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Poorly controlled diabetes increases risk of metastases and castration-resistant prostate cancer in men undergoing radical prostatectomy: results from SEARCH

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Abstract

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Background: While diabetes is inversely related to prostate cancer (PC) risk, the impact of glycemic control on PC progression is unknown. We tested the association between hemoglobin A1c (HbA1c) and long-term PC outcomes among men undergoing radical prostatectomy (RP).

Methods: We retrospectively reviewed data on men undergoing RP from 2000 to 2017 at 8 VA hospitals. We identified diabetic patients by ICD-9 codes (250.x) or by an HbA1c >6.5% at any time before RP. Cox models tested the association between HbA1c and biochemical recurrence (BCR), castration-resistant PC (CRPC), metastases, PC-specific mortality (PCSM), and all-cause mortality (ACM). The model for BCR was adjusted for multiple variable. Due to limited events, models for long-term outcomes were adjusted for biopsy grade and PSA only.

Results: 699 (50%) had HbA1c <6.5%, 631 (45%) had HbA1c 6.5–7.9%, and 79 (6%) had HbA1c ≥8.0%. Men with HbA1c ≥8.0% were younger (p<0.001) and more likely to be black (p=0.013). Median (IQR) follow-up after RP was 6.8 years (3.7–10.6). On multivariable analysis, HbA1c was not associated with BCR. However, higher HbA1c was associated with metastasis (HR 1.21, 95%CI 1.02–1.44, p=0.031) and CRPC (HR 1.27, 95%CI 1.03–1.56, p=0.023). Although not statistically significant, there were trends between higher HbA1c and risk of PCSM (HR 1.24, 95%CI 0.99–1.56, p=0.067) and ACM (HR 1.09, 95%CI 0.99–1.19, p=0.058).

Conclusions: Among diabetic men undergoing RP, higher HbA1c was associated with metastases and CRPC. If validated in larger studies with longer follow-up, future studies should test whether better glycemic control improves long-term PC outcomes.

Precis for use in the Table of Contents:

Among diabetic men undergoing radical prostatectomy, higher HbA1c was associated with metastases and castration-resistant prostate cancer. If validated in larger studies with longer follow-up, future studies should test whether better glycemic control improves long-term prostate cancer outcomes.

Keywords

diabetes; glycemic control; HbA1c; prostate cancer; metastases; castration-resistant prostate cancer

Introduction

Numerous studies, including two meta-analyses, have shown that diabetes mellitus (DM) is inversely correlated with prostate cancer risk [1–5]. However, how DM and specifically, glycemic control affect prostate cancer *progression* is less well studied.

It is estimated that by the year 2050, the total DM prevalence (both diagnosed and undiagnosed cases) will reach 21% in the U.S. adult population [6], making DM one of the most prevalent chronic diseases burdening the United States. The increasing incidence of DM, coupled with the sheer prevalence of prostate cancer as the most common malignancy affecting American men, makes understanding how DM impacts prostate cancer progression an area of clinical importance that remains to be elucidated. We previously showed in a small study that diabetic men with poorer glycemic control, i.e. a higher hemoglobin A1c (HbA1c), undergoing radical prostatectomy (RP) had more aggressive tumors (higher

grade), yet there was no significant association between glycemic control and the risk of PSA recurrence [7]. A smaller study by Hong et al., also among diabetic men undergoing RP, showed that higher HbA1c levels were associated with higher pathological Gleason scores and extraprostatic tumor extension [8]. However, the effect of glycemic control on long-term prostate cancer outcomes has not been well studied. Here, we hypothesized that poorer glycemic control, as defined by a higher HbA1c, would correlate with worse long-term prostate cancer outcomes amongst men undergoing RP. To test this, we identified diabetic men undergoing RP and assessed long-term outcomes using HbA1c as a marker of glycemic control within the Shared Equal Access Regional Cancer Hospital (SEARCH) database.

Materials and Methods

Study Population

After obtaining Institutional Review Board approval, data on patients who underwent RP from 2000 to 2017 at Veterans Affairs Medical Centers in West Los Angeles, San Diego, San Francisco, and Palo Alto, California; Portland, Oregon; Durham and Asheville, North Carolina; and Augusta, Georgia, were entered into the SEARCH database. This database includes patient characteristics at the time of RP, including age at the time of surgery, race, height, weight, clinical stage, grade of cancer on diagnostic biopsies, preoperative serum PSA value, surgical specimen pathology (specimen weight, tumor grade, tumor volume, stage and surgical margin status), and follow-up serum PSA data. Patients undergoing neoadjuvant treatment were excluded from analysis. Outcomes of interest included biochemical recurrence (BCR), castration-resistant prostate cancer (CRPC), metastases, prostate cancer-specific mortality (PCSM), and all-cause mortality (ACM). We defined BCR as two PSA values of 0.2 or one PSA value >0.2, or secondary treatment for an elevated PSA after RP. CRPC was defined as a PSA rise of ≥2 ng/ml and 25% from the post-androgen deprivation therapy (ADT) PSA nadir while receiving continuous ADT. Metastases was defined as the first metastasis determined from any type of imaging test. ACM was determined from medical records. PCSM was defined as death secondary to progressive, metastatic CRPC with no other obvious cause of death.

