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Diabetes and Outcomes after Radical Prostatectomy – Are Results Affected by Obesity and Race? Results from the SEARCH Database

The SEARCH Database Study Group, **Jayakrishnan Jayachandran**[1,2], **William J. Aronson**[3,4], **Martha K. Terris**[5,6], **Joseph C. Presti Jr.**[7,8], **Christopher L. Amling**[9], **Christopher J. Kane**[10], and **Stephen J. Freedland**[1,2]

[1]Division of Urologic Surgery, Departments of Surgery and Pathology, and the Duke Prostate Center, Duke University School of Medicine, Durham, NC

[2] Urology Section, Veterans Affairs Medical Center Durham, NC

[3]Urology Section, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA

[4]Department of Urology, University of California, Los Angeles School of Medicine, Los Angeles, CA

[5]Urology Section, Veterans Affairs Medical Center Augusta, GA

[6]Section of Urology, Medical College of Georgia, Augusta, GA

[7]Department of Urology, Stanford University School of Medicine, Palo Alto, CA

[8]Urology Section, Veterans Affairs Medical Center Palo Alto, CA

[9]Division of Urology, Oregon Health & Science University, Portland, OR

[10]Division of Urology, University of California, San Diego School of Medicine, San Diego, CA

Abstract

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

Materials and Methods: A retrospective analysis of 1262 men treated with RP between 1988 and 2008 within the SEARCH Database. We examined multivariate association between diabetes at surgery and adverse pathology, biochemical recurrence (BCR) and PSA doubling time (PSADT) 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% vs. 15%, p<0.001) and more obese men (p<0.001). Diabetes was associated with higher tumor grade (OR 1.73, p=0.002), seminal vesicle invasion (OR 1.73, p=0.04), but not BCR (p=0.67) or PSADT at recurrence (p=0.12). In secondary analysis, among white obese men, diabetes was associated with 2.5- fold increased BCR risk (p=0.002) and a trend towards shorter PSADT whereas among all other men (non-obese white men and black men), diabetes was associated with 23% lower recurrence risk (p=0.09) and longer PSADT (p=0.04).

Reprint requests to Division of Urology, Box 2626 DUMC, Duke University School of Medicine, Durham, NC 27710; phone (919) 668-8361; fax (919) 668-7093; steve.freedland@duke.edu. (Dr Freedland)..

Conclusion: In a RP cohort, diabetes was not associated with BCR. In 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 PC, the association between diabetes and PC aggressiveness may vary by race and obesity.

Keywords

Prostate cancer; diabetes; obesity; race; radical prostatectomy; biochemical recurrence; PSADT

Introduction

Prostate cancer (PC) 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 diabetes is associated with decreased PC risk.(3) However, the influence of diabetes on PC outcomes is less studied. Among 2,780 men, Chan et al. found diabetes was not associated with biochemical recurrence (BCR) after radical prostatectomy (RP) though there was a non-significant trend towards increased risk in men undergoing radiotherapy.(4) In contrast, Smith et al. found a non-significant trend toward lower PC-specific mortality risk (HR=0.80, 95% CI 0.51-1.26) among diabetic men treated with radiation combined with short-term or long-term hormonal therapy.(5)

Black men in the United States have the highest PC incidence in the world.(6) Also, black race is associated with higher PSA levels,(7-9) higher-grade disease,(8,9) and increased risk for BCR after RP (at least in some series),(10) and PC-specific mortality.(1) Obesity is similarly associated with increased risk of high-grade disease,(11) BCR after RP,(12-14) and PC mortality.(15,16) Also, obesity is a strong risk factor for diabetes,(17,18) while black men bear a disproportionate burden of diabetes (12% vs. 8%).(2)

