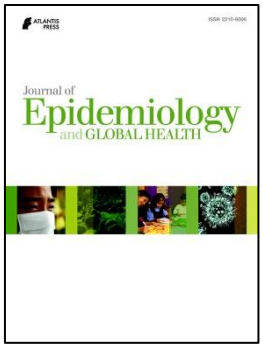

ATLANTIS PRESS

Journal of Epidemiology and Global Health

ISSN (Online): 2210-6014 **ISSN (Print): 2210-6006**
Journal Home Page: https://www.atlantis-press.com/journals/jegh

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To cite this article: Maureen Sanderson, Adriana Pérez, Mirabel L. Weriwoh, Leah R. Alexander, Gerson Peltz, Vincent Agboto, Heather O'Hara, Waseem Khoder (2013) Perinatal factors and breast cancer risk among Hispanics, Journal of Epidemiology and Global Health 3:2, 89–94, DOI: https://doi.org/10.1016/j.jegh.2013.02.004

To link to this article: https://doi.org/10.1016/j.jegh.2013.02.004

Published online: 23 April 2019

Journal of Epidemiology and Global Health (2013) 3, 89–94

http:// www.elsevier.com/locate/jegh

Perinatal factors and breast cancer risk among Hispanics

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Received 6 September 2012; received in revised form 7 February 2013; accepted 10 February 2013
Available online 13 March 2013

KEYWORDS
Breast neoplasms;
Prenatal exposure delayed effects;
Risk factors;
Hispanic Americans;
Case–control studies

Abstract *Purpose:* This study assessed whether perinatal factors were associated with breast cancer among Hispanics, a group with fairly low incidence rates of breast cancer.

Methods: Data were used from a case–control study of breast cancer among Hispanics aged 30–79 conducted between 2003 and 2008 on the Texas–Mexico border. In-person interviews were completed with 188 incident breast cancer cases ascertained through surgeons and oncologists, and 974 controls (with respective response rates of 97% and 78%).

Results: Relative to birth weight 2500–3999 g, there was no elevation in breast cancer risk for birth weight of $\geqslant$4000 g (odds ratio [OR] 0.76, 95% confidence interval [CI] 0.47–1.21).

Conclusions: The results tended to differ slightly from previous studies of this topic perhaps owing to the different hormonal milieu among Hispanics relative to Caucasians, African Americans and Asians in whom all previous studies of this topic

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http://dx.doi.org/10.1016/j.jegh.2013.02.004
0263-2373/$ - see front matter

have been conducted. Confirmation of these findings in larger studies may assist in determining how hormonal mechanisms responsible for breast cancer differ by ethnicity.

1. Introduction

High birth weight and other perinatal factors thought to reflect on a woman's exposure to hormones, growth factors and other endocrine factors have been linked to subsequent breast cancer [1]. Three meta-analyses of the high birth weight-breast cancer association have reported summary relative risks ranging from 1.15 (95% confidence interval [CI] 1.09—1.21) to 1.24 (95% CI 1.04—1.48) [2—4], while a pooled analysis of this association based on birth records reported a pooled relative risk of 1.12 (95% 1.00—1.25) [5]. High birth weight was defined as ⩾4000 g relative to <3000 g for the most part in the meta-analyses [2—4] or relative to 3000—3499 g in the pooled analysis [5]. After restricting the types of studies to cohort studies, two meta-analyses of the association between older maternal age defined as ⩾30 years relative to <25 years and breast cancer reported summary relative risks of 1.13 (95% CI 1.02—1.25) [2] and 0.99 (95% CI 0.82—1.19) [3], respectively. Neither higher birth order (relative risk [RR] 0.91, 95% CI 0.91—1.04) nor maternal smoking (RR 0.98, 95% CI 0.86—1.13) appeared to be associated with breast cancer in a meta-analysis that included studies of all types [3]. Meta-analyses have reported breast cancer to be positively associated with birth length and older paternal age [2], negatively associated with pre-eclampsia/eclampsia and twin membership [2], and not associated with gestational age [2,3], and maternal diethylstilbestrol (DES) use [2]. However, cohort studies have identified a positive association between maternal DES and breast cancer among women diagnosed at age 40 or older [6,7]. None of the studies reported on the meta-analyses or pooled analysis examined the associations between perinatal factors and breast cancer among Hispanic women who have fairly low incidence rates of breast cancer compared with Caucasian women [8].

