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Associations of Physical Activity, Sedentary Time, and Insulin with Percent Breast Density in Hispanic Women

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Abstract

Background—In a previous study of Hispanic women, we reported a positive association between sedentary time and percent breast density, a marker of breast cancer risk. It is unclear whether associations between sedentary time or physical activity and percent breast density are mediated through serum insulin levels or insulin resistance, factors also associated with physical activity and breast cancer risk.

Methods—In the Chicago Breast Health Project phase II pilot study, detailed information on health and lifestyle factors, including sitting time and total physical activity over the previous 7 days, was collected from 95 Hispanic women aged 40–77 years. We also assessed percent breast density and measured fasting serum insulin and glucose to calculate the Homeostasis Model Assessment (HOMA) index, a measure of insulin resistance. Multivariable linear regression was used to assess associations of total physical activity, time spent sitting, serum insulin, and HOMA index with percent breast density.

Results—There was no association between total physical activity and percent breast density ($p = 0.98$), whereas there was a positive association between sedentary time and percent density ($\beta = 0.25\%$ per 100 metabolic equivalent (MET)-minutes/week, $p = 0.06$). Percent breast density was not associated with insulin or with HOMA index. The strength of the association between time spent sitting and percent density was unchanged after inclusion of insulin or the HOMA index in the model.

Conclusions—These results are consistent with our previous finding of an association between sedentary time and percent breast density and suggest that insulin or insulin resistance is unlikely to mediate this relation.

INTRODUCTION

Among Hispanic women, breast cancer is the most commonly occurring nonskin cancer and the most common cause of cancer mortality.^{1,2} Risk of breast cancer is significantly higher

(4–6-fold risk increase) in women with a predominance of radiologically dense breast tissue.^{3,4} In addition, many breast cancer risk factors, including age, menopausal status, use of hormone therapy (HT), and obesity, are associated with mammographic breast density.^{5–9} Although density is a risk factor for breast cancer, previous studies of non-Hispanic white women have found no association of physical activity with percent breast density.^{9–11} The Chicago Breast Health Project (CBHP) examined the relations between lifestyle factors and breast density in Hispanic women. In phase I, we found a higher percent breast density for women who reported at least 3.5 hours/day of sedentary time compared with women who reported 0–1 hour/day.¹² To our knowledge, no study has examined the association of directly measured physical activity with percent breast density in Hispanic women, a population that has been found to have low levels of leisure time physical activity and a high prevalence of obesity,^{13,14} both independent risk factors for breast cancer.¹⁵ Given the increasing size of the female Hispanic population in the United States and potential differences in risk behaviors from non-Hispanic whites, understanding the nature of modifiable breast cancer risk factors, such as physical activity, within the population is of importance. Thus, we examined the association of physical activity, sedentary time, and breast density in a sample of Hispanic women using a previously validated comprehensive self-report physical activity instrument.

One proposed pathway linking lifestyle factors with breast cancer risk is the insulin pathway; both serum insulin levels and measures of insulin resistance have been associated with risk of breast cancer.^{17,18} Insulin levels increase with obesity, whereas weight loss and physical activity can induce a drop in serum insulin. Using data collected as part of the CBHP phase II pilot study, we explored a potential biological mechanism underlying the previously found association between sedentary time and breast density.

MATERIALS AND METHODS

Sample

Healthcare providers from two community health clinics serving a Hispanic community of Chicago referred women to Northwestern University for screening mammography. Eligibility criteria included women who were ≥ 40 years, had no personal history of breast cancer, were not pregnant at the time of the study, had no abnormality detected by a clinical breast examination (CBE), and reported no screening mammography in the past 12 months. Between May 2003 and June 2004, 142 women were referred and 113 consented to participate. Of the 29 women who did not consent, 14 were unreachable, 12 did not want to participate, and 3 were found to be ineligible. Of those who consented, we excluded 9 women who did not identify themselves as Hispanic and 3 who did not undergo digital mammography. In addition, the physical activity instrument used calls for the exclusion of extreme scores,¹⁹ thus excluding an additional 6 women, resulting in a final sample of 95 Hispanic women. Women provided written informed consent. This study was reviewed and approved by the Institutional Review Board of Northwestern University.

