Hyperglycemia and prostate cancer recurrence in men treated for localized prostate cancer

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ABSTRACT:

Introduction: Obesity is consistently linked with prostate cancer (PCa) recurrence and mortality although the mechanism is unknown. Impaired glucose regulation, which is common among obese individuals, has been hypothesized as a potential mechanism for PCa tumor growth. In this study we explore the relationship between serum glucose at time of treatment and risk of PCa recurrence following initial therapy.

Methods: The study group was comprised of 1,734 men treated with radical prostatectomy (RP) or radiation therapy (RT) for localized PCa between 2001-2010. Serum glucose levels closest to date of diagnosis were determined. PCa recurrence was determined based on PSA progression (nadir PSA + 2 for RT; PSA ≥ 0.2 for RP) or secondary therapy. Multivariate Cox regression was performed to determine whether glucose level was associated with BCR after adjusting for age, race, BMI, comorbidity, diagnosis of diabetes, Gleason Sum, PSA, treatment, and treatment year.

Results: Recurrence was identified in 16% of men over a mean follow-up period 41 months (range 1 – 121 months). Those with elevated glucose (≥ 100 mg/dL) had a 50% increased risk of recurrence (HR 1.5, 95% CI: 1.1-2.0) compared to those with a normal glucose level (< 100 mg/dL). This effect was seen in both those undergoing RP (HR 1.9, 95% CI 1.0–3.6) and those treated with RT (HR 1.4, 95% CI 1.0-2.0).

Conclusion: Glucose levels at the time of PCa diagnosis are an independent predictor of PCa recurrence for men undergoing treatment for localized disease.

INTRODUCTION:

Obesity appears to confer an increased risk of prostate cancer (PCa) specific mortality.[1-6] Considering the epidemic of obesity in the United States, understanding mechanisms between obesity and poor cancer prognosis holds great promise for improving patient outcomes. One potential link is impaired glucose regulation, which is a precursor to Type II diabetes mellitus (DM), a commonly co-occurring condition with obesity.[7, 8]

There are several pathways by which alterations in glucose metabolism may lead to cancer progression. Glucose is required for cancer cells for growth,[9] and cancer cells are known to use more glucose than non-cancerous cells. Hyperglycemia leads to elevated insulin levels, and the activation of the insulin/insulin-like growth factor (IGF) pathway has been implicated in PCa growth though positive effects on cellular proliferation and anti-apoptosis.[10] Hyperglycemia also leads to the production of advanced glycosylated end products[11] with resultant oxidative stress which can lead to DNA damage. Finally, chronic inflammation is seen with DM and the metabolic syndrome and results in release of several cytokines that can promote tumor growth.[12]

Although a diagnosis of DM (self-reported or by diagnosis code) has been associated with poor PCa outcomes in some studies, this finding has not been consistent.[13-15] These mixed findings may be due to imprecision in assessment of DM, which typically uses of a diagnostic code and does not adequately describe the severity of DM within an individual. Limited work investigated hemoglobin A1C (HbA1C)[14, 16] levels as more specific measures of severity of DM and glucose control. Whereas HbA1C levels are

typically only obtained for patients with DM, glucose is a commonly collected test that is more widely available for analyses. Studies in breast and colon cancer have found that higher blood glucose levels are associated with a greater risk of disease progression,[17-19] although such studies have not been performed in PCa. We hypothesize that impaired glucose regulation, represented by higher serum glucose levels, is associated with a higher risk of recurrence after primary PCa treatment. In this study we explore the relationship between serum glucose at time of PCa diagnosis and risk of biochemical recurrence (BCR) for men with localized PCa undergoing primary therapy.

METHODS:

Data source:

The Northwest Veterans Integrated Services Network (VISN 20) electronic medical record was used to identify eligible men with PCa. VISN 20 encompasses Washington, Oregon, Alaska, Idaho, western Montana and northern California and includes 7 primary medical centers and 27 community-based outpatient clinics. VISN 20 uses a shared regional electronic medical record system and the data for this study were extracted from the VISN20 regional data warehouse, a system of relational databases that pulls nearly 100% of the information contained in the electronic medical record (including clinic appointments, inpatient stays, pharmacy records, laboratory values, pathology reports, imaging tests, and vital measures).[20, 21] Institution review board approval was obtained.

