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The association of diabetes and obesity with prostate cancer aggressiveness among Black Americans and White Americans in a population-based study

Saira Khan, PhD, MPH^{1,2}, Jianwen Cai, PhD, MS³, Matthew E. Nielsen, MD, MS^{1,4,5}, Melissa A. Troester, PhD, MPH, MS^{1,5}, James L. Mohler, MD^{4,5,6,7}, Elizabeth T. H. Fontham, DrPH, MPH⁸, Laura H. Hendrix, MS⁵, Laura Farnan, PhD, MS⁵, Andrew F. Olshan, PhD, MS^{1,5}, and Jeannette T. Bensen, PhD, MS^{1,5}

¹ Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina-Chapel Hill, 135 Dauer Drive, Chapel Hill, North Carolina, 27599 USA.

² Department of Surgery, Division of Public Health Sciences, Washington University in St. Louis School of Medicine 660 S. Euclid Ave., St. Louis, Missouri, 63110 USA

³ Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina-Chapel Hill, 135 Dauer Drive, Chapel Hill, North Carolina, 27599 USA

⁴ Department of Urology, School of Medicine, University of North Carolina-Chapel Hill, 170 Manning Dr., Chapel Hill, North Carolina, 27599 USA

⁵ Lineberger Comprehensive Cancer Center, School of Medicine, University of North Carolina-Chapel Hill, 450 West Drive, Chapel Hill, North Carolina, 27599 USA

⁶ Department of Urology, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, New York, 14263, USA

⁷ Department of Urology, University of Buffalo School of Medicine and Biotechnology, 100 High Street, Buffalo, New York, 14203, USA

⁸ School of Public Health, Louisiana State University Health Science Center, 2020 Gravier Street, New Orleans, Louisiana 70112, USA

Abstract

Purpose—Few studies have investigated the role of race in the association of diabetes and obesity with prostate cancer aggressiveness. Here we evaluate the independent association

Correspondence: Saira Khan, PhD, MPH, Washington University in St. Louis School of Medicine, Division of Public Health Sciences, Department of Surgery, 660 S. Euclid Ave, Box 8100, St. Louis, MO 63110, khans@wudosis.wustl.edu, Phone: 314-747-0964.

Compliance with Ethical Standards

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent was obtained from all individual participants included in the study.

between diabetes and obesity with prostate cancer aggressiveness in White Americans and Black Americans.

Methods—Our cross-sectional, case-only study consisted of 1058 White Americans and 991 Black Americans from the North Carolina-Louisiana Prostate Cancer (PCaP) project. Diabetes status was determined by self-report. Obesity was determined using body mass index and calculated based on anthropometric measurements. High aggressive prostate cancer was defined as Gleason sum ≥ 8 , or prostate specific antigen >20 ng/ml, or Gleason sum ≥ 7 and clinical stage cT3-cT4. The association between diabetes and obesity with high aggressive prostate cancer at diagnosis was evaluated using multivariable logistic regression and adjusted for potential confounders.

Results—Diabetes was not associated with high aggressive prostate cancer in the overall sample (OR: 1.04; 95% CI: 0.79, 1.37), White Americans (OR: 1.00; 95% CI: 0.65, 1.57), or Black Americans (OR: 1.07; 95% CI: 0.75, 1.53). Obesity, independent of diabetes, was positively associated with high aggressive prostate cancer in White Americans (OR: 1.98; 95% CI: 1.14, 3.43), but not in the overall sample (OR: 1.37; 95% CI: 0.99, 1.92) or Black Americans (OR: 1.09; 95% CI: 0.71, 1.67).

Conclusions—Diabetes was not associated with prostate cancer aggressiveness, overall, or in either race-group. Obesity, independent of diabetes, was associated with high aggressive prostate cancer only in White Americans.

Keywords

prostate cancer; aggressiveness; diabetes; obesity; Black Americans; PCaP

Introduction

Prostate cancer (CaP) is the most common incident cancer among men in the United States. The Surveillance Epidemiology and End Results (SEER) reported that, 14% of men will be diagnosed with CaP during their lifetime [1]. An estimated 180,890 new cases of CaP and 26,120 CaP deaths occurred in the United States during 2016 [2]. CaP is a disease of disparities. Black Americans (Blacks) are more likely to be diagnosed with and die from CaP than White Americans (Whites). The incidence of CaP from 2008-2012 is higher in Blacks at 214.5 cases per 100,000 compared to 130.4 cases per 100,000 in Whites [1]. The age-adjusted death rate in Blacks was more than double that in Whites between 2008-2012 [1].

