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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

The purpose of this Minority Institution Partnership Training Award was to train University of Texas at Brownsville (UTB) faculty to conduct breast cancer research by collaborating with faculty from the University of Texas-Houston School of Public Health (UTSPH). Three UTB faculty underwent intensive training provided by six UTSPH faculty during year 1. To reinforce training, faculty from UTB and UTSPH conducted a clinic-based case-control study of breast cancer to investigate its' association with hormones, diet and body size in years 2 through 4. Specific aims included: 1) to provide UTB faculty training through classes, presentations and seminars to gain knowledge of epidemiology, proposal development, behavioral sciences, and biostatistics offered by UTSPH faculty, and 2) to design and conduct a clinic-based case-control study to include completion of a questionnaire, anthropometry and a blood draw.

During the fifth year of the project, data collection continued for the clinic-based case-control study, the South Texas Women's Health Project. Dr. Sanderson (UTSPH) continued in her role as principal investigator of a project funded by the National Center on Minority Health and Health Disparities to conduct a study of women diagnosed with high risk-human papillomavirus which places them at high risk of cervical cancer, and as principal investigator of a grant from the Texas Cancer Council to investigate the utility of electronic pathology lab reporting the to the Texas Cancer Registry on the Texas-Mexico border. Dr. Sanderson (UTSPH) and Dr. Nair (UTB) submitted a Synergistic Idea Award application to conduct a substudy of the South Texas Women's Health Project to investigate genes associated with obesity and diabetes.

14. Subject Terms (keywords previously assigned to proposal abstract or terms which apply to this award)
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Introduction

The purpose of this Minority Institution Partnership Training Award was to train University of Texas at Brownsville (UTB) faculty to conduct breast cancer research by collaborating with faculty from the University of Texas-Houston School of Public Health (UTSPH). Three UTB faculty underwent intensive training provided by six UTSPH faculty during year 1. Additional training took place in subsequent years. To reinforce training, faculty from UTB and UTSPH conducted a clinic-based case-control study of breast cancer to investigate its' association with hormones, diet and body size in years 2 through 5. Specific aims were: 1) to provide UTB faculty training through classes, presentations and seminars to gain knowledge of epidemiology, proposal development, cancer epidemiology, intervention mapping, field epidemiology, biostatistics, and nutrition epidemiology offered by UTSPH faculty in-person from Brownsville and via ITV from Houston, 2) to design and conduct a clinic-based case-control study to include completion of a questionnaire, anthropometry and a blood draw, 3) to disseminate findings to the Texas Department of State Health Services, the Department of Defense, and local health providers and health clinics, and 4) to submit proposals to conduct larger population-based case-control studies of breast cancer in the Lower Rio Grande Valley.

Body

This project occurred in two phases, the training phase (year 1) and the investigation phase (years 2 through 5). The only training task that was fully completed during the first year of the project was training task 5. The training tasks that were fully completed during the second year of the project were training tasks 4 and 6. The training task that was fully completed during the third year of the project was training task 1. The training tasks that were fully completed during the fourth year of the project were training tasks 3 and 8 in our attempt to include Hidalgo county by teaming up with an investigator from the University of Texas Medical Branch. We obtained institutional review board (IRB) approval from the University of Texas Medical Branch on May 18, 2007, but the Department of Defense IRB never provided their approval due to wording problems with consent forms so we did not add this study site. During the fifth year of the project, we fully completed training task 2 by Dr. Sanderson (UTSPH) continued to receive funding from the Texas Cancer Council to investigate the possibility of utilizing electronic pathology lab reporting to the Texas Cancer Registry on the Texas and Mexico sides of the border. We fully completed training task 7 by obtaining continuing IRB approval for data analysis from the University of Texas at Brownsville on June 4, 2008 and from the University of Texas Health Science Center at Houston on July 31, 2008; however, our continuing IRB approval from the Department of Defense is still pending. We submitted study closure reports to the Texas Department of State Health Services on February 12, 2008, and to Valley Baptist Medical Center-Harlingen on July 8, 2008.

During the fifth year of the project, we fully completed investigation task 1 by identifying and recruiting women with breast cancer and control women through the study completion date of July 8, 2008 (see Table 1). We fully completed investigation task 2 by conducting in-person and telephone interviews on breast cancer risk factors. We fully completed investigation task 3 by collecting anthropometric measurements, blood and urine. We fully completed investigation task 4 by abstracting medical records for diagnosis, and breast cancer screening, diagnosis and treatment. We fully completed investigation task 5 by processing and storing blood and urine samples. We fully completed investigation task 6 by completing enzyme-linked immunosorbent assays on hormones and growth factors. We fully completed

investigation task 7 by completing high-performance liquid chromatography analysis for urinary phytoestrogen. We fully completed investigation task 8 by entering data for all questionnaires and assays. We fully completed investigation task 9 by performing interim statistical analysis to assess data quality. We fully completed investigation task 10 by performing final statistical analysis to test study hypotheses at the end of the study. We fully completed investigation task 11 by Dr. Sanderson (UTSPH) presenting on cancer registration at the University of Texas Medical Branch Cancer Stop Clinic on February 13, 2008. We fully completed investigation task 12 by Dr. Sanderson (UTSPH) serving as principal investigator of a project funded by the National Center on Minority Health and Health Disparities to conduct a study of women diagnosed with high risk-human papillomavirus which places them at high risk of cervical cancer. We fully completed investigation task 13 by Dr. Sanderson presenting to representatives of the Texas Department of State Health Services and local health providers and clinics on February 22, 2008, and by Dr. Peltz (UTB) and Dr. Sanderson (UTSPH) presenting at the Department of Defense Breast Cancer Research Program meetings on June 24 and 25, 2008. We fully completed investigation task 14 by preparing and submitting an initial manuscript of the project to *Cancer Causes and Control* on September 15, 2008 (see Appendix). We fully completed investigation task 15 by archiving datasets for future analyses and future patient follow-up. We fully completed investigation task 16 by Dr. Sanderson (UTSPH) and Dr. Nair (UTB) submitting a Synergistic Idea Award application to the Department of Defense to conduct a substudy of the South Texas Women's Health Project to investigate genes associated with obesity and diabetes.

Key Research Accomplishments

- Completed training task 1 by Dr. Peltz (UTB) taking epidemiology (introductory, nutrition, advanced epidemiologic methods I, and cancer), biostatistics, behavioral sciences, community health assessment, proposal development, individual study and practicum, and receiving his Master's of Public Health; and by Drs. Estrada (UTB) and Johnson (UTB) auditing proposal development, epidemiology, biostatistics, and behavioral sciences. Dr. Peltz (UTB) received a grant from the University of Texas Health Science Center at San Antonio to conduct a pilot study of body composition and leptin concentration. Dr. Peltz (UTB) worked with Dr. Sanderson (UTSPH) in publishing two cancer-related manuscripts in *Ethnicity and Disease* in 2006 and in *Annals of Epidemiology* in 2006 (see Appendix), and in publishing two breast cancer-related abstracts in the *American Journal of Epidemiology* in 2006 and 2007. Dr. Peltz (UTB) conducted his master's thesis using data from the leptin project which was subsequently published in the *Archives of Medical Research* in 2007 (see Appendix). Dr. Peltz published abstracts on the leptin project in *Obesity Research* in 2005, 2006 and 2007, in *Diabetes and Vascular Disease Research* in 2007.

- Completed training task 2 by Dr. Sanderson (UTSPH) co-chairing the Texas Cancer Registry Data Utilization Subcommittee to encourage timely reporting of breast cancer cases to the Texas Cancer Registry, and by Dr. Sanderson (UTSPH) received a grant from the Texas Cancer Council to investigate the possibility of utilizing electronic pathology lab reporting to the Texas Cancer Registry on the Texas and Mexico sides of the border.

- Completed training tasks 3 through 8 by identifying study sites and designing the South Texas Women's Health Project to include completion of a questionnaire, anthropometry, a blood draw, and a urine collection; developing a questionnaire appropriate for use with the

local Hispanic population; designing the protocols for data collection, laboratory work, tracking system, data entry programs, and by writing the manual of operations; obtaining institutional review board approval from several entities; conducting a pilot study, and revising the study design as needed. Dr. Sanderson (UTSPH) received a grant from the National Center on Minority Health and Health Disparities to conduct a pilot study of the South Texas Women's Health Project. Dr. Peltz (UTB) unsuccessfully submitted a grant to the National Institute of General Medical Sciences to add urinary excretion of phytoestrogen to the South Texas Women's Health Project, but did receive a supplemental grant from the Department of Defense to add urinary excretion of phytoestrogen to the South Texas Women's Health Project.

- Completed investigation tasks 1 through 11 by recruiting breast cancer cases and controls; conducting in-person and telephone interviews; collecting anthropometric measurements, blood, and urine; abstracting medical records; processing and storing blood and urine samples; completing enzyme-linked immunosorbent assays; completing high-performance liquid chromatography analysis; entering data for all questionnaires and assays; performing interim statistical analysis to assess data quality; performing final statistical analysis to test study hypotheses; and consulting with local health providers and clinics regarding cancer reporting. With regard to investigation task 10, we hypothesized that we would not find an association between diabetes and breast cancer among Hispanic women in our study; although non-significant, we saw a reduced risk of breast cancer among women who had a history of diabetes (OR 0.70, 95% CI 0.49-1.09) after adjustment for age, menopausal status, body mass index, and mammography screening (see Table 2 of the initial manuscript in the Appendix). Since physical activity is known to reduce the risk of breast cancer and diabetes, we also hypothesized that physical activity would modify the effect of diabetes on breast cancer. Relative to women who had no history of diabetes and did not engage in physical activity, women who had a diabetes history and did not exercise were at somewhat reduced breast cancer risk (OR 0.66, 95% CI 0.42-1.04) while those with diabetes who did exercise had greatly reduced breast cancer risk (OR 0.31, 95% CI 0.15-0.65) (see Table 3 of the initial manuscript in the Appendix). Dr. Sanderson (UTSPH) unsuccessfully submitted a grant to the Susan G. Komen Foundation to conduct a validation study and awareness campaign of family history of breast cancer among South Texas Women's Health Project subjects.

- Completed investigation task 12 by Dr. Sanderson (UTSPH) receiving a grant from the National Center on Minority Health and Health Disparities to conduct a study of women diagnosed with high risk-human papillomavirus which places them at high risk of cervical cancer, and by Dr. Sanderson (UTSPH) unsuccessfully submitting a grant to the National Cancer Institute to conduct a case-only study of prostate cancer utilizing the newly gold certified Texas Cancer Registry as a source of cases.

- Completed investigation tasks 13 through 15 by disseminating project findings to the Texas Department of State Health Services, the Department of Defense, and local health providers and clinics; by preparing and submitting an initial manuscript to *Cancer Causes and Control* (see Appendix); and by archiving the dataset for future analyses. Drs. Peltz and Sanderson presented findings at the Department of Defense Breast Cancer Research Program meetings in 2005 and 2008, and at the Department of Defense Historically Black Colleges and Universities/Minority Institutions Breast Cancer Research Program meetings in 2006 and 2008. Drs. Peltz and Sanderson presented on developing and maximizing effective

collaborations at the Department of Defense Historically Black Colleges and Universities/Minority Institutions Breast Cancer Research Program meetings in 2008.

- Completed investigation task 16 by Dr. Sanderson (UTSPH) and Dr. Nair (UTB) unsuccessfully submitting and resubmitting a Synergistic Idea grant to the Department of Defense to conduct a substudy of the South Texas Women's Health Project to investigate genes associated with obesity and diabetes.

Reportable Outcomes

1) Manuscripts

Sanderson M, Fernandez ME, Dutton RJ, Ponder A, Sosa D, Peltz G. Risk behaviors by ethnicity and Texas-Mexico border residence. Ethnicity Dis 2006;16:514-520.

Sanderson M, Coker AL, Perez A, Du XL, Peltz G, Fadden MK. A multilevel analysis of socioeconomic status and prostate cancer risk. Ann Epidemiol 2006;16:901-907.

Peltz G, Sanderson M, Perez A, Sexton K, Caceres D, Fadden MK. Serum leptin concentration, adiposity, and body fat distribution in Mexican Americans: A cross-sectional study. Arch Med Res 2007;563-570.

Sanderson M, Peltz G, Perez A, Johnson M. Diabetes, physical activity and breast cancer among Hispanic women. Cancer Causes Control (under review).

2) Abstracts

Peltz G, Sanderson M, Perez A, Estrada JK, Johnson M. Use of mammography by Texas-Mexico border residence and ethnicity. 4th Department of Defense Breast Cancer Research Program Meeting, Philadelphia, PA, June 2005.

Peltz G, Casares DO, Fadden MK, Calil R, Perez A, Sanderson M. The use of body mass index for the diagnosis of obesity in Mexican Americans: A comparative study with bioelectrical impedance analysis. Obes Res 2005;13:A62.

Peltz G, Garcia ER, Calil R, Fadden MK, Sanderson M. Self-perception of body image and body area dissatisfaction in Mexican Americans. Obes Res 2005;13:A130.

Peltz G, Sanderson M. South Texas Women's Health Project: Training partnership and preliminary results. Department of Defense Historically Black Colleges and Universities/Minority Institutions Breast Cancer Research Program Reverse Site Visit, Baltimore, MD, April 2006.

Sanderson M, Sparrow P, Peltz G, Perez A, Johnson M. Association between breast and cervical cancer screening and self-rated health by ethnicity. Am J Epidemiol 2006;163:S143.

Peltz G, Sanderson M, Perez A, Ochoa D, Fadden MK. Leptin and body composition in Mexican Americans. Obes Res 2006;14:A.

Sanderson M, Peltz G, Perez A, Johnson M, Dutton RJ. Influence of Mexican health care on breast and cervical cancer screening. Am J Epidemiol 2007;165:S31.

Peltz G, Sanderson M, Calil R, Aguirre MT, Casares DO, Chavez-Reyes J, Fadden MK. Association of leptin with insulin: effects of body fat and waist circumference. Diabetes Vasc Dis Res 2007; 4(Suppl 1):s87.

