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THE INFLUENCE OF ANTIDIABETIC MEDICATIONS ON THE DEVELOPMENT AND PROGRESSION OF PROSTATE CANCER

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THESIS

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ABSTRACT OF THESIS

THE INFLUENCE OF ANTIDIABETIC MEDICATIONS ON THE DEVELOPMENT AND PROGRESSION OF PROSTATE CANCER

The development of prostate tumors has been linked to co-morbid diabetes mellitus (DM) in several studies, potentially through the stimulation of insulin-like growth factor receptor (IGFR). This study evaluates the effect of anti-diabetic medication use on the development of high grade tumors and time to tumor progression compared to non-diabetics. This retrospective, nested case control study identified patients with prostate cancer (PCa) from the Kentucky Medicaid Database. Cases were diagnosed with PCa and DM and using at least one of the following antidiabetic medications; sulfonylureas, insulin, metformin or TZDs. Cases were further stratified on their insulin exposure resulting from therapy. Controls were those with PCa without DM or any anti-diabetic medications. No statistically significant effects on insulin exposure was found on tumor grade and time to progression. Trends identified that use of metformin or TZDs potentially decreased the odds of high-grade tumors and decreased the risk of progression, while sulfonylureas and high-dose insulin may increase the odds of high-grade tumors and increase the risk of progression compared to non-diabetics. Future studies should be conducted to further evaluate the effects of anti-diabetic medications on tumor grade and time to prostate cancer progression.

KEYWORDS: Prostate Cancer, Prostate Tumor, Diabetes, Insulin, IGFR

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SECTION ONE: BACKGROUND

Prostate cancer (PCa) is the most common cancer of men in the United States, affecting nearly 2.4 million men in 2008.[1] Currently 11.8% of the adult male population (13 million men) are estimated to have a diagnosis of diabetes, 90-95% of which is considered to be type II (T2DM).[2] While the most prominent long term effects of diabetes are cardiovascular complications, recent studies have demonstrated a relationship between diabetes, diabetes treatments and cancer risk.[3-9]

In investigating the association, the presence of diabetes was found to independently correlate with lower prostate specific antigen (PSA) levels.[10] Looking at how this may translate into overall cancer risk, the Physician's Health Study found that diabetics were 36% less likely to develop prostate cancer than non-diabetics, a finding that has been supported in other trials.[3,6,11,12] Interestingly, the duration of diabetes diagnosis also appears to affect this relationship, with those with long-standing T2DM having a lower risk than newly diagnosed patients, namely due to the progressive nature of insulin resistance.[13,14] Furthermore, in those that do develop cancer, diabetes appears to have an effect on tumor grade, with some studies reporting a direct relationship in prostate tumors while others demonstrate inverse correlation.[6,15-19] Although numerous hypothesis have been proposed to explain this causal

relationship, one prominent rationale focuses on the role of insulin exposure and the insulin-like growth factor receptor (IGF-1R) in tumorgenesis.[4,5,7]

Insulin-like growth factor

IGF-1R is a dimeric type 2 tyrosine kinase receptor expressed on both normal tissue as well as numerous cancer cell lines. It is structurally similar to the insulin receptor (IR) and may form hetero-dimer hybrids with IR on cells that co-express both receptors.[20,21] Stimulation of IGF-1R is associated with numerous downstream actions including the activation of mitogenic and anti-apoptotic mechanisms such as the P13K/AKT and RAS/RAF/MAPK signaling pathways, stimulation of which have a known effect on oncogenesis. These activations are essential in cell growth, proliferation and survival; mutations in these pathways have been shown to lead to aberrant uncontrolled cell growth.[22] The effects of IGF-1R and its primary ligand, insulin-like growth factor (IGF-1) on the development of cancer have been evaluated in numerous cell and animal models.[21-24]

Specifically IGF-1R, insulin receptors and hetero-dimers have been shown to be over-expressed in both normal and malignant prostate tissue. Studies have demonstrated a trend of increasing levels of expression being associated with increased levels of prostate specific antigen (PSA) and higher Gleason score values, both of which indicate increased aggressiveness and poorer prognosis.[25-

[27] Recent evaluation of IGF-1R antagonism in prostate tumor cells has demonstrated a decrease in both androgen dependant and androgen independent cell growth, furthering the hypothesis that IGF-1R activation may accelerate tumor progression.[23]

While IGF-1 is the most common cause of IGF-1R stimulation, insulin has also been demonstrated to bind and activate the IGF-1 receptor, leading to increased cellular proliferation and anti-apoptosis.[21,22,28] Increased measured insulin levels have been linked to not only a higher incidence of prostate cancer, but also potentially increased Gleason scores and cancer-related mortality.[7,16,29] Lehrer et al. found that men presenting with higher grade tumors had higher measured circulating insulin, although the diabetic status of these patients was not noted.[16] Further in a study by Venkateswaran et al. mice with a diet-induced measured hyperinsulinemic state had an increase in prostate tumor size over those with normal levels.[30] These studies support the hypothesis that the acute elevation in insulin seen in initial diabetes development impacts tumor growth, while the overall long term decrease in circulating insulin affects tumor development.

Serum insulin levels and PCa

Antidiabetic pharmacotherapy can influence the levels of exogenous and endogenous insulin, potentially impacting tumor development.[31] Weinstein et al. found that insulin analogues (glargine, detemir) increased mitogenic growth

similar to direct application of IGF-1 on tumor cells. In these cells, the rate of proliferation increased by 14-16% in glargine and detemir treated cells, while the percentage of apoptotic cells decreased by 5.1-8.3% compared to controls ($p<0.05$).[28] This finding was confirmed in an epidemiologic study by Hemkens et al. that found a dose-dependent OR 1.09-1.31 times ($p<0.0001$) greater risk of cancer for those using insulin glargine over regular human insulin.[32] This increase in cellular proliferation, especially prominent with the increased exposure of longer acting agents provides further evidence of the relationship of insulin and prostate cancer cell growth.