We identified patients diagnosed with DM at any time before RP using ICD-9 codes (250.x) or by an HbA1c value >6.5% at any point prior to surgery. We limited our analysis to patients who had an HbA1c within one year of RP. Patients were stratified based on their level of glycemic control, with HbA1c values <6.5% representing very well controlled DM, 6.5–7.9% representing moderately controlled DM, and values ≥8% representing poorly controlled DM [9, 10]. Of the 5,424 patients in the SEARCH Database treated since 2000, 2022 patients were diabetic at the time of RP (Figure 1). Of those, we excluded 520 patients with no HbA1c labs available within one year of RP. Another 91 patients were excluded due to missing follow-up, race, BMI, PSA, grade group, clinical stage information, and two patients with HbA1c values >14% were excluded in order to eliminate outliers from our data pool. This resulted in a study population of 1409 patients, of which 1017 met the criteria for diabetes diagnosis using both ICD-9 codes and an HbA1c value. Though SEARCH includes patients treated since 1988, we *a priori* selected men treated since 2000 due to the widespread availability of electronic records to accurately verify DM status after this date.

Statistical Analyses

Patient characteristics by HbA1c groups were compared using Kruskal-Wallis tests for continuous variables and chi-squared tests for categorical variables. Kaplan-Meier estimates were graphed to show the relationship between HbA1c group and time to BCR. Survival differences were calculated using a log-rank test. Cox proportional hazard models were used to test the association between HbA1c (continuous and categorical) and BCR, metastases, CRPC, PCSM, and ACM. The model for BCR was adjusted for age, race, BMI, PSA, year, biopsy grade group, clinical stage, and surgical center. Due to limited events, models for long-term outcomes were adjusted for biopsy grade group and PSA only. P-values for trend were calculated by assigning the median value for HbA1c to all patients in that group and treating it as a continuous variable. Statistical significance was two sided and defined as $p<0.05$.

Results

Baseline Patient Characteristics

Of the 1409 patients included, at the time of RP, 699 had HbA1c values <6.5%, 631 had HbA1c values 6.5–7.9%, and 79 had HbA1c values ≥8.0% (Table 1). The highest HbA1c group was younger ($p<0.001$) and more likely to be black ($p=0.013$). There was no difference in BMI, PSA, year of surgery, pre-operative biopsy grade group, clinical stage, or follow-up time among the 3 groups.

Association Between HbA1c and BCR

During a median 81–85 months of follow-up among the 3 groups, 443 men developed a BCR. Overall, there was no difference in time to BCR among HbA1c groups (log-rank, $p=0.30$, Figure 2). On both univariable and multivariable analyses, higher HbA1c values as a categorical variable did not correlate to an increased risk of BCR (p-trend=0.13 and 0.45 respectively, Table 2). Similar null results were seen when HbA1c was treated as a continuous variable.

Association Between HbA1c and Long-Term Prostate Cancer Outcomes

During follow-up, 59 men developed metastases, 37 developed CRPC, and 261 died, of which, 31 were due to prostate cancer (Table 3). Overall, there was no difference in time to metastasis among HbA1c groups (log-rank, $p=0.15$, Figure 2). When treated as a continuous variable, higher HbA1c was associated with higher risk of metastases on both univariable (HR 1.25, $p=0.008$) and multivariable (HR 1.21, $p=0.031$, Table 3) analyses. As a categorical variable, there were trends for higher HbA1c category to be associated with increased risk, though the p-trend was not significant.

Among HbA1c groups, there was a significant difference in time to CRPC (log-rank, $p=0.047$). As a continuous variable, higher HbA1c was associated with CRPC on both univariable (HR 1.33, $p=0.005$) and multivariable (HR 1.27, $p=0.023$, Table 3) analyses, though again when treated as a categorical variable, there were trends for higher HbA1c category to be associated with increased risk, though the p-trend was not significant on multivariable analysis.

There was no significant difference in time to PCSM among the three groups (log-rank, p=0.063, Figure 2). However, there was a significant association between glycemic control and PCSM when treated as a continuous variable on univariable (HR 1.30, p=0.018) analysis, although results were no longer significant on multivariable analysis (HR 1.24, p=0.067, Table 3). In-line with this, when treated as a categorical variable, HRs were increased for the higher categories, but the p-trend was not significant.

