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A pooled analysis of breast-feeding and breast cancer risk by hormone receptor status in parous Hispanic women

Meera Sangaramoorthy[1], **Lisa M. Hines**[2], **Gabriela Torres-Mejía**[3], **Amanda I. Phipps**[4,5], **Kathy B. Baumgartner**[6], **Anna H. Wu**[7], **Jocelyn Koo**[1,8], **Sue A. Ingles**[7], **Martha L. Slattery**[9], and **Esther M. John**[1,8,10]

[1]Cancer Prevention Institute of California, Fremont, CA 94538

[2]Department of Biology, University of Colorado at Colorado Springs, Colorado Springs, CO 80918

[3]Instituto Nacional de Salud Puública, Population Health Research Center, Cuernavaca Morelos, Mexico

[4]Department of Epidemiology, University of Washington, Seattle, WA 98195

[5]Epidemiology Program, Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109

[6]Department of Epidemiology and Population Health, School of Public Health & Information Sciences, James Graham Brown Cancer Center, University of Louisville, Louisville, KY 40202

[7]Department of Preventive Medicine, Keck School of Medicine of USC, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA 90089

[8]Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA 94304

[9]Department of Medicine, University of Utah, Salt Lake City, UT 84108

[10]Department of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, CA 94304

Abstract

Background: Data on breast-feeding and breast cancer risk are sparse and inconsistent for Hispanic women.

Methods: Pooling data for nearly 6,000 parous Hispanic women from four population-based studies conducted between 1995 and 2007 in the U.S. and Mexico, we examined the association of breast-feeding with risk of breast cancer overall and subtypes defined by estrogen receptor (ER) and progesterone receptor (PR) status, as well as the joint effects of breast-feeding, parity, and age

Corresponding author: Esther M. John, Ph.D., Stanford University School of Medicine, 780 Welch Road, Suite CJ250C, Stanford, CA 94304-5769. Phone: 650-497-1221. emjohn@stanford.edu.

Conflict of interest

The authors do not have any conflict of interest to report.

Data availability

Data may be obtained contingent upon approval by appropriate Institutional Review Boards and study Principal Investigators. The data and computing code may be obtained from the corresponding author on request.

at first birth. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression.

Results: Among parous Hispanic women, older age at first birth was associated with increased breast cancer risk, whereas parity was associated with reduced risk. These associations were found for hormone receptor positive (HR+) breast cancer only and limited to premenopausal women. Age at first birth and parity were not associated with risk of ER-PR-breast cancer. Increasing duration of breast-feeding was associated with decreasing breast cancer risk (≥25 vs. 0 months: OR=0.73, 95% CI=0.60–0.89, P_{trend} =0.03), with no heterogeneity by menopausal status or subtype. At each parity level, breast-feeding further reduced HR+ breast cancer risk. Additionally, breast-feeding attenuated the increase in risk of HR+ breast cancer associated with older age at first birth.

Conclusions: Our findings suggest that breast-feeding is associated with reduced risk of both HR+ and ER-PR-breast cancer among Hispanic women, as reported for other populations, and may attenuate the increased risk in women with a first pregnancy at older ages.

Keywords

Breast cancer; breast-feeding; Hispanic; Latina; hormone receptor status

Introduction

Worldwide changes in reproductive patterns towards older ages at first birth and lower parity have put women at an increased risk of developing breast cancer.[1,2] There is some evidence that this risk may be mitigated by breast-feeding,[1,3–7] a potentially modifiable behavior that is associated with lower risk of breast cancer,[8] particularly among premenopausal women.[1,9] In the United States (U.S.), Hispanic women have higher initiation and longer duration of breast-feeding than non-Hispanic white women.[10] Differences in breast-feeding behaviors may contribute to the lower breast cancer incidence in Hispanic women compared to non-Hispanic white women.[11,12]

To our knowledge only five studies have evaluated the relation between breast-feeding and breast cancer risk in Hispanic women, and results are inconsistent.[13–17] These studies had relatively small sample sizes, not all of them stratified by menopausal status, and only one reported on associations with breast cancer defined by estrogen receptor (ER) and progesterone receptor (PR) status.[17] Assessment of breast cancer by hormone receptor status is important because studies, primarily in non-Hispanic white populations, have shown that risk factors for breast cancer differ by ER and PR status.[18] Furthermore, Hispanic women are more likely than NHWs to be diagnosed with ER and PR negative (ER-PR-) breast cancer,[11] a tumor subtype that is more difficult to treat, has poorer survival, and for which few risk factors have been identified.[18,19]

Given that Hispanic women have reproductive characteristics[20] and breast cancer incidence rates[21] that are distinct from those of NHW women, we pooled data from four studies conducted in the U.S. and Mexico and investigated the relation of breast-feeding with breast cancer risk overall and by menopausal status, as well as the joint effects of breast-feeding,

parity, and age at first birth. In a subset of women, we also examined differences in associations by tumor ER and PR status. This is the largest study to date of breast-feeding and breast cancer risk in Hispanic women.

