Research Article

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Diabetes and Outcomes After Radical Prostatectomy: Are Results Affected by Obesity and Race? Results from the Shared Equal-Access Regional Cancer Hospital Database

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Abstract

Background: Diabetes is associated with lower prostate cancer risk. The association of diabetes with prostate cancer outcomes is less clear. We examined the association between diabetes and outcomes after radical prostatectomy and tested whether associations varied by race and/or obesity.

Materials and Methods: This study is a retrospective analysis of 1,262 men treated with radical prostatectomy between 1988 and 2008 within the Shared Equal-Access Regional Cancer Hospital database. We examined the multivariate association between diabetes at surgery and adverse pathology, biochemical recurrence (BCR), and prostate-specific antigen doubling time at recurrence using logistic, proportional hazards, and linear regression, respectively. Data were examined as a whole and stratified by race and obesity.

Results: Diabetes was more prevalent among black (22% versus 15%, $P < 0.001$) and more obese men ($P < 0.001$). Diabetes was associated with higher tumor grade (odds ratio, 1.73; $P = 0.002$), seminal vesicle invasion (odds ratio, 1.73; $P = 0.04$), but not BCR ($P = 0.67$) or PSADT at recurrence ($P = 0.12$). In the secondary analysis, among white obese men, diabetes was associated with 2.5-fold increased BCR risk ($P = 0.002$) and a trend toward shorter PSADT, whereas among all other men (nonobese white men and black men), diabetes was associated with 23% lower recurrence risk ($P = 0.09$) and longer PSADT ($P = 0.04$).

Conclusion: In a radical prostatectomy cohort, diabetes was not associated with BCR. In the secondary analysis, diabetes was associated with more aggressive disease in obese white men and less aggressive disease for all other subsets. If externally validated, these findings suggest that among men with prostate cancer, the association between diabetes and prostate cancer aggressiveness may vary by race and obesity. *Cancer Epidemiol Biomarkers Prev; 19(1); 9–17. ©2010 AACR.*

Introduction

Prostate cancer is the most common malignancy among men (1). Diabetes is also a major public health concern with nearly 25 million affected and 1.6 million new cases in 2007 alone (2). There is a general consensus that diabetes is associated with decreased prostate cancer risk (3). However, the influence of diabetes on prostate cancer outcomes is less studied. Among 2,780 men, Chan et al. (4) found that diabetes was not associated with biochemical recurrence (BCR) after radical prostatectomy, although there was a nonsignificant trend toward increased risk in men undergoing radiotherapy. In contrast, Smith et al. (5) found a nonsignificant trend toward lower prostate cancer–specific mortality risk [hazard ratio (HR), 0.80; 95% confidence interval (95% CI), 0.51-1.26] among diabetic men treated with radiation combined with short- or long-term hormonal therapy.

Black men in the United States have the highest prostate cancer incidence in the world (6). In addition, black race is associated with higher prostate-specific antigen (PSA) levels (7-9), higher grade disease (8, 9), and increased risk for BCR after radical prostatectomy (at least in some series; ref. 10), and prostate cancer–specific mortality (1). Obesity is similarly associated with increased risk of high-grade disease (11), BCR after radical prostatectomy (12-14), and prostate cancer mortality (15, 16). In addition, obesity is a strong risk factor for diabetes (17, 18), whereas black men bear a disproportionate burden of diabetes (12% versus 8%; ref. 2).