Numerous studies have shown that diabetes is associated with a reduced risk of incident CaP [3-10]. Insulin is a known growth factor for CaP cells [11,12]. Thus diabetics, with potentially lower levels of circulating insulin, may be less likely to develop CaP [11]. Other possible explanations for this inverse association include changing levels of testosterone and decreased CaP detection among diabetic men [6,13,14]. Diabetics are more likely to be obese than their non-diabetic counterparts [15]. Digital rectal exam (DRE) CaP detection and prostate biopsy are both more difficult in obese men, and obese men may have lower levels of prostate specific antigen (PSA), any of which could contribute to lower rates of CaP diagnosis [6,14,16,17].

By contrast, studies among men already diagnosed with CaP show that diabetes and obesity are positively associated with CaP aggressiveness [13,17-25]. Jayachandran et al. hypothesized that the positive association between diabetes and CaP aggressiveness is a result of a “selection pressure” where only high aggressive prostate CaP can survive in a low-insulin, poor growth environment [13]. In addition, the insulin profile of diabetics changes throughout the diabetes disease-course [13,14]. Newly diagnosed diabetics, in particular, likely have high insulin levels that create an environment that promotes CaP growth [14]. The positive association between diabetes and CaP aggressiveness observed in the literature is limited to studies with clinic or hospital-based populations or patients undergoing a single treatment type. Few studies have included sufficient numbers of Black men to examine the role of race on the diabetes-CaP aggressiveness association, and the two existing studies have yielded different results [13,22].

We examined the association of diabetes and obesity, independent of diabetes, with high aggressive CaP at diagnosis, defined as a Gleason sum ≥ 8 , or PSA >20 ng/ml, or Gleason sum ≥ 7 and clinical stage cT3-cT4. This analysis adds to the literature by examining the association between diabetes and CaP aggressiveness at diagnosis in racially-diverse sample-group from the Southern U.S. Specifically, our study population was a large, population-based sample of men who had incident CaP, were over-sampled for Blacks, were diagnosed in the PSA screening era, and participated in the North Carolina-Louisiana Prostate Cancer Project (PCaP). This analysis builds on previous PCaP research that found obesity was associated with CaP aggressiveness at diagnosis, by accounting for the diabetic status of PCaP research subjects [23]. We further expand this research by presenting prevalence differences, in addition to odds ratios (ORs).

Methods

Study Population and data collection

PCaP has been described in detail [26]. PCaP is a population-based cross-sectional, case-only study of research subjects with incident CaP. All research subjects were diagnosed with adenocarcinoma of the prostate between July 2004 and August 2009, and were identified using state tumor registries. Eligibility criteria for PCaP research subjects included: resident of North Carolina or Louisiana- study areas, first diagnosis of histologically confirmed adenocarcinoma of the prostate, 40-79 years old at diagnosis, could complete the study interview in English, did not live in an institution (i.e. nursing home), not cognitively impaired or in a severely debilitated physical state, and not under the influence of alcohol, severely medicated, or apparently psychotic at the time of the interview. Moreover, eligible men had to self-identify as African American/Black or Caucasian/White in response to the open-ended question, “What is your race?”.

PCaP enrolled Blacks and Whites at an equal rate using a randomized recruitment method [27]. Participation rates were 62% in North Carolina, 73% in pre-hurricane Katrina Louisiana, and 63% in post-hurricane Katrina Louisiana. 1,130 Blacks and 1,128 Whites enrolled in PCaP.

We excluded 25 research subjects that were underweight [body mass index (BMI) < 18.5] and 84 research subjects with missing information on the outcome (CaP aggressiveness) from our analytic group. Furthermore, 17 research subjects were excluded due to missing information on diabetes (4 research subjects responded they did not know their diabetes status and 13 research subjects did not have their diabetes status recorded). Additional research subjects were excluded due to missing covariate information (CaP screening history, body mass index (BMI), or education) (n=83). Our final analytical sample included a total of 2049 research subjects (94% of PCaP research subjects with CaP aggressiveness defined at diagnosis) of which 1058 were White and 991 were Black. Although Black research subjects were more likely to be excluded than White research subjects, the distribution of CaP aggressiveness, diabetes, and covariates was similar for Blacks in the full PCaP sample and Blacks in the analytic sample.

The primary outcome was high aggressive CaP based on a composite of diagnostic PSA, clinical stage and Gleason sum. We also evaluated CaP aggressiveness solely based on Gleason sum. The sample consisted of 2207 research subjects (98% of all PCaP research subjects) when the analysis was restricted to Gleason sum.