Peltz G, Sanderson M, Cortez E, Calil R, Aguirre M. Comparative study between waist circumference and trunk fat mass using segmental bioelectrical impedance analysis. Obes Res 2007;15:A.

Peltz G, Sanderson M, Wittenburg D, Bailey M, Aguirre K, Reyes-Chaves J, Aguirre MT, Calil R, Fadden MK. Body composition by bioelectrical impedance analysis and air-displacement plethysmography: a comparative study. Obes Res 2007;15:A.

Peltz G, Sanderson M. Preliminary results from the South Texas Women's Health Project. Building Networks: The CDMRP Minority and Underserved Populations Program Facilitates Progress to Eliminate Health Disparities, Baltimore, MD, June 2008.

Peltz G, Sanderson M. Developing and maximizing effective collaborations. Building Networks: The CDMRP Minority and Underserved Populations Program Facilitates Progress to Eliminate Health Disparities, Baltimore, MD, June 2008.

Sanderson M, Peltz G, Perez A, Johnson M. Diabetes, physical activity and breast cancer among Hispanic women. 5th Department of Defense Breast Cancer Research Program Era of Hope Meeting, Baltimore, MD, June 2008.

Peltz G, Sanderson M, Perez A, Johnson M. Body composition and breast cancer among Hispanic women. 5th Department of Defense Breast Cancer Research Program Era of Hope Meeting, Baltimore, MD, June 2008.

3) Grants

Name:	Insulin Resistance and Breast Cancer (Sanderson, PI)
Funding Agency:	National Center on Minority Health and Health Disparities
Period of Funding:	March 1, 2003 – February 28, 2005
Amount: (total direct)	
Status:	Funded

Name:	Cancer Disparities, Reporting and Prevention among Texas-Mexico Border Hispanics (Sanderson, PI)
Funding Agency:	National Institute on Minority Health and Health Disparities
Period of Funding:	March 1, 2003 – February 28, 2008
Amount: (total direct)	
Status:	Funded

Name:	Serum Leptin Values in Mexican Americans: Association with Body Fat, Body Mass Index, and Obesity (Peltz, PI)
Funding Agency:	University of Texas Health Science Center at San Antonio

Period of Funding: September 1, 2004 – August 31, 2005
Amount: (total direct)
Status: Funded

Name: Partnership between the Texas Cancer Registry and the UTSPH-B for Assuring Timely, Complete and Accurate Cancer Data in the LRGV (Sanderson, PI)
Funding Agency: Texas Cancer Council
Period of Funding: March 1, 2005 – August 31, 2008
Amount: (total direct)
Status: Funded

Name: Urinary Excretion of Phytoestrogen in Breast Cancer among Hispanic Women (Peltz, PI)
Funding Agency: National Institute of General Medical Sciences, MBRS-SCORE
Period of Funding: April 1, 2005 – March 31, 2006
Amount: (total direct)
Status: Unfunded

Name: Supplement - Interrelationships of Hormones, Diet, Body Size, and Breast Cancer Among Hispanic Women (Peltz, PI)
Funding Agency: Department of Defense
Period of Funding: August 8, 2005 – August 31, 2007
Amount: (total direct)
Status: Funded

Name: Using the Texas Cancer Registry to Conduct a Multiethnic Prostate Cancer Study (Sanderson, PI)
Funding Agency: National Cancer Institute
Period of Funding: April 1, 2006 – March 31, 2008
Amount: (total direct)
Status: Unfunded

Name: Accuracy of Reporting of Family History of Breast Cancer among Hispanic Women (Sanderson, PI)
Funding Agency: Susan G. Komen Foundation
Period of Funding: April 1, 2007 – March 31, 2009
Amount: (total direct)
Status: Unfunded

Name:	Obesity, Diabetes and Breast Cancer in Mexican American Women (Sanderson and Nair, PIs)
Funding Agency:	Department of Defense
Period of Funding:	April 1, 2008 – March 31, 2010
Amount: (total direct)	
Status:	Unfunded

Name:	Obesity, Diabetes and Breast Cancer in Mexican American Women (Sanderson and Nair, PIs)
Funding Agency:	Department of Defense
Period of Funding:	April 1, 2009 – March 31, 2011
Amount: (total direct)	
Status:	Pending

Conclusions

The overall goal of this Minority Institution Partnership Training Award was to further strengthen the collaborative relationship between the minority institution, UTB, and the collaborating institution, UTSPH. The UTSPH established a regional campus on the UTB campus in 2001, and the Co-Principal Investigator of the partnership from UTSPH was located in Brownsville. The vision of UTB and the UTSPH, Brownsville regional campus was to conduct community-based participatory research in areas deemed important by the community.

The training program focused on breast cancer etiology, specifically the interrelationships between hormones, diet, body size and breast cancer among Hispanic women. The Lower Rio Grande Valley (LRGV) of Texas is an exceptional location to perform breast cancer research because 85 percent of the population is Hispanic. Hispanic women in the LRGV have a relatively low incidence of breast cancer compared with non-Hispanic white women. In comparison with Hispanic women in the US, Hispanic women residing in the LRGV have a higher mortality from breast cancer. In contrast, Hispanic women are at greater risk of insulin resistance. This research will allow us to investigate whether the reduced risk of breast cancer among Hispanic women in the LRGV may be related to their higher genetic susceptibility to insulin resistance. Women tend to develop insulin resistance if they are genetically susceptible, gain excess weight due to physical inactivity, and consume a high-fat, low-fiber diet during adolescence and adulthood. It is clear that this area of research has promise with regard to explaining the different breast cancer incidence and mortality rates by ethnicity. We hypothesized that the South Texas Women's Health Project conducted as part of the training program would be useful in identifying factors associated with decreased breast cancer risk among Hispanic women.

While faculty from UTSPH have expertise in breast cancer research, faculty from UTB have strong ties with the medical and lay community in Brownsville and Cameron County. Prior to the project, no breast cancer research has been conducted in Cameron County. By partnering together, these institutions hoped to achieve the following goals: 1) develop a regional cancer registry, 2) build infrastructure to conduct population-based case-control studies of breast cancer, 3) initiate studies to investigate factors which may protect Hispanic women from breast cancer, and 4) establish an outstanding breast cancer research program.

References

Sanderson M, Fernandez ME, Dutton RJ, Ponder A, Sosa D, Peltz G. Risk behaviors by ethnicity and Texas-Mexico border residence. Ethnicity Dis 2006;16:514-520.

Sanderson M, Coker AL, Perez A, Du XL, Peltz G, Fadden MK. A multilevel analysis of socioeconomic status and prostate cancer risk. Ann Epidemiol 2006;16:901-907.

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Sanderson M, Peltz G, Perez A, Johnson M. Diabetes, physical activity and breast cancer among Hispanic women. Cancer Causes Control (under review).

Statement of Work

Interrelationships of Hormones, Diet, Body Size and Breast Cancer among Hispanic Women

Phase 1: Training phase (Year 1)

1) Complete coursework toward Master's of Public Health degree
2) Liaise with local medical providers, health clinics and state health agencies to encourage reporting of breast cancer to the Texas Cancer Registry
3) Identify sites for data collection with local health providers and health clinics
4) After consultation with local health providers design a case-control study to include completion of a questionnaire, urine collection, anthropometry and a blood draw
5) Develop a questionnaire appropriate for use with the local Hispanic population
6) Design protocols for data collection, laboratory work, tracking system, data entry programs, and write manual of operations
7) Initiate institutional review board approval through local and federal channels
8) Pilot test study methods and revise the study design as needed

Phase 2: Investigation Phase (Years 2 through 4)

1) Identify and recruit 500 breast cancer cases and 1000 controls identified by mammography centers
2) Complete questionnaires to obtain information on breast cancer risk factors, personal health history (e.g., type 2 diabetes), medication history (e.g., estrogen and insulin), and diet
3) Collect anthropometric measurements and pre-diagnostic blood
4) Abstract medical records for relevant health history and pathology data
5) Process and store blood samples
6) Complete enzyme-linked immunosorbent assays for insulin, insulin-like growth factor-I, insulin-like growth factor binding protein-3, and sex hormone-binding globulin, enzyme immunoassays for estradiol and estrone, and measure glucose on a biochemistry analyzer
7) Complete high-performance liquid chromatography (HPLC) analysis for urinary phytoestrogens
8) Complete data entry of all questionnaires and assays
9) Perform interim statistical analyses at end of year 2 to assess data quality
10) Perform final statistical analyses to test study hypotheses
11) Consult with local health providers and health clinics regarding the cancer reporting mechanism and provide training as needed
12) Expand data collection to cancers other than breast cancer as a means of developing a regional Lower Rio Grande Valley cancer registry.
13) Disseminate findings to the Texas Department of Health, the Department of Defense, and local health providers and health clinics
14) Prepare manuscripts to report study results
15) Archive dataset for future analyses and future patient follow-up
16) Submit proposals to conduct larger population-based case-control studies of breast cancer in the Lower Rio Grande Valley

RISK BEHAVIORS BY ETHNICITY AND TEXAS-MEXICO BORDER RESIDENCE

Maureen Sanderson, PhD; Maria E. Fernandez, PhD; Ronald J. Dutton, PhD; Arlette Ponder, MPH; Dina Sosa, BS; Gerson Peltz, MD

Objective: To determine whether residence on the Texas-Mexico border would modify the effect of ethnic differences on risk behaviors.

Design: We performed an analysis of 1999–2003 cross-sectional data from the Texas Behavioral Risk Factor Surveillance System (BRFSS).

Setting: Fifteen Texas-Mexico border counties compared with 239 Texas non-border counties.

Participants: 521 White and 1722 Hispanic residents of Texas-Mexico border counties and 16,904 White and 4933 Hispanic residents of Texas non-border counties.

Main Outcome Measures: Health risk behaviors including overweight, obesity, physical inactivity, fruit or vegetable consumption, heavy drinking, binge drinking, and smoking.

Results: Hispanic women and men were more likely to be overweight, obese, and physically inactive, and less likely to consume fewer than five fruits or vegetables per day than Whites regardless of residence. Ethnic differences in heavy and binge drinking differed by residence and sex. After adjustment for age, educational level, annual household income, perceived general health, and diabetes, most behaviors that were higher or lower remained significant among non-border residents but were no longer significant among border residents.

Conclusions: The only evidence of effect modification was binge drinking among males and most associations were weaker among border residents than among non-border residents. (*Ethn Dis*. 2006;16:514–520)

Key Words: Ethnicity, Risk Behaviors, Texas-Mexico Border

From the University of Texas-Houston School of Public Health at Brownsville (MS), University of Texas at Brownsville (GP), Brownsville; University of Texas-Houston School of Public Health, Houston (MF); Office of Border Health, Texas Department of State Health Services, Austin (RJD, AP); Public Health Region 11, Texas Department of State Health Services, Harlingen (DS); Texas.

INTRODUCTION

The prevalence of conditions and behaviors that place persons at risk of chronic disease differs by ethnicity. Myers et al[1] conducted a review of existing literature in 1995 of behavioral risk factors by ethnic group in comparison with White non-Hispanics, henceforth referred to as White. As indicated in the review, substantial evidence of obesity was found among female African Americans, Hispanics, Native Americans, and Pacific Islanders. Among African-American females and males >40 years of age, Asians/Pacific Islanders, and Hispanic females, some evidence of no regular exercise was seen. With regard to poor diet, defined as excess intake of dietary fat and inadequate intake of dietary fiber, strong evidence was seen among female African Americans, and some evidence was seen among Asians/Pacific Islanders, Hispanics, and Native Americans. Strong evidence of heavy drinking, defined as consuming more than two alcoholic drinks per day, was seen among African Americans and Native Americans, and some evidence was seen among Southeast Asian males and Hispanic males. Strong evidence of higher smoking rates was seen among African American males >40 years of age, immigrant Asian/Pacific Islander males, Hispanic males, and Native American males; however, strong evidence of lower smoking rates was seen among Hispanic females. Using data from the 2001–2002 Behavioral Risk Factor Surveillance System (BRFSS), Denny et al[2] reported that American Indians/Alaska Natives had higher prevalence of obesity, physical inactivity, and smoking than Whites.

Winkleby et al[3] posited that lower socioeconomic status may explain ethnic disparities in risk behaviors. In subsequent studies with data from the National Health and Nutrition Examination Survey III, Winkleby et al found higher prevalence of obesity and physical inactivity in African American and Hispanic women[4] and smoking in African American men[5] compared to Whites <65 years of age after adjustment for age and educational level or family income. Winkleby and Cubbin[6] assessed changes in health behaviors from 1990 to 2000 by ethnicity, sex, and age by using national BRFSS data. After adjusting 2000 data for educational attainment and annual household income, they found ethnic differences in various age groups (18–24 years, 25–44 years, 54–64 years, 64–74 years) for obesity, sedentary behavior, low vegetable or fruit intake, and smoking.

Few previous studies have investigated the proximity to the US-Mexico border as a community-level measure of socioeconomic status. The US-Mexico border region is one of the poorest in the United States. In 2000, it was the location of 6 of the 10 metropolitan areas with the lowest per capita income, and the three poorest metropolitan areas were located on the Texas-Mexico border.[7] Using BRFSS data, Coughlin et al[8] found that Hispanic women in US-Mexico border counties were less likely to have had a recent mammogram or Pap test than White women in

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The purpose of the present study was to determine whether residence on the Texas-Mexico border would modify the effect of ethnic differences on risk behaviors.

border counties and Hispanic and White women in non-border counties. In a study of elderly Mexican Americans, Patel et al[9] reported that the effect of neighborhood disadvantage on poorer self-rated health was two to three times higher among persons living within 50 miles of the US-Mexico border than among other persons. The purpose of the present study was to determine whether residence on the Texas-Mexico border would modify the effect of ethnic differences on risk behaviors. We used data from the BRFSS conducted statewide in Texas to investigate our hypothesis that ethnic differences would be more striking among border residents than among non-border residents.