Materials and Methods

Study Population

We analyzed data for U.S. Hispanic and Mexican women from four population-based studies that were harmonized for other pooled analyses.[22,23] In the San Francisco Bay Area Breast Cancer Study (SFBCS), Hispanic women ages 35 to 79 years newly diagnosed with a first primary invasive breast cancer between 1995 and 2002 were identified through the Greater Bay Area Cancer Registry.[24] Controls were identified through random-digit dialing and were frequency matched to cases on Hispanic ethnicity and 5-year age group. In the Northern California site of the Breast Cancer Family Registry (NC-BCFR), a prospective family cohort, Hispanic women ages 18 to 64 years newly diagnosed with breast cancer were identified through the Greater Bay Area Cancer Registry. All cases with indicators of increased genetic susceptibility (i.e., diagnosis at age <35 years, prior ovarian or childhood cancer, prior breast cancer before age 50 years, or a first-degree family history of breast, ovarian or childhood cancer) were recruited; cases not meeting these criteria were randomly sampled at 33%.[25] For this analysis, we included cases from Phase I and II recruitment periods (diagnoses 1995 to 2003), as well as all controls identified through random-digit dialing and frequency matched to cases diagnosed from 1995 to 1998 on Hispanic ethnicity and 5-year age group. In the 4-Corners Breast Cancer Study (4-CBCS), Hispanic and Native American women ages 25 to 79 years with newly diagnosed breast cancer between 1999 and 2004 were identified through state-wide cancer registries in Arizona, Colorado, New Mexico, and Utah.[26] Controls were selected from the populations living in the four states and frequency matched to cases on Hispanic/Native American ethnicity and 5-year age group. In the Mexico Breast Cancer Study (MBCS), women ages 28 and 74 years with newly diagnosed breast cancer between 2004 and 2007 were identified through 12 hospitals from three main health care systems in Monterrey, Veracruz, and Mexico City.[27] Controls were randomly selected from the hospitals' catchment area using a probabilistic multistage design and frequency matched to cases on 5-year age group, healthcare institution, and place of residence.

All study participants provided written informed consent. The respective institutional review boards approved each study. Interview data for U.S. Hispanic women were collected from SFBCS for 1,119 cases and 1,462 controls; from NC-BCFR for 591 cases and 73 controls; and from 4-CBCS for 846 cases and 924 controls; and for Mexican women from MBCS for 1,000 cases and 1,074 controls. The Hispanics in 4-CBCS include 55 cases and 73 controls who self-identified as Native American. Hereafter, we refer to Hispanics to include both U.S. Hispanic and Mexican women.

Data collection and harmonization

Trained professional interviewers or nurses conducted in-person interviews using similar structured questionnaires in English or Spanish. We collected information on breast cancer

risk factors up to the reference year, defined as the calendar year before diagnosis for cases or selection into the study for controls. We obtained data on ER and PR status from the respective cancer registries for most cases in SFBCS (85%), NC-BCFR (82%), and 4-CBCS (76%), but these were not available for cases in MBCS. Therefore, hormone receptor-specific analyses included U.S. Hispanic women only.

We harmonized the data from the four studies and derived analytic variables as described elsewhere.[22,28] Parity was defined as the total number of live births. We calculated lifetime duration of breast-feeding, summing duration of breast-feeding reported for each live birth. Breast-feeding was collected as a continuous measure in all studies except NC-BCFR which assessed breast-feeding as a categorical measure (<1, 1–5, 6–11, 12–24, >24 months). For NC-BCFR, we assigned the midpoint of the category to each episode of breast-feeding, using 30 months for the >24 months category. We calculated body mass index (BMI) as self-reported weight (kg) in the reference year divided by squared height (m) measured at interview, using methods previously described[26,29,30] and classified the result as underweight/normal weight (<25.0 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥30.0 kg/m^2). For NC-BCFR, only self-reported weight and height were collected, and for MBCS, [30] only measured weight and height were collected. For the studies that collected self-reported measures, weight was not known for a small proportion of cases (1%) and controls (2%); in such instances, measured weight was used. Alcohol consumption was defined as average lifetime intake for participants in 4-CBCS, NC-BCFR, and MBCS, and for SFBCS cases diagnosed from 1999 to 2002 and their matched controls. For SFBCS cases diagnosed from 1995 to 1998 and their matched controls, average alcohol consumption in the reference year was used. Each study defined menopausal status during the reference year based on the available menstrual history data. We determined ‘study-specific age at menopause’ based on the 95th percentile of age at menopause of women with a natural menopause for each study. This age was 56 years in SFBCS and 4-CBCS, 54 years in MBCS, and 55 years in NC-BCFR. Women were classified as premenopausal if they still had menstrual periods or were pregnant or breast-feeding and were younger than the ‘study-specific age at menopause’; or as postmenopausal if 1) they reported their periods stopped naturally or due to surgery or other medical treatment, or 2) they still had periods with or without hormone therapy use and were at or above the ‘study-specific age at menopause’.