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Given that race and obesity are risk factors for both diabetes and aggressive prostate cancer, we sought to understand whether diabetes itself was associated with aggressive prostate cancer. To accomplish this, we sought to investigate the association between diabetes and outcomes after radical prostatectomy, a common treatment for early-stage prostate cancer. As radical prostatectomy entails complete removal of prostate, even slight increases in an accurate biomarker (PSA) can be used to detect cancer recurrence years before metastases are found (19, 20). Moreover, once the PSA starts to increase, the rapidity with which it increases, measured by the time it takes for the PSA to double (i.e., PSA doubling time or PSADT) can be used to predict the risk of cancer-specific death (21). Thus, time to recurrence and the PSADT can be used as intermediate end points of disease aggressiveness. Moreover, we believe that a radical prostatectomy cohort is a valuable population in which to study prostate cancer outcomes in the PSA-era, as BCR and PSADT provide valuable intermediate end points that can be accurately measured over several years rather than the decades needed when the outcome is prostate cancer death. As such, we specifically sought to examine whether diabetes was associated with adverse pathologic features, BCR, and short PSADT at recurrence among a racially diverse cohort undergoing radical prostatectomy. We hypothesized that the association between diabetes and aggressive disease may vary by either race and/or obesity, and thus, we performed analyses stratified by both race and obesity.

Materials and Methods

After obtaining Institutional Review Board approval from each institution, we combined data from patients undergoing radical prostatectomy between 1988 and 2008 at the Veterans Affairs Medical Centers in West Los Angeles and Palo Alto, California, Augusta, Georgia, and Durham, North Carolina into the Shared Equal-Access Regional Cancer Hospital database (10). Data about diabetic status at radical prostatectomy (yes versus no; and date of diabetes diagnosis if yes) were abstracted from clinical notes and were based on clinical diagnosis from a physician. Likewise, body mass index (BMI; height divided by weight squared) was abstracted from the preoperative medical records. All patients were followed with serial PSA determinations and clinical visits at intervals according to attending physician discretion. Typical follow-up including PSA values every 3 mo for the first year, every 4 mo for the next year, every 6 mo for the third year, and yearly thereafter. Patients were censored at the last date of a known PSA. For patients who died as assessed by the electronic medical records of the Veterans Affairs, the date of the last known PSA was used as the censoring date.

Within the Shared Equal-Access Regional Cancer Hospital database, patients treated with preoperative androgen deprivation or radiation were excluded. Of the 1,974 patients, those with missing data about diabetes status at surgery (n = 241), whose race was neither black nor white (n = 128 patients), or unknown (n = 8 patients) or missing BMI (n = 229 patients) were excluded. Men with unknown clinical stage (n = 60 patients), biopsy Gleason score (n = 22 patients), or PSA level (n = 24 patients) were also excluded, resulting in a study population of 1,262. A total of 22 patients (2%) had missing follow-up but were included in analyses evaluating diabetes and adverse pathology, but were excluded from analysis evaluating BCR. Thus, 98% had at least one postoperative PSA value.

BCR was defined as a single PSA of >0.2 ng/mL, two concentrations at 0.2 ng/mL, or secondary treatment for an elevated postoperative PSA. Men who received adjuvant treatment for an undetectable PSA were censored as not recurred at the time of treatment. PSADT at recurrence was calculated assuming first-order kinetics by dividing the natural log of 2 (0.693) by the slope of the linear regression line of the natural log of PSA over time. To be eligible to calculate PSADT, patients must have had a minimum of 2 PSA values, separated by at least 3 mo, and within 2 y after BCR. All PSA values within the first 2 y after BCR were used to calculate PSADT. For patients beginning salvage hormone or radiation therapy within this time, only PSA values before salvage therapy were used to compute PSADT. Patients with a PSADT of <0 (i.e., no increase/decline in PSA) or those with long PSADT (>100 mo; n = 35) were assigned a PSADT of 100 mo for ease of calculations.

Statistical Analysis

We explored differences in clinicopathologic characteristics by diabetes status using the rank-sum test for continuous variables and χ^2 test for categorical variables. We determined the odds ratio of the following adverse pathologic features associated with diabetes using a logistic regression analysis: high-grade disease (Gleason $\geq$7), positive margins, extracapsular extension, and seminal vesicle invasion. There were few men with lymph node metastasis. Analysis were adjusted for age (continuous), race (black versus white), BMI (kg/m^2; continuous), year of surgery (continuous), clinical stage (cT1 versus T2/3), biopsy Gleason score (2-6, 3 + 4, $\geq$4 + 3), center (categorical), and preoperative PSA (continuous). BMI and PSA were not normally distributed and were examined after logarithmic transformation.