METHODS

Each year ≈5000–6000 Texas residents complete the cross-sectional statewide BRFSS.[10] Random digit dialing is used to select adults ≥18 years of age who live in a private household to complete a telephone interview. Questions are taken from the Centers for Disease Control and Prevention BRFSS and cover risk behaviors that contribute to morbidity and mortality.[11] The BRFSS does not break down Hispanic ethnicity into its component parts, but 76% of Hispanics in Texas are of Mexican origin.[12] For most risk behaviors, we used the combined 1999–2003 Texas BRFSS consisting of ≈5613 adults annually reflecting ≈15.2 million persons residing in the 254 counties in the state. We excluded persons of ethnicities other than White or Hispanic (n=3,688) and those with missing information on place of residence (n=298) resulting in 24,080 adults for this analysis. Border residence was for the 15 counties contiguous with the Mexico border, and non-border residence was for the remaining 239 counties. Response rates to the Texas BRFSS were 36.2% in 1999, 33.5% in 2000, 39.7% in 2001, 46.2% in 2002, and 41.2% in 2003.

Self-reported weight and height were used to calculate body mass index (BMI=weight in kilograms/height in meters squared). Overweight was defined as a BMI ≥25 kg/m^2, and obese was defined as BMI ≥30 kg/m^2 (obese is a subset of overweight). Physical inactivity was no leisure-time physical activity in the past month. To calculate fruit or vegetable consumption, respondents were asked how many servings of six different fruits and vegetables (fruit juices, fruit, green salad, potatoes, carrots, and other vegetables) they usually consumed per day, week, month or year; consumption of fewer than five servings per day was considered a risk factor. Heavy drinking was defined differently for men and women: averaging two or more alcoholic beverages on a daily basis for men and averaging one or more alcoholic beverage on a daily basis for women during the past month.[11] Binge drinking was having five or more alcoholic beverages on one or more occasions in the past month. Smoking was defined as having smoked ≥100 cigarettes and currently smoking.

Probability sample weights were applied to the sample to reflect the population of non-border and border residents for each year of the survey. Weights were derived by multiplying factors accounting for the probability of selection within strata (subsets of area code/prefix combinations), the number of adults in the household, and the number of phones in the household by a post-stratification weight reflecting the age and sex distribution of Texas' adult population (age ≥18 years). The post-stratification weight adjusts for non-coverage and non-response. Data were analyzed by using Survey Data Analysis (SUDAAN) to account for sampling within strata and multiple years of data.[13] Unconditional logistic regression was used to assess the association between ethnicity and risk behaviors while controlling for confounding.[14] An interaction term between ethnicity and border residence was included in logistic regression models, and likelihood ratio tests were performed to examine effect modification. Although the only behavior to exhibit effect modification was binge drinking among males (P value for interaction=.03), we present analyses stratified by border residence for ease of interpretation. We added all theoretically relevant variables as defined in Table 1 as potential confounders, including age, educational level, annual household income, perceived general health, and diabetes. These variables were selected because they address socioeconomic status, perceived health status, and morbidity, which may impact risk behaviors. We also stratified by sex since the effect of ethnicity on risk behaviors appears to differ by sex.

RESULTS

The distribution of potential confounding factors by ethnicity, residence, and sex is presented in Table 1. In comparison to Whites, Hispanics tended to be younger, to be less educated, to have a lower annual household income, and to rate their general health as poor or fair regardless of residence or sex. The prevalence of diabetes was higher among Hispanic than White non-border females, while the reverse was true among border males.

Table 2 shows the prevalence of risk behaviors by ethnicity, residence, and

Table 1. Distribution of potential confounding factors among non-border and border Whites and Hispanics by sex

	WOMEN			
	Non-Border		Border	
	White (*n*=10,046)	Hispanic (*n*=2979)	White (*n*=306)	Hispanic (*n*=1131)
Variable	Weighted %	Weighted %	Weighted %	Weighted %
Age group (years)				
18–24	9.9	20.4	5.2	15.1
25–44	35.6	51.0	29.3	44.7
45–64	32.2	22.0	29.8	29.7
≥65	22.3	6.6	35.7	10.5
Educational level				
<High school	9.0	45.2	9.0	44.2
High school graduate	28.2	25.8	22.8	25.1
Some college	30.7	18.1	33.2	18.8
College graduate	32.1	10.9	35.0	11.9
Annual household income				
<$15,000	10.5	24.4	13.1	33.9
$15,000–$24,999	16.0	33.0	15.1	30.7
$25,000–$44,999	33.7	27.5	37.4	26.2
$45,000–$74,999	17.5	8.6	20.1	5.7
≥$75,000	22.3	6.5	14.3	3.5
Poor or fair perceived general health	15.8	32.1	19.4	34.6
Diabetes	5.9	8.0	8.3	8.1
	MEN			
	Non-Border		Border	
	White (*n*=6858)	Hispanic (*n*=1954)	White (*n*=215)	Hispanic (*n*=591)
Variable	Weighted %	Weighted %	Weighted %	Weighted %
Age group (years)				
18–24	11.4	22.7	10.6	20.0
25–44	38.2	54.0	28.1	46.0
45–64	33.8	20.1	30.0	24.7
≥65	16.6	3.2	31.3	9.3
Educational level				
<High school	7.7	44.5	4.9	34.0
High school graduate	25.2	28.0	23.9	32.2
Some college	27.2	17.2	31.6	21.5
College graduate	39.9	10.3	39.6	12.3
Annual household income				
<$15,000	5.6	20.4	6.8	30.3
$15,000–$24,999	12.8	33.3	16.6	30.5
$25,000–$44,999	33.0	31.5	37.0	26.8
$45,000–$74,999	20.3	8.0	16.1	7.8
≥$75,000	28.3	6.8	23.5	4.6
Poor or fair perceived general health	13.6	27.8	11.5	25.1
Diabetes	6.8	6.4	9.7	7.0

sex. Hispanics of both sexes and residences were more likely to be overweight, obese, physically inactive, and consume fewer than five fruits or vegetables per day than Whites. Hispanic females were less likely to engage in heavy drinking and smoking than White females, little difference was seen in the prevalence of binge drinking comparing Hispanic and White females regardless of residence. In comparison with White males, Hispanic males were more likely to drink heavily, to binge drink, and to smoke than Whites, regardless of residence.

Table 3 presents the unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for risk beha-

Table 2. Prevalence of risk behaviors among non-border and border Whites and Hispanics by sex

	WOMEN			
	Non-Border		Border	
	White	Hispanic	White	Hispanic
Behavior	Weighted %	Weighted %	Weighted %	Weighted %
Overweight	46.3	63.1	50.3	65.4
Obese	19.1	29.9	21.8	31.5
Physically inactive	24.9	42.0	24.4	38.6
Consumed <5 fruits or vegetables per day	71.8	74.1	67.6	73.8
Heavy drinking	5.5	3.0	2.8	2.3
Binge drinking	8.6	9.0	5.9	5.9
Smoking	22.4	12.6	19.8	11.5
	MEN			
	Non-Border		Border	
	White	Hispanic	White	Hispanic
Behavior	Weighted %	Weighted %	Weighted %	Weighted %
Overweight	68.4	70.2	72.2	72.7
Obese	23.0	27.4	18.3	27.8
Physically inactive	20.5	38.3	15.0	25.6
Consumed <5 fruits or vegetables per day	81.3	82.8	80.4	84.9
Heavy drinking	7.5	9.3	6.2	7.7
Binge drinking	24.0	35.3	25.4	30.7
Smoking	25.1	29.2	19.8	25.6

Table 3. Odds ratios for risk behaviors among non-border and border Hispanics relative to Whites by sex

	WOMEN			
	Non-Border		Border	
Behavior	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Overweight	1.98 (1.73–2.27)	1.79 (1.48–2.17)	1.86 (1.32–2.62)	1.36 (.89–2.09)
Obese	1.81 (1.57–2.08)	1.48 (1.29–1.70)	1.65 (1.24–2.20)	1.15 (.72–1.86)
Physically inactive	2.19 (1.77–2.71)	1.35 (1.14–1.58)	1.95 (1.73–2.19)	1.44 (.89–2.33)
Consumed <5 fruits or vegetables per day	1.12 (.87–1.45)	.77 (.63–.94)	1.35 (.72–2.54)	.82 (.39–1.72)
Heavy drinking	.54 (.41–.70)	.60 (.39–.94)	.81 (.19–3.48)	1.41 (.23–8.68)
Binge drinking	1.05 (.82–1.35)	.83 (.70–.99)	1.01 (.47–2.18)	.62 (.25–1.57)
Smoking	.50 (.39–.64)	.26 (.18–.38)	.53 (.30–.93)	.30 (.15-.62)
	MEN			
	Non-Border		Border	
Behavior	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Overweight	1.09 (.82–1.45)	1.36 (1.02–1.81)	1.03 (.68–1.55)	1.20 (.70–2.08)
Obese	1.26 (.98–1.63)	1.26 (.94–1.68)	1.72 (1.05–2.81)	1.43 (.84–2.45)
Physically inactive	2.41 (2.13–2.71)	1.33 (1.10–1.60)	1.95 (1.43–2.66)	.97 (.47–2.02)
Consumed <5 fruits or vegetables per day	1.10 (.90–1.36)	.81 (.68–.97)	1.36 (.77–2.42)	.83 (.46–1.51)
Heavy drinking	1.27 (.94–1.73)	.97 (.66–1.44)	1.27 (.67–2.42)	1.06 (.70–1.62)
Binge drinking	1.73 (1.39–2.14)	1.21 (.99–1.49)	1.30 (.86–1.97)	.90 (.49–1.63)
Smoking	1.23 (1.05–1.45)	.57 (.49–.67)	1.39 (.59–3.25)	.78 (.28–2.18)

OR=odds ratio; CI=confidence interval.

* Adjusted for age, educational level, annual household income, perceived general health, and diabetes.

viors associated with ethnicity and residence among women and men, respectively. Adjustment weakened most associations, strengthened some associations (smoking in women and overweight in men), and reversed some associations (consumption of fewer than five fruits or vegetables per day, heavy drinking in border women, binge drinking in border men, and smoking in men). With the exception of physical inactivity in border males, Hispanics of each sex were more likely than Whites to be overweight, obese, and physically inactive. In contrast, Hispanics were less likely than Whites to consume fewer than five fruits or vegetables per day and to smoke. After adjustment these findings were significant among non-border residents but not among border residents. The findings for heavy and binge drinking were mixed by residence and sex. Although the *P* value for interaction was not significant for heavy drinking among females ($P=.49$), the odds ratios are on either side of the null-value of 1.0 indicating Hispanic women who did not live on the border were less likely to drink heavily than White women, while Hispanic women who did live on the border were more likely to drink heavily than White women. The opposite pattern was seen for binge drinking in men (*P* value for interaction$=.03$) with non-border Hispanics more likely to binge drink than Whites and border Hispanics less likely to drink than Whites. Hispanic women were less likely to binge drink than White women regardless of residence, and little difference in heavy drinking was seen by ethnicity or residence among men.

DISCUSSION

Our findings of higher rates of overweight and obesity among Hispanics of both sexes than among Whites regardless of border residence are comparable to results from several studies. The Stanford Five-City Project reported higher mean values of BMI among Mexican Americans overall,[15] the San Antonio Heart Study reported higher mean values of BMI among Mexican Americans of both sexes,[16] and an analysis of the NHANES III reported higher mean values of BMI among Mexican American females[4] than their White counterparts. The New York City BRFSS defined overweight as >110% ideal Metropolitan relative weight and obesity as >120% of ideal weight.[17] They found elevations in overweight and obesity among Hispanic females relative to White females but not among males. In an analysis of changes in health behaviors between 1990 and 2000 that used national BRFSS data, Winkleby and Cubbin[6] found higher prevalences of obesity among Hispanics than among Whites; however, the differences appeared to be narrowing between 1990 and 2000. With the exception of obesity among men, our study found smaller differences among border than non-border residents for overweight and obesity, which may reflect a narrowing of the White-Hispanic gap on the border that is not evident in the non-border region.

We saw higher levels of physical inactivity among Hispanics relative to Whites, limited to non-border males, which is similar to the findings of most other studies. A modified BRFSS telephone survey conducted in San Francisco reported significantly higher levels of no leisure-time physical activity among Latinos of both sexes compared to Whites.[18] Burchfiel et al[19] completed personal interviews as part of the San Luis Valley Diabetes Study and reported higher levels of physical inactivity, defined as work-related, among Hispanics of both sexes compared to Whites in Colorado. In the New York City BRFSS, Hispanics had higher levels of physical inactivity, defined as exercise fewer than three times per week, than Whites.[17] No significant ethnic differences in physical inactivity were seen, which incorporated work and leisure-time, in the Stanford Five-City Project.[15] An analysis of NHANES III that focused on women reported that Hispanic women were more likely to do no leisure-time physical activity than White women.[4] In a comparison of no leisure-time physical activity that used national BRFSS data for 2000, Hispanics were more likely to be sedentary than Whites for all persons except those age 65–74 years.[6] Like other studies, we were unable to incorporate work-related activity into our measure of physical inactivity, which tends to underestimate total amount of physical activity because Hispanics' employment is more likely to be physically active than Whites' employment.

The higher consumption of fruits or vegetables among Hispanics compared to Whites in our study differs from most, but not all, studies of ethnic differences of fruit or vegetable consumption. A comparison of the Hispanic Health and Nutrition Examination Survey (HHANES) with NHANES II showed that Mexican American women consumed fewer servings of fruits or vegetables than White women.[20] Shea et al[21] completed telephone interviews modeled after the BRFSS in New York City and reported lower consumption of vegetables among Latinos than among Whites. Otero-Sabogal et al[22] conducted telephone interviews in the San Francisco Bay Area Study and found that Latinos were more likely to eat fewer than three servings of fruits or vegetables on the previous day than Whites. Using personal interview data from the Stanford Five-City Project, Winkleby et al[23] reported no difference in fruit or vegetable consumption by ethnicity. Winkleby and Cubbin[6] used national BRFSS data in 2000 to assess low fruit or vegetable intake, defined as less than three servings per day, and found, with the exception of the 45- to 64-year-old age group, Hispanics had lower levels of low fruit or vegetable intake than

Whites.[6] Our findings, like those of Winkleby and Cubbin,[6] may reflect the greater contribution of socioeconomic status than that of ethnicity for fruit or vegetable intake, since adjustment for socioeconomic status reversed the unadjusted positive associations.