Statistical analyses

We excluded from the analysis 185 cases from NC-BCFR who also participated in SFBCS, 99 cases whose cancer was not a first primary breast cancer, and 168 cases with known *in situ* breast cancer. Restricting the dataset to parous women and excluding 21 cases and 24 controls with missing age at first birth, the analyses was based on 2,703 cases and 3,254 controls. Missing data for covariates, shown in Table 1, were imputed by multiple imputation for 285 cases and 320 controls with missing values for one or more covariates.[31] We used SAS multiple imputation procedures to impute missing covariate data and generate 20 data sets which were each analyzed. We combined the results of the analyses to derive valid statistical inferences.

We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for all women combined, and separately for premenopausal and postmenopausal women, using unconditional logistic regression. Multivariable models were adjusted for study and age, and factors associated with breast cancer risk in our dataset. Covariates and their categorizations are shown in the footnotes of the tables. For U.S. Hispanics, we compared ER+ and/or PR+ (hereafter referred to as hormone receptor positive, HR+) and ER-PR-case groups to a common control group. We used logistic regression analyses to estimate ORs and 95% CIs for each subtype and adjusted for factors associated with each subtype, as shown in the footnotes of the tables. Linear trends were assessed across ordinal values of categorical variables. Binary logistic regression, adjusting for covariates for breast cancer overall, was used to test for differences in associations by menopausal status. To test for heterogeneity by subtype, we used polytomous logistic regression, adjusting for covariates for HR+ breast cancer, to compare each case subtype to a common control group. Differences in ORs between groups were evaluated as departure from multiplicative effects using the Wald statistic *P* value. Two-sided *P* values are reported for tests of trend and tests of heterogeneity. Analyses were conducted using SAS version 9.4 software (SAS Institute, Inc., Cary, NC).

Results

Characteristics of parous Hispanic women are shown in Table 1. Greater proportions of cases than controls had higher education, a first-degree family history of breast cancer, early menarche, a history of hormonal contraceptive use, higher alcohol consumption, lower BMI, and, among postmenopausal cases, were more likely to be current users of hormone therapy. Cases were also older at first live birth, had fewer live births, and were less likely to have a history of breast-feeding than controls.

Among all Hispanic women from the U.S. and Mexico combined (Table 2), older age at first birth was associated with increased breast cancer risk (≥30 vs. <20 years: OR=1.41, 95% CI=1.15–1.74, P_{trend}=0.001), but limited to premenopausal women (≥30 vs. <20 years: OR=1.81, 95% CI=1.30–2.54, P_{trend}=0.001, $P_{heterogeneity\ by\ menopausal\ status}$=0.01). Higher parity was associated with decreasing breast cancer risk (≥4 vs. 1 live births: OR=0.70, 95% CI=0.56–0.86, P_{trend}=0.001), with similar risk reductions for premenopausal and postmenopausal women ($P_{heterogeneity}$=0.30).

Among U.S. Hispanic women (eTable 1), age at first birth was not associated with breast cancer risk overall; a positive association was seen for premenopausal women only (≥30 vs. <20 years: OR=1.59, 95% CI=1.05–2.40, P_{trend}=0.03, $P_{heterogeneity\ by\ menopausal\ status}$=0.02). The association of parity with overall breast cancer risk was similar to that found for all Hispanics combined.

Age at first birth and parity were associated with HR+ but not ER-PR-breast cancer risk ($P_{heterogeneity\ by\ subtype}$=0.04 and 0.02, respectively; eTable 2), and for both characteristics, associations with HR+ breast cancer risk were limited to premenopausal women ($P_{heterogeneity\ by\ menopausal\ status}$=0.02 and 0.01, respectively).

Among U.S. Hispanic and Mexican women combined (Table 2), a history of breast-feeding was associated with reduced breast cancer risk (ever vs. never: OR=0.83, 95% CI=0.73–0.94), with similar risk reductions for premenopausal and postmenopausal women ($P_{\text{heterogeneity by menopausal status}}$=0.50). There was a trend of decreasing risk with longer duration of breast-feeding, with a 37% risk reduction for breast-feeding for ≥25 vs. 0 months (OR=0.73, 95% CI=0.60–0.89; P_{trend}=0.03 for women who breast-fed), with no heterogeneity by menopausal status ($P_{\text{heterogeneity}}$=0.81). Similar results were seen for U.S. Hispanic women (eTable 1), for whom inverse associations with longer duration of breast-feeding did not differ by subtype ($P_{\text{heterogeneity}}$=0.64; eTable 2). ORs per 12 months of breast-feeding were 0.94 (95% CI=0.90–0.99) for HR+ breast cancer and 0.93 (95% CI=0.86–1.00) for ER-PR-breast cancer. Furthermore, longer duration of breast-feeding was associated with reduced risk of HR+ breast cancer for both premenopausal and postmenopausal women ($P_{\text{heterogeneity by menopausal status}}$=0.30).