Looking at the use of oral agents, conflicting data exists regarding the role that oral anti-diabetic agents play in the development of prostate tumors. Bowker et al. linked the use of insulin and insulin-secretagogue agents (i.e. sulfonylureas) with an increased risk of cancer-related mortality across all cancer types. Patients with any use of sulfonylureas had a 1.3 times higher cancer-related mortality than those on metformin, a non-secreting agent, while any use of insulin increased the risk by 1.9 times versus non-insulin users.[33] Compared to insulin-stimulating agents, thiazolidinediones (TZDs) appear to have little to no effect on the development of any cancer type, although the results are inconsistent.[34,35]

Specifically evaluating prostate tumors, Murtola et al. reported a lower risk of prostate tumor development with all users of oral antidiabetic therapy (metformin, sulfonylureas, or other oral agents) compared to non-diabetic non-users,

although this did not differentiate between disease effect versus the effect of the medications used to managed diabetes. Currie et al. reported a non-statistically significant increase in prostate cancer risk for those treated with sulfonylurea monotherapy, sulfonylurea + metformin therapy or insulin-based therapies compared to those using metformin as a single agent.[36] On the contrary, a large cohort analysis from the Kaiser Permanente Northern California Diabetes Registry, the ever-use of any oral antidiabetic therapy (sulfonylureas, metformin and TZDs) was not associated with any change in the development of prostate tumors.[37] From this information it is clear that the interaction of these agents with tumor development and growth is unclear and more investigation is needed to guide prudent medication selection in diabetic men at-risk for prostate tumors.

Covariate relationship

In addition to these observed relationships, other factors may also impact the complex interactions of prostate cancer and diabetes and should be accounted for in future study. Bisphosphonates are often used to prevent and treat bone metastases and may reduce the adhesion and invasion of metastasized tumor cells, potentially prolonging the time to progression.[38] Other concurrent medications, such as corticosteroids, are commonly used in the management of prostate tumors and may lead to hyperglycemia.[39] The increased presence of serum glucose stimulates insulin production in non-diabetic patients and may necessitate increased medication doses in diabetic patients. Additionally, recent

research has suggested that obesity, hypertension, hypercholesterolemia, either individually or as metabolic syndrome may also play a role in the development of higher-grade cancer (Gleason score ≥ 7) as well as increased progression.[8,40] These findings appear to be independent of concurrent diabetes and are thought to potentially be through alterations in sex-hormones.[8] Finally, use of androgen deprivation therapy (ADT) in the treatment of prostate tumors has also been linked to the increased development of diabetes and metabolic syndrome in previously undiagnosed patients and may also affect tumor development.[41]

Aside from concurrent medication use and medical diagnoses, social factors may also influence the development and progression of prostate cancer. Numerous studies have cited that patients living in more rural areas have reduced access to health, leading to poorer outcomes across disease states. Specifically, how far patients live from their treating physician has been associated with worsening overall glycemic control and may impact the presence of serum insulin.[42] In regards to prostate cancer outcomes, men in rural areas away from treatment centers are less likely to undergo more aggressive radiation therapy as those living in more metropolitan areas.[43,44] In addition to the decreased access to care seen in rural patients, other, non-medical exposures may also impact the characteristics of prostate tumors in more agrarian areas. While not commonly encountered, several occupational investigations have cited that farmers have an increased risk and mortality of prostate tumors.[45-47]

The relationship between insulin, diabetes and prostate cancer is complex with multiple modifying factors. An improved characterization of this association on the development and progression of prostate tumors could potentially impact thousands of patients. Based upon previous epidemiologic, animal and in vitro studies we hypothesize that increased insulin exposure induced by endogenous insulin or oral insulin secretagogues will increase the initial tumor invasiveness as measured by Gleason score and shorten the time to disease progression.

SECTION TWO: METHODS

Study Design

This was a retrospective nested case-control study of the Kentucky Medicaid population. The Kentucky Medicaid (KM) database contains billing information on the healthcare utilization, including procedures, medication use and diagnoses, of low-income patients. Data within the KM database is available through the International Disease Classification 9th revision (ICD-9) and Current Procedural Terminology (CPT) codes. Data prior to January 1, 2000 was not available and after December 31, 2005, outpatient prescription drug coverage of patients >65 years of age was transitioned to coverage through the national Medicare Part D program and was no longer available through the Kentucky Medicaid (KM) database.

In addition to information from the KM database, the Kentucky Cancer Registry (KCR) was also used for data collection and validation. The KCR is a mandatory state cancer reporting system that is part of the National Cancer Institute's Surveillance Epidemiology End Results (SEER) program. All state healthcare facilities are required by law to report all new cancer diagnoses to the registry. Through participation in SEER, cases are validated and additional demographic, pathologic, and survival information is collected.[48]

This study protocol was reviewed and approved through the Institutional Review Board (IRB) at the University of Kentucky and the Kentucky Cabinet for Health and Family Services (KCHFS). An independent board at the Kentucky Cancer Registry also approved the use of this protocol upon recommendation from the University of Kentucky and KCHFS.