The ethnic differences we saw for drinking differed by residence and sex. Hispanic females who lived on the border were more likely to drink heavily than White females, while Hispanic females who did not live on the border were less likely to drink heavily than White females. Binge drinking was lower among Hispanic women than White women regardless of residence. Little difference in ethnicity for heavy drinking was seen among men. Hispanic men who lived on the border were less likely to binge drink than White men, but Hispanic men who did not live on the border were more likely to binge drink. Results of other studies of ethnic differences in drinking have been mixed. Otero-Sabogal et al[22] reported lower rates of any drinking in the past month and higher rates of binge drinking among Latinos overall than among Whites in the San Francisco Bay Area Study. The San Francisco BRFSS found lower rates of any drinking in Latinos than Whites of both sexes but no difference in binge drinking.[18] In a nationally representative survey that used personal interviews, Caetano and Clark[24] reported higher rates of binge drinking among Hispanic men than among White men. No significant differences in drinking were seen between Mexican Americans and Whites in the Stanford Five-City Project.[15] Guendelman and Abrams[20] reported much lower levels of drinking among Mexican American women in HHANES than among White women in NHANES II. In a study conducted on the US-Mexico border that used personal interviews, Holck et al[25] reported that Mexican American women were more likely to abstain from alcohol than White women. The differing effect of residence on heavy drinking in females and on binge drinking in males in our study may be a function of socioeconomic status since adjustment for socioeconomic status reversed the negative association among females and the positive association among males.

We found a lower likelihood of current smoking among Hispanics compared with Whites regardless of border residence. This finding is in agreement with most studies of this topic.[4,6,15,17,18,20,23] One exception is the San Francisco Bay Area Study, which reported no ethnic differences for current smoking but did find that Latinos were more likely to be never-smokers than Whites.[22] Another exception is the San Luis Valley Diabetes Study, which reported a non-significantly higher prevalence of current smoking among Hispanic females than among White females.[19] In our study, Hispanic men were more likely to smoke than White men before adjusting for socioeconomic status, which indicates that smoking among males may be related more to socioeconomic status than to ethnicity.

This study was not without limitations. Incomplete telephone coverage (2000 Texas Whites 98%; Hispanics 94%),[26] and low response rates may have introduced selection bias, especially if persons less likely to engage in risk behaviors were more likely to respond to the survey. We were unable to determine whether response rates differed by ethnicity or border residence, which would have resulted in substantial bias. Risk behaviors are based on self-report and are prone to misclassification. An additional limitation of our study is the failure of the BRFSS to break down Hispanic ethnicity into its component parts. Although most Hispanics in the Texas BRFSS are Mexican American, other Hispanic groups with differing risk profiles are included. Small numbers of border residents limited study power to assess effect modification. Analysis at the county level may be a limitation since socioeconomic status of census tracts within counties tends to vary substantially. Future research of this issue should examine census tracts or distance from the border as a community-level measure of socioeconomic status.

To our knowledge, this is the first study to assess ethnic differences in health behaviors with proximity to the US-Mexico border as a community-level measure of socioeconomic status. We hypothesized that ethnic differences would be more striking among border residents than among non-border residents because of the extreme poverty of the Texas-Mexico border region. This was not the case, and most associations were weaker for border residents than for non-border residents. The one behavior that exhibited effect modification, binge drinking among males, showed a negative association among border residents and a positive association among non-border residents. Possible explanations for these findings are: 1) Whites on the border are of lower socioeconomic status than non-border Whites, which may influence risk behaviors; or 2) Whites on the border engage in risky health behaviors more often than non-border Whites. The average median household income for 1999 among Whites for the 15 border counties ($36,563) was similar to that among Whites for the remaining 239 counties ($37,246), which was not the case for Hispanics (border $21,442, non-border $26,640).[26] Acculturation may be defined as a non-dominant group adopting the cultural attitudes, values, and behaviors of a dominant group. The dominant group on the Texas-Mexico border is Hispanic and accounts for 85% of residents of the 15 Texas counties bordering Mexico in 2000.[12] Thus, Whites living on the border may have adopted the risk behaviors of the dominant Mexican culture. Future studies of ethnic differences should assess adoption of the

Mexican culture by Whites living in predominantly Hispanic areas. Results of this study would argue against targeting specific ethnic groups for behavioral risk factor interventions in favor of universal interventions that can be adapted to be culturally appropriate for all people.

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ELSEVIER

A Multilevel Analysis of Socioeconomic Status and Prostate Cancer Risk

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PURPOSE: We investigated whether prostate cancer was associated with socioeconomic status (SES) at the individual level, area level, or a combination of both levels.
METHODS: This population-based case–control study of prostate cancer in men aged 65 to 79 years was conducted between 2000 and 2002 in South Carolina. Complete interviews were available for 407 incident prostate cancer cases and 393 controls (with respective response rates of 61% and 64%). We used educational level to measure individual-level SES and a composite variable capturing income and education from 2000 Census data to measure area-level SES.
RESULTS: After adjustment for race, age, geographic region, and prostate-specific antigen testing, men with some college were at reduced risk for prostate cancer (odds ratio [OR], 0.44; 95% confidence interval [CI], 0.27–0.72), as were men in the highest quartile of area-level SES (OR, 0.52; 95% CI, 0.34–0.80). When assessing individual-level and area-level SES simultaneously and accounting for their nonindependence, the independent negative associations persisted and appeared to be more striking for men with a diagnosis of localized disease, rather than advanced disease.
CONCLUSION: The independent effects of area-level and individual-level SES on prostate cancer risk seen in our study may help explain the conflicting results of previous studies conducted at both levels.
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KEY WORDS: Prostate Cancer, Socioeconomic Status, Multilevel Analysis, Case–Control Studies.

INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer in the United States and the second leading cause of cancer deaths among men. Little is understood about the cause of prostate cancer, and we do not know what factors might explain why African-American men are at greater risk relative to white men. Several studies investigated prostate cancer incidence associated with individual-level socioeconomic status (SES) based on income, occupation, or educational level, with conflicting results. We limit our review to studies conducted in the United States because SES levels differ across countries. Two of the four studies that evaluated the association between individual-level SES and prostate cancer incidence in the United States reported positive associations (1, 2), whereas two studies reported no association (3, 4). Of the seven studies that investigated area-level SES and prostate cancer incidence in the United States, three studies each reported a positive association (5–7) or no association (8–10), whereas one study reported a negative association (11). Proposed mechanisms for explaining the positive association between individual-level and area-level SES and prostate cancer are consuming a healthy diet (4), engaging in exercise (4), and increased access to screening (12).

Studies of SES and prostate cancer must account for screening because the effect of high SES on prostate cancer risk may have differed before and after the advent of prostate-specific antigen (PSA) testing. Before PSA testing, men with higher SES were more likely to have lower rates of prostate cancer as a result of engaging in healthy behaviors (4). After PSA testing, men with higher SES were more likely to be screened annually (12) and thus the disease was more likely to be diagnosed, especially at an earlier stage (13). Using 1987 as the year that PSA testing became widespread, the majority of individual-level (1, 2, 4) and half the area-level (8–11) studies of SES and prostate cancer were conducted before screening, which may help explain the mixed results.

Along with the failure to account for PSA testing, another possible explanation for the mixed results of the SES and prostate cancer association is the failure to account for area-level SES in studies of individual-level SES, and vice versa. Several studies investigated the joint effects of

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Selected Abbreviations and Acronyms

CI = confidence interval
OR = odds ratio
PSA = prostate-specific antigen
SES = socioeconomic status

individual-level and area-level SES and cardiovascular disease incidence (14, 15) and mortality (16, 17); however, few focused on cancer (17–19). Robert et al. (18) recently investigated the joint effect of individual-level and area-level SES on breast cancer incidence and found that area-level SES was associated positively with breast cancer after adjustment for individual-level SES, whereas the reverse was not true. Conversely, Steenland et al. (19) found little effect of area-level SES on prostate cancer mortality after adjustment for individual-level SES. Borrell et al. (17) found greater rates of cancer mortality among blacks and whites in the Atherosclerosis Risk in Communities Study who resided in neighborhoods with the lowest SES score that was weakened by adjustment for individual-level SES. To our knowledge, no other study simultaneously investigated the effect of individual-level and area-level measures of SES on prostate cancer risk. We assess joint effects of area-level and individual-level SES to indirectly determine whether conflicting results for prostate cancer incidence associated with individual-level SES may have been caused by the unmeasured influence of area-level SES.

METHODS

Detailed methods of this population-based case–control study conducted in South Carolina from 2000 to 2002 appear elsewhere (20). Briefly, cases diagnosed with primary invasive prostate cancer between October 1999 and September 2001 were identified through the South Carolina Central Cancer Registry. During this time, the South Carolina Central Cancer Registry was certified as silver by the North American Association of Central Cancer Registries, with a case ascertainment rate between 90% and 95% (21). Eligible cases were South Carolina residents who were Caucasian or African American, aged 65 to 79 years, and had histologically confirmed prostate cancer and for whom physicians had given permission for research staff to contact the patient. We selected all eligible cases with advanced disease (stages III and IV) and a random sample of men with localized disease (stages I and II). We had insufficient funding to study all men with localized disease. Because we wanted approximately equal numbers of men with localized disease by race, we performed stratified sampling by race and oversampled African-American men by randomly selecting 82% of men with localized disease compared with 40% of Caucasian men with localized disease. Of 692 eligible prostate cancer cases, 425 (61.4%) completed a standardized telephone interview. Of the remaining eligible cases, 90 physicians refused (13.0%), 71 patients refused (10.3%), 24 patients died before the interview (3.5%), 59 patients were not located (8.5%), and 23 patients were too sick to participate (3.3%).

Control subjects were randomly sampled from the 1999 Health Care Financing Administration Medicare beneficiary file. Controls were frequency matched to cases for age (5-year age groups), race (Caucasian and African American), and geographic region (western 14 counties, middle 19 counties, and eastern 13 counties of the state). Eligible controls were South Carolina residents aged 65 to 79 years with no history of prostate cancer. Of 756 eligible controls, 482 (63.8%) completed the interview. Of the remaining eligible controls, 108 controls refused (14.3%), 22 controls died before the interview (2.9%), 112 controls were not located (14.8%), and 32 controls were too sick to participate (4.2%). We eliminated 59 subjects (7 cases and 52 controls) who upon review of medical records were determined to have prevalent prostate cancer. After excluding an additional 48 subjects (11 cases and 37 controls) who completed fewer than 10 questions, the final sample size was 800 subjects (407 cases and 393 controls).

Institutional Review Boards of the University of South Carolina, Centers for Disease Control and Prevention, and National Cancer Institute approved this project's data collection procedures. Interviewing began in June 2000 and was completed in August 2002. Trained interviewers from the University of South Carolina Survey Research Laboratory conducted computer-assisted telephone interviews with subjects who provided verbal consent with the understanding that written consent would be obtained. The questionnaire collected information on demographic characteristics, SES, stress, coping, alcohol and tobacco use, physical activity, diet, medical history, family history of cancer, history of sexually transmitted diseases, and farm-related work activities and exposures. Most exposures pertained to the period before a reference date, the date of diagnosis for cases and an assigned date for controls that was similar to the distribution of diagnosis dates among cases.

We used the generalized linear latent and mixed models macro in STATA 8 (StataCorp LP, College Station, Texas) to estimate the odds ratio (OR) of prostate cancer associated with individual-level and area-level SES while accounting for their nonindependence and controlling for potential confounding factors (22). We had a two-level hierarchical structure; therefore, we fit a two–random level intercepts logistic model and used RESET diagnostic test to evaluate misspecification of error or inappropriate link function (23). Because the majority of men were retired, we used educational level to measure individual-level SES, rather than annual household income 1 year before diagnosis.

There were five categories of educational level: (i) less than eighth grade, (ii) 9th to 11th grade, (iii) high school graduate, (iv) some college or technical school, and (v) college graduate or more. To measure area-level SES, we created a composite variable consisting of median household income, percentage of persons living below the poverty level, percentage unemployment, and percentage of college or higher educational attainment addressing four of the six domains thought to comprise socioeconomic position in the United States (24). Subjects' addresses were not geocoded; therefore, this information was available at the ZIP code level from the 2000 census (25). Of the total of 919 ZIP codes in South Carolina, 265 were represented in the study. To ensure sufficient sample sizes and minimize overdispersion of estimates, we collapsed ZIP codes of homogeneous geographic and demographic characteristics into groups with a minimum of 25 subjects in each. There were 21 groupings ranging from 29 to 57 subjects (median = 41). We reversed the coding of poverty level and unemployment, summed the four area-level measures of SES, and categorized the composite variable by using the quartile distribution among controls. Cronbach α for this composite variable was 0.83 among controls, indicating these items went together in measuring the area-level SES construct.

Individual-level variables assessed as confounders included marital status, family history of prostate cancer, body mass index, and frequency of PSA testing, as categorized in Table 1. Body mass index, defined as self-reported weight in kilograms before reference date divided by the square of self-reported height in meters, was categorized by using the quartile distribution among controls. PSA testing was categorized as frequency within the past 5 years, with men who reported they had a PSA test performed, but did not remember the number of tests, categorized as one to two tests (53 local cases, 10 advanced cases, 90 controls). Controls were frequency matched to cases on age, race, and geographic region; thus, we adjusted for these three factors based on the study design. We also adjusted for PSA testing because it was the only variable to materially change unadjusted ORs. Although PSA testing may be in the causal pathway between SES and prostate cancer, we adjusted for it to investigate the association between SES and prostate cancer, accounting for the effect of SES on PSA testing. In analyses by stage at diagnosis, men with stages I and II were classified as having localized disease, and men with stages III and IV were classified as having advanced disease. Stages I and II correspond to tumors that were clinically unapparent or confined within the prostate with no nodal involvement or metastases (26). Stages III and IV correspond to tumors that extended through the prostatic capsule or invaded adjacent structures with or without nodal involvement or metastases. Linear trend was assessed by treating categorical variables as continuous variables.