Data collection

Data collection research interviewers were bilingual (Spanish/English) and bicultural (Hispanic) and were trained in interviewing and anthropometry measurements. All questionnaires were translated using a back-translation approach, which employed two independent translations in sequence, from English to Spanish and then Spanish to English. A questionnaire on health and lifestyle was administered in person by the interviewer and included information on birth date, race/ethnicity, highest grade of education completed, and smoking.

Physical activity was assessed via the International Physical Activity Questionnaire—Long Form (IPAQ), available for download at the IPAQ website.¹⁹ This 27-item survey queries participants on the frequency and duration of physical activity in the last 7 days across five domains: (1) job related, (2) transportation, (3) housework, house maintenance, and caring for family, (4) recreation, sport, and leisure time, and (5) time spent sitting. The intensity of each item within the activity domains was assigned a metabolic equivalent (MET) intensity level (for leisure time and work: moderate = 4, vigorous = 8, walking = 3.3, sitting = 1).²⁰ The IPAQ was scored by multiplying the frequency (days/week), duration (minutes/session), and the intensity (MET) of the activities performed, resulting in a MET-min/wk score. MET-min/wk were computed for all domains, except time spent sitting, which was expressed as min/wk, and summed to create a total physical activity score. The detailed scoring protocol for the IPAQ—Long Form is posted on the IPAQ website.¹⁹

Weight was measured to the nearest 0.25 pounds and height to the nearest 0.25 inches with the use of a balance beam. Body mass index (BMI) was calculated as weight (kg) divided by the height squared (m²). Measurements were taken in duplicate, and the average was used.

Fasting blood samples were drawn by veni-puncture. Radioimmunoassay (human insulin specific RIA kit, Linco Research, Inc., St Charles, MO) was used to measure serum insulin levels. The YSI glucose analyzer (YSI 2300 STAT PLUS, YSI Inc., Yellow Springs, OH) was used to measure glucose levels, which were then used to calculate a measure of insulin resistance using the Homeostasis Model Assessment (HOMA) score: (fasting serum insulin (β U/mL)* fasting plasma glucose (mmol/L)/22.5). HOMA score provides an estimate of insulin sensitivity, with a high score reflecting insulin resistance. Our quality control evaluation had coefficients of variation (CV) for glucose and insulin of 1.04% and 13.32%, respectively.

Screening mammography was conducted using a full-field digital mammography system (GE Senograph 2000D, GE Medical Systems, Milwaukee, WI). Clinical mammography results were provided to the subject and her physician, and efforts were made for appropriate follow-up care. Percent breast density was determined using the NIH ImageJ software (rsb.info.nih.gov/ij/) as described in our previous report.⁵ A reviewer blinded to the radiologist report and patient history analyzed the digital image to determine the total and percentage of breast fibroglandular dense tissue by examining the craniocaudal and mediolateral oblique images and determining (1) the area of the entire breast, excluding nipple markers and pectoralis major muscle along the chest wall, by summing the number of pixels containing breast area (BA), (2) a threshold signal value that best separated fibroglandular regions from the fatty background, and (3) the area of fibroglandular tissues (FA) within the breast by summing the number of pixels within the fibroglandular region. Percent breast density was then calculated for each woman as FA/BA. This calculation was done separately for the craniocaudal and mediolateral oblique views of both right and left breasts, and percent breast density was determined by calculating the mean of the percent density from both views of both breasts.

Statistical methods

For bivariate analysis, age was stratified into 5-year age groups. Associations with mean percent density were examined by comparing the age-adjusted mean percent density across levels of the exposure variables using analysis of covariance (ANCOVA). Because of the small numbers, the use of cigarettes was classified as never/past or current. BMI, total physical activity, sedentary time, insulin, and HOMA were stratified into quartiles. The dependent variable, percent breast density, was treated as a continuous variable.