Study population:

We identified men diagnosed with localized prostate cancer during the years 2001 – 2010 who were treated with either radical prostatectomy (RP) or radiation therapy (RT) in the form of brachytherapy or external beam radiation therapy. We excluded men treated with active surveillance/watchful waiting and men with distant metastases at diagnosis. We also excluded men who received primary androgen deprivation therapy (ADT) or long-term continuous ADT as part of their primary treatment as ADT impacts glucose regulation.[22] In order to ensure that complete follow-up would be likely within the VA system, we included only those men who had an established relationship with a primary care provider in VISN20 prior to diagnosis and had a previously assessed PSA value measured within the network.

Data collection and coding:

The primary exposure of interest was serum glucose closest to date of diagnosis. Diabetes mellitus (DM) was coded based on provider recorded ICD9 diagnosis codes in the 12 month period prior to diagnosis. Recurrence following RP was defined as any PSA 6 months or more after surgery ≥ 0.2 ng/mL (after achieving an undetectable PSA post-RP). For RT patients, PSA recurrence was defined by nadir PSA + 2.0 ng/mL. Initiation of salvage therapy was also considered as evidence of progression (salvage RT, salvage RP or salvage ADT). Salvage RT was defined as radiation received > 1 year after primary treatment date. Several covariates were also identified from the EMR including demographic characteristics (age, race), clinical measures (body mass index (BMI), Charlson Comorbidity Index[23] scores in the 12 month period prior to diagnosis) and tumor characteristics (year of diagnosis, Gleason score, clinical stage (available for all subjects), and pathologic stage (available for subjects treated with RP)).

Statistical analysis:

Descriptive statistics, including Chi-square tests, were conducted to compare demographic and clinical characteristics by initial treatment and by glucose level. Glucose level was analyzed using three different approaches. First, quartiles of glucose were determined and the lowest quartile served as the referent group. Second, the categories established by the American Diabetes Association (ADA) for normal (< 100 mg/dL) impaired glucose (100 – 125 mg/dL) and diabetes (> 125 mg/dL) were used with the normal category serving as the referent group. Finally, a binary analysis was

performed using the normal ADA glucose level as the cutoff (< 100 mg/dL vs. ≥ 100 mg/dL). All three approaches are reported. Patients who may have moved or stopped using VA care were censored at the end of the calendar year of their last visit if they had no VA utilization in the subsequent calendar year. Multivariate Cox proportional hazards regression was performed adjusting for all covariates above (*age, race, BMI, Charlson Comorbidity Index, year of diagnosis, treatment type, Gleason score and tumor stage)* included in the analysis. The proportional hazards assumption was assessed by examining the slope of the Schoenfeld residuals. Models including all patients and stratified by treatment were performed. Effect modification by treatment and by the National Comprehensive Cancer Network (NCCN®) risk strata[24] were evaluated with the likelihood ratio test comparing the full model (with the interaction term) to the reduced model. Two additional analyses were performed: first, excluding those with a clinical diagnosis of DM and/or a glucose level which would qualify for the diagnosis of DM by the ADA (> 125 mg/dL); and second, excluding patient with high risk disease who did not received concomitant ADT as this may impact risk of disease recurrence. All statistical analyses were conducted using STATA software, Version 12 (Stata, Inc., College Station, TX).

RESULTS:

A total of 1,734 men were identified during the study period undergoing treatment with either RP (n = 722) or RT (n = 1,012). Table 1 presents the demographic and pathologic features of these men by disease recurrence status. As expected, pathologic factors (PSA, Gleason and stage were highly associated with recurrence. Several differences between men undergoing RP or RT were identified (data not shown). Men treated with RT were older (15% vs. 1% over age 75, $p<0.001$) had higher Charlson Comorbidity scores ($p<0.001$) and were more likely to have been diagnosed with DM prior to diagnosis ($p<0.001$). Men receiving RT had higher pretreatment PSA values compared to the RP group (35% ≥ 10 ng/mL vs. 19%, $p<0.001$). The median follow-up time was 41 months (range 1 – 121 months). Recurrence was observed in 281 men (16%). Cumulative recurrence was similar following RT (15%) and surgery (17%). Recurrence events occurred in 7%, 14% and 33% of low, intermediate and high risk cases (as defined by the National Comprehensive Cancer Network (NCCN®)),[24] respectively.