Given race and obesity are risk factors for both diabetes and aggressive PC, we sought to understand whether diabetes itself was associated with aggressive PC. To accomplish this, we sought to investigate the association between diabetes and outcomes after RP, a common treatment for early-stage prostate cancer. As RP entails complete removal of prostate, even slight rises 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 rise, the rapidity with which it rises, 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 an RP 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 pathological features, BCR, and short PSADT at recurrence among a racially diverse cohort undergoing RP. We hypothesized 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 RP between 1988 and 2008 at the Veterans Affairs (VA) Medical Centers in West Los Angeles and Palo Alto, California, Augusta, Georgia, and Durham, North Carolina into the Shared Equal Access Regional Cancer Hospital (SEARCH) database.(10) Data regarding diabetic status at RP (yes vs. no; and date of diabetes diagnosis if yes) were

abstracted from clinical notes and based upon clinical diagnosis from a physician. Likewise, BMI (height divided by weight squared) was abstracted from the pre-operative 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 months for the first year, every 4 months for the next year, every 6 months for the 3rd 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 VA, the date of the last known PSA was used as the censoring date.

Within SEARCH, patients treated with preoperative androgen deprivation or radiation were excluded. Of the 1974 patients, those with missing data regarding diabetes status at surgery (n=241), whose race was neither black nor white (n=128 patients) or unknown (n=8 patients) or missing body mass index (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 1262. 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 post-operative PSA value.

BCR was defined as a single PSA >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 months, and within 2 years after BCR. All PSA values within the first 2 years 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 <0 (i.e., no increase/decline in PSA) or those with long PSADT (>100 months, n=35) were assigned a PSADT of 100 months for ease of calculations.

Statistical Analysis

We explored differences in clinicopathological characteristics by diabetes status using the ranksum test for continuous variables and chi-squared test for categorical variables. We determined the odds ratio (OR) of the following adverse pathological features associated with diabetes using a logistic regression analysis: high-grade disease (Gleason ≥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 vs. white), BMI (kg/m^2; continuous), year of surgery (continuous), clinical stage (cT1 vs. T2/3), biopsy Gleason score (2−6, 3+4, ≥4+3), center (categorical), and pre-operative 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 (RR) of progression associated with diabetes, we used a Cox proportional hazards model adjusted for the pre-operative characteristics of age, race, BMI, year of surgery, clinical stage, biopsy Gleason score, center, and pre-operative PSA.

We evaluated the association between diabetes and PSADT at recurrence using a linear regression. PSADT was modeled as a logarithmically transformed continuous variable and results were adjusted for the preoperative features described above and the geometric mean was back-transformed for ease of interpretation.

Given we hypothesized the association between diabetes and outcome may vary as a function of obesity and race, we performed secondary analysis by repeating all multivariate analyses stratified by both obesity and race. For these analyses, obesity was defined as BMI ≥ 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 ≥30 kg/m^2.

All statistical analyses were performed using STATA 10.1 (Stata Corp., College Station, TX).

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 univariate analysis, diabetic men had significantly lower PSA levels (p=0.01), higher BMI (p<0.001) were more likely to be treated recently (p<0.001), had higher RP tumor grade, (p<0.001), and more lymph node involvement (p=0.04). 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 pathological characteristics

Similar to univariate analysis above, when adjusted for multiple pre-operative 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 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), though the interaction was not statistically significant (p-interaction=0.17, table 2). The associations between diabetes and other adverse features appeared similar between black and white men. When stratified by obesity, there were no significant interactions implying the association between diabetes and adverse pathology was not significantly different between obese and non-obese 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) (Figure 1). After adjusting for multiple pre-operative characteristics, diabetes remained not significantly associated with BCR (p=0.67) (Table 3). However, when stratified by race in secondary analysis, we observed diabetes was associated with a trend towards increased BCR among white men (HR 1.28, p=0.28) but a decreased risk among black men (HR 0.79, p=0.26), though neither trend was significant. The interaction between race and obesity 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) while among non-obese 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. non-obese white men,