Study Population

All male patients >18 years age who were found to have a diagnoses of prostate cancer between July 1, 2000 and December 31, 2005, as defined below, were established for inclusion. Patients were followed from diagnosis until the last date of contact or August 31, 2009, whichever came first. Patients must have had Medicaid enrollment for >11 months to allow for medication use analysis.

Diagnosis of prostate cancer was determined through the identification of the ICD-9 diagnosis codes for primary prostate gland cancer (PGC) (ICD9 185.x) and primary prostate utricle cancer (PUC) (ICD9 189.3) within the KM database. Patients with benign lesions or carcinoma in situ were excluded. Patients must have had at least two cancer related visits to a healthcare provider within 1 year. Patients with a diagnosis of prostate cancer through the KM database were then linked to information from the KCR to validate diagnosis dates and provide pathologic and staging data. In the event of a discrepancy for diagnosis date between the two databases, the date given by KCR was utilized due to the independent validation of this dataset.

Diagnosis of diabetes mellitus was determined using the Healthcare Effectiveness Data and Information Set (HEDIS) definition. Patients with two type II diabetes (T2DM) related healthcare visits (defined by the presence of ICD 250.x2 or 250.x0) and a prescription for an antidiabetic medication filled within 1 year were considered to have diabetes. The presence of type I diabetes was not eligible for study inclusion due to the lack of endogenous insulin and inability to use oral antidiabetic medications of this patient population.

Insulin exposure groups were determined based on the use of antidiabetic medications within the KM database. Medications were determined through the use of NDC codes; a complete list of medications used within the study is available in Appendix Table 1.. Patients with the use of sulfonylureas, insulin at

doses >0.8 units/kg/day (high-dose; utilized an average weight of 85kg determined from internal data on the weight of prostate cancer patients in Kentucky) or combination therapy for >2/3 the entire study period involving either of these agents were considered to have elevated insulin exposure. Patients using metformin, TZDs, insulin at doses ≤0.8 units/kg/day, or combination therapy for >2/3 of the study period without high-dose insulin or sulfonylureas were considered to have physiologic insulin exposure. Those without the use of a clear combination medication therapy for >2/3 the study period, one-time medication use or poor diabetes medication compliance were considered to have indeterminate insulin exposure. Patients without a diagnosis of type I or type II diabetes, or the receipt of an antidiabetic medication at any time during the study observation were considered control subjects. Since age is a key determinate in the progression of aggressive of prostate tumors and a well known confounder, cases were age-matched to controls in randomized blocks of 2, allowing for up to 2 controls present in the analysis for every case.

Patients with an ICD-9 diagnosis of diabetes, but who do not have a prescription for diabetes treatment during the study period were excluded. These include patients who may be utilizing therapeutic lifestyle changes for glucose control and may have less predictable insulin exposure. Patients utilizing therapy with repaglinde, nateglindine, α-glucosidase inhibitors were not included due to variable insulin exposure. Newer agents such as exenatide, pramlintide or sitagliptin were not present in the Medicaid population during the study period.

In addition to the diagnosis of prostate cancer and diabetes, information on age, presence of diabetes, medication use (including steroid and bisphosphonate use), geography, comorbid disease, tumor grade, tumor stage, metastatic sites, surgical information, time with diagnosis of diabetes within the study period and compliance was collected. Medication use was defined as use prior to diagnosis (for primary analysis) or recurrence (for secondary analysis); steroid use was limited to those with use for ≥30 days. Geography was determined through the use of the United States Department of Agriculture (USDA) Rural-Urban continuum codes.[49] Based on their primary residence, patients were divided into urban, suburban and rural areas based on their proximity to large metro areas. Co-morbid disease was primarily measured in the KM database through the use of the Charlson score. The Charlson score is a weighted composite score that evaluates the presence of 22 conditions (e.g. heart disease, hypertension, pulmonary dysfunction, diabetes, AIDS, renal dysfunction, etc.).[50] For this analysis, the Charlson score calculated prior to the diagnosis of cancer was utilized to reduce falsely elevated comorbid disease. Charlson data was not available for all patients, so in addition the the presence of a hypertension or hypercholesterolemia diagnosis in the Medicaid database with subsequent prescription medication treatment was also included as a separate measure of comorbid disease Medication Possession Ratio (MPR) was used to evaluate medication compliance of diabetes medications and determine study inclusion. MPR is calculated as the sum of the days supply medication over a time period

divided by the time period of evaluation.[51] An MPR of <80% was used to determine poor diabetes medication compliance and led to study exclusion.

Determination of endpoints

Gleason score information is available as part of the KCR database from pathology reports at the time of diagnosis. Patients with a Gleason score <7 were considered to have low grade, less aggressive disease while those with a Gleason score ≥7 were considered to have high grade, more aggressive tumors.

Time to progression was defined as a composite endpoint classified through the use of ICD-9 and CPT codes within the KM database. Patients that experienced any of the following events ≥ 60 days after the diagnosis of prostate cancer were considered to have progressed:

1. Appearance of elevation of PSA ICD-9 code (790.93) at any point after the index date of PSA normalization.
2. Initiation of chemotherapy determined through CPT codes 96401-96549 or the presence of chemotherapy within the KM prescription database (low dose oral methotrexate was excluded).
3. Development of a secondary cancer diagnosis in patients who were not diagnosed at a metastatic stage. This was determined through ICD9 codes and based on reasonable sites of metastatic spread of prostate cancer including bone/spine, regional lymph nodes, bladder, kidney, liver, lung, colon/rectum and other pelvic/genital structures.[52]

Statistical Analysis

Demographic variables were evaluated using descriptive statistics. Simple comparisons of continuous variables between the study groups was conducted using ANOVA testing for normally distributed data and Kruskal-Wallis testing for non-parametric variables. Categorical variables were evaluated using chi-square testing of independence; however, when low cell counts were found, Fisher's exact testing was utilized instead.