Table 2 shows the distribution of demographic and pathologic features by different ADA glucose levels. A total of 514 (30%), 623 (36%) and 597 (34%) had glucose levels of < 100, 100-125 and > 125 mg/dL, respectively. Men in the highest glucose category were more commonly obese, with higher Charlson scores and having a diagnosis of diabetes mellitus (all $p < 0.001$). Gleason sum scores of 7-10 were more common in the highest category of glucose (68%) compared to 57% and 59% for the lower two categories, respectively ($p = 0.001$). Similarly, higher clinical stage (T2b-T3) was more common in those with glucose > 125 mg/dL (23%) than those with lower glucose levels (16 and 17%

respectively, p = 0.04). Surgery was more common in those with the highest glucose levels.

The hazard ratios (HR) and 95% CI for risk of recurrence by quartile of glucose level are presented in Table 3 for the entire cohort. The lowest quartile (range 31 – 98 mg/dL) served as the referent group in the multivariate analysis adjusting for age, race, BMI, diagnosis of DM, treatment type and year of treatment, stage, Gleason and Charlson Score. In the overall cohort, we observed a modest trend in increased risk (range 35 – 57%) of recurrence for each of the glucose quartiles compared to the lowest quartile, although this was not significant. There was no evidence for effect modification by treatment or NCCN risk category (both likelihood ratio test p-value > 0.6). In the RP group, all three higher quartiles had a more than 2-fold increased risk of recurrence compared to the lowest quartile, with p-values ranging from 0.01 to 0.04, data not shown). In the RT group, there were non-significant differences in risk of recurrence with higher glucose levels (range 18 – 48%). The risk of recurrence by the three ADA glucose categories is presented in Table 4 along with dichotomous ADA categories. In the entire cohort, those with an abnormal glucose (> 100mg/dL) had a 46% increased risk of recurrence (HR: 1.46: 95% CI 1.09 – 1.95). This observed risk was present in both the RP group (HR 1.91, 95% CI 1.03 – 3.55) and the RT group (HR 1.42, 95% CI 1.00 – 2.01). Excluding those with either a clinical diagnosis of DM or a serum glucose which would qualify for the diagnosis of DM by the ADA (> 125 mg/dL) did not change the results. In that analysis including both RP and XRT patients, having a glucose of 100-

125 mg/dL was associated with a 44% increased risk of recurrence compared to those with a normal glucose level (HR 1.41, 95% CI 1.01 –1.97).

DISCUSSION:

In this study, we found that men with elevated glucose levels at the time of PCa diagnosis have a greater risk of PCa recurrence following primary treatment compared to men with a normal glucose level. Considering the growing obesity epidemic and the consistent relationship between obesity and adverse PCa outcomes,[7, 8] these findings are important in helping to identify modifiable risk factors for men undergoing treatment for newly diagnosed PCa.

Glucose and cancer outcomes have been evaluated in breast and colorectal cancer.[17-19, 25] In a study of 202 women with breast cancer, there was a similar increased risk of recurrence in the 2nd (HR 1.9, 95% CI 1.1-3.2) and 3rd (HR 1.8 (95% CI 1.0-3.1) tertiles compared to the lowest tertile.[17] In colorectal cancer, those with the highest quartile of glucose (HR 1.8, 95% CI 1.1-3.1)[19] or post load plasma glucose (HR 1.6, 95% CI 1.1-2.4)[18] had higher risk of disease-specific mortality compared to those in the lowest quartile. These studies support the role of abnormal glucose regulation and cancer outcomes.

Small studies have evaluated serum biomarkers of glucose regulation and PCa. In a study of 89 men with DM treated with RP, a higher HbA1C pre-operatively was associated with the risk of extracapsular disease (pT3) and higher Gleason grade (≥ 7).[26] In another study of 247 men undergoing RP, HbA1C levels pre-operatively were associated with higher Gleason grade ($p = 0.001$).[16] Higher HbA1C levels were associated with a non-significant risk of recurrence: compared to those with HbA1C <

6.3, the HR for men with HbA1C of 6.3-7.7 and ≥ 7.8 was 1.5 (95% CI 0.8-2.6) and 1.3 (0.7-2.4), respectively.[16] Both of these studies are limited by their small size and only including men with DM. Studies have found associations between insulin levels and PCa-specific mortality.[1, 27] In one study, a higher mean fasting insulin level at diagnosis was found in those who died of PCa.[27] In a second study, levels of C-peptide (an insulin surrogate) were determined from PCa cases from the Physicians Health Study.[1] Those in the highest C-peptide quartile had a more than 2-fold increased risk of PCSM (HR 2.4, 95% CI 1.3 – 4.3) compared to those in the lowest C-peptide quartile. We do not have insulin or C-peptide levels available in our study and thus rely on serum glucose levels as an indicator of an individual's glucose regulation.