Research subjects who agreed to participate were visited by a Registered Nurse. The nurse administered a questionnaire, took biologic samples, and made anthropometric measures during an in-home visit. The nurse also obtained informed consent for the interview and specimen collection and release of tumor tissue and medical records. The study questionnaire included questions on comorbidities (e.g. diabetes), education level, and CaP screening history. The average time between CaP diagnosis and the nurse visit in our study sample was 4.9 months. The time between the visit and diagnosis was similar in Whites (4.8 months) and Blacks (5.0 months).

Medical records were requested from the physicians (up to 3) of all consenting research subjects for standardized medical record abstraction. Medical record abstraction included information regarding physical examinations and laboratory assays at or near diagnosis, clinical stage, Gleason sum, PSA measures, and initial CaP treatment.

Outcome, Exposure, and Covariate Measurement

Our primary outcome of interest was a composite measure of CaP aggressiveness *at diagnosis* [26]. High aggressive CaP was defined as Gleason sum ≥ 8, or PSA >20 ng/ml, or Gleason sum =7 and clinical stage cT3-cT4. Low aggressive CaP was defined as Gleason sum <7 and clinical stage cT1-cT2 and PSA <10 ng/ml. Other CaP was defined as intermediate aggressive. Low aggressive and intermediate aggressive CaP were collapsed into a single category in all our analytic models. We also analyzed CaP aggressiveness using Gleason sum alone to allow comparison with previous studies. Gleason sum was analyzed as a binary variable with high aggressiveness defined as Gleason sum ≥ 7.

Our primary exposures of interest are diabetes and obesity, independent of diabetes. PCaP research subjects self-reported diabetes status when asked the question, “Has a doctor or other health professional ever told you that you had diabetes or sugar diabetes?”. Responses were recoded as “yes”, “no”, “refused”, or “don't know”. Research subjects who did not

know their diabetes status or refused to answer were excluded from our analysis (n=17, 0.8% of all PCaP research subjects). Obesity was determined using body mass index (BMI). BMI was calculated using standardized anthropometric measurements at the home visit, and research subjects were categorized as normal (BMI 18.5 to <25), overweight (BMI 25 to <30), or obese (BMI ≥ 30) using World Health Organization classifications.

Covariates were selected based on known confounders in the literature and to maintain consistency with prior PCaP studies and included race, age, CaP screening history, education, and study site. Race was based on self-report, and all research subjects were categorized as either White or Black. Age was calculated based on age at diagnosis and coded as a continuous variable. Education was based on self-report and categorized as less than high school, high school graduate or some college, or college graduate and above. Study site was categorized as North Carolina or Louisiana. CaP screening history was based on self-report and defined as having at least one PSA or Digital Rectal Exam (DRE) prior to CaP diagnosis

Statistical Analysis

Logistic regression was used to assess the association of diabetes and BMI with the composite binary outcome (aggressive CaP at diagnosis) in our primary analysis. Multivariable models were adjusted for race, age, CaP screening history, education, and study site. Models were stratified by race to examine race differences and adjusted for age, CaP screening history, education, and study site. Because the outcome of high aggressive CaP does not meet the rare disease assumption, prevalence ORs obtained from logistic regression should not be interpreted as prevalence ratios.

We conducted several sensitivity analyses. First, we ran multivariable models without adjustment for BMI, because weight gain may be risk factor for and a result of having diabetes. Obesity is known risk factor for diabetes, and diabetics may also gain weight as a result of certain diabetes medications [15,28]. Second, we examined the interaction between diabetes and CaP screening history, because it is possible that men with diabetes are more likely to receive CaP screening as they may have more contact with the healthcare system to manage their diabetes. Third, we restricted our analyses only to men that did not receive CaP screening. Finally, we stratified by diabetes status to further elucidate the independent effect of diabetes and obesity.

In secondary analyses, we modeled Gleason sum ≥ 7 (vs. <7) rather than using our composite outcome measure of CaP aggressiveness. Logistic regression was used to assess the association of diabetes and BMI with our dichotomous Gleason sum variable using the same adjustment set as the analysis using our composite outcome. Models were stratified by race.

Prevalence differences were calculated to allow for comparisons in the relative frequency of high aggressive CaP across races. Prevalence differences were calculated using the method suggested by Spiegelman and Hertzmark [29]. Diabetes and BMI were our exposures of interest. Models were adjusted for race, age, CaP screening history, education, and study

site. Models were stratified by race to examine race differences and adjusted for age, CaP screening history, education, and study site.

All analyses were conducted using SAS 9.4 (Cary, NC).