Joint associations of breast-feeding, parity, and age at first birth are shown in Table 3. Among all Hispanic women combined, compared to a single reference group of women with parity=1 and no history of breast feeding, increasing parity in the absence of a breast-feeding history was associated with decreasing risk of breast cancer, and at each parity level (1, 2–3, ≥4), breast-feeding contributed to a further estimated reduction in risk. For women with parity ≥4 and no breast-feeding history, the OR was 0.65 (95% CI=0.47–0.89) compared to OR=0.49 (95% CI=0.37–0.65) for parity ≥4 and breast-feeding for ≥13 months. Similar patterns were found for U.S. Hispanic women overall and for women with HR+ breast cancer (eTable 3).

Breast-feeding attenuated the increased risk associated with older age at first birth. Among all Hispanic women combined (Table 3), compared to a single reference group of women with first birth at age <20 years and breast-feeding for ≥13 months, those with a first birth at age ≥30 years and no history of breast-feeding experienced a nearly two-fold increased risk (OR=1.88, 95% CI=1.32–2.67). However, in the presence of breast-feeding for ≥13 months, late age at first birth was no longer associated with increased breast cancer risk (OR=1.23, 95% CI=0.83–1.85). A similar pattern was seen for U.S. Hispanic women overall and for those with HR+ breast cancer (eTable 3).

Discussion

In this pooled analysis of nearly 6,000 parous Hispanic women, older age at first birth was associated with increased risk of breast cancer but limited to HR+ breast cancer among premenopausal women, whereas high parity was associated with a substantial reduction in risk of HR+ breast cancer among premenopausal women. Neither age at first pregnancy nor parity was associated with ER-PR-breast cancer. A history of breast-feeding was associated with reduced breast cancer risk, independent of parity, with similar risk reductions for premenopausal and postmenopausal women and for HR+ and ER-PR-subtypes. Risk decreased with increasing duration of breast-feeding, and there was no heterogeneity by subtype. For HR+ breast cancer, at each level of parity risk reductions were larger in the presence of breast-feeding, and breast-feeding attenuated the increase in risk associated with older age at first birth.

Data on reproductive factors and breast cancer risk among Hispanic women are sparse. Two case–control studies outside of the U.S., one in Costa Rica[13] and one in Mexico,[15] found large risk reductions associated with high parity, as we did in our pooled analysis, particularly for postmenopausal women. The Costa Rican study did not stratify by menopausal status, whereas the Mexican study found larger risk reductions for premenopausal than postmenopausal breast cancer. Results for U.S. Hispanic women, however, are inconsistent. The Cancer and Steroid Hormone Study did not detect associations with parity in their sample of younger, mostly premenopausal women.[14] The New Mexico Women's Health Study found a large increased risk of postmenopausal breast cancer associated with high parity,[16] whereas the 4-CBCS previously reported reduced risk associated with high parity for postmenopausal breast cancer and limited to ER+ disease.[17] Only two prior studies in Hispanic women found linear trends of increased risk of breast cancer with older age at first birth; one for postmenopausal women from the New Mexico Women's Health Study,[16] and the other for premenopausal women from the 4-CBCS,[17] as corroborated in our larger pooled analysis.

Our results on parity and age at first birth for Hispanic women align with findings from prior studies, primarily in non-Hispanic populations.[32] Furthermore, our findings of associations with parity for HR+ but not ER-PR-breast cancer agree with a majority of previously published reviews and meta-analyses.[18,19,33–36] Unlike some studies that reported positive associations between parity and risk of ER- or ER-PR-subtypes in both younger[4,6,7] and older[3,6] women, we saw no evidence of this in our analysis of ER-PR-breast cancer.