Finally, HbA1c category was significantly correlated with overall survival times (log-rank, p=0.043, Figure 2). Similarly, whether treated as a continuous (HR 1.11, p=0.024) or categorical variable (p-trend=0.014), HbA1c was correlated with ACM on univariable analysis. Although there was a suggestion that this correlation remained after adjustment for biopsy grade group and PSA, results were attenuated and no longer statistically significant when treated as a continuous variable (HR 1.09, p=0.058) but did remain significant for p-trend of HbA1c as a categorical variable (p-trend=0.043, Table 3).

Discussion

Prostate cancer remains the second most common cause of cancer death in men. Although there is an increasing body of evidence showing an inverse relationship between DM and prostate cancer risk [1–5], the impact of glycemic control on prostate cancer outcomes remains largely unknown. Given the rapidly increasing incidence of DM, it is important to identify and understand its impact on the clinical course of prostate cancer. Here, we used HbA1c as a marker of glycemic control to examine the correlation between DM severity and long-term prostate cancer outcomes among men undergoing RP. We found that higher HbA1c, as a continuous variable, was significantly associated with greater risk of metastases and CRPC and suggestively linked with higher PCSM and ACM. As HbA1c is a good marker of glycemic control, these data suggest serum glucose levels may significantly influence prostate cancer progression and long-term clinical outcomes. If validated in larger studies with longer follow up, our results would support clinical trials to test whether better glycemic control can improve long-term clinical outcomes in men undergoing RP.

Among men undergoing RP, two prior studies both found higher HbA1c was associated with higher pathological Gleason score and extracapsular extension, but neither found an association with BCR [7, 8]. Our results are consistent with these previous findings in that higher HbA1c was not related to BCR. Our study has the advantage of a larger sample size and longer follow-up period, enabling us to examine longer-term outcomes. Importantly, we found a correlation between higher HbA1c and higher metastases and CRPC risk, when HbA1c was treated as a continuous variable. Although we found a suggested increased risk in PCSM, this relationship was not significant after adjustment for biopsy grade group. Larger studies with more follow-up are needed to further understand this potential correlation.

HbA1c remains the most widely used clinical marker of glycemic control, signifying the extent of glycosylation at the cellular level caused by excess circulating glucose [11–14]. As such, our findings of higher HbA1c being linked with worse prostate cancer outcomes suggest glucose may be key for prostate cancer growth. Indeed, a recent *in vitro* study using

two prostate cancer cell lines cultured in media containing different glucose concentrations found that a higher glucose concentration led to increased androgen receptor expression and an increased rate of cellular growth [15]. Conversely, in human prostate cancer, uptake of fluorodeoxyglucose (FDG) is low, leading to a lack of utility of FDG positron emission tomography (FDG-PET) scans in prostate cancer management [16–19], which suggests glucose may not be important in human prostate cancer. Interestingly, there is increasing data that suggests that insulin, rather than excess glucose, may play a more significant role in prostate cancer. A study by Ma et al. showed that among men diagnosed with prostate cancer, those with the highest C-peptide concentration, a marker of insulin secretion, had a higher risk of prostate cancer mortality, and that this risk was increased four-fold when coupled with a BMI > 25kg/m^2 [20]. Another study showed that patients at the highest risk of prostate cancer recurrence exhibited higher levels of serum insulin compared to those at medium and low-risk [21]. As HbA1c is a surrogate marker of insulin resistance [22], it is possible that the impact of poor glycemic control on prostate cancer progression is due to higher circulating insulin levels required to counter insulin resistance in those with long-standing hyperglycemia, and not the excess glucose itself. An alternative explanation may be that higher circulating glucose levels may be a marker of other processes, such as metabolic syndrome or a lack of physical activity, both of which have been shown to be correlated with poor clinical outcomes in some studies [23, 24]. Although our results suggest that poor glycemic control is associated with increased metastatic disease risk and CRPC, the causal mechanisms underlying these findings require further study. If there is indeed a causal relationship between poor glycemic control and worse prostate cancer outcomes, then future studies should test whether improved glycemic control can lead to better prostate cancer outcomes.

Our study has several strengths in design, including a large sample size and the robust nature of the SEARCH database. The SEARCH database offers a wide set of cancer progression metrics, allowing us to analyze multiple long-term outcomes over a follow-up period of at least 6 years. However, limitations in electronic record availability on HbA1c values prior to the year 2000 required that we exclude patients in the SEARCH database prior to this timepoint, thus limiting our study population to patients being treated since 2000. As such, this likewise limited the number of events and thus longer follow-up studies are needed. Additionally, our database has HbA1c values from only one timepoint prior to RP, preventing us from analyzing long-term trends in glycemic control amongst diabetic men undergoing RP or whether changes in glycemic control impacts long-term clinical outcomes in prostate cancer. Finally, as the number of men with HbA1c ≥8% was small, additional studies are needed to better define risks of progression for this group.