non-obese black men, and obese black men) (n=1080; diabetic men, n=188 or 17%), diabetes was associated with a slightly reduced BCR risk (11-31% lower risk), though 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 vs. 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 secondary analysis, diabetes was associated with longer PSADT among black men (p=0.02), but not white men (p=0.71), though the test of interaction was not significant (p=0.11). When the subjects were grouped as described above (i.e. black men combined with non-obese white men), diabetes was associated with a significantly longer PSADT (28.3 vs. 17.0 months, p=0.04) whereas among white obese men PSADT tended to be shorter (11.0 vs. 22.7 months) though this was not significant (p=0.24), though there were only 10 white obese men with diabetes. The interaction between diabetes and patient group (white obese vs. all others) for predicting PSADT was not significant (p=0.8 with 3 degrees of freedom), though 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 vs. <5 years vs. ≥ 5 year 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 pathological or biochemical end-point between men with diabetes <5 years vs. ≥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 RP, overall there was no significant association between diabetes and BCR. However, when stratified by obesity and race in secondary analysis, diabetes was associated with *increased* recurrence risk among white obese men and a trend toward shorter PSADT, thereby suggesting diabetes may be associated with more aggressive disease in this subset. In contrast, among all other subsets (i.e. black men and non-obese white men) diabetes was associated with a trend toward *decreased* recurrence risk and significantly longer PSADT, suggesting 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 PC progression, these findings require validation. If confirmed, these findings suggest race and BMI modify the influence of diabetes on PC progression perhaps giving novel insights into the mechanisms through which race, BMI, and diabetes affect PC growth.

Two meta-analyses found diabetes was associated with 9% and 16% lower risk of PC diagnosis. (3,22) While there is general agreement diabetes is associated with lower PC risk, few studies have explored the influence of pre-existing diabetes on PC outcomes after primary treatment. Chan et al., among men treated with primary radiotherapy, found a non-significant trend for poorer outcomes among diabetic men (p=0.08), which was attenuated after multivariate

analysis.(4) However, in stratified analysis, they found among men with low-risk disease or men <70 years old, diabetes was associated with a significantly increased recurrence risk. When examining long-term outcomes, in a study of men with locally advanced PC undergoing radiation therapy with hormone treatment, diabetes was associated with a 2-fold increased risk for overall mortality, but a non-significant risk *reduction* (HR 0.80, p=0.34) in PC-specific mortality.(5) This risk reduction, though non-significant, is similar to the 9-16% risk reduction for diabetes and PC diagnosis.(3,22)

The influence of diabetes on outcomes after RP is less studied. The Chan et al. study reported diabetes was not associated with BCR after RP.(4) However, these men had a short follow-up (median 2 years). Furthermore, other end-points such as pathological findings or PSADT were not presented. Our study had longer follow-up (median 4 years) and included both pathological findings and PSADT. We found 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 RP, present with more aggressive and advanced disease. Interestingly, despite these higher-risk features, our observations were similar to the findings of Chan et al: 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 significant related to disease progression after RP.

Centers for Disease Control and Prevention data demonstrate 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 PC incidence and mortality rates(6) and are arguably higher risk for BCR.(24) Similarly, obesity is a risk-factor for both aggressive PC,(13,14,25) and diabetes. Given race and obesity are related to both aggressive PC and diabetes, we hypothesized the association between diabetes and PC 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 PC aggressiveness. We found the association of diabetes with increased recurrence risk and a trend towards aggressive recurrence (shorter PSADT) was evident only in one sub-group – white obese men. In all other subgroups, diabetes was associated with lower recurrence risk and longer PSADT. While no study has specifically studied this to date, some studies have tested for interactions between diabetes and PC diagnosis not finding any interactions with race.(26,27) However, these studies contained limited number of black men, limiting power to detect clinically important observations. Moreover, both meta-analyses examining diabetes and PC risk did not test whether this association was modified by race and give that the vast majority of studies included in these meta-analyses contained predominantly CM, the effect of diabetes on PC risk among AAM is largely unknown.

Though the current findings require external validation, if validated, they may have important implications. Specifically, in secondary analysis, the current data suggest race and obesity may modify the molecular pathways linking diabetes and aggressive PC. It is postulated the molecular mechanism linking diabetes with lower PC risk is via lower serum levels of insulin, insulin-like growth factor (IGF-1), and testosterone.(28) Thus, diabetes may be thought of as a growth-factor poor environment.