Time to BCR was compared between men with and without diabetes at surgery using Kaplan-Meier plots and the log-rank test. To estimate the relative risk of progression associated with diabetes, we used a Cox proportional hazards model adjusted for the preoperative characteristics of age, race, BMI, year of surgery, clinical stage, biopsy Gleason score, center, and preoperative PSA.

We evaluated the association between diabetes and PSADT at recurrence using a linear regression. PSADT was modeled as a logarithmically transformed continuous

Table 1. Clinical characteristics of men at the time of radical prostatectomy stratified by presence or absence of diabetes

	Diabetic at surgery	Not diabetic at surgery	*P**
No. of patients (%)	233 (19)	1,029 (82)	
Age in years at surgery			0.82†
Mean ± SD	61.6 ± 5.5	61.4 ± 6.5	
Median (range)	62 (43-74)	61 (43-86)	
Median year of surgery	2003	2001	<0.001†
PSA in ng/mL			
Mean ± SD	7.9 ± 6.1	9.5 ± 9.0	0.01†
Median (range)	6.2 (0.9-59.3)	7.1 (0.1-140)	
Obesity in kg/m^2 no (%)			<0.001
Normal weight (<25)	38 (16)	280 (27)	
Overweight (25 to 29.9)	92 (39)	484 (47)	
Mildly obese (30 to 34.9)	71 (30)	196 (19)	
Moderately and severely obese (>35)	32 (14)	69 (7)	
Race no. (%)			0.003
White	103 (44)	567 (55)	
Black	130 (56)	462 (45)	
Biopsy Gleason Score no. (%)			0.07
2-6	128 (55)	650 (63)	
7	61 (26)	220 (21)	
8-10	44 (19)	159 (16)	
Clinical stage no. (%)			0.4
T1	137 (59)	573 (56)	
T2 and above	96 (41)	456 (44)	
Pathologic Gleason Score no. (%)			<0.001
2-6	59 (26)	416 (41)	
3 + 4	111 (48)	400 (39)	
≥4 + 3	61 (26)	205 (20)	
ECE no. (%)	51 (22)	194 (19)	0.3
SVI no. (%)	29 (13)	88 (9)	0.07
PSM no. (%)	110 (48)	447 (44)	0.3
LNI no. (%)	3 (1)	17 (2)	0.04

Abbreviations: ECE, extracapsular extension; SVI, seminal vesicle invasion; PSM, positive surgical margins; LNI, lymph node involvement.

*P value assessed by χ^2 test unless otherwise specified.

†P value assessed by rank sum test.

variable and results were adjusted for the preoperative features described above. The geometric mean was back transformed for ease of interpretation.

Given that we hypothesized the association between diabetes and outcome may vary as a function of obesity and race, we performed a secondary analysis by repeating all multivariate analyses stratified by both obesity and race. For these analyses, obesity was defined as a BMI of ≥30 kg/m^2. We tested for significant interactions in these analyses by introducing two interaction terms, one examining the interaction between diabetes and obesity and the other between diabetes and race, by including the cross-product term in the models along with both primary variables. For these analyses, obesity was defined as a BMI of ≥30 kg/m^2.

All statistical analyses were done using STATA 10.1 (Stata Corp.).

Results

A total of 47% of men were black (n = 592) and nearly one-third were obese (n = 368; 29%). Diabetes was significantly more prevalent among black (22%; n = 130) than white men (15%; n = 103; P = 0.003; Table 1). On the univariate analysis, diabetic men had significantly lower PSA levels (P = 0.01), had higher BMI (P < 0.001), were more likely to be treated recently (P < 0.001), and had higher

Table 2. Odds and 95% CI of adverse pathologic features stratified by race and obesity among men with diabetes at surgery