Although a growing body of work suggests that DM may play a protective role against prostate cancer risk, the impact of glycemic control on prostate cancer *outcomes* is largely unknown. In our study, HbA1c, a marker of glycemic control, is significantly associated with prostate cancer metastasis and CRPC among men undergoing RP. Although our data suggest there may be an association between serum glucose levels and prostate cancer progression, future studies are needed to understand whether insulin or hyperglycemia is of greater clinical significance. Larger studies with longer follow-up are needed to validate our findings.

Acknowledgments

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References

1. Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. Diabetologia. 2004;47: 1071–1078. [PubMed: 15164171]
2. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2006;15: 2056–2062. [PubMed: 17119028]
3. Coker AL, Sanderson M, Zheng W, Fadden MK. Diabetes mellitus and prostate cancer risk among older men: population-based case-control study. Br J Cancer. 2004;90: 2171–2175. [PubMed: 15150583]
4. Kasper JS, Liu Y, Giovannucci E. Diabetes mellitus and risk of prostate cancer in the health professionals follow-up study. Int J Cancer. 2009;124: 1398–1403. [PubMed: 19058180]
5. Baradaran N, Ahmadi H, Salem S, et al. The protective effect of diabetes mellitus against prostate cancer: role of sex hormones. Prostate. 2009;69: 1744–1750. [PubMed: 19676082]
6. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr. 2010;8: 29. [PubMed: 20969750]
7. Kim HS, Presti JC, Aronson WJ, et al. Glycemic control and prostate cancer progression: results from the SEARCH database. Prostate. 2010;70: 1540–1546. [PubMed: 20687228]
8. Hong SK, Lee ST, Kim SS, et al. Significance of preoperative HbA1c level in patients with diabetes mellitus and clinically localized prostate cancer. Prostate. 2009;69: 820–826. [PubMed: 19189299]
9. Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329: 977–986. [PubMed: 8366922]
10. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352: 837–853. [PubMed: 9742976]
11. Bunn HF, Haney DN, Kamin S, Gabbay KH, Gallop PM. The biosynthesis of human hemoglobin A1c. Slow glycosylation of hemoglobin in vivo. J Clin Invest. 1976;57: 1652–1659. [PubMed: 932199]
12. Koenig RJ, Peterson CM, Jones RL, Saudek C, Lehrman M, Cerami A. Correlation of glucose regulation and hemoglobin AIc in diabetes mellitus. N Engl J Med. 1976;295: 417–420. [PubMed: 934240]
13. Gabbay KH, Hasty K, Breslow JL, Ellison RC, Bunn HF, Gallop PM. Glycosylated hemoglobins and long-term blood glucose control in diabetes mellitus. J Clin Endocrinol Metab. 1977;44: 859–864. [PubMed: 858776]
14. Nathan DM, Singer DE, Hurxthal K, Goodson JD. The clinical information value of the glycosylated hemoglobin assay. N Engl J Med. 1984;310: 341–346. [PubMed: 6690962]
15. Antunes HP, Teixo R, Carvalho JA, et al. Diabetes mellitus and prostate cancer metabolism: Is there a relationship? Arch Ital Urol Androl. 2018;90: 184–190. [PubMed: 30362687]
16. Takahashi N, Inoue T, Lee J, Yamaguchi T, Shizukuishi K. The roles of PET and PET/CT in the diagnosis and management of prostate cancer. Oncology. 2007;72: 226–233. [PubMed: 18176088]
17. Salminen E, Hogg A, Binns D, Frydenberg M, Hicks R. Investigations with FDG-PET scanning in prostate cancer show limited value for clinical practice. Acta Oncol. 2002;41: 425–429. [PubMed: 12442917]
18. Effert PJ, Bares R, Handt S, Wolff JM, Büll U, Jakse G. Metabolic imaging of untreated prostate cancer by positron emission tomography with 18fluorine-labeled deoxyglucose. J Urol. 1996;155: 994–998. [PubMed: 8583625]
19. Hofer C, Laubenbacher C, Block T, Breul J, Hartung R, Schwaiger M. Fluorine-18-fluorodeoxyglucose positron emission tomography is useless for the detection of local recurrence after radical prostatectomy. Eur Urol. 1999;36: 31–35.

20. Ma J, Li H, Giovannucci E, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. Lancet Oncol. 2008;9: 1039–1047. [PubMed: 18835745]

21. Lehrer S, Diamond EJ, Stagger S, Stone NN, Stock RG. Increased serum insulin associated with increased risk of prostate cancer recurrence. Prostate. 2002;50: 1–3. [PubMed: 11757030]

22. Singh B, Saxena A. Surrogate markers of insulin resistance: A review. World J Diabetes. 2010;1: 36–47. [PubMed: 21537426]

23. Gacci M, Russo GI, De Nunzio C, et al. Meta-analysis of metabolic syndrome and prostate cancer. Prostate Cancer Prostatic Dis. 2017;20: 146–155. [PubMed: 28220805]