For all Hispanic women combined, we found an inverse trend for breast-feeding, with similar results for premenopausal and postmenopausal Hispanic women and no significant differences by subtype. Of the five prior reports for Hispanic women,[13–17] only two studies found dose-response associations with lifetime duration of breast-feeding,[15,16] limited to premenopausal women in one study[16] and postmenopausal women in the other study.[15] 4-CBCS was the only prior study that considered ER status; no association with breast-feeding was found for either ER+ or ER− disease.[17]

Although evidence for an association between breast-feeding and breast cancer primarily in NHW women has not been consistent,[9,37] many studies found decreased risks associated with breast-feeding.[1,8,9,38] A recent meta-analysis of 27 international studies found a nearly 40% risk reduction for ever vs. never breast-feeding and greater than 50% reduction in risk for longest vs. shortest duration of lifetime breast-feeding.[8] However, this association was found only in case–control studies and was stronger for women from Asian countries, who had historically higher initiation and longer duration of breast-feeding than women from Western countries.[9] The most comprehensive meta-analysis to date of prospective studies found a 2% decrease in breast cancer risk per 5-month duration of breast-feeding, although evidence was less consistent for premenopausal and postmenopausal breast cancer separately.[38] In our large pooled analysis of Hispanic women, ever vs. never breast-feeding was associated with a 17% risk reduction overall, and among U.S. Hispanic women, with risk reductions of 22% and 23% for HR+ and ER-PR-subtypes, respectively. Unlike some studies that reported larger risk reductions for ER-PR- than HR+ breast cancer,[19,39] we

found similar risk reductions for both subtypes (per 12 months of breast-feeding: OR=0.94, 95% CI=0.90–0.99 for HR+ subtype; OR=0.93, 95% CI=0.86–1.00 for ER-PR-subtype).

Few studies have examined the joint effects of breast-feeding, parity, and age at first birth. Our results suggest that breast-feeding further contributes to a reduction in breast cancer risk beyond that associated with high parity for both overall and HR+ breast cancer. This finding is in agreement with a collaborative analysis of 47 international studies.[1] In our study, parity was associated with decreased risk of overall and HR+ breast cancer in the absence of breast-feeding, whereas the Nurses' Health Study cohort[5] of primarily Caucasian women and the Women's CARE case–control study[3] of white and African American women saw a decrease in risk associated with parity only for those with a history of breast-feeding, with similar findings for overall and HR+ breast cancer. In contrast, the Black Women's Health Study cohort and the larger AMBER Consortium of studies in African Americans did not find that breast-feeding further reduced risk of HR+ breast cancer beyond the protection afforded by parity alone.[4,6] A case–control analysis from the Breast Cancer Family Registry also found that breast-feeding further reduced risk of HR+ disease associated with parity, with stronger results for postmenopausal women than premenopausal women.[7] Thus, the joint effects of parity and breast-feeding warrant further analyses in larger datasets.

Similar to the CARE study,[3] we found a positive association between age at first birth and breast cancer risk among women who never breast-fed; for those with a history of breast-feeding, age at first birth was not associated with breast cancer risk. These findings suggest that breast-feeding may reduce elevated breast cancer risk in women who have their first child at older ages. Given the growing number of women who postpone childbearing to older ages, this finding is of public health importance.

Pregnancies and breast-feeding may affect breast cancer risk by several mechanisms. Pregnancy and breast-feeding inhibit ovulation, thereby reducing the number of ovulatory cycles over the lifetime and lowering exposure to cancer-stimulating endogenous hormones, such as estradiol and progesterone.[40] The stronger associations with breast-feeding for HR- disease in some studies suggest that perhaps non-hormonal pathways, such as drainage of toxins and possible carcinogens in the breast during lactation, contribute to the decrease in breast cancer risk.[41] It has also been proposed that differentiation of breast cells during pregnancy and breast-feeding after birth may protect against genetic mutations and the earlier that this protection occurs in a woman's lifetime, the lower the chance of carcinogenic changes.[37]

Furthermore, breast-feeding may reduce circulating estrogen levels through mechanisms involved in the physical stimuli of suckling.[42] Women who breast-feed exclusively experience a higher frequency of suckling, have longer post-partum amenorrhea,[43] lower levels of circulating estrogens,[42] and greater protection against breast cancer[44] than women who do not exclusively breast-feed.[42,44] However, at 6 months after birth, due to pediatric recommendations of supplementation with solid food, there is a decrease in exclusive breast-feeding practices.[45] Therefore, if breast-feeding affects breast cancer risk through hormonal pathways, the first six months of exclusive breast-feeding per child may be most critical for reducing breast cancer risk. A recent meta-analysis found stronger associations in women

who breast-fed exclusively compared to women who supplemented,[44] but in our study we were not able to distinguish exclusive breast-feeding from breast-feeding with supplementation.

Our study has several strengths, including a population-based design; the largest study to date that examined reproductive factors and breast cancer risk in Hispanic women, an understudied minority group; a comprehensive assessment of breast cancer risk factors by in-person interview; and availability of tumor ER and PR status for most cases in the U.S.-based studies. Our results should also be viewed in light of some limitations. Being a retrospective study, our findings are vulnerable to inaccurate recall. Given that breast-feeding is a discrete event in a woman's reproductive history, any recall bias is likely to be non-differential by case–control status, which would bias the OR estimates towards the null. The NC-BCFR offered response categories of breast-feeding per child in 6- and 12-month intervals and did not collect more detailed breast-feeding information. However, we did not detect differences in ORs associated with breast-feeding when excluding NC-BCFR. The number of controls in the NC-BCFR was small; in order to have comparable population controls from all studies, we opted to not include unaffected sisters as controls in this analysis. Another limitation is that our ER-PR-case counts were small, precluding analyses by menopausal status. Larger studies of ER-PR-breast cancer in Hispanic women are needed to examine associations with breast-feeding.