Results

Characteristics of PCaP Research Subjects (Table 1)

The mean age of research subjects at diagnosis was 63 years. The majority of research subjects had CaP screening using PSA or DRE prior to CaP diagnosis. Research subjects were enrolled in approximately equal numbers in North Carolina and Louisiana. Approximately half of research subjects were high school graduates or had some college education. PCaP research subjects were more likely to be overweight or obese than normal weight. 21.6% of the sample had diabetes, and 17.9% of the sample had high aggressive CaP using our composite measure of aggressiveness.

Blacks (n=991) were slightly younger than Whites (n=1058). Whites were more likely than Blacks to have undergone CaP screening prior to diagnosis. The CaP screening prevalence in research subjects with diabetes (89.5%) and research subjects without diabetes (90.3%) was similar. There were approximately equal numbers of Whites and Blacks at each study site. Whites were more likely to be college graduates or above, while blacks were more likely to have less than a high school education. Blacks were more likely to have diabetes (26.8%) than Whites (16.7%), and were more likely to have high aggressive CaP at diagnosis (20.6% vs. 15.3%).

Diabetes and Obesity (Table 2)

The OR for diabetes and high aggressive CaP was close to the null after adjustment for age, race, CaP screening history, study site, education, and BMI (OR: 1.04; 95% CI: 0.79, 1.37). The association of diabetes and high aggressive CaP was similar in race-specific models adjusted for age, CaP screening history, study site, education, and BMI among Whites (OR: 1.00; 95% CI: 0.65, 1.57) or Blacks (OR: 1.07; 95% CI: 0.75, 1.53). Obesity, adjusted for diabetes, was associated with an elevated odds of high aggressive CaP in the overall sample (OR: 1.37; 95% CI: 0.99, 1.92) and Whites (OR: 1.98; 95% CI: 1.14, 3.43), but not Blacks (OR: 1.09; 95% CI: 0.71, 1.67) in adjusted models. Multivariable models without diabetes adjustment, showed a similar association between obesity and high aggressive CaP as our primary model [Overall (OR: 1.38; 95% CI: 1.00, 1.92), Whites (OR: 1.98; 95% CI: 1.15, 3.42), or Blacks (OR: 1.10; 95% CI: 0.72, 1.69)].

Sensitivity Analyses

Models *not* adjusted for BMI in a sensitivity analysis did not show an association between diabetes and high aggressive CaP [Overall (OR: 1.10; 95% CI: 0.84, 1.45), Whites (OR: 1.14; 95% CI: 0.73, 1.76), or Blacks (OR: 1.09; 95% CI: 0.77, 1.55)]. In multivariable models with an additional interaction term for diabetes and CaP screening history, no significant interaction was observed in the overall sample (p-value for interaction = 0.28), Whites (p-value = 0.61), or Blacks (p-value = 0.37). Due to the small number of research

subjects that did not receive CaP screening, analyses restricted to non-screened men were highly imprecise, although the ORs were further above the null than in the overall sample [Non-screened overall (OR: 1.59, 95% CI: 0.77, 3.26); Non-screened Whites (OR: 1.89, 95% CI: 0.33, 10.70); Non-screened Blacks (OR 1.54, 95% CI: 0.68, 3.47)]. Multivariable models stratified by diabetes status, showed no association between obesity and high aggressive CaP in diabetics (OR: 1.16, 95% CI: 0.52, 2.59), and were suggestive of a positive association in non-diabetics (OR: 1.43, 95% CI: 0.99, 2.06) after adjustment for race, age, CaP screening history, study site, and education. To further examine the potential association among non-diabetics, we stratified by race. Results were consistent with our overall findings, and showed that obesity was associated with high aggressive CaP among non-diabetic Whites (OR: 2.48, 95% CI: 1.35, 4.56), but not non-diabetic Blacks (OR: 0.97, 95% CI: 0.60, 1.57) after adjustment for age, CaP screening history, study site, and education. We did not have adequate statistical power to examine the association of obesity and high aggressive CaP stratified by race among diabetics only.

Secondary analyses with Gleason sum as our outcome were consistent with analyses using the composite outcome of high aggressive CaP. The observed ORs for Gleason sum ≥ 7 (in diabetics vs. non-diabetics) were similar for the overall sample (OR: 0.93; 95% CI: 0.75, 1.16), and race-specific groups [Whites (OR: 0.96, 95% CI: 0.68, 1.34); Blacks (OR 0.92, 95% CI: 0.69, 1.23)]. Obesity, independent of diabetes, was associated with Gleason sum ≥ 7 in both the overall sample (OR: 1.36; 95% CI: 1.06, 1.76) and Whites (OR: 1.51; 95% CI: 1.03, 2.20), but not Blacks (OR: 1.23; 95% CI: 0.87, 1.75).