24. Benke IN, Leitzmann MF, Behrens G, Schmid D. Physical activity in relation to risk of prostate cancer: a systematic review and meta-analysis. Ann Oncol. 2018;29: 1154–1179. [PubMed: 29788165]

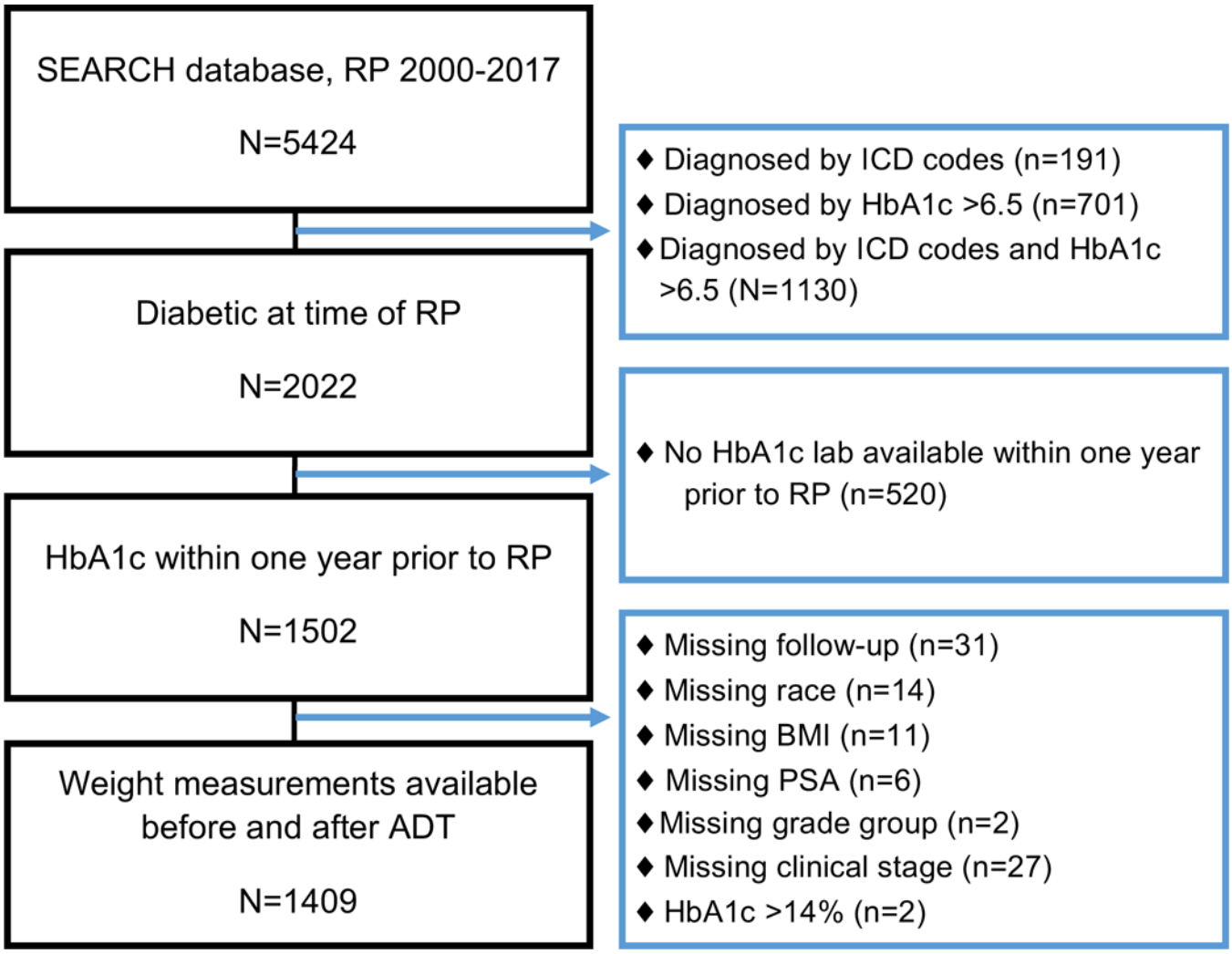
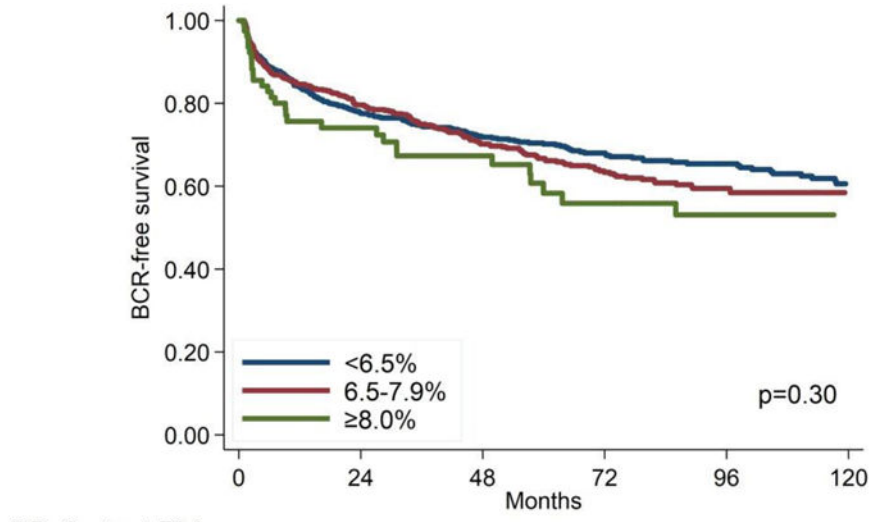
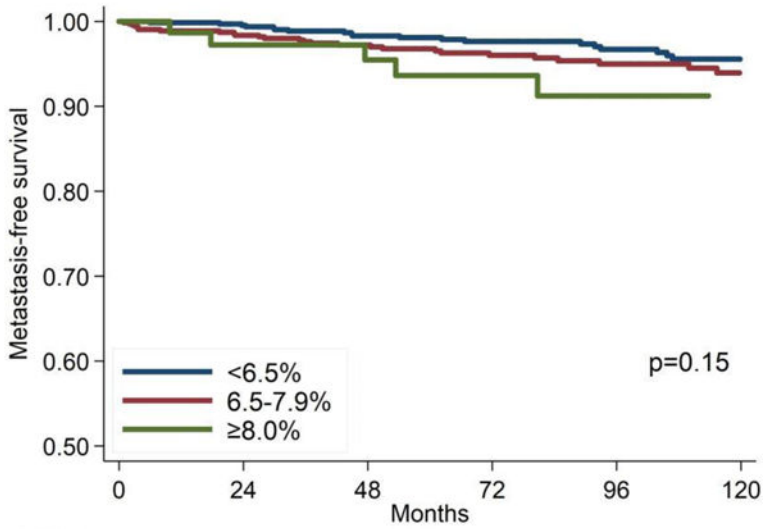