In the U.S., foreign-born Hispanic women have more children and longer breast-feeding duration than those who are U.S.-born.[24,46] These reproductive behaviors change, however, with longer residence in the U.S. and adoption of Western patterns of lower parity, older age at first birth, and shorter periods of breast-feeding.[24,46–48] In Mexico, rates of breast-feeding have also declined rapidly due to changing socioeconomic factors.[49] Our findings suggest that breast-feeding is associated with reduced risk of both HR+ and ER-PR-breast cancer among Hispanic women, as reported for other populations, and that the increase in risk may be attenuated in women with a first pregnancy at older ages. Given the high incidence of breast cancer in Hispanic women and other populations, identifying lifestyle behaviors that are modifiable, like breast-feeding, is important to breast cancer prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of U.S. Hispanic and Mexican Parous Women

	Cases N=2,703		Controls N=3,254	
	N	%[a]	N	%[a]
Study				
San Francisco Bay Area Breast Cancer Study (SFBCS)	980	36	1,357	42
Northern California Breast Cancer Family Registry (NC-BCFR)	262	10	63	2
4-Corners Breast Cancer Study (4-CBCS)	596	22	831	26
Mexico Breast Cancer Study (MBCS)	865	32	1,003	31
Estrogen receptor (ER) and progesterone receptor (PR) status[b]				
ER+ and/or PR+	1,139	62		
ER-PR-	382	21		
Unknown	317	17		
Age (years)				
< 40	305	11	337	10
40–44	386	14	472	15
45–49	464	17	537	17
50–54	428	16	489	15
55–59	387	14	448	14
60–64	319	12	385	12
≥65	414	15	586	18
Education				
Some high school or less	1,425	53	1,963	60
High school graduate	523	19	558	17
Some college or higher	752	28	731	22
Unknown	3	<1	2	<1
Family history of breast cancer in first-degree relatives				
No	2,333	86	2,925	90
Yes	331	12	260	8
Unknown	39	1	69	2
Age at menarche (years)				
<12	638	24	670	21
12	679	25	732	22
13	633	23	757	23
≥14	753	28	1,095	34
Unknown	0		0	
Hormonal contraceptive use				
Current	100	4	92	3
Former	1,370	51	1,551	48
Never	1,085	40	1,463	45
Unknown	148	5	148	5

	Cases N=2,703		Controls N=3,254	
	N	%[a]	N	%[a]
Menopausal status				
Premenopausal	1,073	40	1,217	37
Postmenopausal	1,547	57	1,928	59
Unknown	83	3	109	3
Hormone therapy use (postmenopausal women)				
Current	378	24	333	17
Former	295	19	510	26
Never	874	56	1,085	56
Average daily alcohol consumption (grams)[c]				
0	1,762	65	2,429	75
0.1–4.9	604	22	519	16
≥ 5.0	303	11	279	1
Unknown	34	1	27	1
Body mass index (kg/m^2) (premenopausal women)[d]				
< 25.0	340	32	278	23
25.0–29.9	401	37	470	39
≥ 30.0	314	29	451	37
Unknown	18	2	18	1
Body mass index (kg/m^2) (postmenopausal women)[d]				
< 25.0	326	21	340	18
25.0–29.9	569	37	712	37
≥30.0	617	40	838	43
Unknown	35	2	38	2
Age at first live birth (years)				
<20	755	28	1,096	34
20–24	1,015	38	1,248	38
25–29	557	21	614	19
≥30	376	14	296	9
Mean	23.4		22.7	
Range	11–46		12–50	
Parity[e]				
1	400	15	316	10
2	774	29	755	23
3	688	25	823	25
4	374	14	492	15
5	196	7	319	10
≥6	271	10	549	17
Mean	3.0		3.6	
Range	1–12		1–17	

	Cases N=2,703		Controls N=3,254	
	N	%[a]	N	%[a]
Duration of lifetime breast-feeding (months)				
0	783	29	776	24
1–6	922	34	964	30
7–12	360	13	479	15
13–24	343	13	500	15
≥25	295	11	535	16
Mean	11.0		15.9	
Range	0–166		0–188	

Abbreviations: 4-CBCS, 4-Corners Breast Cancer Study; ER, estrogen receptor; MBCS, Mexico Breast Cancer Study; NC-BCFR, Northern California Breast Cancer Family Registry; PR, progesterone receptor; SFBCS, San Francisco Bay Area Breast Cancer Study.