TABLE 1. Comparison of cases by stage at diagnosis and controls for demographic and socioeconomic factors

	Localized cases (n = 314) N (%)	Advanced cases (n = 102) N (%)	Controls (n = 429) N (%)
Race			
Caucasian	175 (55.7)	70 (68.6)	258 (60.1)
African-American	139 (44.3)	32 (31.4)	171 (39.9)
Age (years)			
65–69	138 (44.0)	54 (52.9)	186 (43.4)
70–74	102 (32.5)	32 (31.4)	125 (29.1)
75–79	74 (23.5)	16 (15.7)	118 (27.5)
Geographic region			
Eastern counties	180 (57.3)	55 (53.9)	243 (56.6)
Middle counties	81 (25.8)	26 (25.5)	92 (21.5)
Western counties	53 (16.9)	21 (20.6)	94 (21.9)
Marital status[a]			
Single/separated/ divorced/widowed	56 (18.6)	17 (17.0)	80 (20.6)
Married/living as married	245 (81.4)	83 (83.0)	308 (79.4)
Missing	5	1	5
Family history[a]			
None	212 (70.9)	66 (66.7)	329 (84.6)
First-degree	63 (21.1)	23 (23.2)	43 (11.0)
Second-degree	24 (8.0)	10 (10.1)	17 (4.4)
Missing	7	2	4
Body mass index (quartiles)[a]			
<24.4	77 (25.9)	13 (13.1)	90 (23.5)
24.4–27.2	83 (28.0)	31 (31.3)	101 (26.3)
27.3–29.8	69 (23.2)	27 (27.3)	96 (25.1)
⩾29.9	68 (22.9)	28 (28.3)	96 (25.1)
Missing	9	2	10
No. of prostate-specific antigen tests in past 5 years			
0	43 (13.7)	18 (17.7)	98 (22.9)
1–2	102 (32.5)	29 (28.4)	154 (36.0)
3–4	48 (15.3)	19 (18.6)	66 (15.4)
⩾5	121 (38.5)	36 (35.3)	110 (25.7)
Missing	1	0	0
Educational level			
Elementary education	84 (26.8)	22 (22.2)	89 (20.7)
Some high school	44 (14.1)	11 (11.1)	69 (16.1)
High school graduate	78 (24.9)	23 (23.2)	102 (23.8)
Some college or technical school	37 (11.8)	17 (17.2)	77 (18.0)
College graduate	70 (22.4)	26 (26.3)	92 (21.5)
Missing	1	3	0
Composite socioeconomic status (quartiles)			
Low	105 (33.4)	30 (29.4)	118 (27.5)
Medium	94 (29.9)	18 (17.7)	115 (26.8)
High	71 (22.6)	35 (34.3)	106 (24.7)
Very high	44 (14.0)	19 (18.6)	90 (21.0)

[a]Consists of 306 local cases, 101 advanced cases, and 393 controls.

RESULTS

Table 1 lists cases by stage at diagnosis and controls for demographic and socioeconomic factors. Compared with controls, prostate cancer cases were more likely to be younger, reside in the middle portion of the state, be married or living

as married, have a family history of prostate cancer, have undergone PSA testing, have a lower educational level themselves, and live in a community with a lower composite SES. A greater percentage of men with a diagnosis of localized disease were African American and in the lowest quartile of body mass index than men with a diagnosis of advanced disease, whereas the reverse was true of men with a diagnosis with advanced disease.

ORs and 95% confidence intervals (CIs) for prostate cancer associated with individual-level and area-level SES are listed in Table 2. There were significant correlations between PSA testing and individual-level (Spearman $r = 0.30$; $p < 0.0001$) and area-level (Spearman $r = 0.09$; $p = 0.007$) SES (data not shown). After adjustment for race, age, geographic region, and PSA testing, men with some college or technical school were at significantly reduced risk (OR, 0.44; 95% CI, 0.27–0.72) and college graduates were at borderline reduced risk (OR, 0.67; 95% CI, 0.42–1.05) for prostate cancer. Combining these upper two categories resulted in a significantly reduced risk for prostate cancer (OR, 0.55; 95% CI, 0.35–0.87). Similarly, men in the highest quartile of area-level SES (OR, 0.52; 95% CI, 0.34–0.80) were at reduced prostate cancer risk. In both measures of SES, there was a trend of decreasing risk with increasing educational level. Although the trend test was significant for individual-level SES, it must be noted that the referent group was markedly higher than all other educational groups and the trend test is driven by this group. Additional adjusting for individual-level or area-level SES and accounting for the nonindependence of these measures resulted in independent negative associations for prostate cancer in men with some college (OR, 0.45; 95% CI, 0.27–0.78) and men in the highest quartile of area-level SES (OR, 0.52; 95% CI, 0.25–1.10).

Risk for prostate cancer associated with socioeconomic factors by stage at diagnosis is listed in Table 3. With one exception, the third quartile of area-level SES in men diagnosed with advanced disease, there were reductions in risk associated with individual-level and area-level SES regardless of stage at diagnosis. The decreased risk for men with some college or technical school and men who lived in the highest quartile of area-level SES was weaker for men with a diagnosis of advanced cancer than those with a diagnosis of localized cancer, but remained reduced even after adjustment for the other level measure of SES.

DISCUSSION

We found a significantly reduced risk for prostate cancer associated with having some college or technical school and a borderline reduced risk for the highest category of our individual-level SES measure, educational level. In addition, there was a significant trend of decreasing risk with increasing educational level. A possible explanation for the trend is the greater percentage of cases (especially those with localized disease) with an elementary education than controls. Although not limited to men with a diagnosis of localized disease, the reduction in risk in the two highest SES categories was more pronounced for this group. Our results are in conflict with the majority of studies of individual-level SES and prostate cancer risk, which reported a positive (1, 2) or no association (3, 4). Possible explanations for our findings relate to the educational level and race of men in our study. Men in our study had a fairly low SES; 36.8% of our controls aged 65 and older had less than a high school education in comparison to 31.2% of men in the United States in 1999 (27). The only study of

TABLE 2. Odds ratios for prostate cancer associated with individual-level and area-level socioeconomic factors

	OR[a] (95% CI)	OR[b] (95% CI)	OR[c] (95% CI)
Educational level			
Elementary education	1.00 (Referent)	1.00 (Referent)	
Some high school	0.60 (0.37–0.95)	0.57 (0.34–0.94)	
High school graduate	0.69 (0.45–1.06)	0.70 (0.44–1.11)	
Some college or technical school	0.44 (0.27–0.72)	0.45 (0.27–0.78)	
College graduate	0.67 (0.42–1.05)	0.65 (0.39–1.07)	
p for trend	0.05	0.08	
Composite socioeconomic status (quartiles)			
Low	1.00 (Referent)		1.00 (Referent)
Medium	0.79 (0.53–1.17)		0.78 (0.38–1.59)
High	0.86 (0.58–1.28)		0.96 (0.42–2.23)
Very high	0.52 (0.34-0.80)		0.52 (0.25–1.10)
p for trend	<0.01		0.13

OR = odds ratio; CI = confidence interval.
[a]Adjusted for race, age, geographic region, and prostate-specific antigen testing.
[b]Adjusted for race, age, geographic region, composite socioeconomic status, and prostate-specific antigen testing.
[c]Adjusted for race, age, geographic region, educational level, and prostate-specific antigen testing.

TABLE 3. Odds ratios for prostate cancer associated with individual-level and area-level socioeconomic factors by stage at diagnosis

	OR[a] (95% CI)	OR[b] (95% CI)	OR[c] (95% CI)
Localized			
Educational level			
Elementary education	1.00 (Referent)	1.00 (Referent)	
Some high school	0.60 (0.36–0.98)	0.54 (0.31–0.93)	
High school graduate	0.70 (0.44–1.11)	0.70 (0.43–1.16)	
Some college or technical school	0.39 (0.22–0.67)	0.41 (0.23–0.73)	
College graduate	0.62 (0.38–1.02)	0.61 (0.35–1.05)	
p for trend	0.03	0.06	
Composite socioeconomic status (quartiles)			
Low	1.00 (Referent)		1.00 (Referent)
Medium	0.87 (0.58–1.32)		0.88 (0.40–1.96)
High	0.72 (0.47–1.11)		0.80 (0.35–1.83)
Very high	0.48 (0.30–0.76)		0.51 (0.21–1.21)
p for trend	<0.01		0.10
Advanced			
Educational level			
Elementary education	1.00 (Referent)	1.00 (Referent)	
Some high school	0.54 (0.24–1.21)	0.61 (0.26–1.42)	
High school graduate	0.67 (0.33–1.34)	0.69 (0.32–1.45)	
Some college or technical school	0.58 (0.27–1.25)	0.54 (0.24–1.26)	
College graduate	0.77 (0.37–1.59)	0.74 (0.34–1.64)	
p for trend	0.62	0.49	
Composite socioeconomic status (quartiles)			
Low	1.00 (Referent)		1.00 (Referent)
Medium	0.56 (0.28–1.10)		0.57 (0.24–1.36)
High	1.32 (0.72–2.40)		1.41 (0.63–3.17)
Very high	0.72 (0.37–1.39)		0.66 (0.26–1.65)
p for trend	0.84		0.74

OR = odds ratio; CI = confidence interval.
[a]Adjusted for race, age, geographic region, and prostate-specific antigen testing.
[b]Adjusted for race, age, geographic region, composite socioeconomic status, and prostate-specific antigen testing.
[c]Adjusted for race, age, geographic region, educational level, and prostate-specific antigen testing.

individual-level SES and prostate cancer conducted since the advent of PSA testing found no association after adjustment for PSA testing for the highly educated, younger American Cancer Society Nutrition Cohort Study; 8% of their participants aged 55 years and older had less than a high school education (3) compared with 26% of men in the United States in 1999 (27). A large percentage of men in our study were African American (40.8% of cases; 42.2% of controls). Yu et al. (2) reported a weak positive association between college education and prostate cancer risk for Caucasian men, but not African-American men.

Similarly, prostate cancer was associated negatively with area-level SES measured by using our composite variable. Again, the reduction in risk was stronger for men with a diagnosis of localized disease than those with a diagnosis of advanced disease. The negative association we found was in contrast to most previous studies of area-level SES and prostate cancer that reported a positive association (5–7) or no association (8–10). In their study of area-level SES and prostate cancer mortality using the American Cancer Society Nutrition Cohort Study, Steenland et al. (K. Steenland, personal communication, February 9, 2006) found a positive association. Possible explanations for our findings relate to the race of men in our study and the different measures of area-level SES used by different studies. As indicated, more than 40% of our participants were African American. One study identified a positive association in all racial groups except whites (6), another study found a positive association in all racial groups except Asians (8), and another study reported no association in African-American or Caucasian men (9). Studies of area-level SES used a variety of measures, including a combination of occupation and poverty level (5), median household income (6), a combination of median household income and educational attainment (7), and a combination of household income, home value, occupation, and education (19).

After performing a multilevel analysis, there was little effect on either measure of SES with approximately the same reduction in prostate cancer risk associated with the two highest levels of individual-level SES combined (OR, 0.55; 95% CI, 0.35–0.87) as the highest quartile of area-level SES (OR, 0.52; 95% CI, 0.25–1.10). These results were evident for men with a diagnosis of localized and advanced disease; however, the association was more

pronounced for men with localized disease. This is in contrast to the majority of studies of SES and cardiovascular disease incidence and mortality, which reported stronger associations for individual-level SES than area-level SES after simultaneous adjustment (14–17). In the American Cancer Society Nutrition Cohort Study, Steenland et al. (K. Steenland, personal communication, February 9, 2006) found no association between individual-level SES and prostate cancer mortality after adjustment for area-level SES and vice versa. However, the only study of cancer incidence to examine the joint effects of individual-level and area-level SES reported a stronger effect of area-level SES than individual-level SES (18). These investigators hypothesized that the stronger positive effect of area-level than individual-level SES they saw on breast cancer risk may have been caused by greater access to mammograms in higher SES areas (28) or to physical and environmental characteristics common in the community that may increase a woman's breast cancer risk. One possible explanation for the reduced prostate cancer risk associated with higher individual-level and area-level SES we saw is that men with higher SES and those living in higher SES areas are less likely to undergo PSA testing. This was not the case in our study in which PSA testing positively and significantly correlated with both measures of SES (individual-level SES, Spearman $r = 0.30, p < 0.0001$; area-level SES, Spearman $r = 0.09, p = 0.007$). An alternative explanation for the reduced risk for prostate cancer associated with high individual-level and area-level SES is that men with higher SES and those from higher SES areas have greater access to healthful diets and physical activity.

This study was not without limitations. Our response rates were less than desired, and we sampled men with localized disease, somewhat limiting the generalizability of our results and possibly resulting in some nonsignificant reductions in prostate cancer risk. African-American men with advanced disease were less likely to participate than African-American men with localized disease, which limited study power to statistically assess effect modification by race and stage. We were unable to determine whether nonparticipation rates of cases and controls differed by SES. However, similar percentages of nonrespondents (22.6%) and respondents (25.2%) had diagnoses of advanced disease, which would argue against selective survival of cases. The average time between diagnosis and interview was 8.7 months, which may have led to misclassification. Another source of misclassification was the memory problems common in men aged 65 years and older. Our study power was limited for some joint effects because of small numbers. We were unable to assess race as an effect modifier of the association between SES and prostate cancer because of small numbers. Analysis at the grouped ZIP code level in our study may not reflect the area-level SES accurately because SES of block groups and census tracts within ZIP codes tend to vary substantially (24). Although block groups and census tracts may better represent area-level SES than grouped ZIP codes, we chose to group ZIP codes to provide stable estimates.

Our study is the first population-based case–control study of prostate cancer to simultaneously assess the effect of individual-level and area-level SES on prostate cancer risk. Additional strengths of the study include the fairly large number of men with advanced disease, which allowed us to perform analyses by stage at diagnosis, and use of an accepted measure of area-level SES (24). We adjusted for the frequency of PSA testing in an attempt to isolate the effect of SES apart from its influence on access to care. Area-level SES may be a more comprehensive measure of SES than individual-level SES because it captures social characteristics of communities that are not typically measured (29). The independent effects of area-level and individual-level SES on prostate cancer risk seen in our study may help explain the conflicting results of previous studies conducted at both levels and would argue for the measurement of both levels in future studies.

