				Mexico (n = 2,039)			
	Case		Control		Case		Control		Case		Control	
	n	%	n	%	n	%	n	%	n	%	n	%
Smoking status												
Never	839	55.0	938	58.9	839	66.3	1,008	67.4	741	74.9	820	78.2
Former	482	31.6	452	28.4	271	21.4	324	21.7	123	12.4	80	7.6
Current	204	13.4	203	12.7	155	12.3	163	10.9	126	12.7	149	14.2
Pack-years of smoking												
0	875	57.5	969	61.1	894	71.0	1,069	71.6	807	83.0	899	86.7
≤10	249	16.4	218	13.8	199	15.8	243	16.3	125	12.9	110	10.6
11–20	132	8.7	143	9.0	71	5.6	79	5.3	20	2.1	17	1.6
≥21	266	17.5	256	16.1	96	7.6	102	6.8	20	2.1	11	1.1
Duration of smoking, years												
0	843	55.4	942	59.3	843	66.8	1,011	67.7	751	76.9	836	80.5
≤10	178	11.7	155	9.8	135	10.7	150	10.1	75	7.7	76	7.3
11–20	154	10.1	131	8.2	80	6.3	104	7.0	47	4.8	47	4.5
21–30	184	12.1	174	11.0	107	8.5	120	8.0	56	5.7	60	5.8
≥31	163	10.7	187	11.8	97	7.7	108	7.2	48	4.9	20	1.9
Cigarettes/day												
0	841	55.2	942	59.3	839	66.4	1,008	67.4	787	80.6	863	83.1
0 to <10	180	11.8	163	10.3	232	18.4	297	19.9	138	14.1	144	13.9
10–19	191	12.5	193	12.1	96	7.6	90	6.0	31	3.2	13	1.3
≥20	313	20.5	292	18.4	96	7.6	100	6.7	21	2.2	19	1.8
Age of smoking initiation												
Never smoked	839	55.0	938	58.9	839	66.3	1,008	67.4	741	75.2	820	79.1
<20	465	30.5	468	29.4	267	21.1	272	18.2	113	11.5	108	10.4
≥20	221	14.5	187	11.7	159	12.6	215	14.4	132	13.4	109	10.5
Initiated smoking before first full-term pregnancy												
Never smoked	692	54.7	804	58.7	750	66.2	935	68.4	644	75.5	766	79.2
No	85	6.7	86	6.3	100	8.8	137	10.0	76	8.9	76	7.9
Yes	488	38.6	479	35.0	283	25.0	296	21.6	133	15.6	125	12.9
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
BMI (kg/m ²)	26.8	6.1	27.0	6.2	28.9	5.8	29.9	6.2	29.3	5.5	30.6	5.5
WHR	0.80	0.07	0.80	0.07	0.84	0.07	0.84	0.07	0.90	0.10	0.91	0.10
WC (cm)	86.8	14.5	86.8	15.2	91.4	13.5	92.2	91.5	96.3	14.2	99.3	14.0

Missing data: NA ancestry ($N = 1,378$); education $n = 54$; menopausal status $n = 85$; parity $n = 1$; age at first birth $n = 32$; family history $n = 239$; alcohol $n = 79$; BMI $n = 63$; WHR $n = 172$; WC $n = 169$; pack years $n = 47$; duration of smoking $n = 35$; average cigarettes per day $n = 28$; age at initiation $n = 16$; initiated smoking before first full-term pregnancy $n = 962$ missing (exclusion of nulliparous women).

^aEthnic group comparison, based on controls, p -value based on chi-square tests.

^bEthnic group comparison, based on controls, p -value based on one-way ANOVA.

BMI, body mass index; 4-CBCS, 4-Corners Breast Cancer Study; NA, Native American; NHW, non-Hispanic white; SFBCS, San Francisco Bay Area Breast Cancer Study; WC, waist circumference; WHR, waist-hip ratio.