The primary endpoint was the presence of low Gleason score at diagnosis. An odds ratio of the presence of low Gleason score between cases and controls was evaluated through bivariate and multivariate conditional logistic regression to control for confounders. Conditional logistic regression allows for comparison between matched groups; using this test provided for appropriate analysis between the age-matched cases and controls. The conditional multivariate regression included known confounders of geography, comorbidity measure and steroid use prior to diagnosis regardless of the results of the bivariate model. The secondary endpoint was the time to progression as defined above. Kaplan Meier survival curves and log-rank testing was used to evaluate the differences in time to progression between insulin exposure groups. To account for potential confounding covariates, a Cox Proportional Hazard regression model was created to evaluate the overall hazard ratios, again accounting for known

confounders of geography, comorbidity, stage/metastatic spread, and steroid and bisphosphonate use prior to recurrence. Patient with missing data used in the regression models were excluded from the regression analysis. Statistical analysis was performed using STATA v.10 (StataCorp LP, College Station, TX, USA).

SECTION THREE: RESULTS

Out of 1272 patients initially identified, 722 patients were eligible for inclusion. A diagram of exclusion is provided in Figure 1. Of these patients, 50 were found to have physiologic insulin exposure, 103 had elevated insulin exposure, and 16 had indeterminate exposure. The remaining 569 patients had no evidence of diabetes. From this, 338 were randomly age-matched and selected as controls. Those with indeterminate exposure were excluded from the final analysis due to low numbers, leading to a total of 491 patients evaluated. Demographic information is listed in Table 1.

Within the 491 patients, 236 were found to have evaluable pathologic information, including Gleason score, provided by the Kentucky Cancer Registry. One-hundred forty-nine (59.36%) were found to have a low Gleason score (<7), while 102 (40.64%) were diagnosed with high-grade disease. A breakdown of this by insulin exposure group is in Figure 2. Overall diabetic patients, regardless of insulin exposure, presented with lower Gleason scores, although this was not

statistically significant. Compared to those without diabetes, patients with elevated exposure had a 5% lower odds (95% CI: 0.47-1.91; p=0.887) of developing high-grade disease, while those with physiologic exposure had a 45% lower odds (95% CI: 0.21-1.46; p=0.233). When adjusted for geography, co-morbidity (measured as Charlson score), and corticosteroid use prior to prostate cancer diagnosis, elevated insulin exposure appeared to slightly increase the odds of presenting with high-grade disease (OR=1.04 (0.44-2.44); p=0.685), while physiologic insulin exposure decreased the odds (OR=0.62 (0.22-1.70); p=0.929) compared to controls (Table 2).

Only 299 patients had complete information using the Charlson score as the measure of comorbidity; 133 had evaluable Gleason scores. Eliminating the Charlson score measure of comborbidity from the model to increase the evaluable population to 236, both elevated and physiologic insulin exposure was found to slightly lower the odds of being diagnosed with a low Gleason score (Appendix Table 2). Hypercholesterolemia and hypertension are the most clinically significant comorbid diseases; through the substitution of these variables as the measure of comorbidity, the evaluable population in the model was retained at 236 patients, while still allowing for adjustment of the effect of comorbid disease. Through this, elevated insulin exposure appeared to have no effect on high-grade disease, while physiologic insulin exposures trended to lower Gleason scores at diagnosis (elevated insulin OR=1.00 (0.49-2.08); p=0.988) (physiologic insulin OR=0.59(0.22-1.60); p=0.304)) compared with

those without diabetes. (Appendix Table 3). Additionally, the duration of diabetes diagnosis prior to prostate cancer was also evaluated, but was found to have a non-significant impact on the development of high-grade prostate cancer (Appendix Table 4).

Evaluating the secondary endpoint (Figure 3), 122 patients were found to have recurrence. Median time to recurrence was 31.4 (0.03-98.1) months for those with physiologic exposure compared to 27.6 (1.38-92.7) months for those with elevated insulin exposure and 26.6 (0.92-96.2) for those without diabetes ($p=0.8623$). Adjusting for potential confounders, there was no significant effect of insulin exposure on the time to tumor progression, although it appeared that elevated insulin exposure may increase the risk of progression, while physiologic exposure decreases the risk of progression compared to non-diabetics (Table 3). Only the use of steroids prior to recurrence was found to have a statistically significant impact on the time to tumor progression. A 68% decrease ($p=0.019$) in the risk of progression over the five years studied was found in patients that used corticosteroids when controlling for other factors.