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ORIGINAL ARTICLE

Serum Leptin Concentration, Adiposity, and Body Fat Distribution in Mexican-Americans

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Background. Leptin is strongly associated with adiposity and few studies have investigated its role in Mexican-Americans. The aims of this study were to examine the association of serum leptin concentration with adiposity and body fat distribution in Mexican-Americans and to develop a predictive model of serum leptin concentration for this ethnic group.

Methods. Three hundred fifty-two college students (242 women, 110 men; age 18–30 years) were evaluated in this cross-sectional study. Body fat content was assessed using bioelectrical impedance analysis. Correlation between serum leptin levels and several markers of adiposity and body fat distribution were examined in both men and women. Multiple regression analysis was performed to create the predictive model.

Results. Women had higher serum leptin concentrations than men for the same levels of adiposity. After controlling for gender and body fat, only fat mass (FM) expressed in kg, was significantly correlated with serum leptin concentration in men (partial $rho = 0.811$, $p < 0.001$), whereas body mass index (BMI), hip circumference (HC), and FM expressed in kg, were significantly correlated with serum leptin concentration in women (partial $rho = 0.214$, $p < 0.001$; partial $rho = 0.201$, $p < 0.01$; and partial $rho = 0.818$, $p < 0.001$, respectively). Percent body fat (PBF) was the only significant predictor of serum leptin concentration among men, explaining 42% of the variance in serum leptin concentration. In addition to PBF, waist circumference (WC) and HC were significant predictors of serum leptin concentration among women explaining 65% of the variance in serum leptin concentration.

Conclusions. Serum leptin concentration is a function of adiposity as determined by PBF in both Mexican-American men and women. HC and WC are associated with serum leptin concentration in Mexican-American women but not in men. BMI alone should not be used in evaluating the association of serum leptin concentration with body fatness in Mexican-Americans.

Key Words: Leptin, Adiposity, Body fat distribution, Mexican-Americans.

Introduction

The past decade has seen an important advance in the understanding of the regulation of energy balance and food intake, providing significant knowledge regarding the pathogenesis of obesity. Adipocyte-derived cytokines including leptin, adiponectin, adipsin, and resistin have been extensively investigated for their association with obesity, and very strong evidence exists that such cytokines play a critical role in regulating body weight (1–3). Leptin, a protein encoded by the *ob* gene (4), is produced by adipocytes and is secreted into the circulation (3). It regulates food intake and energy expenditure (3), binding mainly to receptors in the hypothalamus and influencing the expression of several

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neuropeptides (5). Free leptin, the form present in cerebrospinal fluid, has been shown to be the biologically active form of leptin (6). Evidence points out that leptin-binding proteins are saturated in states of increased adiposity (7). At high concentrations, leptin provides a negative feedback signal to the brain, which in turn reduces food intake and increases energy expenditure (5). However, elevated serum leptin levels have been reported in a large proportion of obese individuals, which implies resistance to endogenous leptin in human obesity (8,9). Leptin concentration in both plasma and cerebrospinal fluid is higher in women than in men, which raises the possibility that women are relatively leptin resistant (10). It has been suggested that the higher serum leptin concentration in women is, at least partially, the result of higher body fat content compared to men (11).

Serum and plasma leptin concentrations have been associated with body mass index (BMI) (8,12–15). However, BMI (measured as weight in kilograms divided by height in meters squared) takes into account body weight and body height instead of body fat content defined as the fat component of the body weight (16). Limited attention has been paid to the relationship of leptin concentrations with body composition measures other than BMI. Because BMI does not accurately measure adiposity, the effects of body fatness on leptin concentration may be more pronounced when more reliable methods such as bioelectrical impedance analysis (BIA), underwater weighing (UWW), dual-energy X-ray absorptiometry (DXA), computed tomography, and magnetic resonance imaging are used to measure total body fat content. In the few studies when adiposity was measured using such tools, the effect of adiposity on leptin concentration was more evident in both men and women (17–20). Among the accurate methods of body composition, BIA is the simplest, cheapest, fastest, and least invasive method suitable for clinical and field epidemiologic research. BIA has been validated as an indicator of adiposity against gold-standard methods such as UWW and DXA (21,22) and has been used in large multiethnic nationally representative surveys such as the National Health and Nutrition Examination Survey III (23).

Body fat distribution has been shown to play an important role in many metabolic disorders (24). Studies examining the association of leptin concentration with body fat distribution have shown conflicting results. Both subcutaneous (25–29) and visceral adipose tissue depots (30) have been associated with high serum leptin levels. The San Antonio Heart Study, a population-based cohort study of type-2 diabetes and cardiovascular disease, has found that serum leptin concentrations are associated with all adipose tissue depots and not disproportionately with upper body or central adiposity in a sample of 147 Mexican-Americans (31). In another study, serum leptin concentrations were not associated with waist circumference (WC) after adjustment for fat mass but were associated with hip circumference (HC) in women (32). Although waist/hip ratio (WHR) is the most frequent marker of body fat distribution pattern (16), WC has been considered a surrogate for central obesity (33–35), whereas HC is a proxy measure of peripheral obesity (31,32,36). In summary, the relationship between serum leptin levels and body fat distribution in different ethnic groups remains unclear.

The objectives of this study were to determine the association of serum leptin concentration with (i) several anthropometric parameters including body fat content and (ii) body fat distribution in a large sample of Mexican-Americans. In addition, we sought to develop a predictive model of leptin concentration for Mexican Americans that could be used for clinical and epidemiological purposes.

Materials and Methods

Subjects

From September 2004 to December 2005, 359 Mexican-American college students (248 women and 111 men) attending the University of Texas at Brownsville & Texas Southmost College (UTB/TSC) volunteered to participate in this cross-sectional study. Seven participants were excluded due to extremely high values of serum leptin concentration (>200 ng/mL) resulting in 242 women and 110 men for analysis. Recruitment activities such as classroom presentations and posting of flyers throughout campus were accomplished by research staff. Information on self-reported ancestry was used to define subjects as Mexican-Americans. Participants were enrolled if all four grandparents were of Mexican ancestry. Pregnancy was the sole criterion for exclusion of participants. The response rate was 90% among those who indicated they were interested in participating in the study. The study protocol was approved by the UTB/TSC Institutional Review Board and the University of Texas–Houston Health Science Center Committee for the Protection of Human Subjects. All participants were required to sign written informed consent before participating in the study. All anthropometric, bioelectrical impedance analysis and serum leptin concentration measurements were performed in duplicate during weekdays from 7:30 to 10:30 AM at the Student Health Services at UTB/TSC by trained research staff.

Weight and Height Measurements

Each subject's body weight in kilograms and body height in meters was measured while subjects were wearing an examining gown and no shoes. Body weight was measured to the nearest 0.1 kg with portable electronic digital scales (Tanita BWB-800S, Arlington Heights, IL). Body height was measured using a vertical wall-mounted stadiometer (Tanita HR-100) and was recorded to the nearest 0.1 cm. BMI was calculated as weight in kilograms divided by height in

meters squared. Obesity is defined as BMI $\geq$30.0 kg/m^2 and overweight is defined as BMI $\geq$25.0$-<$30.0 kg/m^2 (37).

Waist Circumference and Waist-to-Hip Ratio

WC and HC were taken with a non-elastic tape measure. WC was measured at the smallest circumference between the costal margin and the iliac crest, and HC was measured at the widest circumference between the waist and the thigh. WHR was calculated as WC divided by HC. Central obesity was defined as WC $\geq$102 cm in men and $\geq$88 cm for women (38).

Bioelectrical Impedance Analysis

A BIA analyzer (BIA Quantum II; RJL Systems, Detroit, MI) was used to measure resistance (R) and reactance (Xc) at 50 kHz frequency. All subjects were asked to refrain from eating, drinking, and exercising for 6 h before testing. Participants were asked to urinate within 30 min of the test and not to consume alcohol within 48 h or use diuretics within 7 days of the test. Female subjects who perceived they were retaining water due to their menstrual cycle were not tested and were missing from the BIA analysis. Subjects were placed in a supine position with arms and legs abducted approximately 45° to each other, assuring no contact between the thighs and between the arms and trunk. Shoes and socks were removed, and contact areas were scrubbed with alcohol immediately before electrode placement. Source electrodes were placed proximal to the phalangeal–metacarpal joint on the dorsal surfaces of the right hand and distal to the transverse arch on the superior surface of the right foot. Sensor electrodes were placed at the midpoint between the distal prominence of radius and ulna of the right wrist and between the medial and lateral malleoli on the right ankle. R and Xc were recorded to the nearest ohm (Ω). The following fat-free mass (FFM) prediction equations validated for Mexican-Americans (39) were applied to individual BIA resistance data in order to estimate FFM for each subject:

$$\text{Men: FFM} = -10.68 + 0.65\,\text{height}^2/\text{resistance} + 0.26\,\text{weight} + 0.02\,\text{resistance}$$

$$\text{Women: FFM} = -9.53 + 0.69\,\text{height}^2/\text{resistance} + 0.17\,\text{weight} + 0.02\,\text{resistance}$$

where FFM is measured in kg, height^2/resistance in cm^2/Ω, and resistance in Ω. Body fat mass (FM) and percent body fat (%BF) were calculated as follows:

$$\text{FM (kg)} = \text{body weight (kg)} - \text{FFM (kg)}$$

$$\%\text{BF} = [\text{FM (kg)}/\text{body weight (kg)}] \times 100$$

Obesity was defined as %BF $>$25 and $>$30 in men and women, respectively (40,41).

Serum Leptin Concentration

Each participant was asked to provide a fasting blood sample when scheduled to arrive at the Student Health Services. Using standard, sterile phlebotomy procedures, a blood specimen was drawn from the antecubital vein into a tube with no anti-coagulant. Blood was allowed to clot at room temperature for 30 min and then centrifuged at 3000 $\times$ g for 15 min. Serum was aliquoted into 2-mL cryo-vials and stored at −70°C until analysis. Quantitative measurement of leptin in serum was performed using a leptin enzyme immunoassay kit (ELISA) (Diagnostic Systems Laboratories, Inc., Webster, TX), according to the manufacturer's instructions. Briefly, 25 μL of the standards, controls, and serum samples were dispensed into the appropriate wells. Using a semi-automatic dispenser, 100 μL of the assay buffer E was added to each well. The well was incubated, shaking at fast speed (500–700 rpm) on an orbital microplate shaker, at room temperature (~25°C) for 2 h. Each well was aspirated and washed five times with wash solution using an automatic microplate washer (1575 Immunowash Microplate Washer; Bio-Rad Laboratories, Hercules, CA) and blotted dry by inverting the plate on absorbent material. The antibody–enzyme conjugate concentrate was diluted in the solution and 100 μL of the diluted solution was added to each well of the microtiter plate using a semi-automatic dispenser. The wells were incubated, shaking at a fast speed (500–700 rpm) on an orbital microplate shaker, at room temperature for 1 h. The wells were aspirated and rinsed five times with wash solution using the automatic microplate washer and blotted dry by inverting the plate on absorbent material. Using a semi-automatic dispenser, 100 μL of tetramethylbenzidine chromogen solution was added to each well. Each well was incubated, shaking at a fast speed (500–700 rpm) on an orbital microplate shaker, at room temperature (~25°C) for 10 min. Exposure to direct sunlight was avoided; 100 μL of the stopping solution (0.2 M sulfuric acid) was added to each well using a semi-automatic dispenser. Finally, using a microplate reader (Benchmark Plus System; Bio-Rad Laboratories) the degree of enzymatic turnover of the substrate was determined by dual wavelength absorbance measurement at 450 and 620 nm. The absorbance measured is directly proportional to the concentration of human leptin present. A set of human leptin standards was used to plot a standard curve of absorbance vs. human leptin concentration from which the human leptin concentration in the serum was calculated. Serum leptin concentration was expressed in ng/mL. Hemolyzed and lipemic specimens were not used because these specimens may give false values. In this assay, the intra-assay precision (% coefficient of variation) using ten replicates of three subjects was 8.1% (2.77 ng/mL), 6.6% (67.79 ng/mL) and 4.2% (143.77 ng/mL);

the inter-assay precision from five different runs of three subjects was 8.2%, 2.6%, and 3.1% at concentrations of 2.57 ng/mL, 64.58 ng/mL, and 124.59 ng/mL, respectively. These results are comparable to those found in similar studies using either radioimmunoassay (8,19,20,26,31,32,42) or ELISA (43) methodology.

Statistical Analysis

All statistical analyses were performed using STATA 8 (College Station, TX). Non-normally distributed variables according to the Wilk-Shapiro test were transformed after identifying the function that would transform the original variable into a normally distributed variable. Serum leptin concentration was non-normally distributed and was log transformed. Measures of central tendency and variability were computed accordingly.

Statistical analyses are presented by gender and included Mann-Whitney *U* test for independent samples to compare the medians between groups, and Spearman correlation coefficients (*rho*) for measuring the correlation between serum leptin concentration and each independent variable. Partial Spearman correlation coefficients (partial *rho*) are reported adjusting these correlation coefficients for gender and adiposity (FM measured in kg). Fisher's z transformation was used to compute the significance of the difference between correlation coefficients. In addition, we performed multiple linear regression analysis using backwards elimination with the log of serum leptin concentration as the dependent variable to create a predictive model of serum leptin concentration for Mexican-Americans. The following independent variables were assessed: age, body weight, body height, BMI, PBF, FM, FFM, WC, HC, and WHR. Effect modification was expected to occur between sex and potential determinants, so the analyses were performed separately for women and men (11). Diagnostic measures including influence of collinearity statistics were examined. Power estimation for the regression model was confirmed using the method of Hsieh et al. (44). We also report the multiple regression correlation coefficient (R^2) as a measure of the proportion of variability of serum leptin concentration explained by the independent variables in the multiple regression model. To test whether the equations adequately predict serum leptin concentration in our entire study sample we randomly split the dataset into two in order to a) derive predictive equations in one dataset, and b) predict serum leptin concentration in the other dataset. The equations effectively predicted serum leptin concentration with $<8\%$ difference compared to the final predictive equations.