[a] Percentages may not add up to 100% due to rounding.

[b] Excluding participants in the MBCS for whom data on ER and PR status were not available.

[c] Average daily lifetime consumption for participants in the NC-BCFR, 4-CBCS, MBCS, and SFBCS participants diagnosed/selected into the study after April 1999; and average daily consumption in reference year for SFBCS participants diagnosed/selected into the study before May 1999.

[d] In reference year (calendar year before diagnosis for cases or before interview or selection into the study for controls).

[e] Number of live births.

Table 2.

Reproductive History, Breast-feeding, and Breast Cancer Risk among Parous U.S. Hispanic and Mexican Women by Menopausal Status

	U.S. Hispanic and Mexican Women Combined								
	All Women			Premenopausal Women			Postmenopausal Women		
	Cases N=2,703	Controls N=3,254		Cases N=1,073	Controls N=1,217		Cases N=1,547	Controls N=1,928	
	N	N	OR 95% CI[a]	N	N	OR 95% CI[b]	N	N	OR 95% CI[c]
Age at first live birth (years)[d]									
<20	755	1,096	1.0	256	418	1.0	480	641	1.0
20–24	1,015	1,248	1.11 0.97–1.27	390	434	1.38 1.10–1.73	594	772	0.98 0.82–1.16
25–29	557	614	1.13 0.96–1.34	253	241	1.53 1.17–2.00	280	358	0.91 0.73–1.13
≥30	376	296	1.41 1.15–1.74	174	124	1.81 1.30–2.54	193	157	1.27 0.96–1.68
			P_{trend} = 0.001			P_{trend} = 0.001			P_{trend} = 0.10
						$P_{heterogeneity\ by\ menopausal\ status}$ = 0.01			
Parity[e,f]									
1	400	316	1.0	210	151	1.0	175	153	1.0
2	774	755	0.86 0.71–1.04	370	373	0.79 0.60–1.04	368	348	0.94 0.71–1.24
3	688	823	0.78 0.64–0.96	301	358	0.80 0.59–1.04	363	438	0.80 0.60–1.07
≥4	841	1,360	0.70 0.56–0.86	192	335	0.73 0.51–1.03	641	989	0.72 0.54–0.97
			P_{trend} = 0.001			P_{trend} = 0.07			P_{trend} = 0.03
						$P_{heterogeneity\ by\ menopausal\ status}$ = 0.30			
per live birth			0.91 0.88–0.95			0.94 0.87–1.02			0.90 0.86–0.94
History of breast-feeding[g]									
Never	783	776	1.0	244	221	1.0	504	523	1.0
Ever	1,920	2,478	0.83 0.73–0.94	829	996	0.83 0.66–1.03	1,043	1,405	0.82 0.69–0.96
						$P_{heterogeneity\ by\ menopausal\ status}$ = 0.50			
Duration of lifetime breast-feeding (months)[g]									
0	783	776	1.0	244	221	1.0	504	523	1.0
1–6	922	964	0.92 0.79–1.07	411	434	0.88 0.68–1.13	486	504	0.94 0.78–1.14
7–12	360	479	0.80 0.73–0.96	182	201	0.90 0.68–1.21	170	264	0.69 0.54–0.88

U.S. Hispanic and Mexican Women Combined									
	All Women			Premenopausal Women			Postmenopausal Women		
	Cases N=2,703	Controls N=3,254		Cases N=1,073	Controls N=1,217		Cases N=1,547	Controls N=1,928	
	N	N	OR 95% CI[a]	N	N	OR 95% CI[b]	N	N	OR 95% CI[c]
13–24	343	500	0.77 0.64–0.93	132	189	0.72 0.53–0.99	201	295	0.77 0.61–0.98
≥25	295	535	0.73 0.60–0.89	104	172	0.70 0.50–0.99	186	342	0.73 0.57–0.93
			P_{trend} = 0.002			P_{trend} = 0.05			P_{trend} = 0.01
			P_{trend} = 0.03[h]			P_{trend} = 0.14[h]			P_{trend} = 0.09[h]
						$P_{heterogeneity\ by\ menopausal\ status}$ = 0.81			
Per 12 months			0.94 0.90–0.98			0.90 0.83–0.98			0.95 0.91–0.99

Abbreviations: 4-CBCS, 4-Corners Breast Cancer Study; ER, estrogen receptor; MBCS, Mexico Breast Cancer Study; NC-BCFR, Northern California Breast Cancer Family Registry; SFBCS, San Francisco Bay Area Breast Cancer Study.