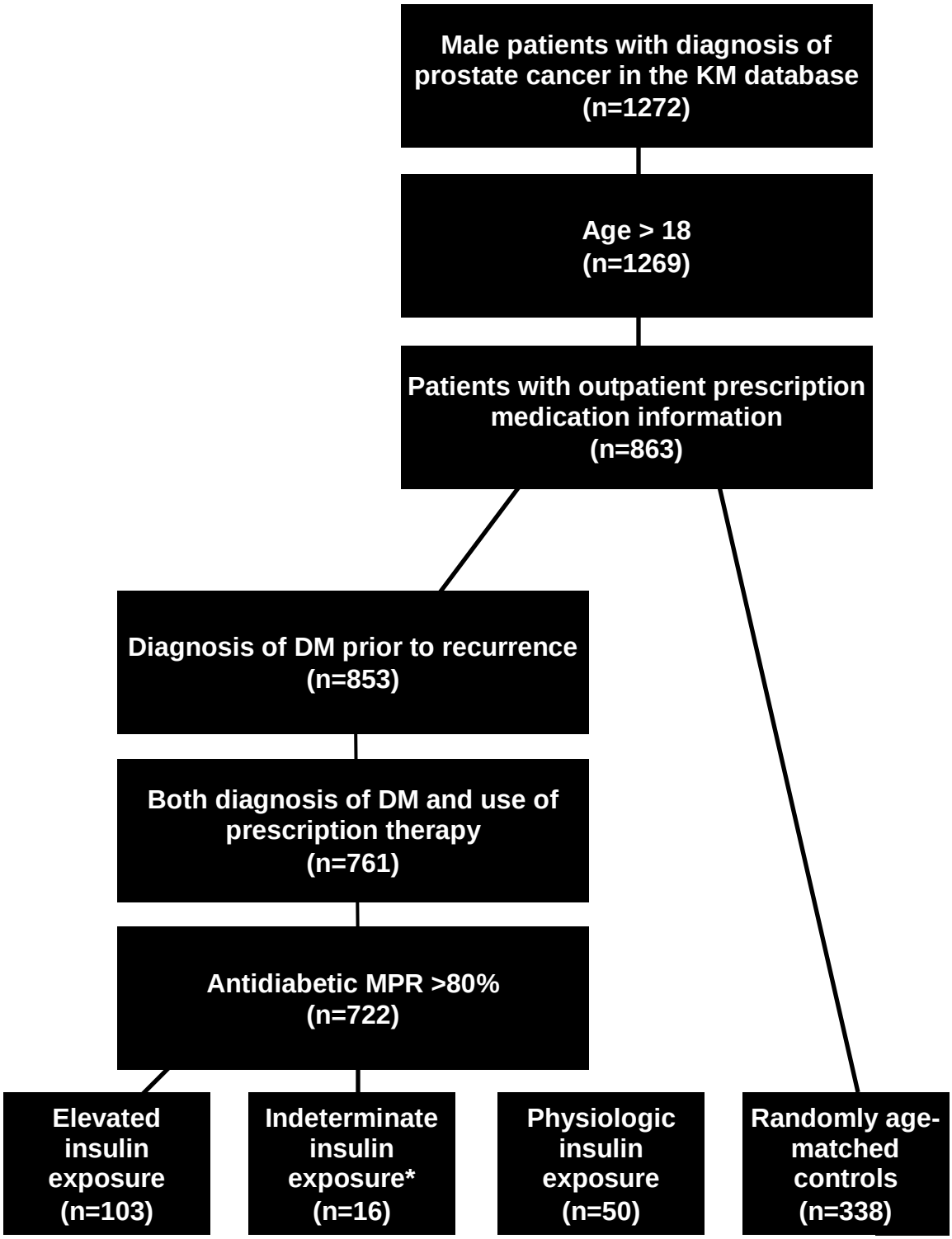
Similar to the primary endpoint analysis, the covariates containing incomplete data were eliminated from the model to improve the evaluable population. In eliminating the effects of Charlson score and stage, the use of bisphosphonates was found to increase the risk of recurrence by 1.21-4.59 times compared with those that did not have bisphosphonate exposure ($p=0.001$-0.012) (Appendix

Tables 5-6). Adjusting for comorbidities and stage through evaluating hypercholesterolemia, hypertension, and the presence of metastases at diagnosis revealed similar effects. Bisphosphonate use appeared to significantly increase the risk of progression, despite controlling for comorbidities. Within this analysis, bisphosphonates were used across all stages of disease. Further investigation of interaction between Charlson score and bisphosphonate use demonstrated no interaction. (Appendix Table 7)

Finally, the duration of diabetes prior to prostate cancer development appeared to increase the risk of progression by 30% for every year diagnosed (95% CI: 1.09-1.73; p=0.007), although this analysis was only available in a small population (Appendix Table 8).

In evaluating the effect of the presence of DM, regardless of medication use, on cancer development and progression, diabetics appeared to have no difference in the grade of tumor at diagnosis, but may have reduced risk of progressive disease when HTN and hypercholesterolemia are controlled for. The complete analysis of the effects of DM regardless of medication treatment can be found in Appendix Tables 9-16.

Figure 1: Patient selection for cases and randomly selected controls



* Patients with indeterminate exposure were excluded from the final analysis

Table 1: Patient Demographic Information

	Elevated insulin exposure	Physiologic insulin exposure	No evidence of DM	Total	p-value
N	103 (20.98%)	50 (10.18%)	338 (68.84%)	491	
Age, *years* (mean,SD)	70.8 (±9.78)	71.2 (±9.32)	70.6 (±10.18)	70.7 (±9.99)	0.9250
Geography					0.651
Urban	32 (31.07%)	10 (20.00%)	96 (28.40%)	138 (28.11%)	
Suburban	16 (15.53%)	11 (22.00%)	61 (18.05%)	88 (17.92%)	
Rural	55 (53.40%)	29 (58.00%)	181 (53.55%)	265 (53.97%)	
Stage*	n=62	n=30	n=202	n=294	0.281
Localized	46 (74.19%)	26 (86.67%)	142 (70.30%)	214 (72.79%)	
Regional	4 (6.45%)	0 (0%)	11 (5.45%)	15 (5.10%)	
Distant Metastases	7 (11.29%)	2 (6.67%)	39 (19.31%)	48(16.33%)	
Unknown/unstageable	5 (8.06%)	2 (6.67%)	10 (4.95%)	17 (5.78%)	
Presence of metastases at diagnosis					0.159
No	96 (93.20%)	48 (96.00%)	299 (88.46%)	443 (90.22%)	
Yes	7 (6.80%)	2 (4.00%)	39 (11.54%)	48 (9.78%)	
Metastatic sites					0.119
No metastatic sites	96 (93.20%)	48 (96.00%)	299 (88.46%)	443 (90.22%)	
Bone/Spine	1 (0.97%)	2 (4.00%)	15 (4.44%)	18 (3.67%)	
Other sites	6 (5.83%)	0 (0%)	24 (7.10%)	30 (6.11%)	
Comorbidity Information					
Charlson scores (median, range)*	2 (1-7) n=86	2 (1-5) n=40	1 (1-12) n=173	2 (1-12) n=299	0.0351
Presence of Hypertension					<0.001
No	5 (4.85%)	1 (2.00%)	62 (18.34%)	68 (13.85%)	
Yes	98 (95.15%)	49 (98.00%)	276 (81.66%)	423 (86.15%)	