Statistical significance was set using a type I error level of 0.05. For convenience and comparability with previous authors, summary statistics are presented as mean ± standard deviation in addition to median and interquartile range for non-normally distributed variables.

Results

Descriptive statistics of the study variables for men and women are shown in Table 1. Approximately 53% of participants were either overweight (27.6%) or obese (24.7%) based on BMI, whereas all participants were considered obese based on body fatness estimated by BIA (data not shown). In the whole group of subjects, median serum leptin concentration was 32.5 ± 51.4 ng/mL. Despite similar values of BMI by gender, median serum leptin concentrations were higher in women compared with men (48.1 ± 59.7 ng/mL vs. 10.6 ± 17.5 ng/mL; $p < 0.001$). Age, BMI, and HC had similar median values among men and women. Men had statistically significantly higher body weight, body height, WC, WHR, FFM, FM, and PBF than their female counterparts. Table 2 shows that men and women in higher BMI categories had higher median serum leptin concentration.

Table 1. Descriptive statistics of demographic, anthropometric, and hormonal parameters in 352 participants

	Median (iqr)		Mean (±SD)	
Variable	Men $n = 110$	Women $n = 242$	Men $n = 110$	Women $n = 242$
Age (years)	21 (6)	21 (5)	22.1 ± 3.5	22.1 ± 3.6
BW (kg)	79.5 (27.3)	62.8* (21.9)	83.9 ± 18.1	67.1 ± 16.9
BH (cm)	174.0 (8.8)	159.8* (8.2)	174.5 ± 6.1	160.2 ± 5.9
BMI (kg/m^2)	26.5 (7.5)	24.5 (7.7)	27.5 ± 5.3	26.1 ± 6.3
WC (cm)	89.0 (19.5)	78.8* (17.3)	90.2 ± 12.1	81.3 ± 13.9
HC (cm)	103.0 (13.2)	101.5 (14.9)	104.1 ± 10.1	103.6 ± 11.9
WHR	0.86 (0.07)	0.77* (0.09)	0.86 ± 0.05	0.78 ± 0.07
FFM (kg)	46.2 (11.8)	32.4* (10.9)	47.9 ± 9.2	34.0 ± 8.2
FM (kg)	34.3 (15.5)	30.3* (11.1)	36.0 ± 10.9	33.2 ± 9.7
PBF (%)	43.2 (7.0)	49.2* (5.4)	42.6 ± 5.7	49.1 ± 3.7
Serum leptin (ng/mL)	10.6 (17.5)	48.1* (59.7)	17.4 ± 18.5	60.8 ± 46.6

BW, body weight; BH, body height; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist/hip ratio; FFM, fat-free mass; FM, fat mass; PBF, percent body fat; iqr, interquartile range; SD, standard deviation.
*$p < 0.001$; men vs. women using Mann-Whitney *U* test.

Table 2. Serum leptin concentration in 352 participants based on BMI

	Men (n = 110)			Women (n = 242)		
BMI group	n	Median (iqr)	Mean (± SD)	n	Median (iqr)	Mean (± SD)
BMI <18.5	2	4.02 (5.2)	4.02 (3.71)	7	13.45 (15.6)	17.62 (8.45)
18.5 ≤ BMI <25	36	5.79‡ (6.4)	6.88 (4.34)	123	29.01† (29.6)	33.63 (20.73)
25 ≤ BMI <30	35	8.54¶ (7.3)	13.3 (14.9)	62	65.71¶ (37.6)	68.85 (27.72)
BMI ≥30	37	29.24* (17.8)	32.12 (21.60)	50	107.30* (48.1)	112.39 (39.78)

All differences using Mann-Whitney U test
*p <0.001; BMI ≥30 vs. 25 ≤ BMI <30.
¶p <0.001; 25 ≤ BMI <30 vs. 18.5 ≤ BMI <25.
‡p <0.05; 18.5 ≤ BMI <25 vs. BMI <18.5 for men.
†p <0.001; 18.5 ≤ BMI <25 vs. BMI <18.5 for women.

Table 3 reports the Spearman correlation coefficients for men and women between serum leptin concentration and independent variables. Prior to adjustment for FM measured in kg, most anthropometric variables were significantly correlated with serum leptin concentration and FM was most strongly correlated among men (rho = 0.811, p <0.001) and women (rho = 0.818, p <0.001). After controlling for FM in kg, no variables were significantly correlated with serum leptin concentration among men, whereas among women BMI (partial rho = 0.214, p <0.001) and HC (partial rho = 0.201, p <0.01) were significantly correlated with serum leptin concentration.

Because of the high correlation between BMI and WC (r = 0.82, p <0.001) and BMI and FM (0.93, p <0.001), we did not examine these variables simultaneously in any regression model due to multicollinearity. However, BMI was included separately as independent variable in every model. Table 4 shows correlation matrix of independent variables examined for potential collinearity. The logarithm of serum leptin concentration was significantly predicted by PBF in men and by PBF, WC, and HC in women (Table 5). These variables explained approximately 42% of the variance of logarithm of serum leptin concentration in men and approximately 65% of the variance of logarithm of serum leptin concentration in women. Substituting PBF with FM did not materially change the results.

Table 3. Spearman correlation coefficients between serum leptin concentration and independent variables

	Men		Women	
Variable	rho	Partial rho[1]	rho	*Partial rho*[1]
Age (years)	0.183	−0.068	0.097	0.001
BW (kg)	0.725*	−0.099	0.778*	0.083
BH (m)	0.045	−0.204	0.016	−0.117
BMI (kg/m^2)	0.766*	0.058	0.804*	0.214*
WC (cm)	0.729*	−0.097	0.777*	0.127
HC (cm)	0.739*	−0.016	0.775*	0.201**
WHR	0.489*	−0.107	0.456*	0.017
FFM (kg)	0.422	−0.099	0.651	0.084
PBF (%)	0.607*	0.086	0.390*	0.052
FM (kg)	0.811*	–	0.818*	–

BW, body weight; BH, body height; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio; PBF, percent body fat; FM, fat mass; rho, Spearman correlation coefficient.
[1]Partial Spearman correlation coefficient adjusted for adiposity (FM measured in kg).
*p <0.001.
**p <0.01.

Discussion

We addressed the question of whether serum leptin concentrations are related to body fat distribution and adiposity as measured by BIA in a large sample of Mexican-American college students. To our knowledge, no previous study has examined the correlation of serum leptin concentrations with adiposity assessed by a measure other than BMI or skinfold thickness in Mexican-Americans.

Our data showed that serum leptin concentrations are highly correlated with body fatness expressed as FM in kg confirming previous results that degree of adiposity is a key determinant of leptin concentration (19,20,26,31,42). Serum leptin concentrations were positively correlated with body fatness in both men and women, although women had the higher median serum leptin concentration. This finding is in agreement with other studies showing that women have higher leptin concentrations than men at any level of adiposity (19,20,31,43). In a study of Mexican-Americans where the sum of triceps and subscapular skinfold thickness were used to assess overall adiposity, the correlations of serum leptin concentration in both men and women were higher with BMI than with the sum of skinfold thicknesses after adjustment for age (31). Conversely, our data showed a slightly higher but not statistically significant difference in the correlation coefficients of serum leptin concentration with FM compared to serum leptin concentration with BMI in both men and women prior to controlling for adiposity measured as FM in kg (rho = 0.811 vs. rho = 0.766, p = 0.09, and rho = 0.818 vs. rho = 0.804, p = 0.12, respectively). In addition, we found that adiposity expressed as

Table 4. Correlation matrix of independent variables examined for potential collinearity

	PBF	BMI	WC	HC	WHR	FM
Men						
PBF	1.0000					
BMI	0.5061	1.0000				
WC	0.4923	0.9380	1.0000			
HC	0.3897	0.5889	0.5366	1.0000		
WHR	0.2754	0.3660	0.4819	−0.1182	1.0000	
FM	0.7179	0.9210	0.9024	0.8235	0.3405	1.0000
Women						
PBF	1.0000					
BMI	0.4387	1.0000				
WC	0.3499	0.9042	1.0000			
HC	0.3060	0.6471	0.7137	1.0000		
WHR	0.1413	0.1580	0.2267	0.0867	1.0000	
FM	0.4838	0.9489	0.9348	0.9290	0.1720	1.0000

PBF, percent body fat; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist/hip ratio; FM, fat mass.

FM in kg was a significant predictor of serum leptin concentration in both Mexican-American men and women.

Several studies have investigated the relationship of body fat distribution with leptin concentrations (25–32,45). Surprisingly, our data show that there was no statistically significant difference in HC values between men and women, although WC was larger in men than in women. In agreement with studies of whites and African-Americans (42) and of Mexican-Americans (31), our data showed that serum leptin concentration is not a function of a specific pattern of body fat distribution in men, although we observed a statistically significant correlation of HC with serum leptin concentration in women even after adjusting for fat mass measured in kg. It is interesting to note that in our sample, gynoid pattern determined by WHR $\geq$1.0 for men and $\geq$0.8 for women (38) was the most prevalent pattern of body fat distribution in both men and women (92% and 63%, respectively).

In agreement with a study in Asian individuals (20), we found that HC helped to predict serum leptin concentration in women. However, our data showed that both HC and WC were predictors of serum leptin concentration in women. These results suggest there is no specific body fat distribution pattern determining serum leptin concentration in both Mexican-American men and women.

In this study we performed the statistical analysis in two distinct groups, men and women, because we found evidence of effect modification by gender. The sample size was large enough to provide the necessary power for gender-based analysis.

This study was not without limitations. Although the study population was relatively large, it was a convenience sample of college students at UTB/TSC. Therefore, our sample may not be representative of Mexican-Americans. Considering the fact that the study participants were students 18–30 years old, we were not able to investigate the effect of age in other age groups. The discrepancy between BMI values and body fatness measured by BIA in both men and women is of concern. We hypothesize the occurrence of BIA- and BMI-related reasons for this finding. In the former, the assessment of adiposity was performed using validated equations for BIA in Mexican Americans. BIA equations tend to overestimate adiposity in lean individuals and underestimate adiposity in obese individuals (39). In the latter, it has been shown that specific BMI cutoff points should be set for different ethnic groups (46) due to differences in average height among groups. For instance, lower BMI cutoff points have been proposed for Mexicans (47) and Asians (48,49). It is important to note that the mean height of our study population was lower than the average of Americans at same age and gender (50). Therefore, taken together, it seems that we cannot rule out misclassification bias. Other limitations are the lack of information on smoking status, diet and alcohol intake, lactation status, and use of oral contraceptives, as well as physical activity levels.

In summary, the findings of our study that serum leptin concentrations were higher in women than men are in

Table 5. Multiple linear regression analysis with backwards elimination of log of serum leptin concentration

Independent variable	Coefficient	Standard error	*p* value
Men (R^2 = 42.3)			
PBF	0.10	0.012	<0.001
Age	0.02	0.007	0.08
Constant	−1.754	0.452	0.001
Women (R^2 = 65.4)			
PBF	0.03	0.009	<0.001
WC	0.02	0.005	<0.001
HC	0.03	0.005	<0.001
Age	0.01	0.004	0.1
Constant	−2.241	0.265	<0.001

PBF, percent body fat; WC, waist circumference; HC, hip circumference; R^2, multiple regression correlation coefficient.

agreement with the literature. We demonstrated that higher serum leptin concentrations were correlated with the physiological higher adiposity seen in Mexican-American women. In addition, BMI, HC, and WC are associated with serum leptin concentration in Mexican-American women even after adjusting for fat mass measured in kg. Therefore, it seems there is no preferential pattern of body fat distribution related to serum leptin concentration in Mexican-Americans. We suggest that BMI alone should not be used in evaluating the association of serum leptin concentration with body fatness in Mexican-Americans. Further studies using more accurate methods of body composition should be carried out to confirm our findings. Also, we suggest that further studies be conducted to evaluate if our predictive equation is applicable to similar populations of Mexican Americans.

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Diabetes, Physical Activity and Breast Cancer among Hispanic Women

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Abstract

Objective: We assessed whether physical activity modified the effect of diabetes on breast cancer in Hispanic women.

Methods: We used data from a case-control study of breast cancer among Hispanic women aged 30 to 79 conducted between 2003 and 2008 on the Texas-Mexico border. In-person interviews were completed with 190 incident breast cancer cases ascertained through surgeons and oncologists, and 468 controls who had two consecutive negative screening mammograms (with respective response rates of 97% and 74%).

Results: After adjustment for age, menopausal status, body mass index, and mammography screening, there was a reduction in breast cancer risk associated with diabetes (odds ratio [OR] 0.70, 95% confidence interval [CI] 0.45-1.09). Relative to women who had no history of diabetes and did not engage in physical activity, diabetic women who did not exercise were at somewhat reduced breast cancer risk (OR 0.66, 95% CI 0.42-1.04) while diabetic women who exercised were at greatly reduced breast cancer risk (OR 0.31, 95% CI 0.15-0.65).

Conclusions: Our study is one of the first studies to investigate the association between diabetes and breast cancer among Hispanic women. In addition to hormonal mechanisms, potential mechanisms that warrant exploration are related to physical activity and treatment of diabetes.

Keywords: breast cancer, diabetes, physical activity, case-control study

Introduction

Current breast cancer incidence rates in the United States (US) are lower among Hispanic women (90.1/100,000) than among non-Hispanic White women (130.6/100,000) (1). We conducted the South Texas Women's Health Project in the Lower Rio Grande Valley (LRGV) located at the southern tip of Texas on the Mexico border to elucidate factors that might account for this lower breast cancer risk among Hispanic women relative to non-Hispanic White women. One factor which may help explain the lower breast cancer risk is the higher prevalence of early-onset diabetes among Hispanics than among non-Hispanic Whites (2), which has been linked to reduced breast cancer risk in one study of primarily non-Hispanic White women (3) and another study of Hispanic and Native American women combined (4). In addition, since physical activity is known to reduce the risk of breast cancer (5) and diabetes (6), we assessed whether physical activity modified the effect of diabetes on breast cancer.