The present analysis is the first to specifically evaluate glucose levels and outcomes in men with PCa. We found that men with an elevated glucose at the time of PCa diagnosis had an almost 50% increased risk of PCa recurrence even after adjusting for clinical and pathologic factors. Whether it is hyperglycemia, or subsequent elevated levels of insulin/IGF, which affect tumor recurrence cannot be determined from this study. Studies have not found a significant relationship between the diagnosis of DM (self-reported or diagnosis code)[13-15] and PCa recurrence, but the diagnosis of DM may not reflect an individual's current glycemic control. This could lead to misclassification as men with well controlled DM may have glucose and insulin levels similar to men without DM and vice-versa. Thus, using a serum biomarker is more sensitive for accurately determining the relationship between glucose regulation and disease outcomes. Our analysis is also unique in that we include both surgical and radiation patients. Although

the magnitude of influence with hyperglycemia on recurrence is less in the XRT group, the direction of the effect is the same and there was no evidence for effect modification by treatment. Potential reasons for this attenuation include regression to the mean, differences in BCR definitions, unmeasured confounding and the concomitant use of ADT in the radiation group alone.

There are limitations to our study. We only use a single glucose measurement which may not reflect an individual's ongoing glucose regulation during their post-treatment time. A hemoglobin A1C measurement does represent one's recent glucose regulation, however such values were only available in those with DM, and similar to the pre-operative glucose level, will not necessarily reflect subsequent glucose regulation. Further, we cannot be certain that these glucose levels were drawn fasting, however the median glucose for men without the diagnosis of DM was 107 (interquartile range 96 – 126). Data from the Center for Disease Control and Prevention Diabetes Fact Sheet 2011, state that 35% of adults over aged 20 (and 50% of adults over the age of 65) had prediabetes based on fasting glucose levels.[28] Thus our data, in which 72% of the patients are over age 60 years and 82% of patients are overweight or obese, are consistent with this distribution. Our population reflects Veterans who are consistent users of VA care and may not be generalizable to other men. Because the VA is an open system, some men may go to non-VA providers for follow-up care which may not get reported back to the VA. This appears to happen infrequently, a prior study of men with elevated PSA tests, 8% of men received subsequent care outside of the VA,[29] and we specifically restricted our cohort to men who had an established primary care relationship prior to diagnosis to

help reduce this potential limitation. Our definitions of biochemical recurrence may misclassify some men as not having evidence of recurrence and we cannot rule out Type 1 error in this analysis. We also do not include medication usage for treatment of DM which may impact glucose levels and we cannot rule out additional sources of unmeasured confounding. Future study of medication usage for DM may be informative. Finally, recurrence after PCa is a heterogeneous event with many individuals not progressing to PCa-specific mortality (PCSM). Although PCSM is a more robust endpoint, we did not have enough events to study this relationship. Use of national VA data in the future may allow such an analysis.

In conclusion, men with an elevated glucose level at the time of treatment for localized PCa have a higher risk of recurrence than men with a normal glucose level. This analysis provides evidence that disease progression may be influenced by glucose, suggesting that glucose control could be a modifiable risk factor for PCa recurrence and progression.

Table 1. Demographic and Tumor Characteristics of Men Treated for Localized Prostate Cancer by Disease Recurrence Status

	Disease Recurrence		
	No	**Yes**	**P – value***
	N (%)	**N (%)**	
Age			
< 65	815 (84)	154 (16)	0.11
65 – 74	509 (85)	91 (15)	
≥ 75	129 (78)	36 (22)	
Race			
Caucasian	1,231 (84)	236 (16)	0.69
African-American	124 (82)	28 (18)	
Other	98 (85)	17 (15)	
Year of Diagnosis			
2001 – 2003	317 (78)	88 (22)	< 0.001
2004 – 2006	499 (82)	112 (18)	
2007 – 2010	637 (89)	81 (11)	
BMI			
< 25	240 (81)	57 (19)	0.11
25 – 29	589 (83)	121 (17)	
≥ 30	620 (86)	103 (14)	
Charlson Score			
None	636 (84)	119 (16)	0.61
1	426 (85)	78 (15)	
2 – 3	263 (82)	58 (18)	
≥ 4	102 (81)	24 (19)	
Diabetes Mellitus			
No	1,127 (83)	223 (17)	0.51
Yes	326 (85)	58 (15)	
Diagnostic PSA			
< 4.0	132 (90)	14 (10)	< 0.001
4.0 – 9.9	940 (86)	153 (14)	
10 – 19.9	311 (80)	76 (20)	
≥ 20	70 (65)	38 (35)	
Gleason Sum			
6	602 (90)	65 (10)	< 0.001
7	643 (85)	115 (15)	
8 – 10	201 (67)	101 (33)	
Clinical T-stage			
T1 – T2a	1,198 (85)	207 (15)	< 0.001
T2b – T2c	239 (80)	60 (20)	
Treatment			
Surgery	596 (83)	126 (17)	0.23
Radiation	857 (85)	155 (15)	