Table 1: Patient Demographic Information continued on page 20

Presence of Hypercholesterolemia					<0.001
No	51 (49.51%)	23 (46.00%)	233 (68.93%)	307 (62.53%)	
Yes	52 (50.49%)	27 (54.00%)	105 (31.07%)	184 (37.47%)	
Medication Use					
Chemotherapy Use					0.088
No	90 (87.38%)	49 (98.00%)	308 (91.12%)	447 (91.04%)	
Yes	13 (12.62%)	1 (2.00%)	30 (8.88%)	44 (8.96%)	
Antiandrogen/GNRH agonist use					0.869
No	82 (79.61%)	38 (76.00%)	266 (78.70%)	386 (78.62%)	
Yes	21 (20.39%)	12 (24.00%)	72 (21.30%)	105 (21.38%)	
Bisphosphonate Use					0.706
No	96 (93.20%)	48 (96.00%)	311 (92.01%)	455 (92.67%)	
Yes	7 (6.80%)	2 (4.00%)	27 (7.99%)	36 (7.33%)	
Corticosteroid Use‡					0.118
No	82 (79.61%)	45 (90.00%)	262 (77.51%)	389 (79.23%)	
Before diagnosis	5 (4.85%)	1 (2.00%)	8 (2.37%)	14 (2.85%)	0.346
Spanning diagnosis	12 (11.65%)	4 (8.00%)	43 (12.72%)	59 (12.02%)	0.722
After diagnosis	4 (3.88%)	0 (0.00%)	25 (7.40%)	29 (5.91%)	0.068
Diabetes Information					
Time diagnosed with DM, *years* (median, range)	4.2 (0.16-9.61)	3.9 (0.16-9.59)	0 (0)	4.1 (0.16-9.61)	0.5147
Time from diagnosis of DM to diagnosis of PCa, *years* (mean, SD)	1.8 (±1.89)	1.8 (±2.01)	0 (0)	1.8 (±1.93)	0.8507

Table 1: Patient Demographic Information continued on page 21

Antidiabetic Medication Use					
Sulfonylurea use					
No sulfonylurea use	10 (9.71%)	38 (76.00%)	338 (100%)	386 (78.62%)	
Sulfonlyurea + other DM	69 (66.99%)	12 (24.00%)	0 (0%)	81 (16.50%)	<0.001
Exclusive sulfonylurea	24 (23.30%)	0 (0%)	0 (0%)	24 (4.89%)	<0.001
Thiazolendione use (TZD)					
No TZD use	69 (66.99%)	26 (52.00%)	338 (100%)	433 (88.19%)	
TZD + other DM med	34 (33.01%)	18 (36.00%)	0 (0%)	52 (10.59%)	<0.001
Exclusive TZD	0 (0%)	6 (12.00%)	0 (0%)	6(1.22%)	<0.001
Metformin use					
No metformin use	48 (46.60%)	19 (38.00%)	338 (100%)	405 (82.48%)	
Metformin + other DM	55 (53.40%)	17 (34.00%)	0 (0%)	72 (14.66%)	<0.001
Exclusive metformin	0 (0%)	14 (28.00%)	0 (0%)	14 (2.85%)	<0.001
Insulin use					
No insulin use	60 (58.25%)	31 (62.00%)	338 (100%)	429 (87.37%)	
Insulin+ other DM	37 (35.92%)	14 (28.00%)	0 (0%)	51 (11.88%)	<0.001
Exclusive insulin	6 (5.83%)	5 (10.00%)	0 (0%)	11 (2.24%)	<0.001
Average Medication Possession Ratio (MPR) of Diabetic Meds (median, range)	1.00 (0.80-4.72)	0.99 (0.82-3.53)	0 (0)	1.00 (0.80-4.72)	0.7974
Use of antidiabetic medications after PCa dx (as percent of total DMgrp)	14 (13.59%)	11 (22.00%)	0 (0%)	25 (5.09%)	

*Not available for all patients; number evaluated listed

‡Differences between the steroid group overall listed first; differences listed with each point of steroid use (before, during, after) are listed at the point of use – these were determined from dichotomous values (e.g. used/did not use steroid before diagnosis)