Materials and Methods

This clinic-based case-control study was conducted in the LRGV from 2003-2008. Cases diagnosed with primary invasive breast cancer between November 2003 and August 2008 were identified through surgeons and oncologists shortly after diagnosis or treatment. Eligible cases were Hispanic, aged 30-79, whose breast cancer was histologically confirmed and who had no history of cancer, other than nonmelanoma skin cancer. A total of 190 breast cancer cases (96.9% of eligible cases) completed a standardized in-person interview. Of potentially eligible cases, 3 refused (1.5%) and 3 were lost to follow-up (1.5%).

Control subjects were randomly selected from women receiving a diagnostic or screening mammogram at the mammography center where the case received her diagnostic mammogram. Two control groups were selected, a high-risk group of women receiving a diagnostic mammogram, and a low-risk group of women with no family history of breast cancer, no history of breast biopsy, and negative screening mammograms for the past two years. Two women from each control group were selected per case**.** Eligible controls were Hispanic, aged 30-79 who had with no history of cancer, other than nonmelanoma skin cancer. A total of 513 high-risk control subjects (83.0% of eligible high-risk controls) and 468 low-risk control subjects (73.6% of eligible low-risk controls) completed the interview. Of potentially eligible high-risk controls, 61 refused (9.9%) and 44 (7.1%) were lost to follow-up. Of potentially low-risk controls, 127 refused (20.0%) and 41 (6.4 %) were lost to follow-up. The present analysis is restricted to low-risk control subjects.

Institutional Review Boards of the University of Texas at Brownsville, the University of Texas Health Science Center at Houston, the Department of Defense, the Texas Department of

State Health Services and hospitals housing the mammography centers approved this project's data collection procedures. Cases and controls were recruited through flyers that described the study posted in the waiting rooms of the surgeons, oncologists, and mammography centers.

Interviewing began in November 2003 and was completed in August 2008. Trained interviewers conducted in-person interviews with subjects who provided consent. The questionnaire collected information on demographic characteristics, suspected breast cancer risk factors, medical history including diabetes, physical activity, diet, and body size. Exposures pertained to the period prior to a reference date, the date of diagnosis for the cases and an assigned date for controls comparable to the date of diagnosis for the cases. The in-person interview took approximately 40 minutes to complete. All information in the present analysis is based on self-report with the exception of body mass index (BMI) which is based on actual measurements. Diabetes was defined as reporting that a doctor indicated the subject had diabetes, borderline diabetes or high blood sugar. Diabetes was further defined as having it during pregnancy, other than pregnancy, or both during and other than pregnancy. One diabetic control was excluded because her age at diagnosis of 15 suggested she had type 1 diabetes. If women received both insulin and oral medications to treat diabetes they were classified as having used insulin. Metabolic equivalents were calculated from leisure-time vigorous and moderate physical activity.

We used unconditional logistic regression to estimate the relative risk of breast cancer associated with the main effect of diabetes and the joint effects of diabetes and physical activity wile controlling for potential confounding factors (7). Interaction terms, the product of diabetes and putative effect modifiers (menopausal status and physical activity), were added to logistic regression models and likelihood ratio tests were performed to test for effect modification.

There was no evidence of effect modification by menopausal status; however, there was a suggestion that physical activity modified the effect of diabetes on breast cancer risk. Age, family history of breast cancer, age at menarche, menopausal status, age at menopause, parity, age at first live birth, BMI, use of oral contraceptives, use of hormone replacement therapy, alcohol use, physical activity, and mammography screening as categorized in Table 1 were evaluated as potential confounders. Age, menopausal status, BMI and mammography screening were considered confounders of the relationship between diabetes and breast cancer risk because their addition to the model changed the unadjusted odds ratio by 10 percent or more.

Results

Table 1 provides a comparison of cases and controls for suspected breast cancer risk and protective factors in the South Texas Women's Health Project. 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 have an older age at menopause, not to have used oral contraceptives or hormone replacement therapy, and to have fewer mammograms in the past 6 years.

Table 2 presents the odds ratios for breast cancer associated with diabetes. Although non-significant, we saw a reduced risk of breast cancer among women who had a history of diabetes (OR 0.70, 95% CI 0.49-1.09) after adjustment for age, menopausal status, BMI, and mammography screening. The reduction in risk was more pronounced for gestational diabetes (OR 0.16, 95% CI 0.02-1.31) than for type 2 diabetes (OR 0.75, 95% CI 0.48-1.18); however, this finding was based on very small numbers. Women treated with insulin had an elevated breast cancer risk (OR 1.42, 95% CI 0.76-2.65), while women treated with oral medications were at somewhat reduced risk (OR 0.63, 95% CI 0.34-1.19) and women treated with neither insulin nor oral medication were at substantially reduced risk (OR 0.30, 95% CI 0.11-0.83). There was little effect of age at diabetes onset or of family history of diabetes on breast cancer risk.

Table 3 presents the odds ratios for breast cancer associated with the joint effects of diabetes and physical activity. Relative to women who had no history of diabetes and did not engage in physical activity, women who had a diabetes history and did not exercise were at somewhat reduced breast cancer risk (OR 0.66, 95% CI 0.42-1.04) while those with diabetes who did exercise had greatly reduced breast cancer risk (OR 0.31, 95% CI 0.15-0.65).

Discussion

Although a recent meta-analysis of the association between diabetes and breast cancer reported a summary relative risk of 1.20 (95% CI 1.12-1.28) (8), we hypothesized we would not find an association between diabetes and breast cancer based on the Four Corners Breast Cancer Study, the one study that included sufficient Hispanic women to stratify by ethnicity (4). Unfortunately those investigators grouped Hispanic and Native American women so our studies are not strictly comparable. Our findings differ from the Four Corners Study which reported an odds ratio of 0.92 for the association between diabetes and breast cancer (4), in that our odds ratio of 0.70 was a non-significant reduction in breast cancer risk. In agreement with the Four Corners Study (4), we found a stronger negative relation for gestational diabetes than for type 2 diabetes, and for early-onset diabetes than for late-onset diabetes. Nor were our findings on diabetes treatment comparable with the Four Corners Study because that study grouped insulin and oral medications. However, they reported odds ratios of 0.91 for either treatment and 1.84 for neither treatment, while we found odds ratios of 1.42 for insulin, 0.63 for oral medications, and 0.30 for neither treatment. Lastly, neither the Four Corners Study (4) nor our study found an association between family history of diabetes and breast cancer.

The meta-analysis of diabetes and breast cancer stratified by physical activity and found a slightly lower relative risk of 1.16 among women who exercised than the relative risk of 1.20 among women who did not exercise (8). While we did not find a statistically significant interaction between diabetes, physical activity and breast cancer, the odds ratio of 0.30 we found for the joint effect of diabetes and physical activity on breast cancer is striking and must be confirmed in additional studies.

Plausible biological mechanisms for the negative association we found between diabetes and breast cancer are the use of the oral medication Metformin which may reduce insulin levels (9) or activate AMP-dependent protein kinase thereby suppressing protein synthesis (10), and hyperinsulinemia induced chronic anovulation (11). A plausible biological mechanism for our finding of a substantially reduced breast cancer risk resulting from the joint effect of diabetes and physical activity may be the reduction in insulin resistance that accompanies physical activity (6).

In addition to non-comparable ethnicities, another possible explanation for our differing findings from the Four Corners study includes misclassification of breast cancer or diabetes. Of the four states that participated in the Four Corners Study two have Surveillance, Epidemiology and End Results registries, and the one most similar to South Texas is New Mexico. For 2000-2004 New Mexico breast cancer incidence rates were 133/100,000 for non-Hispanic Whites and 91/100,000 for Hispanics (12), which are similar to Texas rates for 2001-2005 (non-Hispanic Whites 124.4/100,000, Hispanics 84.6/100,000) and slightly higher than LRGV rate for 2001-2005 (non-Hispanic Whites 104.2/100,000, Hispanics 77.5/100,000) (13). In 2004, the Texas Department of State Health Services conducted a Behavioral Risk Factor Surveillance System survey in three border counties, two of which are in the LRGV (personal communication, R.J. Dutton, Texas Department of State Health Services, 2007). Diagnosed diabetes prevalence based on self-report was much higher in Texas border counties (12.0%) than in Texas (7.7%), New Mexico (6.5%), and the US (7.1%) (14). Higher diabetes prevalence in Texas border counties may be partially explained by not having met recommendations for moderate to vigorous physical activity which was much lower in Texas border counties (31.7%) than in Texas (55.3%) and the US (52.8%) (14).

Additional limitations of our study were its clinic-based nature which may have introduced selection bias, the delay of more than six months following initial diagnosis before contacting the majority of cases which may have introduced misclassification of exposures, relying on self-report of diabetes which is often times undiagnosed, our failure to distinguish between type 1 and type 2 diabetes, and our lack of study power to detect some main and joint effects. Nevertheless, we do not expect misclassification of exposures to differ by case-control status meaning our point estimates may be attenuated.

Our study is one of the first studies to investigate the association between diabetes and breast cancer among Hispanic women. The analysis of the interaction between diabetes, physical activity and breast cancer contributes to the sparse body of knowledge in this area. Additional strengths of the study were the focus on Hispanic women, a population that is at high-risk of the diabetes, but low risk of the breast cancer, high response rates, and adjusting for mammography screening to reduce the likelihood of detection bias.

Hispanic women possess a number of breast cancer risk factors and yet have a relatively low incidence of the disease. Very few breast cancer studies have focused on Hispanic women; however, the identification of protective factors against breast cancer may contribute to our understanding of the biological mechanisms of the disease. Stoll (15-16) hypothesized that the higher risk for postmenopausal breast cancer among some ethnic groups within the US may be related to their higher genetic susceptibility to diabetes brought on by excess weight gain, and a high-fat, low-fiber diet. Although Hispanic women have higher rates of insulin resistance than non-Hispanic Whites (17), women in our study did not have resulting higher rates of breast cancer. Preventive measures such as the use of Metformin and physical activity should be explored as a means of reducing breast cancer risk in diabetic women.

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

Characteristic	Cases (n=190)		Controls (n=468)	
Age (years)	n	%	N	%
30-49	59	31.0	129	27.5
50-64	91	47.9	269	57.5
65-79	40	21.1	70	15.0
Breast cancer among first-degree relatives				
No	169	89.9	440	95.6
Yes	19	10.1	20	4.4
Missing	2		8	
Age at menarche (years)				
<12	50	26.5	104	22.3
≥12	139	73.5	363	77.7
Missing	1		1	
Menopausal status				
Premenopausal	36	19.3	77	16.7
Postmenopausal	150	80.7	383	83.3
Missing	4		8	
Age at menopause (years)				
<45	68	45.3	191	49.9
45-49	37	24.7	103	26.9
≥50	45	30.0	89	23.2
Parous				
No	10	5.3	26	5.6

Yes	180	94.7	442	94.4
Age at first pregnancy (years)				
<20	59	32.8	160	36.6
20-24	69	38.3	174	39.8
25-29	38	21.1	70	16.0
30-34	10	5.6	23	5.3
≥35	4	2.2	10	2.3
Missing	0		5	
Body mass index				
<25	21	11.3	62	13.4
25-29.9	56	30.1	138	29.8
30-34.9	57	30.6	145	31.3
≥35	52	28.0	118	25.5
Missing	4		5	
Use of oral contraceptives				
No	66	35.1	131	28.1
Yes	122	64.9	336	71.9
Missing	2		1	
Use of hormone replacement therapy				
No	127	66.8	222	47.8
Yes	63	33.2	243	52.2
Missing	0		4	
Alcohol intake				
No	153	80.5	385	82.4
Yes	37	19.5	82	17.6

Missing	0		1	
Physical activity in past 3 years				
No	153	80.5	385	82.4
Yes	37	19.5	82	17.6
Missing	0		1	
Number of mammograms in past 6 years				
0-1	39	20.5	6	1.3
2-3	54	28.4	55	11.9
4-5	36	19.0	101	21.8
≥6	61	32.1	301	65.0
Missing	0		4	

Table 2. Odds ratios for breast cancer associated with diabetes

Characteristic	Cases (n=190)		Controls (n=468)			
History of diabetes	n	%	n	%	OR[a]	(95% CI)
No	137	72.1	314	67.5	1.00	(referent)
Yes	53	27.9	151	32.5	0.70	(0.45-1.09)
Missing	0		2			
Type of diabetes						
Gestational	3	1.6	12	2.6	0.16	(0.02-1.31)
Type 2	49	25.9	137	29.6	0.75	(0.48-1.18)
Missing	1		4			
Age at diabetes onset (years)						
<35	3	1.6	10	2.2	0.68	(0.17-2.74)
≥35	43	23.5	122	27.4	0.74	(0.47-1.19)
Missing	3		5			
Diabetes treatment						
Insulin	25	13.4	36	8.0	1.42	(0.76-2.65)
Oral medication	20	10.7	66	14.6	0.63	(0.34-1.19)
No insulin or oral medication	5	2.7	37	8.2	0.30	(0.11-0.83)
Missing	3		12			
Family history of diabetes						
No	58	31.0	154	33.4	1.00	(referent)
Yes	129	68.9	307	66.6	1.28	(0.84-1.94)
Missing	3		6			

[a]Adjusted for age, menopausal status, body mass index and mammography screening.

Table 3. Odds ratios for breast cancer associated with joint effects of diabetes and physical activity

Characteristic	Cases (n=190)		Controls (n=468)			
Did not engage in physical activity						
History of diabetes	n	%	n	%	OR[a]	(95% CI)
No	79	66.9	141	63.5	1.00	(referent)
Yes	39	33.1	81	36.5	0.66	(0.42-1.04)
Did engage in physical activity						
History of diabetes						
No	58	80.6	173	71.2	0.79	(0.46-1.36)
Yes	14	19.4	70	28.8	0.31	(0.15-0.65)
P for interaction						0.27

[a]Adjusted for age, menopausal status, body mass index and mammography screening.