	No. total patients	No. diabetics	Odds ratio* (95% CI)	*P*	$P_{interaction}$ by race†	$P_{interaction}$ by obesity‡
High-grade disease						
Overall	1,262	233	1.73 (1.22-2.45)	0.002	0.17	
White	670	103	2.28 (1.33-3.91)	0.003		0.47
Nonobese	488	58	2.08 (1.07-4.05)	0.03		
Obese	182	45	2.52 (0.96-6.60)	0.06		
Black	592	130	1.45 (0.90-2.33)	0.13		0.88
Nonobese	406	72	1.48 (0.80-2.73)	0.21		
Obese	186	58	1.56 (0.71-3.44)	0.27		
ECE						
Overall	1,262	233	1.25 (0.85-1.83)	0.27	0.49	
White	670	103	0.93 (0.53-1.63)	0.81		0.94
Nonobese	488	58	1.04 (0.50-2.19)	0.91		
Obese	182	45	0.68 (0.27-1.70)	0.41		
Black	592	130	1.64 (0.94-2.85)	0.08		0.41
Nonobese	406	72	2.00 (1.02-3.94)	0.04		
Obese	186	58	1.25 (0.43-3.66)	0.68		
PSM						
Overall	1,262	233	1.11 (0.81-1.52)	0.50	0.3	
White	670	103	1.31 (0.82-2.10)	0.25		0.07
Nonobese	488	58	0.92 (0.50-1.71)	0.79		
Obese	182	45	2.07 (0.93-4.59)	0.08		
Black	592	130	1.01 (0.65-1.55)	0.98		0.32
Nonobese	406	72	0.86 (0.49-1.53)	0.61		
Obese	186	58	1.28 (0.63-2.59)	0.50		
SVI						
Overall	1,262	233	1.73 (1.04-2.90)	0.04	0.78	
White	670	103	1.44 (0.64-3.25)	0.38		0.35
Nonobese	488	58	1.16 (0.36-3.80)	0.80		
Obese	182	45	1.31 (0.37-4.66)	0.67		
Black	592	130	2.01 (1.02-3.99)	0.05		0.18
Nonobese	406	72	2.78 (1.21-6.40)	0.02		
Obese	186	58	0.93 (0.26-3.38)	0.92		

NOTE: Obesity was defined as a BMI of ≥30 kg/m^2.

*Adjusted for age, year of surgery, race, BMI, clinical stage, biopsy Gleason score (except analysis of high-grade disease), center, and preoperative PSA.

†$P_{interaction}$ by race assessed by including the cross-product term between diabetes and race in the model.

‡$P_{interaction}$ by obesity assessed by including the cross-product term between diabetes and obesity in the model.

radical prostatectomy tumor grade, ($P < 0.001$). There were trends, which did not reach significance, for diabetic men to have higher tumor grades at biopsy ($P = 0.07$) and more seminal vesicle invasion ($P = 0.07$). Extracapsular extension and positive margins were not associated with diabetes.

Diabetes and Adverse Pathologic Characteristics

Similar to univariate analysis above, when adjusted for multiple preoperative clinical features, diabetic men had over a 70% higher risk of high-grade disease ($P = 0.002$) and seminal vesicle invasion ($P = 0.04$; Table 2). As in univariate analysis, extracapsular extension and positive margins were not significantly associated with diabetes.

In the secondary analysis, when stratified by race, diabetes was more strongly associated with high-grade disease among white ($P = 0.003$) than black men ($P = 0.13$), although the interaction was not statistically significant ($P_{interaction} = 0.17$; Table 2). The associations between diabetes and other adverse features seemed similar between black and white men. When stratified by obesity, there were no significant interactions implying that the association between diabetes and adverse pathology was not significantly different between obese and nonobese men.

Diabetes and BCR

Mean and median follow up for men without BCR were 56 and 46 months, respectively. During this time, 401 men (32%) developed a BCR. Overall, there was no significant association between diabetes and BCR (log-rank, $P = 0.33$; Fig. 1). After adjusting for multiple preoperative characteristics, diabetes remained not significantly associated with BCR ($P = 0.67$; Table 3). However, when stratified by race in the secondary analysis, we observed that diabetes was associated with a trend toward increased BCR among white men [hazard ratio (HR), 1.28; $P = 0.28$] but a decreased risk among black men (HR, 0.79; $P = 0.26$), although neither trend was significant. The interaction between diabetes and race approached, but did not reach, significance ($P_{interaction} = 0.09$).