Based on mothers who delivered between 1974 and 1977, the birth characteristics of Hispanic women also differ from those of Caucasian women [9]. In comparison with Caucasians, Hispanics weigh slightly less (3.48 vs. 3.42 kg), are born to younger mothers (26.5 vs. 25.7 years), are of higher birth order (18.6% ⩾2 vs. 26.0% ⩾2), and are born to mothers who do not smoke during pregnancy (70.1% vs. 79.4%). Given the differences in perinatal factors and breast cancer incidence rates of Hispanics relative to Caucasians, it was assessed whether perinatal factors were associated with breast cancer among Hispanic women in the current study.

2. Materials and methods

Detailed methods of this clinic-based case—control study conducted in the Lower Rio Grande Valley located at the southern tip of Texas on the Mexico border appear elsewhere [10]. Briefly, cases of self-reported Hispanic ethnicity, aged 30—79, diagnosed with primary invasive breast cancer between November 2003 and August 2008 were identified through surgeons and oncologists shortly after diagnosis or treatment ($n = 190$, response rate 97.0%). Controls of Hispanic ethnicity, aged 30—79, were randomly selected from women receiving a diagnostic or screening mammogram at the mammography center where the case received her diagnostic mammogram. Interviews were completed with approximately five controls per case ($n = 979$, response rate 78.0%). Women who were adopted were excluded resulting in 188 cases, and 974 controls for analysis.

Written informed consent was obtained from subjects and the Institutional Review Boards of the University of Texas at Brownsville and the University of Texas Health Science Center at Houston approved this study's protocol. Trained interviewers conducted in-person interviews on demographic characteristics, suspected breast cancer risk and protective factors, medical history, physical activity, diet, body size and perinatal factors. Exposures were for a period before a reference date, the date of diagnosis for the cases and an assigned date for controls comparable to the date for the cases. For example, controls recruited early in the study were assigned reference dates ranging from November 2003 to December 2005, while controls recruited later in the study were assigned reference dates ranging from January 2006 to August 2008.

Statistical analyses were completed in SAS version 9.2. There were large percentages of missing

data for some perinatal factors (birth weight 14.2%, maternal age 13.7%, and maternal hormone use 18.1%). It was assumed that these missing values were missing at random and multiple imputation for handling these missing values were implemented. The variables listed in Tables 1 and 2 were used to perform 10 imputations under a multivariate normal model. An assumption of multiple imputation is that all variables are normally distributed which, based on a normal probability plot, was not the case for body mass index (BMI). BMI was log transformed for the imputation models and retransformed for presentation in Table 1. Logistic regression was used to estimate the relative risk of breast cancer associated with perinatal factors while controlling for potential confounding factors [11]. To assess the fit and any influential observations of the logistic regression models, Pregibon's diagnostics measures were implemented, including index plots and delta-betas [12]. Some observations were influential, but their impact on the fit was negligible. Overall, there were no concerns regarding the fitted models. Age, family history of breast cancer, age at menarche, menopausal status, parity, BMI, use of oral contraceptives, use of hormone replacement therapy, alcohol intake, number of mammograms in past 6 years, physical activity and other perinatal factors were evaluated as potential confounders. An alpha level of 0.05 was used to determine statistical significance of all two-sided statistical tests, and final analyses are presented using Rubin's rules for reporting summary statistics, odds ratios, confidence intervals, test statistics and diagnostic measures from the 10 multiple imputations [13].

3. Results

Table 1 presents the distribution of suspected breast cancer risk and protective factors by case—control status following the imputation of missing values. Cases were more likely than controls to be older, to have a family history of breast cancer, to have an earlier age at menarche, to be postmenopausal, not to have used oral contraceptives or hormone replacement therapy, to have had fewer mammograms in the past 6 years, and not to have engaged in physical activity.