Figure 2: Gleason score based on insulin exposure

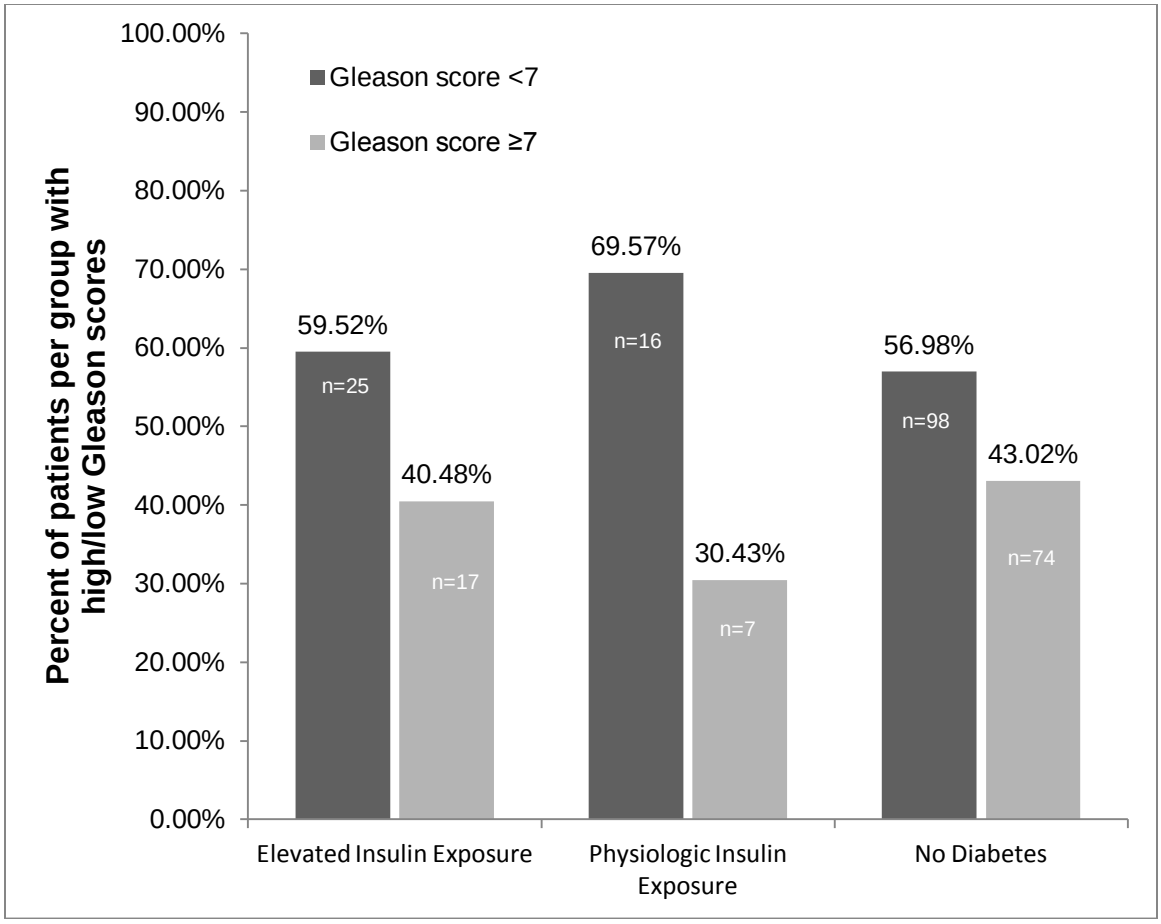


Table 2: Multivariate Analysis of Odds of Developing High Gleason Score Based on Insulin Exposure (n=133)

	Odds Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	0.50	(0.17-1.52)	0.222
Rural	0.74	(0.30-1.80)	0.500
Charlson score	1.07	(0.79-1.44)	0.670
Corticosteroid Use (before dx)			
No	Reference		
Yes	1.47	(0.23-9.46)	0.685
Diabetes Group			
No Diabetes	Reference		
Elevated insulin exposure	1.04	(0.44-2.44)	0.929
Physiologic insulin exposure	0.61	(0.22-1.70)	0.350
Physiologic compared to elevated	0.61	(0.23-1.62)	0.320