On further stratification by obesity categories, we found the increased recurrence risk associated with diabetes among white men was only in obese men. Specifically, among obese white men ($n = 182$; diabetic men, $n = 45$ or 25%), diabetes was associated with a 2.5-fold increased BCR risk ($P = 0.002$), whereas among nonobese white men ($n = 488$; diabetic men, $n = 58$ or 12%), diabetes was associated with a 31% reduced BCR risk ($P = 0.26$; Table 3). Among white men, the interaction between obesity and diabetes for predicting BCR was significant ($P_{interaction} = 0.006$). Among all subsets except obese white men (i.e., nonobese white men, nonobese black men, and obese black men; $n = 1,080$; diabetic men, $n = 188$ or 17%), diabetes was associated with a slightly reduced BCR risk (11-31% lower risk), although this did not reach significance in any single subset. When these three groups were combined (i.e., all men except obese white men), diabetes was associated with a 23% lower risk of BCR (HR, 0.77; 95% CI, 0.56-1.04; $P = 0.09$). The interaction between diabetes and patient group (white obese versus all others) for predicting BCR was significant ($P = 0.01$ with three degrees of freedom).

Diabetes and Aggressive Recurrence

Among 401 men with BCR, PSADT was calculable in 192 (48%). Among these 192 men, only 33 had diabetes at surgery. On univariate analysis, there was no significant association between PSADT and diabetes ($P = 0.18$). Similarly, after adjusting for multiple preoperative characteristics, there was no significant differences in mean adjusted PSADT among men with (23.4 months) or without (16.7 months) diabetes ($P = 0.12$; Table 4). When stratified by race in the secondary analysis, diabetes was associated with longer PSADT among black men ($P = 0.02$), but not white men ($P = 0.71$), although the test of interaction was not significant ($P = 0.11$). When the subjects were grouped as described above (i.e., black men combined with nonobese white men), diabetes was associated with a significantly longer PSADT (28.3 versus 17.0 months; $P = 0.04$), whereas among white obese men, PSADT tended to be shorter (11.0 versus 22.7 months), although this was not significant ($P = 0.24$) and there were only 10 white obese men with diabetes. The interaction between diabetes and patient group (white obese versus all others) for predicting PSADT was not significant ($P = 0.8$ with 3 degrees of freedom), although the number of men with diabetes in these analyses was small.

Diabetes Duration

To assess the influence of diabetes duration on our findings, we reran all multivariate models including diabetes coded as none versus <5 years versus ≥5 years of duration. We found that the general associations described above were similar for men regardless of diabetes duration. Specifically, there were no significant differences in the multivariate adjusted risk of any pathologic or biochemical end point between men with diabetes for <5 years versus men with diabetes for ≥5 years when the data were examined as a whole or in the secondary analyses stratified by race and obesity (all $P > 0.05$; data not shown).

Discussion

In a multi-institutional cohort treated with radical prostatectomy, overall, there was no significant association between diabetes and BCR. However, when stratified by obesity and race in the secondary analysis, diabetes was associated with *increased* recurrence risk among white obese men and a trend toward shorter PSADT, thereby suggesting that diabetes may be associated with more aggressive disease in this subset. In contrast, among all other subsets (i.e., black men and nonobese white men), diabetes was associated with a trend toward *decreased* recurrence risk and significantly longer PSADT, suggesting that diabetes may be associated with less aggressive disease in this subset. As this is the first study to examine racial and BMI differences in the association between diabetes and prostate cancer progression, these findings require validation. If confirmed, these findings may suggest that race and BMI modify the