* p-value for Chi-2 test between surgery and radiation

Table 2. Demographic and Tumor Characteristics of Men Treated for Localized Prostate Cancer Stratified by American Diabetes Association Serum Glucose Categories

	Glucose Level			
	< 100 mg/dL N (%)	**100-125 mg/dL N (%)**	**> 125 mg/dL N (%)**	**P – value***
Age				
< 65	256 (50)	349 (56)	364 (61)	<0.001
65 – 74	190 (37)	218 (35)	192 (32)	
≥ 75	68 (13)	56 (9)	41 (7)	
Race				
Caucasian	433 (84)	524 (84)	510 (85)	0.49
African-American	42 (8)	54 (9)	56 (9)	
Other	39 (8)	45 (7)	31 (5)	
Year of Diagnosis				
2001 – 2003	133 (26)	155 (25)	117 (20)	0.004
2004 – 2006	198 (39)	198 (32)	215 (36)	
2007 – 2010	183 (36)	270 (43)	265 (44)	
BMI				
< 25	109 (21)	110 (18)	78 (13)	<0.001
25 – 29	243 (47)	255 (41)	212 (36)	
≥ 30	162 (32)	256 (41)	305 (51)	
Charlson Score				
None	255 (50)	289 (47)	211 (36)	<0.001
1	143 (28)	289 (28)	187 (32)	
2 – 3	82 (16)	113 (18)	126 (21)	
≥ 4	28 (6)	35 (6)	63 (10)	
Diabetes Mellitus				
No	460 (89)	541 (87)	349 (58)	<0.001
Yes	54 (11)	82 (13)	248 (42)	
Diagnostic PSA				
< 4.0	37 (7)	51 (8)	58 (10)	0.1
4.0 – 9.9	307 (60)	406 (65)	380 (64)	
10 – 19.9	138 (27)	130 (21)	119 (20)	
≥ 20	32 (6)	36 (6)	40 (7)	
Gleason Sum				
6	217 (43)	258 (42)	192 (32)	0.001
7	220 (43)	259 (42)	279 (47)	
8 – 10	73 (14)	104 (17)	125 (21)	
Clinical T-stage				
T1 – T2a	429 (83)	516 (83)	460 (77)	0.04
T2b – T2c	78 (15)	95 (15)	126 (21)	
T3+	7 (1)	12 (2)	11 (2)	
Treatment				
Surgery	105 (20)	246 (39)	371 (62)	<0.001
Radiation	409 (80)	377 (61)	226 (38)	

* p-value for Chi-2 test

Table 3: Adjusted Risk of Prostate Cancer Recurrence by Quartiles of Serum Glucose

Quartile	Range (mg/dL)	N	Events (%)	Overall HR (95% CI)*
1st	31 – 98	464	61 (13)	1.00 (referent)
2nd	99 – 111	416	68 (16)	1.35 (0.95 -- 1.92)
3rd	112 – 137	414	76 (18)	1.57 (1.10 – 2.24)
4th	138 – 1015	438	76 (17)	1.44 (0.97 – 2.14)

*HR adjusted for age, race, body mass index, diagnosis of diabetes, treatment year, treatment, clinical stage, diagnostic PSA, Gleason Sum

Table 4: Risk of Recurrence after Prostate Cancer Treatment by American Diabetes Association Serum Glucose Categories

	N	Events N (%)	HR (95% CI)*
3 Categories			
< 100 mg/dL	445	69 (13)	1.00 (referent)
100 – 125 mg/dL	513	110 (18)	1.50 (1.10 – 2.04)
> 125 mg/dL	495	102 (17)	1.36 (0.95 -- 1.95)
2 Categories			
< 100 mg/dL	445	69 (13)	1.00 (referent)
≥ 100 mg/dL	1006	212 (17)	1.46 (1.09 -- 1.95)

*HR adjusted for age, race, body mass index, diagnosis of diabetes, treatment year, treatment, clinical stage, diagnostic PSA, Gleason Sum

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