Prevalence Differences

ORs are interpretable as measures of association and may mask the relative differences in prevalence between Whites and Blacks in our case-only study. We calculated prevalence differences as an estimate of the relative frequency of high aggressive CaP in Whites and Blacks (Table 3). Prevalence differences showed directions of association that were consistent with the results based on ORs. Namely, diabetes was not associated with a higher prevalence of aggressive CaP in the study sample as a whole, nor in Whites or Blacks after adjusting for age, race (overall sample only), CaP screening history, study site, education, and BMI. However, obesity, independent of diabetes, was associated with a 7% (PD: 0.07; 95% CI: 0.01, 0.14) increase in the prevalence of high aggressive CaP in Whites and a 4% increased prevalence in the sample as a whole (PD: 0.04; 95% CI: 0.00, 0.09). The prevalence difference in Blacks was close to the null (PD: 0.01; 95% CI: -0.06, 0.08), although the estimate is imprecise.

Discussion

Self-reported diabetes was not associated with a composite measure of CaP aggressiveness at diagnosis in this population-based study of Whites and Blacks with CaP. We did not observe any differences in this association between Whites and Blacks. However, we found that obesity, independent of diabetes, was associated with high aggressive CaP in Whites using our composite measure of CaP aggressiveness.

Several studies have reported a positive association between diabetes and CaP aggressiveness at diagnosis [13,22,24,25]. However, unlike our study, these studies were restricted to clinical patient sets receiving a common treatment, with an outcome of Gleason sum alone [13,22,24,25]. Moreover, only one of these studies accounted for obesity in their analyses [13]. D'Amico et al. reported a positive association between diabetes and Gleason sum 8-10 (OR: 1.85, 95% CI: 1.25, 2.74) among radiation patients [25]. Kang et al reported that both type 1 diabetes (OR: 2.05, 95% CI: 1.28, 3.27) and type 2 diabetes (OR: 1.58, 95% CI: 1.26, 1.99) were associated with Gleason sum 8-10 in another study that used the same patient population [24]. Jayachandran et al. reported that diabetes was associated with Gleason sum 7 (OR: 1.73, 95% CI: 1.22, 2.45) among RP patients from the Shared Equal Access Regional Cancer Hospital Database (SEARCH) [13]. By contrast, we did not find an association between diabetes and our composite outcome of CaP aggressiveness or Gleason sum 7 in our population-based study sample.

Our results were consistent with the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) study. Chan et al. reported that a history of diabetes was not associated with higher Gleason score in multivariate analysis [30]. Although Chan et al. is not population-based, it is similar to our study in its inclusion of men treated with either radiation or RP and use of a self-reported measure of diabetes. However, this study modeled diabetes at baseline as the outcome of interest with Gleason score as a covariate in a multivariable model, and as such their analytic approach differed from ours[30].

Only two studies examined racial differences among men *diagnosed with CaP* [13,22]. Mitin et al. reported that diabetes was associated with a Gleason sum 8-10 in Blacks (OR: 1.84, 95% CI: 1.08, 3.13) and nonblacks (OR: 1.59, 95% CI: 1.33, 1.89) treated with radiation [22]. By contrast, Jayachandran et al. reported that diabetes was associated with high-grade disease (Gleason sum 7) in Whites (OR: 2.28, 95% CI: 1.33, 3.91), but not Blacks (OR: 1.45, 95% CI: 0.90, 2.23) treated with RP [13]. Our results did not show a positive association between diabetes and our composite measure of high aggressive CaP in either Whites or Blacks. Secondary analyses with Gleason sum 7 as our outcome were consistent with our CaP aggressiveness composite outcome, and we did not observe an association between diabetes and Gleason sum 7 in the overall sample or either race-group. Some studies only reported association between diabetes and a higher Gleason sum cut-point (i.e. Gleason sum 8). Therefore we examined the association using this higher cut-point [22,25]. The higher cut-point did not impact our results, and no significant associations were observed in either race-group (data not shown).