While this growth-factor poor environment may reduce PC development, the effect on already established tumors is unclear. Moreover, by only studying men already diagnosed with PC, we are examining tumors which were able to grow despite this poor environment. As such, one could postulate diabetes may actually be associated with more aggressive tumors among men

with PC (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 overweight and obese white men had lower free IGF-1 levels than normal weight white men or black men.(30) Perhaps, in obese white men, the compounded effects of lower free IGF-1 *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-1 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-1, 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 PC as well as men with PC. Specifically, serum levels of these factors should be measured among men with known PC undergoing treatment and followed to assess the complex association between diabetes, serum hormonal levels, obesity, and race and PC progression.

This study shares the shortcomings of all retrospective studies – selection bias, temporal changes in both disease and treatment modalities and unknown confounders. Though diabetic men sometimes are discouraged from RP due to concerns about complications, the percentage of diabetic men was greater than the population prevalence, reflecting the increased comorbidities seen in a VA population. However, being a cohort of men treated with RP, the current population is likely to have 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 (non-insulin dependent) diabetes. However, since Type 2 diabetes constitutes 90-95% of adult cases, it is unlikely 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 the risk of PC may vary by diabetes duration.(26,31,32) This may be due to the fact that our study had fewer diabetic men compared to the aforementioned studies and therefore may not be powered enough to detect modest changes in effect sizes. We do not have 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 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 SEARCH 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 like metastases or PC mortality. Our end-points were BCR and aggressive recurrence (i.e. PSADT): clinically

relevant intermediate end-points correlated with metastasis-free and PC-specific survival. (21)

Conclusion

In a racially diverse multi-institutional cohort treated with RP, we found diabetes was not associated with PC progression. However, in stratified secondary analysis, we found 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 (non-obese white men and black men). To our knowledge, this is the first study to examine the association of diabetes and PC outcome as a function of obesity and race. Thus, these findings require verification in external datasets. If verified, these findings may further our understanding of how diabetes, race and obesity influence PC outcomes.

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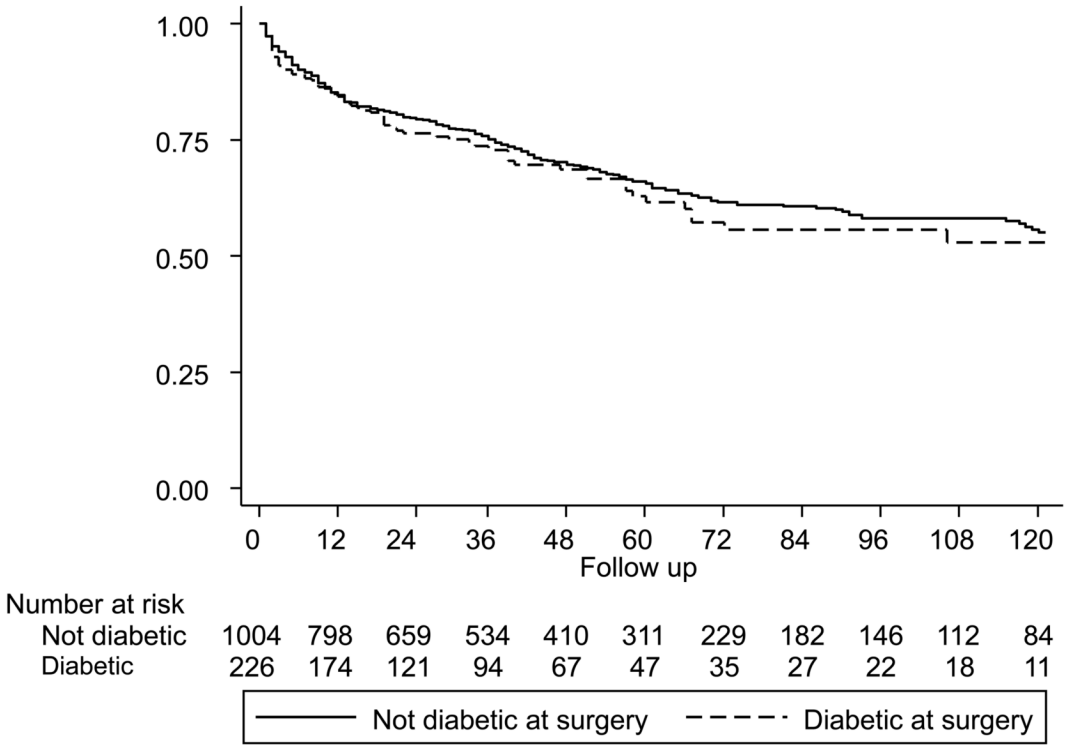

Figure 1.
Kaplan-Meier estimates of PSA-free survival stratified by diabetic status at surgery.