The associations between the lifestyle (BMI, total physical activity, and time spent sitting) and hormonal (insulin, HOMA index) factors were examined using age-adjusted Pearson partial

correlations, with age as a continuous variable. We considered adjusting for menopausal status, parity, postmenopausal hormone use, BMI, and smoking status. The variables in the final model were those that appeared to be associated ($p \leq 0.1$) with percent breast density in the age-adjusted analyses or we had on *a priori* reason for including. Therefore, multivariable associations were adjusted for age (continuous), BMI (continuous), and smoking status. Analyses of breast density with total physical activity or sedentary time were additionally adjusted for insulin and HOMA. Reanalysis using a square root transformation of total physical activity and sedentary time to normalize the distributions did not alter the conclusions.

RESULTS

In this sample of 95 Hispanic women, the overall mean (SD) percent breast density was 20.5% (10.1%) and ranged from 2.3% to 49.7% (Table 1). The mean BMI was 30.9 kg/m²; 88% of the subjects were overweight or obese (BMI ≥ 25 kg/m²). Less than one tenth (7%) of women smoked. The average time spent sitting was 1478 min/wk, which is equivalent to approximately 25 hours. The average total physical activity score was 3321 MET-min/wk; this is equivalent to approximately 14 hours of moderate and vigorous intensity and walking across four domains (work, transportation, household, and recreation/leisure) of physical activity per week. One tenth of the women (11%) reported ≥ 150 minutes of moderate intensity work physical activity, and nearly one third (32%) reported ≥ 150 minutes of moderate intensity household physical activity in the last week. In contrast, no women reported 150 minutes of moderate intensity leisure physical activity, and only 13 reported any leisure physical activity of any duration.

In age-adjusted analyses, quartiles of total physical activity and sedentary time were not associated with percent breast density (Table 2). Neither insulin nor HOMA index score were associated with percent breast density. Total physical activity was not correlated with insulin ($r = -0.03$, $p = 0.78$) or HOMA index ($r = -0.05$, $p = 0.64$) (data not shown). Similarly, sedentary time was not correlated with insulin ($r = 0.07$, $p = 0.53$) or HOMA score ($r = 0.02$, $p = 0.84$) (data not shown).

In multivariable analysis, the association between time spent sitting and percent density approached significance for all women ($\beta = 0.25$, $p = 0.06$) (Table 3). This can be interpreted as a 0.25% increase in breast density for each 100 minute increase in sedentary time per week. There was no significant association of total physical activity with percent breast density. Percent breast density was not associated with insulin or HOMA. Additional adjustment for insulin and HOMA did not change the association of sedentary time or total physical activity with percent breast density.

DISCUSSION

The positive relationship between sedentary time and percent breast density that was initially documented in CBHP phase I was confirmed in the current study¹²: for every increase of 100 minutes of sitting per week, percent breast density increased by 0.25%. However, we noted no association between total physical activity and percent breast density. These results are consistent with previous studies in non-Hispanic women that found no association of physical activity MET min/wk and breast density in larger samples of European and U.S. women.^{9–11} These studies employed a range of physical activity measures from past year physical activity to physical activity at age 20. This is the first study to examine the association of physical activity and breast density in Hispanic women, a population with traditionally higher levels of obesity and lower levels of leisure time physical activity than non-Hispanic white women.^{13, 14} It is also the first study to measure both physical activity and sedentary time in order to determine their association with breast density. This study expands on our previous pilot

research in phase I by including a more comprehensive measure of sedentary time as well as a comprehensive physical activity questionnaire.

In attempts to understand the biological mechanisms underlying the previously found association of physical inactivity with percent breast density in Hispanic women,¹² the roles of insulin and insulin resistance were examined. No significant relationships between these factors and percent breast density were noted. This is contrary to other studies that found significant correlations between insulin-like growth factor-1 (IGF-1) or IGF-binding protein-3 (IGFBP-3) with breast density.^{21–24} Moreover, our data suggest that serum insulin might not account for the association of time spent sitting with breast density, as the association of time spent sitting with percent breast density was unchanged following adjustment for insulin or HOMA index. It is possible, however, that other biological markers (e.g., sex hormones) linked to physical inactivity and breast cell proliferation might mediate this relationship.