Among the two studies that looked at race differences, Mitin et al. included men treated with radiation between 1991 and 2010 and Jayachandran et al. included men treated with RP between 1988-2008. Our study, by contrast, included men diagnosed with CaP between 2004-2009. The FDA did not approve use of PSA as a screening test in asymptomatic men until 1994 [31]. Thus Mitin et al. and Jayachandran et al. included men from the pre-PSA and PSA screening eras, while our study sample came entirely from the PSA-screening era. Studies that include men from the pre-PSA screening era may be more likely to detect a positive relationship between diabetes and CaP aggressiveness at diagnosis as a larger proportion of men were diagnosed with high aggressive (later stage) CaP in the pre-PSA

screening era. We observed a consistent, strong inverse association between a positive history of PSA or DRE screening prior to CaP diagnosis and high aggressiveness CaP at diagnosis in the overall sample (OR: 0.42, 95% CI: 0.31, 0.59), Whites (OR: 0.40, 95% CI: 0.22, 0.74), and Blacks (OR: 0.43, 95% CI: 0.29, 0.63). Neither of the other two studies that examined race differences adjusted for CaP screening history [13,22].

Given the close relationship between diabetes and obesity, we investigated the role of obesity, independent of diabetes, on CaP aggressiveness. This analysis builds on a previous PCaP study that found obesity, *not* adjusted for diabetes, was associated with high aggressive CaP in Whites [Obese (OR: 2.00; 95% CI: 1.13, 3.54), Severely obese (OR: 2.09; 95% CI: 1.06, 4.14)] but not Blacks [Obese (OR: 1.38; 95% CI: 0.85, 2.23), Severely obese (OR: 1.71; 95% CI: 1.00, 2.90)] [23]. Our results, which were consistent with previous PCaP reports, showed that obesity, independent of diabetes, was positively associated with our composite measure of high aggressive CaP in Whites, but not in Blacks. Obesity, independent of diabetes, was associated with Gleason sum ≥ 7 both in the overall sample and Whites. The association observed in the overall sample is likely driven by Whites, since no association was observed with obesity, independent of diabetes, and Gleason sum ≥ 7 in Blacks.

Our results are consistent with those observed in an earlier study utilizing the SEARCH database [19]. This study reported that moderate and severe obesity were significantly associated with pathologic Gleason sum ≥ 7 in Whites (OR: 2.35; 95% CI: 1.12, 4.91), but not Blacks (OR: 1.48; 95% CI: 0.71, 3.12) [19]. Spangler et al., by contrast, reported that obesity was not associated with Gleason sum in Whites or Blacks [32]. This inconsistency may result from Spangler et al. having a study sample that was derived from a single, academic health system that may not be as representative as population-based samples [32].

Our results suggest the impact of obesity may vary across race, so we examined prevalence differences to further elucidate the role of race. This adds to the current literature, which is largely limited to measures of association. Prevalence differences were consistent with the direction of association for ORs. We found that obesity, independent of diabetes, was associated with a 7% increase in the prevalence of high aggressive CaP in Whites and no significant difference was observed in Blacks.

Our results show differing associations for diabetes and obesity with high aggressive CaP. This finding highlights the complex disease profile of diabetics. The inverse association between diabetes and risk of developing CaP has been well established [3-10]. Several possible underlying reasons have been suggested for this inverse association, and a 2012 review by Pierce summarized many of these reasons [14]. Insulin is a known growth factor for CaP, and it is hypothesized that the lower insulin levels in diabetics may slow the development of *incident* CaP [11]. However, the changing insulin, testosterone, and glucose levels over the diabetes disease-course complicates any potential association between diabetes and CaP aggressiveness among men who have already been diagnosed with CaP [11,12]. Early stages of diabetes are marked by hyperinsulinemia while in later stages of diabetes there is decreased insulin production [14]. Moreover, diabetes is also associated with lower testosterone levels [33,34]. In contrast to traditional understanding, lower

testosterone levels have recently been shown to be associated with CaP aggressiveness [34-39]. However, there is some evidence that also suggests testosterone levels may subsequently increase with increasing diabetes duration [11,40,41]. This finding is further complicated by the fact that the ratio of sex hormone binding globulin (SHBG) to testosterone has also been shown to increase with the duration of diabetes, thereby reducing the free testosterone available as diabetes progresses [11,14]. As such, depending on diabetes duration, how well diabetes is controlled, diabetics may have high insulin levels and low testosterone levels, creating an environment that promotes the growth of high aggressive CaP.