TABLE 2. ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR MEASURES OF CIGARETTE SMOKING WITH BREAST CANCER RISK STRATIFIED BY ETHNICITY AND ASSOCIATED TWO-WAY INTERACTIONS, THE BREAST CANCER HEALTH DISPARITIES STUDY

Measure of smoking	All women (N=7,917)		U.S. NHWs (n=3,118)		U.S. Hispanics/ NAs (n=2,760)		Mexicans (n=2,039)		p for interaction
	OR ^a	95% CI	OR ^b	95% CI	OR ^b	95% CI	OR ^b	95% CI	
Smoking status									
Never	1.00		1.00		1.00		1.00		
Former	1.10	0.98–1.24	1.13	0.95–1.35	0.99	0.81–1.22	1.43	1.04–1.96	0.03
Current	1.00	0.87–1.16	1.04	0.83–1.32	1.06	0.82–1.38	0.82	0.62–1.08	
Wald <i>p</i> -value	0.28		0.40		0.88		0.02		
Pack-years of smoking									
≤10	1.06	0.93–1.22	1.18	0.94–1.47	0.91	0.73–1.15	1.15	0.83–1.49	0.17
11–20	0.99	0.80–1.21	0.95	0.72–1.23	1.00	0.70–1.45	1.14	0.56–2.30	
≥21	1.11	0.94–1.32	1.12	0.91–1.40	1.09	0.79–1.50	1.63	0.73–3.65	
<i>p</i> -Trend	0.27		0.40		0.82		0.18		
Duration of smoking, years									
≤10	1.10	0.94–1.30	1.19	0.93–1.54	1.07	0.81–1.41	0.91	0.64–1.3	0.04
11–20	1.04	0.87–1.26	1.22	0.93–1.59	0.86	0.62–1.20	1.00	0.64–1.56	
21–30	1.04	0.87–1.24	1.05	0.82–1.35	1.06	0.78–1.46	0.88	0.58–1.33	
≥31	1.06	0.89–1.27	1.00	0.78–1.27	1.03	0.75–1.40	1.95	1.13–3.35	
<i>p</i> -Trend	0.43		0.72		0.91		0.24		
Cigarettes/day									
<10	0.96	0.84–1.12	1.10	0.86–1.42	0.91	0.73–1.12	0.91	0.69–1.19	0.15
10–19	1.18	0.98–1.41	1.05	0.83–1.32	1.32	0.95–1.85	2.07	1.04–4.10	
≥20	1.13	0.96–1.41	1.17	0.95–1.43	1.06	0.76–1.47	1.16	0.59–2.29	
<i>p</i> -Trend	0.08		0.16		0.47		0.40		
Age at initiation									
<20	1.06	0.94–1.20	1.04	0.87–1.24	1.12	0.91–1.39	1.05	0.78–1.43	0.16
≥20	1.08	0.94–1.25	1.26	1.00–1.58	0.89	0.69–1.13	1.09	0.81–1.46	
<i>p</i> -Trend	0.21		0.08		0.62		0.53		
Initiated smoking before first full-term pregnancy									
No	1.08	0.90–1.30	1.16	0.83–1.62	0.96	0.71–1.29	1.10	0.77–1.57	0.74
Yes	1.08	0.95–1.22	1.07	0.89–1.28	1.10	0.90–1.36	1.07	0.80–1.42	
Wald <i>p</i> -value	0.41		0.61		0.59		0.82		

^aModels are adjusted for age, ethnicity, study, history of alcohol consumption, menopausal status, parity, education, family history of breast cancer, and BMI at referent year.

^bModels are adjusted for age, study, history of alcohol consumption, menopausal status, parity, education, family history of breast cancer, and BMI at referent year; study is only included when modeling U.S. Hispanic/NA women; the referent group for all models is “never smoked.”

CI, confidence interval; OR, odds ratio.

Although a number of studies have examined the association of smoking with breast cancer by menopausal status over the past decade,^{18,34–39} overall, findings are inconsistent. In general, the association appears to be stronger in premenopausal women, although some studies of postmenopausal women have reported an increased risk also.^{40–42} In the present study, the modification of risk by menopausal status appeared to depend on ethnicity. Risk was increased in premenopausal NHW women who reported smoking 20 or more cigarettes per day (OR 1.61, 95% CI 1.07–2.41) and in postmenopausal Mexican women who reported smoking for more than 30 years (OR 2.13, 95% CI 1.18–3.86). The mechanism by which menopause alters the association of smoking with breast cancer risk remains to be established, but may involve changes in hormone metabolism and the resulting sensitivity of breast tissues to tobacco carcinogens.⁴³ It is unclear how ethnicity might further modify this association, although ethnic differences have been observed in serum concentrations of estradiol and follicle-stimulating

hormone during menopause.⁴⁴ In our study, a greater proportion of Mexican and Hispanic/NA cases were premenopausal compared to NHW cases. Hispanic women have been reported to be more likely than NHW women to develop premenopausal, estrogen receptor-negative breast cancer⁴⁵ and to have an earlier age at menopause.⁴⁶ We did not find significant associations among pre- or postmenopausal Hispanic/NA women. Further investigations into these ethnic differences are warranted.