The addition of age modeled continuously, menopausal status and number of mammograms in the past 6 years to the perinatal factors-breast cancer models changed the crude odds ratio by 10% or more, so adjustment was made for these confounding variables. There appeared to be no association with breast cancer among women whose birth weight was 4000 g or more relative to women whose birth weight was 2500—3999 g (odds ratio [OR] 0.76, 95% CI 0.47—1.21 after adjustment for age, menopausal status and mammography screening) (Table 2). Nor were women who were born preterm at risk of breast cancer relative to women who were born at term (OR 0.32, 95% CI 0.08—1.40). Although there did appear to be an increased risk odds of breast cancer associated with twin birth (OR 2.83, 95% CI 1.08—7.37) and maternal smoking (OR 1.44, 95% CI 0.85—2.45), the wide confidence intervals argue for cautious interpretation. There was no association with breast cancer risk odds for older maternal age or higher birth order.

4. Discussion

The results of this study, which were not statistically significant and tended to differ only slightly from previous meta-analyses [2—4] and a pooled analysis [5] of this topic, are scientifically interesting. A possible explanation for these results may be the different hormonal milieu among Hispanics relative to Caucasians, African Americans and Asians in whom all previous studies of this topic have been conducted. A recent study in the southwestern United States found that two estrogen-related factors — hormone replacement therapy and younger age at menarche — do not function as risk factors for breast cancer diagnosed after menopause among Hispanic women as they do among Caucasian women [14]. Hines et al. [14] hypothesized that the ethnic differences in postmenopausal breast cancer associated with estrogen exposure may be modified by genetic, environmental and/or lifestyle factors. They speculated this may be reflected in the higher proportion of estrogen receptor positive tumors in Caucasian women than in Hispanic women [15].

Another possible explanation for the different findings from previous studies is that *in utero* exposures may not act directly on the breast, but may alter other physiologic pathways that affect risk later in life. Terry et al. [16] investigated the cohort of daughters whose mothers participated in the New York site of the Collaborative Perinatal Project from 1959 to 1963 and found no differences in age at menarche by birth weight, maternal age, birth order, gestational age, or maternal smoking. Troisi et al. [1] indicated there is insufficient evidence to establish associations between perinatal factors and premenopausal estrogen or adult insulin-like growth factor levels, both thought to be related to breast cancer risk.

Table 1 Comparison of cases and controls for suspected breast cancer risk and protective factors.

Characteristic	Cases (n = 188)		Controls (n = 974)	
	N	%	*N*	%
Age (years)				
30–49	61	32.4	391	40.1
50–64	87	46.3	472	48.5
65–79	40	21.3	111	11.4
Breast cancer among first-degree relatives				
No	168	89.4	905	92.9
Yes	20	10.6	69	7.1
Age at menarche (years)				
<12	50	26.7	228	23.4
⩾13	138	73.3	746	76.6
Menopausal status				
Premenopausal	39	21.0	281	28.8
Postmenopausal	149	79.0	693	71.2
Full-term pregnancy				
No	10	5.3	60	6.2
Yes	178	94.7	914	93.8
Body mass index				
<25	13	7.1	69	7.1
25–29.9	44	23.6	230	23.6
30–34.9	77	41.2	401	41.2
⩾35	54	28.1	274	28.1
Oral contraceptive use				
No	66	35.3	267	27.4
Yes	122	64.7	707	72.6
Hormone replacement therapy use[a]				
No	90	60.3	431	44.3
Yes	59	39.7	543	55.7
Alcohol intake				
No	154	81.9	798	81.9
Yes	34	18.1	176	18.1
Number of mammograms in past 6 years				
0–1	39	20.7	97	10.0
2–3	54	28.7	187	19.2
4–5	34	18.1	186	19.1
⩾6	61	32.4	504	51.7
Physical activity				
No	115	61.2	485	49.8
Yes	73	38.8	489	50.2

[a] Among postmenopausal women.

Lastly, these results may have been explained by insufficient study power. This study power was limited for all main effects; in order to achieve 80% power for the high birth weight-breast cancer association, this study would have required 725 cases and 2900 controls.

This study was limited by self-report of perinatal factors which is prone to misclassification and resulted in many missing values. Several validation studies of perinatal factors have been performed, including one that was conducted on women born in Washington State in which very high correlations comparing self-report with birth certificate for maternal age (r = 0.95), and comparing self-report with mother report for birth order (r = 0.89) and for birth weight (r = 0.85) [17] were found.