Although we found an association between percent breast density and sedentary time, no association was observed for total physical activity. Several possible explanations for these observations may exist. First, concerns have been noted about the methods used (IPAQ—Long Form) to assess physical activity. The international validation study, which included a sample of non-Hispanic whites in the United States, showed the IPAQ—Long Form had acceptable validity (pooled $r = 0.33$) when compared with activity counts from Actigraph accelerometers.²⁵ IPAQ sitting minutes were significantly correlated (range $r = 0.22–0.49$, $p < 0.05$) with the minutes of inactivity assessed by the accelerometers, but the validity of the IPAQ—Long Form has not been evaluated in minority populations in the United States. Women in our study reported high levels of occupational and household physical activity but comparatively lower levels of leisure time physical activity. The high level of physical activity reported by our participants (approximately 3300 mean MET min/wk) is consistent with recent preliminary data from the NHANES accelerometer study, which indicates that total physical activity is highest among Mexican-American participants.²⁶ This may be a function of the accumulation of high amounts of lower intensity occupational or transportation activity, which the IPAQ—Long Form assesses as well. Future research is needed to determine the validity of the IPAQ among Hispanics in the United States.

Second, studies suggest that inactivity is a potentially powerful mechanism for disease risk. Indeed, research suggests measures of sedentary time provide more accurate measures of physical activity (via inactivity) than self-report of physical activity.^{27,28} One study found no association for physical activity but a positive association between time spent sitting and risk of ovarian cancer,²⁸ whereas another showed an inverse association between self-reported inactivity and objectively measured physical activity but noted that their findings fail to support the notion that time spent sitting displaces time that would otherwise be spent in physical activity.²⁹ These inconclusive findings may be related to the patterns of physical activity performed by some women. Some women may do a lot of low intensity physical activity throughout the day (scurriers) and sit very little, whereas others may exercise sufficiently to meet public health recommendations of 30+ min/day of moderate or vigorous activity and then sit for the rest of the day (squatters). These patterns should be explored in relation to measures of sitting time and health outcomes. It is also possible that the observations in our study could be the result of measurement error or imprecision in self-report of physical activity performed in the various domains. Little is known about the response patterns for overestimation or underestimation of physical activity in occupation, household, and transportation physical activities. The role of measurement error may be further supported by our failure to find an association between either physical activity or sitting time and insulin or HOMA index; previous research^{30,31} found significant associations of both leisure time physical activity and television watching with blood glucose levels in women. In an exploratory analysis in this

study, we found no associations between leisure time physical activity from the IPAQ—Long Form with insulin ($r = -0.06$) or HOMA ($r = -0.04$).

Third, it is also possible that negative health behaviors associated with time spent sitting are associated with percent breast density. For example, if women engage in poor dietary practices while sitting, greater time spent sitting could be associated with a dietary pattern of increased risk. Research in children has suggested an association between poor diet and increased television viewing.³² Given that specific elements of the diet, such as fat intake, are positively associated with breast density³³ independent of BMI or physical activity, future research should consider whether sedentary time is serving as a proxy for unhealthy dietary practices. Our hypothesis that sedentary time and physical activity may be related but distinct concepts is supported by the low correlation ($r = 0.05$, $p = 0.65$) between the two in our study.

Several factors may influence the interpretation of our results. As noted, there are concerns about the validity of the physical activity and sedentary time measures in minority women. Our physical activity and sedentary time measures reference the last 7 days of behavior, whereas previous studies that have used previous year, usual, lifetime, or past physical activity have similarly found no association. The biologically relevant time period is unknown, although we have argued previously that recent physical activity is more relevant.¹² Given that the other study to look at recent physical activity found no association,¹⁰ additional research on the relevant period of exposure is needed. Furthermore, the pilot nature of the study resulted in a small sample size, which may have limited our ability to find statistically significant findings. Future research in larger samples is clearly necessary before conclusions can be drawn about the association between physically active lifestyles and breast density. However, given that our findings approached statistical significance with a small sample and the measurement error intrinsic in physical activity and inactivity measurement, these findings are noteworthy. The generalizability of our findings to nonurban Hispanic women is not known. That said, our study employed measures of both physical activity and sedentary time, allowing findings to be compared and contrasted. The nature of the relationship between both physical activity and breast density in Hispanic women, a population with low leisure time physical activity levels and high rates of obesity, has not previously been explored.