Table 1

Clinical characteristics of men with diabetes at the time of radical prostatectomy stratified by race and obesity categories

	Diabetic at surgery	Not diabetic at surgery	p value*
No of patients (%)	233 (19)	1029 (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)	
Pathological 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 (34)	17 (26)	0.04

ECE – extracapsular extension, PSM – positive surgical margins SVI – seminal vesicle invasion LNI – lymph node involvement

*p value assessed by chi squared test unless otherwise specified

†p value assessed by rank sum test

Table 2

Odds and 95% CI of adverse pathological 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	1262	233	1.73 (1.22 - 2.45)	0.002	0.17	
White	670	103	2.28 (1.33 - 3.91)	0.003		0.47
Non Obese	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
Non Obese	406	72	1.48 (0.80 - 2.73)	0.21		
Obese	186	58	1.56 (0.71 - 3.44)	0.27		
ECE						
Overall	1262	233	1.25 (0.85 - 1.83)	0.27	0.49	
White	670	103	0.93 (0.53 - 1.63)	0.81		0.94
Non Obese	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
Non Obese	406	72	2.00 (1.02 - 3.94)	0.04		
Obese	186	58	1.25 (0.43 - 3.66)	0.68		
PSM						
Overall	1262	233	1.11 (0.81 - 1.52)	0.50	0.3	
White	670	103	1.31 (0.82 - 2.10)	0.25		0.07
Non Obese	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
Non Obese	406	72	0.86 (0.49 - 1.53)	0.61		
Obese	186	58	1.28 (0.63 - 2.59)	0.50		
SVI						
Overall	1262	233	1.73 (1.04 - 2.90)	0.04	0.78	
White	670	103	1.44 (0.64 - 3.25)	0.38		0.35
Non Obese	488	58	1.16 (0.36 - 3.80)	0.80		

	No. total patients	No. diabetics	Odds Ratio** (95% CI)	p	p – interaction: by race†	p – interaction: by obesity††
Obese	182	45	1.31 (0.37 - 4.66)	0.67		
Black	592	130	2.01 (1.02 - 3.99)	0.05		0.18
Non Obese	406	72	2.78 (1.21 - 6.40)	0.02		
Obese	186	58	0.93 (0.26 - 3.38)	0.92		

ECE – extracapsular extension, PSM – positive surgical margins SVI – seminal vesicle invasion

*Obesity was defined as a BMI ≥ 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 pre-operative 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 obesity and race in the model

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	Hazard Ratio† (95% CI)	p	p – interaction by race††	p – interaction by obesity†††
Overall**	1240	226	0.94 (0.72 - 1.23)	0.67	0.09	
White	659	99	1.24 (0.84 - 1.85)	0.28		0.006
Non obese	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
Non obese	402	71	0.75 (0.45 - 1.25)	0.27		
Obese	179	56	0.89 (0.52 - 1.54)	0.68		

*Obesity was defined as a BMI $\geq$ 30 kg/m^2

**22 men were missing follow-up and not included in these analyses

†Adjusted for age, year of surgery, race, BMI, clinical stage, biopsy Gleason score, center, and pre-operative 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 obesity and race in the model

Table 4

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

	No. Patients		Mean adjusted PSADT † (95% CI)		p		
	Total	Diabetic	Diabetic at surgery	Not diabetic at surgery		p – interaction by race††	P – interaction by obesity‡
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
Non obese	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
Non obese	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		

*Using log transformed PSA doubling time as a continuous variable in a linear regression model

**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 pre-operative 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 obesity and race in the model