A controversial question in the smoking/breast cancer relationship is whether alcohol consumption is a confounding factor. Some studies have reported that alcohol consumption and cigarette smoking are positively correlated.⁴⁷ Previous studies have shown that alcohol consumption is a risk factor for breast cancer, and several have included Hispanic women.^{20–22,48,49} We previously reported a modest nonsignificant increase in breast cancer risk among Mexican women who were ever drinkers (OR 1.25, 95% CI 0.99–1.58).²¹ In the present analyses, adjustment for alcohol changed the point

TABLE 3. ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR MEASURES OF CIGARETTE SMOKING WITH BREAST CANCER RISK, STRATIFIED BY MENOPAUSAL STATUS AND ETHNICITY, THE BREAST CANCER HEALTH DISPARITIES STUDY

Measure of smoking	Premenopausal						Postmenopausal					
	U.S. NHWs (n = 1,030)			U.S. Hispanics/NAAs (n = 1,048)			U.S. NHWs (n = 2,085)			U.S. Hispanics/NAAs (n = 1,630)		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Smoking status												
Never	1.00			1.00			1.00			1.00		
Former	1.35	0.97–1.87		1.18	0.84–1.67		1.03	0.83–1.26		0.92	0.71–1.19	
Current	1.38	0.91–2.09		1.15	0.76–1.75		0.89	0.67–1.18		1.07	0.76–1.50	
Wald <i>p</i> -value	0.11			0.56			0.64			0.72		
Pack-years												
≤10	1.08	0.75–1.54		1.19	0.84–1.69		1.23	0.93–1.63		0.78	0.58–1.06	
11–20	1.55	0.93–2.60		1.14	0.60–2.19		0.76	0.56–1.05		1.01	0.65–1.56	
≥21	1.64	1.00–2.71		1.02	0.52–1.98		1.00	0.78–1.27		1.15	0.80–1.66	
<i>p</i> -Trend	0.02			0.57			0.60			0.74		
Duration of smoking, years												
≤10	1.25	0.84–1.88		1.27	0.85–1.89		1.17	0.84–1.62		0.93	0.63–1.37	
11–20	1.38	0.89–2.14		0.84	0.52–1.37		1.11	0.79–1.55		0.92	0.59–1.45	
21–30	1.52	0.97–2.39		1.27	0.76–2.11		0.85	0.62–1.16		1.02	0.69–1.52	
≥31	1.73	0.61–4.93		1.87	0.65–5.36		0.92	0.71–1.19		0.99	0.71–1.38	
<i>p</i> -Trend	0.02			0.32			0.36			0.95		
Cigarettes/day												
<10	1.22	0.80–1.87		1.19	0.85–1.66		1.04	0.76–1.43		0.77	0.58–1.01	
10–19	1.27	0.82–1.98		1.30	0.74–2.28		0.93	0.70–1.23		1.42	0.94–2.13	
≥20	1.61	1.07–2.41		0.99	0.54–1.80		1.01	0.80–1.28		1.12	0.76–1.66	
<i>p</i> -Trend	0.02			0.49			0.92			0.43		
Age at initiation												
<20	1.33	0.97–1.83		1.31	0.94–1.86		0.90	0.73–1.11		1.03	0.78–1.36	
≥20	1.48	0.93–2.37		0.87	0.56–1.34		1.16	0.89–1.52		0.89	0.66–1.19	
<i>p</i> -Trend	0.04			0.90			0.55			0.52		
Initiated smoking before first full-term pregnancy												
No	1.38	0.63–3.03		0.73	0.40–1.36		1.07	0.74–1.56		1.03	0.73–1.45	
Yes	1.39	0.99–1.96		1.23	0.88–1.72		0.93	0.75–1.16		1.03	0.78–1.35	
Wald <i>p</i> -value	0.14			0.23			0.72			0.97		

Models adjusted for age, study, BMI at referent year, parity, education, family history, and history of alcohol consumption; study is only included when modeling U.S. Hispanic/NA women; the referent group for all models is “never smoked.”