CONCLUSIONS

The current study lends support to the hypothesis that sedentary time is positively related to percent breast density; this relation does not appear to be explained by BMI, cigarette smoking, and insulin. Although the biological mechanism underlying this association is not clear, this finding is significant, given the high levels of sedentary behavior in the U.S. female population.³⁴ Because of the known strong relationship between breast density and breast cancer risk,³ culturally sensitive lifestyle modifications aimed at reducing time spent sitting in Hispanic women might help to reduce their risk of breast cancer. Given the pilot nature of this study, however, these findings need to be replicated in larger samples.

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Table 1Sociodemographic, Health, and Lifestyle Characteristics, Chicago Breast Health Project, Phase II Pilot Study ($n = 95$)

Characteristics	Mean or %	Range
Percent breast density	20.5	2.3–49.7
Age (years)	53	40–77
Cigarette smoking		
Never or past	93%	
Current	7%	
BMI (kg/m^2)	30.9	21.7–49.5
Sitting (min/wk)	1,478	275–4,800
Total physical activity (MET-min/wk)	3,321	0–13,536

Table 2

Age-Adjusted Mean (SE) Percent Breast Density According to Strata of Sociodemographic, Hormonal, and Lifestyle Characteristics
(*n* = 95)

Characteristic	n	Mean	(SE)	p value ^a
Age, years				0.0002
40–45	24	27.0	1.9	
46–50	14	21.7	2.5	
51–55	23	19.9	1.9	
56–60	19	18.2	2.1	
61	15	12.6	2.4	
Cigarette smoking				0.39
Never or past	88	20.7	1.0	
Current	7	17.5	3.5	
BMI (kg/m ²)				0.008
21.7–26.7	23	24.7	1.8	
26.8–30.5	24	22.3	1.8	
30.6–34.1	24	18.5	1.8	
34.2–49.5	24	16.5	1.8	
Sitting (min/wk)				0.68
275–960	24	19.0	1.9	
961–1,409	24	20.5	1.9	
1,410–1,899	23	22.3	1.9	
1,900–4,800	24	20.2	1.9	
Total physical activity (MET-min/wk)				0.30
0–1,049		23		
1,050–2,699	24	22.5	19.0	2.0
2,700–4,999	24	22.0	1.9	
5,000–13,536	24	18.4	1.9	
Insulin (μU/mL)				0.64
6.6–12.7	23	22.3	1.9	
12.8–18.9	24	18.7	1.9	
19.0–26.4	24	20.6	1.9	
26.5–72.4	24	20.4	1.9	

Characteristic	n	Mean	(SE)	p value ^a
HOMA index				0.66
1.6–3.1	23	21.5	1.9	
3.2–5.2	24	19.0	1.9	
5.3–7.2	24	21.8	1.9	
7.3–37.7	24	19.6	1.9	

^a p value from ANCOVA

Table 3
Multivariable Association of Percent Breast Density with Physical Activity and Insulin, CBHP Phase II (*n* = 95)

Characteristic	β (% breast density) ^a	p value	β (% breast density) ^b	p value	β (% breast density) ^c	p value
Total physical activity (per 100 MET-min/wk)	-0.0007	0.98	-0.002	0.96	-0.002	0.95
Sitting (per 100 min/wk)	0.25	0.06	0.25	0.06	0.25	0.07
Insulin (μ U/mL)	-0.03	0.72				
HOMA	-0.08	0.69				

^a Adjusted for age, BMI, and smoking.
^b Adjusted for age, BMI, smoking, and insulin.
^c Adjusted for age, BMI, smoking, and HOMA.