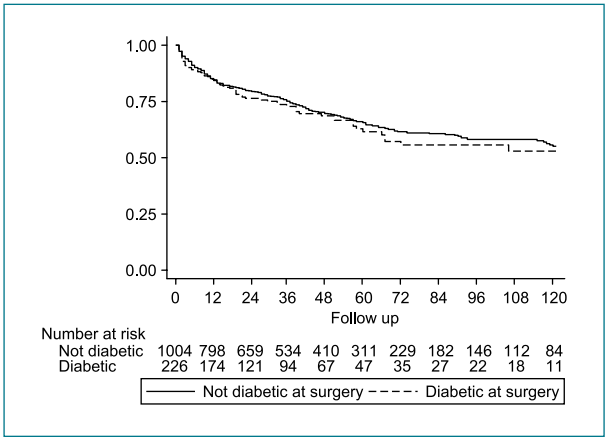

Figure 1. Kaplan-Meier estimates of PSA-free survival stratified by diabetic status at surgery.

Table 3. Relative risk and 95% CI of time to biochemical progression after radical prostatectomy among men with diabetes at surgery stratified by race and obesity

	No. total patients	No. diabetics	HR* (95% CI)	*P*	$P_{interaction}$ by race†	$P_{interaction}$ by obesity‡
Overall§	1,240	226	0.94 (0.72-1.23)	0.67	0.09	
White	659	99	1.24 (0.84-1.85)	0.28		0.006
Nonobese	479	55	0.69 (0.36-1.32)	0.26		
Obese	180	44	2.52 (1.40-4.54)	0.002		
Black	581	127	0.79 (0.55-1.14)	0.21		0.91
Nonobese	402	71	0.75 (0.45-1.25)	0.27		
Obese	179	56	0.89 (0.52-1.54)	0.68		

NOTE: Obesity was defined as a BMI $\geq$ 30 kg/m^2.

*Adjusted for age, year of surgery, race, BMI, clinical stage, biopsy Gleason score, center, and preoperative PSA.

†$P_{interaction}$ by race assessed by including the cross-product term between diabetes and race in the model.

‡$P_{interaction}$ by obesity assessed by including the cross-product term between diabetes and obesity in the model.

§Twenty-two men were missing follow-up and were not included in these analyses.

influence of diabetes on prostate cancer progression, perhaps giving novel insights into the mechanisms through which race, BMI, and diabetes affect prostate cancer growth.

Two meta-analyses found that diabetes was associated with 9% and 16% lower risk of prostate cancer diagnosis (3, 22). Although there is a general agreement that diabetes is associated with lower prostate cancer risk, few studies have explored the influence of pre-existing diabetes on prostate cancer outcomes after primary treatment. Chan et al. (4), among men treated with primary radiotherapy, found a nonsignificant trend for poorer outcomes among diabetic men ($P = 0.08$), which was attenuated after multivariate analysis. However, in stratified analysis, they found among men with low-risk disease or men ages <70 years that diabetes was associated with a significantly increased recurrence risk. When examining long-term outcomes, in a study of men with locally advanced prostate cancer undergoing radiation therapy with hormone treatment, diabetes was associated with a 2-fold increased risk for overall mortality, but a nonsignificant risk *reduction* (HR, 0.80; $P = 0.34$) in prostate cancer–specific mortality (5). This risk reduction, although nonsignificant, is similar to the 9% to 16% risk reduction for diabetes and prostate cancer diagnosis (3, 22).

The influence of diabetes on outcomes after radical prostatectomy is less studied. The Chan et al. (4) study reported that diabetes was not associated with BCR after radical prostatectomy. However, these men had a short follow-up (median, 2 years). Furthermore, other end points such as pathologic findings or PSADT were not presented. Our study had longer follow-up (median, 4 years) and included both pathologic findings and PSADT. We found that diabetes was associated with increased risk of high-grade disease and seminal vesicle invasion, which is novel and has not been reported previously. If verified in further studies, this may suggest that men with diabetes, at least among those who undergo radical prostatectomy, present with more aggressive and advanced disease. Interestingly, despite these higher risk features, our observations were similar to the findings of Chan et al. (4): we found no significant association between diabetes and BCR or PSADT. Thus, the preponderance of the literature to date suggests that in unstratified primary analysis, diabetes is not significantly related to disease progression after radical prostatectomy.