[a]Odds ratios and 95% confidence intervals, adjusted for age (years; continuous), study (SFBCS, NC-BCFR, 4-CBCS, MBCS), education (less than high school, high school graduate, post high school education), family history of breast cancer in first-degree relatives (no, yes), age at menarche (<12, 12, 13, ≥14 years), hormonal contraception use (never, former, current), menopausal status and hormone therapy use (premenopausal, postmenopausal never used HT, postmenopausal past HT use, postmenopausal current HT use, menopausal status unknown), average daily alcohol consumption (0, 0.1–4.9, 5–9.9, ≥10 grams), and body mass index in reference year (<25.0, 25.0–29.9, ≥30.0 kg/m^2).

[b]Odds ratios and 95% confidence intervals, adjusted for age (years; continuous), study (SFBCS, NC-BCFR, 4-CBCS, MBCS), education (less than high school, high school graduate, post high school education), family history of breast cancer in first-degree relatives (no, yes), age at menarche (<12, 12, 13, ≥14 years), hormonal contraception use (never, former, current), average daily alcohol consumption (0, 0.1–4.9, 5–9.9, ≥10 grams), and body mass index in reference year (<25.0, 25.0–29.9, ≥30.0 kg/m^2).

[c]Odds ratios and 95% confidence intervals, adjusted for age (years; continuous), study (SFBCS, NC-BCFR, 4-CBCS, MBCS), education (less than high school, high school graduate, post high school education), family history of breast cancer in first-degree relatives (no, yes), age at menarche (<12, 12, 13, ≥14 years), hormonal contraception use (never, former, current), hormone therapy use (never, past, current), average daily alcohol consumption (0, 0.1–4.9, 5–9.9, ≥10 grams), and body mass index in reference year (<25.0, 25.0–29.9, ≥30.0 kg/m^2).

[d]Adjusted additionally for parity and lifetime breast-feeding.

[e]Number of live births.

[f]Adjusted additionally for lifetime breast-feeding and age at first live birth.

[g]Adjusted additionally for parity and age at first live birth.

[h]Trend for women who breast-fed.

Table 3.

Joint Associations of Breast-feeding, Parity, and Age at First Birth on Overall Breast Cancer Risk among U.S. Hispanic and Mexican Women

	U.S. Hispanic and Mexican Women Combined		
	Cases N=2,703	Controls N=3,254	
	N	N	OR 95% CI[a]
Parity[b] by duration of breast-feeding (months)[c]			
1 birth			
No breast-feeding	183	124	1.0
1–12 months breast-feeding	191	168	0.74 0.54–1.02
≥13 months breast-feeding	26	24	0.65 0.35–1.21
2–3 births			
No breast-feeding	432	436	0.72 0.54–0.95
1–12 months breast-feeding	784	818	0.68 0.52–0.88
≥13 months breast-feeding	246	324	0.54 0.40–0.73
≥4 births			
No breast-feeding	168	216	0.65 0.47–0.89
1–12 months breast-feeding	307	457	0.53 0.40–0.72
≥13 months breast-feeding	366	687	0.49 0.37–0.65
			$P_{interaction} = 0.56$
Age at first live birth (years) by duration of breast-feeding (months)[d]			
<20 years			
≥13 months breast-feeding	245	441	1.0
1–12 months breast-feeding	327	447	1.05 0.84–1.32
No breast-feeding	183	208	1.26 0.96–1.65
20–29 years			
≥13 months breast-feeding	326	526	1.04 0.84–1.30
1–12 months breast-feeding	776	854	1.26 1.02–1.55
No breast-feeding	470	482	1.38 1.11–1.74
≥30 years			
≥13 months breast-feeding	67	68	1.23 0.83–1.85
1–12 months breast-feeding	179	142	1.55 1.14–2.11
No breast-feeding	130	86	1.88 1.32–2.67
			$P_{interaction} = 0.47$

Abbreviations: 4-CBCS, 4-Corners Breast Cancer Study; HR+, hormone receptor positive (estrogen receptor positive and/or progesterone receptor positive); MBCS, Mexico Breast Cancer Study; NC-BCFR, Northern California Breast Cancer Family Registry; SFBCS, San Francisco Bay Area Breast Cancer Study.

[a]Odds ratios and 95% confidence intervals, adjusted for age (years; continuous), study (SFBCS, NC-BCFR, 4-CBCS,MCBS), education (less than high school, high school graduate, post high school education), family history of breast cancer in first-degree relatives (no, yes), age at menarche (<12, 12, 13, ≥14 years), hormonal contraception use (never, former, current), menopausal status and hormone therapy use (premenopausal,

postmenopausal never used HT, postmenopausal past HT use, postmenopausal current HT use, menopausal status unknown), average daily alcohol consumption (0, 0.1–4.9, 5–9.9, ≥10 grams), and body mass index in reference year (<25.0, 25.0–29.9, ≥30.0 kg/m^2).

[b] Number of live births.

[c] Adjusted additionally for age at first live birth.

[d] Adjusted additionally for parity