In this study, however, we did not find an association between diabetes and high aggressive CaP. Obesity, independent of diabetes, was associated with high aggressive CaP in Whites. There are several possible mechanisms by which obesity may impact CaP aggressiveness independent of diabetes. First, obesity has been associated with benign prostatic hyperplasia (BPH) [6,42]. Although BPH does not itself increase the risk of CaP, it is possible that it is harder to detect CaP in an enlarged prostate [6]. Second, obesity is also associated with lower PSA levels [16]. Given that high PSA levels are the primary reason for prostate biopsy referral, lower PSA levels could result in delayed referrals and CaP detection. Third, obesity can result in less effective digital rectal exams (DRE), another important CaP screening test [43]. Factors such as these can all contribute to the diagnosis of CaP at a later, more advanced (aggressive) stage. It is possible that Black men were more likely to have CaP detected at a later, more advanced (aggressive) stage, independent of these obesity-related factors. Our data suggest that this is possible. Blacks with a normal BMI were more likely to have high aggressive CaP (22%) than Whites with a normal BMI (12%) in our study sample. The prevalence of high aggressive CaP in obese Whites is 20%. This prevalence is lower than the prevalence of high aggressive CaP in Blacks with a *normal* BMI. This could explain, in part, why we observed a significant association only in Whites. Our findings suggest that obesity may increase the prevalence of high aggressive CaP only when the baseline prevalence of high aggressive CaP is relatively low.

Finally it is important to note that obese men are at increased risk for both hyperinsulinemia and lower testosterone levels even if they have not been diagnosed with diabetes [44,45]. Both these factors can contribute to CaP aggressiveness at diagnosis. Specifically, insulin-like growth factor (IGF-I), a possible CaP mitogen, is increased in men with hyperinsulinemia [46].

A key strength of our study is that it is a *population-based* study of both Whites and Blacks diagnosed with CaP. PCaP is a large, well-characterized, study sample from the PSA screening era with detailed epidemiologic, interview, and clinical data, which allow for analytic adjustment for factors such as CaP screening history. To our knowledge, previous studies that examined racial differences in the association of diabetes and CaP aggressiveness at diagnosis were not population-based, encompassed both the pre-PSA and PSA screening eras, did not adjust for CaP screening history, and were limited to patients receiving a single treatment modality. Thus our results may provide a more representative assessment of diabetes and CaP aggressiveness at diagnosis, and therefore may be generalized to a broader population of both Blacks and Whites with CaP and diabetes.

According to the National Health and Nutrition and Examination Survey (NHANES), 33.6% of non-Hispanic White adult men and 37.5% of non-Hispanic Black adult men are obese in the U.S. [47]. This is similar to the prevalence of obesity in our study sample, where 37.8% of Whites and 39.8% of Blacks are obese. Moreover, estimates by the Centers for Disease Control and Prevention (CDC) suggest that among men aged 65-74, in the U.S., the diabetes rate is 22.3% for Whites and 29.6% for Blacks [48]. This estimate is similar to the diabetes prevalence observed in our study: 21.9% of Whites and 31.7% of Blacks aged 65-74 report having diabetes.

Our study used self-reported diabetes and therefore has some limitations. An Atherosclerosis Risk in Communities study (ARIC), reported that the sensitivity of prevalent self-reported diabetes ranges from 58.5% to 70.8% and the specificity ranges from 95.6% to 96.8% depending on the reference definition employed [49]. However, as discussed above the prevalence of diabetes in our study sample is representative of national estimates. Another potential limitation of our diabetes measure is that we do not know when research subjects were diagnosed and cannot evaluate the duration of diabetes exposure, or the severity of disease among diabetics, or how well diabetes was controlled. In addition, Black research subjects were more likely than White research subjects to be excluded from our analytic sample due to missing exposure, outcome, or covariate information. However, despite this limitation we retained 87% of Blacks and 94% of Whites in our analytic sample, and almost half our analytic sample consisted of Black men.

The PCaP study allowed us the unique opportunity to make population-based estimates of the association between diabetes and CaP aggressiveness at diagnosis, and to specifically examine this association in a significant number of Black men.

Conclusion

Our results suggest that diabetes may not be associated with CaP aggressiveness at diagnosis in men with CaP. Our results further suggest that association of obesity with CaP aggressiveness in men diagnosed with CaP may be limited to Whites. Future studies with large numbers of both Whites and Blacks with detailed information on diabetes duration and management are needed to further elucidate any racial differences that may exist between in CaP aggressiveness.