Centers for Disease Control and Prevention data show dramatic racial disparities in diabetes prevalence with 11.8% versus 7.5% of the black and white population affected, respectively (2). There are also more diabetic complications among blacks (23). Black men have the highest prostate cancer incidence and mortality rates (6) and are arguably higher risk for BCR (24). Similarly, obesity is a risk factor for both aggressive prostate cancer (13, 14, 25) and diabetes. Given that race and obesity are related to both aggressive prostate cancer and diabetes, we hypothesized the association between diabetes and prostate cancer progression may vary by race and obesity. No study to date has examined this.

To address this, we performed secondary analyses to assess whether race and obesity modify the overall null association between diabetes and prostate cancer aggressiveness. We found the association of diabetes with increased recurrence risk and a trend toward aggressive recurrence (shorter PSADT) was evident only in one subgroup—white obese men. In all other subgroups, diabetes was associated with lower recurrence risk and longer PSADT. Although no study has specifically studied this to date, some studies have tested for interactions between diabetes and prostate cancer diagnosis not finding any interactions with race (26, 27). However, these studies contained a limited number of black men, limiting the power to detect clinically important observations. Moreover, both meta-analyses examining diabetes and

prostate cancer risk did not test whether this association was modified by race, and given that the vast majority of studies included in these meta-analyses contained predominantly White men, the effect of diabetes on prostate cancer risk among Black men is largely unknown.

Although the current findings require external validation, if validated, they may have important implications. Specifically, in the secondary analysis, the current data suggest that race and obesity may modify the molecular pathways linking diabetes and aggressive prostate cancer. It is postulated that the molecular mechanism linking diabetes with lower prostate cancer risk is through lower serum levels of insulin, insulin-like growth factor (IGF-I), and testosterone (28). Thus, diabetes may be thought of as a growth factor–poor environment.

Although this growth factor–poor environment may reduce prostate cancer development, the effect on already established tumors is unclear. Moreover, by only studying men already diagnosed with prostate cancer, we are examining tumors that were able to grow despite this poor environment. As such, one could postulate that diabetes may actually be associated with more aggressive tumors among men with prostate cancer (i.e., their cancers could grow in this poor environment). Indeed, this would parallel the data for obesity in which there are fewer cases detected but an increased risk of aggressive tumors (29). Alternatively, one could postulate that this poor environment also reduces tumor progression/aggressiveness. In fact, we found evidence for both phenomena—significantly increased progression and trends toward more aggressive tumors in white obese men, and trends toward reduced progression and less aggressive recurrences among all others.

What remains unclear are the mechanisms underlying these interactions with race and obesity. However, this would suggest that among white obese men, the selection of more aggressive tumors predominated leading to increased progression. Of note, a prior study found that overweight and obese white men had lower free IGF-I levels than normal weight white men or black men (30). Perhaps, in obese white men, the compounded effects of lower free IGF-I *and* lower insulin from diabetes creates a *very* poor growth factor environment leading to selection pressure such that only aggressive tumors can survive. Among other patient subsets where IGF-I levels are generally higher, the reduced insulin levels of diabetes creates only a *mildly* growth factor–poor environment in which there is minimal selection for aggressive tumors, and yet this mildly poor environment is sufficient to reduce cancer progression. Ultimately, more detailed analysis of insulin, IGF-I, and testosterone levels among the various subsets of men defined by race and obesity are needed to better understand these clinical observations. Ideally, these factors should be analyzed both in cohorts of men without known prostate cancer as well as men with prostate cancer. Specifically, serum levels of these factors should be measured among men with known prostate cancer undergoing treatment, and should be followed to assess the complex association between diabetes, serum hormonal levels, obesity, race, and prostate cancer progression.