Figure 1:
Patient consort diagram. Diabetic patients undergoing RP from 2000–2017 were identified in the SEARCH database. Those with missing follow-up, race, BMI, PSA, grade group, clinical stage, or HbA1c >14% were excluded.



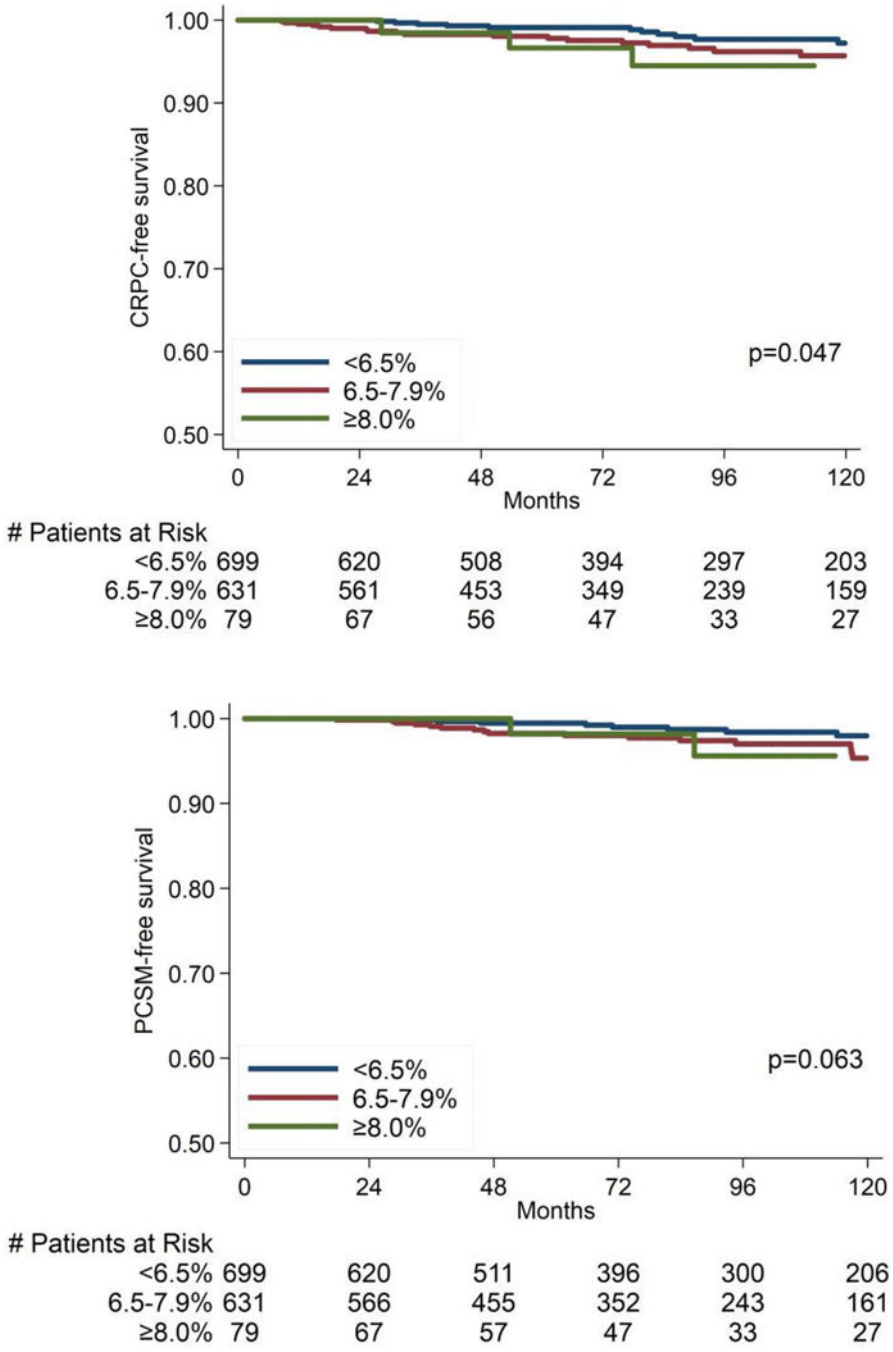
Patients at Risk

<6.5%	699	451	327	233	147	86
6.5-7.9%	631	418	294	195	119	73
≥8.0%	79	44	32	23	14	10



Patients at Risk

<6.5%	699	617	504	391	297	202
6.5-7.9%	631	558	450	344	237	157
≥8.0%	79	65	54	45	32	26