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Table 1

PCaP research subject characteristics

	All research Subjects (n= 2049)	Whites (n=1058)	Blacks (n=991)
Age years (Mean, SD)	63.0 (7.9)	64.1 (7.9)	61.7 (7.8)
Screening History (n, %) ^a			
Yes	1838 (89.7)	996 (94.1)	842 (85.0)
No	211 (10.3)	62 (5.9)	149 (15.0)
Study Site			
North Carolina	973 (47.5)	504 (47.6)	469 (47.3)
Louisiana	1076 (52.5)	554 (52.4)	522 (52.7)
Education (n, %)			
Less than high school	399 (19.5)	100 (9.5)	299 (30.2)
High school graduate or some college	1032 (50.4)	497 (47.0)	535 (54.0)
College graduate or above	618 (30.2)	461 (43.6)	157 (15.8)
BMI (n, %) ^b			
Normal	374 (18.3)	172 (16.3)	202 (20.4)
Overweight	881 (43.0)	486 (45.9)	395 (39.9)
Obese	794 (38.8)	400 (37.8)	394 (39.8)
Diabetes (n, %) ^c			
Yes	443 (21.6)	177 (16.7)	266 (26.8)
No	1606 (78.4)	881 (83.3)	725 (73.2)
CaP Aggressiveness ^d			
Low	1045 (51.0)	586 (55.4)	459 (46.3)
Intermediate	638 (31.1)	310 (29.3)	328 (33.1)
High	366 (17.9)	162 (15.3)	204 (20.6)

^aScreening history was based on self-report and defined as having at least one PSA or DRE prior to CaP diagnosis.

^bResearch subjects were categorized as normal (BMI 18.5 to <25), overweight (BMI 25 to <30), or obese (BMI ≥ 30).

^cBased on self-report.

^dHigh aggressive CaP was defined as Gleason sum ≥ 8, or PSA >20 ng/ml, or Gleason sum =7 and clinical stage cT3-cT4. Low aggressive CaP was defined as Gleason sum <7 and clinical stage cT1-cT2 and PSA <10 ng/ml. All other cases were defined as intermediate aggressive CaP.

Table 2

Prevalence odds ratios (OR) and 95% confidence intervals for high aggressive CaP

All Research Subjects (n=2049)						Whites (n=1058)				Blacks (n=991)			
# of subjects	# with outcome	Unadjusted OR	Adjusted OR ^a	# of subjects	# with outcome	Unadjusted OR	Adjusted OR ^b	# of subjects	# with outcome	Unadjusted OR	Adjusted OR ^b	# of subjects	# with outcome
Diabetes													
No	1606	276	Ref	881	130	Ref	Ref	725	146				
Yes	443	90	1.23 (0.94, 1.60)	177	32	1.28 (0.83, 1.95)	1.00 (0.65, 1.57)	266	58	1.11 (0.79, 1.56)	1.07 (0.75, 1.53)		
BMI													
Normal	374	64	Ref	172	20	Ref	Ref	202	44		Ref		
Over-weight	881	140	0.92 (0.66, 1.27)	486	64	1.15 (0.68, 1.97)	1.29 (0.75, 2.24)	395	76	0.86 (0.56, 1.30)	0.93 (0.60, 1.42)		
Obese	794	162	1.24 (0.90, 1.71)	400	78	1.84 (1.09, 3.12)	1.98 (1.14, 3.43)	394	84	0.97 (0.64, 1.47)	1.09 (0.71, 1.67)		

^aModel included diabetes, age in years, race, screening history, study site, education, and BMI

^bModel included diabetes, age in years, screening history, study site, education, and BMI

Table 3

Prevalence differences (PD) and 95% confidence intervals for high aggressive CaP

	All Research Subjects (n=2049)		Whites (n=1058)		Blacks (n=991)	
	Proportion with outcome (# with outcome/# of subjects)	Adjusted PD ^a	Proportion with outcome (# with outcome/# of subjects)	Adjusted PD ^b	Proportion with outcome (# with outcome/# of subjects)	Adjusted PD ^b
Diabetes						
No	276/1606=0.17	Ref	130/881=0.15	Ref	146/725=0.20	Ref
Yes	90/443=0.20	0.00 (−0.04, 0.04)	32/177=0.18	0.00 (−0.07, 0.06)	58/266=0.22	0.00 (−0.05, 0.06)
BMI						
Normal	64/374 =0.17	Ref	20/172=0.12	Ref	44/202=0.22	Ref
Over-weight	140/881=0.16	−0.01 (−0.05, 0.03)	64/486=0.13	0.01 (−0.05, 0.07)	76/395=0.19	−0.02 (−0.00, 0.01)
Obese	162/794=0.20	0.04 (0.00, 0.09)	78/400=0.20	0.07 (0.01, 0.14)	84/394=0.21	0.01 (−0.06, 0.08)

^a Included diabetes, age in years, race, screening history, study site, education, and BMI^b Model included diabetes, age in years, screening history, study site, education, and BMI