TABLE 4. ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR MEASURES OF CIGARETTE SMOKING WITH BREAST CANCER RISK STRATIFIED BY ETHNICITY AND HISTORY OF ALCOHOL CONSUMPTION, THE BREAST CANCER HEALTH DISPARITIES STUDY

Exposures	No history of alcohol consumption						History of alcohol consumption					
	U.S. NHW (n = 1,572)			U.S. Hispanics/NAs (n = 1,892)			Mexico (n = 1,789)			U.S. NHW (n = 1,503)		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Smoking status												
Never smoked	1.00			1.00			1.00			1.00		
Former smoker	1.13	0.86–1.49		0.99	0.77–1.29		1.27	0.89–1.81		0.98	0.87–1.39	
Current smoker	1.18	0.82–1.68		1.30	0.92–1.83		0.80	0.58–1.10		0.85	0.71–1.33	
Wald <i>p</i> -value	0.51			0.32			0.13			0.75		
No. of pack years												
≤10	1.43	1.00–2.05		1.00	0.75–1.33		1.10	0.79–1.53		1.02	0.76–1.35	
11–20	0.91	0.59–1.41		1.12	0.68–1.85		1.13	0.49–2.63		0.96	0.68–1.35	
More than 20	1.06	0.75–1.49		1.32	0.85–2.06		1.31	0.53–3.28		1.15	0.87–1.52	
<i>p</i> -Trend	0.67			0.25			0.40			0.44		
Total years smoking												
≤10	1.27	0.85–1.90		0.98	0.68–1.40		0.85	0.56–1.27		1.12	0.80–1.57	
11–20	1.13	0.72–1.79		1.01	0.67–1.54		0.97	0.58–1.61		1.21	0.86–1.69	
21–30	1.32	0.87–2.00		1.32	0.86–2.04		0.87	0.54–1.41		0.96	0.69–1.32	
31 years or more	0.88	0.59–1.32		1.15	0.77–1.73		1.72	0.94–3.18		1.06	0.77–1.46	
<i>p</i> -Trend	0.70			0.26			0.53			0.79		
Average No. of cigarettes/day												
<10	1.29	0.84–1.97		0.99	0.76–1.30		0.90	0.66–1.22		1.03	0.75–1.42	
10–20	1.10	0.76–1.60		1.50	0.95–2.38		2.28	1.04–5.00		0.97	0.71–1.32	
≥20	1.12	0.81–1.53		1.03	0.66–1.62		1.16	0.52–2.61		1.18	0.91–1.54	
<i>p</i> -Trend	0.38			0.39			0.42			0.30		
Age at initiation												
<20	1.05	0.82–1.38		1.42	1.07–1.88		1.00	0.74–1.35		1.02	0.81–1.29	
≥20	1.38	0.95–1.99		0.79	0.58–1.07		1.33	1.01–1.76		1.17	0.87–1.59	
<i>p</i> -Trend	0.23			0.01			0.12			0.57		
Initiated smoking before first full-term pregnancy												
No	1.14	0.69–1.89		0.83	0.57–1.21		1.02	0.68–1.53		1.19	0.75–1.88	
Yes	1.04	0.80–1.36		1.24	0.95–1.61		1.03	0.75–1.42		1.08	0.84–1.38	
Wald <i>p</i> -value	0.85			0.14			0.98			0.70		

Models adjusted for age, study, BMI at referent year, parity, education, family history, and menopausal status; study is only included when modeling U.S. Hispanic/NA women; the referent group for all models is “never smoked.”

estimates for smoking by <10%, suggesting minimal confounding; however, we adjusted for alcohol in final models to maintain consistency with previous studies. Various studies have evaluated effect modification by alcohol consumption with the association between smoking and breast cancer risk; results have been mixed with some findings indicating no statistical evidence of effect modification^{50–52} and other studies finding significant associations only among nondrinkers.^{53,54} The CPS-II Nutrition Cohort reported significant associations among current drinkers for current (Hazard Ratio [HR] 1.36, 95% CI 1.14–1.36) and former (HR 1.19, 95% CI 1.09–1.31) smoking status, although the interaction was not statistically significant ($p=0.11$).¹¹ The present analysis is first to investigate this effect modification in U.S. Hispanic and Mexican women. The association that we observed for alcohol consumption and former smoking with breast cancer risk among Mexican women warrants closer examination in other racially/ethnically diverse population-based samples of women.