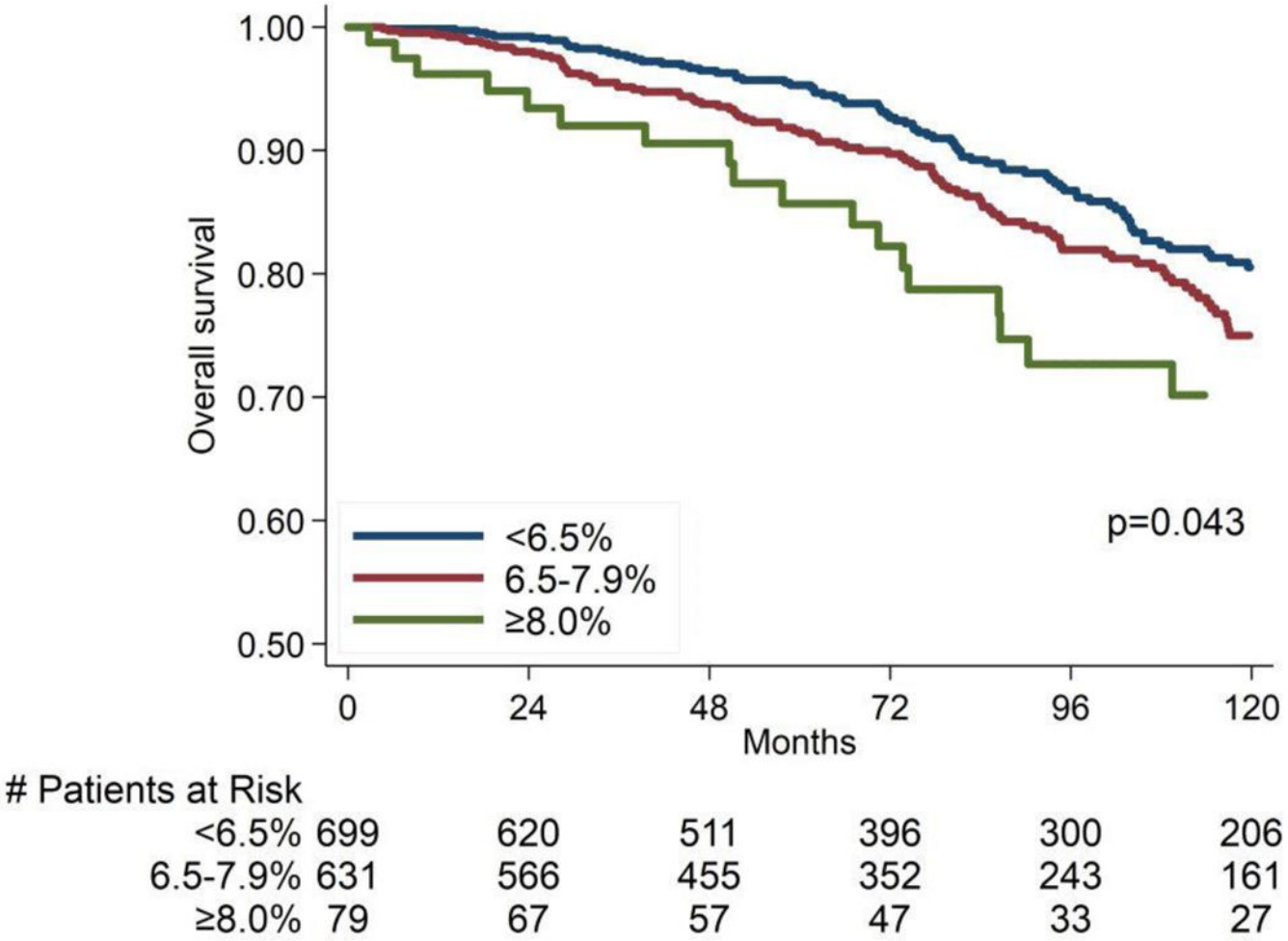


Figure 2:

Kaplan-Meier curves showing the survival distribution of different prostate cancer outcomes by HbA1c values.

Table 1.

Patient characteristics at the time of RP

	HbA1c <6.5% (N=699)	HbA1c 6.5–7.9% (N=631)	HbA1c ≥8% (N=79)	p value
Age				<0.001[1]
Median	62	63	61	
Q1, Q3	58, 66	59, 67	58, 65	
Race				0.013[2]
Non-black	444 (64%)	399 (63%)	37 (47%)	
Black	256 (36%)	232 (37%)	42 (53%)	
BMI				0.291[1]
Median	29.8	30.3	30.6	
Q1, Q3	27.3, 33.3	27.4, 33.6	27.6, 34.1	
PSA (ng/mL)				0.118[1]
Median	6.0	6.0	7.2	
Q1, Q3	4.7, 9.2	4.7, 8.7	4.8, 11.9	
Year of surgery				0.116[1]
Median	2010	2010	2008	
Q1, Q3	2005, 2013	2006, 2013	2004, 2012	
Pre-op grade group				0.168[2]
1	238 (34%)	199 (32%)	27 (34%)	
2–3	339 (48%)	293 (46%)	32 (41%)	
4–5	122 (17%)	139 (22%)	20 (25%)	
Clinical stage				0.165[2]
T1	444 (64%)	370 (59%)	46 (58%)	
T2-T4	255 (36%)	261 (41%)	33 (42%)	
Follow-up				0.395[1]
Median	82	81	85	
Q1, Q3	42, 130	46, 122	45, 146	

[1] Kruskal Wallis

[2] Chi-Square

Table 2:

Hazard ratios for the association between HbA1c and biochemical recurrence

		Univariable			Multivariable*		
	N	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
BCR							
HbA1c							
Continuous	443/1409	1.06	0.98–1.14	0.14	1.02	0.94–1.10	0.63
<6.5	212/689	Ref.			Ref.		
6.5–7.9	202/631	1.06	0.88–1.29		1.05	0.86–1.28	