This study shares the shortcomings of all retrospective studies—selection bias, temporal changes in both disease and treatment modalities, and unknown confounders. Although diabetic men sometimes are discouraged from radical prostatectomy due to concerns about complications, the percentage of diabetic men was greater than the population prevalence, reflecting the increased comorbidities seen in a Veterans Affairs population. However, being a cohort of men treated with radical prostatectomy, the current population is likely to have

Table 4. Mean adjusted estimates and 95% CI of PSADT after recurrence among men with diabetes at surgery stratified by race and obesity

	No. of patients		Mean adjusted PSADT* (95% CI)		*P*	$P_{interaction}$ by race†	$P_{interaction}$ by obesity‡
	Total	Diabetic	Diabetic at surgery	Not diabetic at surgery			
Overall	192	33	23.4 (15.7-34.8)	16.7 (13.0-21.4)	0.12	0.11	
White	99	15	16.4 (8.8-30.3)	18.7 (12.8-27.3)	0.71		0.75
Nonobese	69	5	20.6 (7.4-57.5)	19.8 (12.7-30.9)	0.94		
Obese	30	10	11.0 (4.8-25.0)	22.7 (9.6-53.7)	0.24		
Black	93	18	29.3 (17.0-50.5)	14.9 (10.6-21.0)	0.02		0.87
Nonobese	61	11	42.5 (20.3-89.0)	21.6 (13.7-34.1)	0.06		
Obese	32	7	27.5 (11.3-67.1)	9.6 (6.0-15.3)	0.02		

NOTE: Using log-transformed PSADT as a continuous variable in a linear regression model. Obesity was defined as a BMI ≥ 30 kg/m^2.

*Adjusted for age, year of surgery, race, BMI, clinical stage, biopsy Gleason score, center, and preoperative PSA.

†$P_{interaction}$ by race assessed by including the cross-product term between diabetes and race in the model.

‡$P_{interaction}$ by obesity assessed by including the cross-product term between diabetes and obesity in the model.

had better-controlled diabetes with minimal complications relative to all men with diabetes. Likewise, the cohort consisted of men with early-stage disease. Thus, further study in men with more advanced disease or in those with poorly controlled diabetes is required. The use of multiple stratified analysis increases the chances for spurious associations. To account for this, in our interaction analysis between white obese men and the other groups, we used three degrees of freedom, wherein the interaction between group and diabetes with BCR remained statistically significant. We did not differentiate between type 1 (insulin dependent) and type 2 (noninsulin dependent) diabetes. However, because type 2 diabetes constitutes 90% to 95% of adult cases, it is unlikely that the lack of differentiation would markedly alter our findings (2). We found no difference in the association between diabetes and outcomes as a function of diabetes duration. In contrast, previous studies have noted that the risk of prostate cancer may vary by diabetes duration (26, 31, 32). This may be due to the fact that our study had fewer diabetic men compared with the aforementioned studies and therefore may not be powered enough to detect modest changes in effect sizes. We do not have the information on diabetes management regimens including the use of antidiabetic drugs such as metformin and insulin, and therefore, their influence on outcomes is unknown. Another key limitation is the lack of serum hormone data. Thus, we are unable to explore in further depth the possible mechanistic explanations for our findings. As such, the current results should be viewed as hypothesis generating and further studies as outlined above are needed to confirm these findings and to explore the underlying mechanisms for these observations. In agreement with prior data from the Shared Equal-Access Regional Cancer Hospital database (33), a sizable percentage of men who had a BCR did not have data to calculate PSADT, limiting our ability to detect important associations between diabetes and PSADT. Finally, we did not examine concrete end points such as metastases or prostate cancer mortality. Our end points were BCR and aggressive recurrence (i.e., PSADT): clinically relevant intermediate end points correlated with metastasis-free and prostate cancer–specific survival (21).

Conclusion

In a racially diverse multi-institutional cohort treated with radical prostatectomy, we found that diabetes was not associated with prostate cancer progression. However, in a stratified secondary analysis, we found that diabetes was associated with significantly increased BCR risk and shorter PSADT among obese white men but decreased risk of progression and aggressive recurrence in all other subgroups (nonobese white men and black men). To our knowledge, this is the first study to examine the association of diabetes and prostate cancer outcome as a function of obesity and race. Thus, these findings require verification in external data sets. If verified, these findings may further our understanding of how diabetes, race, and obesity influence prostate cancer outcomes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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