The prevalence of smoking was low in Mexican women compared to NHW and Hispanic/NA women in our study. Tobacco use in Mexico is more common in urban areas and among individuals with higher education.⁵⁵ To date, few studies have examined the association of cigarette smoking with breast cancer risk in Mexico. A previous analysis from the MBCS examined healthy lifestyle associations with risk of breast cancer.⁵⁶ A history of ever smoking by menopausal status was analyzed, in conjunction with other variables considered in a healthy lifestyle index, but results were not statistically significant (premenopausal: OR 1.20, 95% CI 0.83–1.73; postmenopausal: OR 0.82, 95% CI 0.57–1.18).⁵⁶ Smoking duration and intensity were not examined.

The BCHDS constitutes one of the largest population-based case-control studies of breast cancer in Hispanic and NHW women. Moreover, it allows the comparison of Hispanic women in the United States and Mexico who have different environmental exposures and lifestyle factors. It has been proposed that racial/ethnic differences in the joint associations between tobacco smoke, obesity, and alcohol could be based on a differential distribution of genetic variants influencing susceptibility to these risk factors.⁵⁷ Our results suggest that social and cultural factors may contribute to these differences also.

Although there are few data on the association of smoking and breast cancer risk by ethnicity, there is evidence from studies of smoking and lung cancer suggesting that racial differences in cancer risk may be present.⁵⁸ The two studies that have investigated smoking and risk of breast cancer among African American women reported statistically significant associations.^{59,60} Findings from our study allude to the possibility of racial/ethnic differences in the association between smoking and risk of breast cancer as well.

While our study was powered to examine the interactions between smoking and ethnicity, we may not have had adequate power to evaluate the subsequent interactions with menopausal status and alcohol consumption appropriately. Therefore, these statistical interactions were not considered in final results. We did not have data for secondhand smoke exposure for the SFBCS and were unable to assess its impact in our analyses. A recent analysis found that both active and secondhand exposure to cigarette smoke increased risk of both pre- and postmenopausal breast cancer in women from Mexico.⁶¹ Another limitation is that we did not have data

pertaining to the type and brands of cigarettes that smokers in our study smoked. It is possible that national cigarette production in Mexico may be considerably different from the international and U.S. brands, and purchasing of these brands may also differ within Mexico.⁶² Therefore, when making comparisons across countries, we cannot conclude if women in our study are being exposed to the same cigarette smoking exposures, that is, types of chemicals used in cigarette production. These factors pertaining to cigarette types and brands should be considered with future international studies of smoking and breast cancer.

The BCHDS consists of *in situ* and invasive breast cancer cases. In recent studies, the relationship between cigarette smoking and risk of *in situ* breast cancer has been evaluated and results have ranged from an inverse⁶³ to no association.⁶⁴ Approximately 41% of the cases from Mexico can be identified by stage of disease, of which, 3.9% are *in situ* breast cancers; and comparisons of the results without *in situ* cases for the overall sample were not feasible due to Mexico's missing data for stage. With the exclusion of *in situ* cases from subset analyses of the 4-Corners sample for the main effects between smoking and breast cancer risk, we did not observe significant point estimate changes; therefore, we retained *in situ* cases in our analyses.

Conclusions

In summary, we identified ethnic differences in risk of breast cancer associated with intensity and duration of cigarette smoking exposure. These associations were mostly limited to women from Mexico. Menopausal status and alcohol consumption warrant further investigation for their potential modifying effects. The present results suggest the possibility of ethnic differences with the associations between cigarette smoking and breast cancer risk.

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Author Disclosure Statement

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Address correspondence to:

Avonne E. Connor, PhD, MPH

Department of Epidemiology

Johns Hopkins Bloomberg School of Public Health

615 N. Wolfe Street Office E-6137

Baltimore, MD 21205

E-mail: aconnor8@jhu.edu