≥8.0	29/79	1.35	0.92–1.99		1.15	0.77–1.71	
p-trend				0.13			0.45

*Adjusted for age, race, BMI, PSA, year, biopsy grade group, and surgical center

Table 3:

Hazard ratios for the association between HbA1c and prostate cancer outcomes

		Univariable				Multivariable*		
	N	HR	95% CI	P		HR	95% CI	P
Metastases								
HbA1c								
Continuous	59/1409	1.25	1.06–1.48	0.008		1.21	1.02–1.44	0.031
<6.5	23/689	Ref.				Ref.		
6.5–7.9	30/631	1.49	0.87–2.57			1.36	0.79–2.36	
≥8.0	6/79	2.17	0.88–5.36			1.73	0.70–4.26	
p-trend				0.060				0.19
CRPC								
HbA1c								
Continuous	37/1409	1.33	1.09–1.62	0.005		1.27	1.03–1.56	0.023
<6.5	11/689	Ref.				Ref.		
6.5–7.9	22/631	2.26	1.10–4.67			2.16	1.04–4.49	
≥8.0	4/79	2.86	0.90–9.10			2.11	0.66–6.74	
p-trend				0.035				0.12
PCSM								
HbA1c								
Continuous	31/1409	1.30	1.05–1.62	0.018		1.24	0.99–1.56	0.067
<6.5	9/689	Ref.				Ref.		
6.5–7.9	19/631	2.43	1.10–5.37			2.34	1.00–5.00	
≥8.0	3/79	2.66	0.72–9.85			1.90	0.51–7.07	
p-trend				0.065				0.21
ACM								
HbA1c								
Continuous	261/1409	1.11	1.01–1.21	0.024		1.09	0.99–1.19	0.058
<6.5	114/689	Ref.				Ref.		
6.5–7.9	123/631	1.26	0.98–1.62			1.23	0.95–1.59	
≥8.0	24/79	1.65	1.06–2.57			1.50	0.96–2.35	
p-trend				0.014				0.043

*Adjusted for biopsy grade group and PSA

There were only 15 prostate cancer deaths so no model is reported for this outcome.