Table 2 Odds ratios of breast cancer associated with perinatal factors.

Characteristic	Cases (n = 188)		Controls (n = 974)		OR[a]	(95% CI)
	N	%	N	%		
Birth weight (g)						
<2500	28	15.1	164	16.8	0.76	(0.47—1.21)
2500—3999	146	77.3	708	72.7	1.00	(Referent)
⩾4000	14	7.6	102	10.6	0.68	(0.36—1.29)
Maternal age (years)						
<25	84	44.8	392	40.2	1.00	(Referent)
25—29	42	22.3	226	23.2	0.92	(0.58—1.46)
⩾30	62	32.9	356	36.6	0.84	(0.57—1.25)
Birth order						
First	40	21.1	205	21.0	1.00	(Referent)
⩾Second	148	78.9	769	79.0	1.00	(0.95—1.05)
Gestational age (weeks)						
<37	2	1.3	27	2.8	0.32	(0.08—1.40)
⩾37	186	98.7	947	97.2	1.00	(Referent)
Twin birth						
No	180	95.7	962	98.8	1.00	(Referent)
Yes	8	4.3	12	1.2	2.83	(1.08—7.37)
Maternal smoking						
No	164	87.3	893	91.7	1.00	(Referent)
Yes	24	12.7	81	8.3	1.44	(0.85—2.45)

[a] Odds ratio (OR) and 95% confidence interval (95% CI) adjusted for age, menopausal status and number of mammograms in past 6 years.

The percentage of women unable to report some of their perinatal factors ranged from 1.6% for birth order to 18.1% for maternal hormone use. With the exception of gestational age, cases were slightly more likely than controls to have missing values. Although the percentages of missing values tended to be similar for cases and controls, it was not clear as to whether the missing value would have been systematically lower or higher than the obtained value, thus multiple imputations may have resulted in a differential misclassification. Differential misclassification may have biased results toward or away from the null, but in comparing multiple imputations with other methods for analyzing data with large percentages of missing values, multiple imputation produces less biased and more efficient estimates [18]. Additional limitations were the inability to calculate an odds ratio for maternal hormone use because no mothers of cases reported hormone use, and this study's failure to collect information on birth length, paternal age and pre-eclampsia/eclampsia which were associated with breast cancer in a meta-analysis [2]. In addition, this study was unable to assess effect modification by menopausal status owing to the small number of premenopausal cases (n = 39), which is of importance since Sanderson et al. [19] identified differing birth weight-breast cancer associations for premenopausal and postmenopausal women.

As far as this study is concerned, it is the first to investigate the association between perinatal factors and breast cancer among Hispanic women. Given the differing distributions of perinatal factors in Hispanic women relative to women of other ethnicities, it is important to include this group to further clarify the contribution of prenatal exposures to adult-onset diseases. This study was unable to categorize birth weight differently because 35% of women who were unable to report their exact birth weight reported it as less than 2500, 2500—3999 or 4000 g or more. However, a sensitivity analysis was performed comparing women who were first born with those who were second born (OR 1.03, 95% CI 0.61—1.75), third born (OR 0.99, 95% CI 0.56—1.74) and fourth born or higher (OR 0.91, 95% CI 0.59—1.38) which revealed a reduction in risk with higher birth order. Lastly, this study assessed confounding by a number of established breast cancer risk and protective factors, including mammography screening, which reduced the likelihood of detection bias.

Hispanic women have relatively low incidence rates of breast cancer although they possess some of the same risk factors as ethnic groups with higher incidence rates. As Hines et al. [14] suggest, the study of Hispanic women may help us disentangle the effect of the hormonal milieu on breast cancer. Confirmation of these findings in larger studies may assist in determining how hormonal mechanisms responsible for breast cancer differ by ethnicity.

Acknowledgments

This research was supported in part by Grant numbers DAMD-17-03-1-0274 and W81XWH 10 1 0993 from the Department of Defense, U.S. Army Medical Research and Materiel Command, and by Grant number 5 P20 MD000170 from the National Center on Minority Health and Health Disparities (NIH). During the writing of this manuscript, Dr. Pérez was supported by the Michael & Susan Dell Foundation [Grant 8075].

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