Figure 3: Kaplan Meier Analysis of Time to Progression by Insulin Exposure

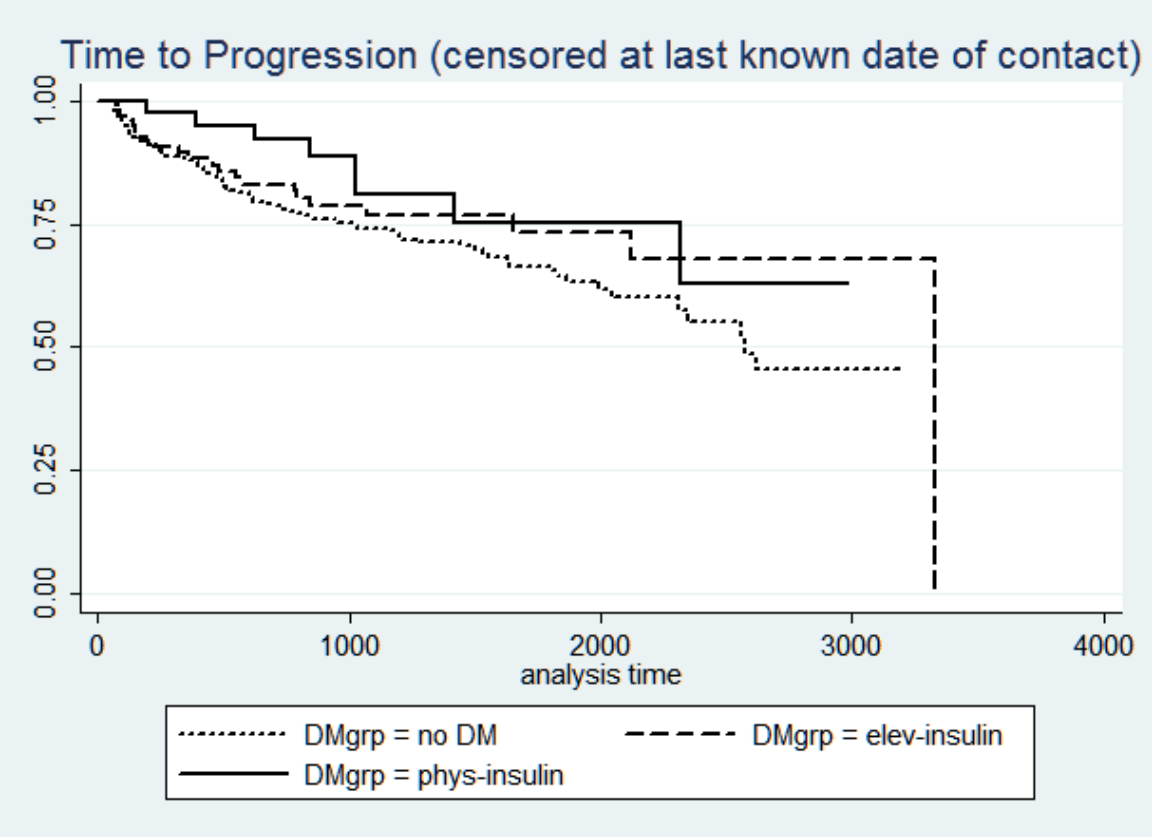


Table 3: Multivariate Analysis of Hazard of Prostate Cancer Progression (n=168)

	Hazard Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	0.82	(0.31-2.15)	0.684
Rural	0.68	(0.30-1.53)	0.351
Charlson score	0.85	(0.62-1.16)	0.313
Stage			
Localized	Reference		
Regional	0.96	(0.28-3.30)	0.945
Distant Metastases	0.96	(0.36-2.53)	0.926
Unknown/unstageable	1.83	(0.42-8.01)	0.421
Corticosteroid Use (prior to recurrence)			
No	Reference		
Yes	0.32	(0.13-0.83)	0.019
Bisphosphonate Use (prior to recurrence)			
No	Reference		
Yes	2.01	(0.64-6.35)	0.232
Antiandrogen/GNRH agonist use (prior to recurrence)			
No	Reference		
Yes	0.91	(0.43-1.93)	0.814
Diabetes Group			
No Diabetes	Reference		
Elevated insulin exposure	1.18	(0.57-2.44)	0.649
Physiologic insulin exposure	0.62	(0.22-1.73)	0.363
Physiologic compared to elevated	0.58	(0.22-1.53)	0.272

SECTION FOUR: DISCUSSION

This study found that management of diabetes with medications which create supra-physiologic insulin exposure does not lead to more aggressive prostate cancers at diagnosis and shorter time to progression. Previous analyses have demonstrated a link between diabetes and developing cancer, an effect which is potentially modified by the choice of antidiabetic treatment.[33-37] In vitro studies clearly demonstrate that insulin can stimulate IGFR-1 receptors in prostate cancer cell lines and stimulate mitogenic and angiogenesis pathways. These findings suggest that this isn't a disease-disease interaction, but rather a disease treatment – disease interaction. While several others have evaluated the association of diabetes and cancer, none have evaluated disease management leading to increased insulin exposure with prostate cancer biology and progression.

The findings in this analysis are consistent with the work reported by Weinstein et al. who evaluated the *in vitro* application of human insulin and human insulin analogs to prostate tumor cells.[28] Here, recombinant human insulin was found to slightly increase growth, but not significantly when compared to control cells. When forming the hypothesis, this data was considered, but the *in-vivo* data presented by Venkateswaran was more compelling. In this, mice with high serum insulin were found to have increased tumor growth over those with low circulating insulin.[30] This data supports the hypothesis that insulin increases cell growth. Based on the major principle of cancer biology, that increased growth

increases cellular instability and increases tumor grade, it is reasonable to then think that insulin may increase the mitogenic growth of prostate tumors and increase tumor grade as further stated in the hypothesis explored.[53]

However, recent data released by the Health Professionals Study suggest that low-grade tumors (Gleason score <7) are associated with higher levels of insulin-like growth factor and binding protein (IGF-1 and IGFBP-3), a finding that is counter to the proposed mechanism seen in this study and previous literature evaluations.[54] The data in the Health Professionals Study suggests that increasing insulin levels may actually lead to lower-grade tumors in patients with high serum insulin who develop cancer. From this, alternate hypothesis for increased high-grade tumors in patients with elevated insulin exposure should be further investigated, including the effect of DM on testosterone. Diabetes is linked with lower levels of circulating testosterone, a known stimulatory agent of prostate cancer growth. Further, testosterone has been associated with higher grade tumors, a finding that supports what was seen in the studies by Hong and DeNuzio.[55-57] As demonstrated there are conflicting reports, and potentially conflicting underlying biochemical mechanisms regarding the effect of diabetes on prostate tumor grade. This highlights the importance of further study in this area with clear measurement of the effect of serum insulin, insulin/IGFR-1 receptors and testosterone on tumor grade.

Looking at the effects between cancer and insulin in diabetic patients in epidemiologic data, the presence of diabetes has been shown to increase the risk of high grade prostate tumor development, a finding that is not supported by this analysis. Hong et al. found that in patients undergoing prostate biopsy, those with self-reported DM were found to have a 1.54 times higher odds of developing tumors with Gleason score ≥7.[15] Similarly, De Nunzio et al. recently published a similar study that found that patients with metabolic syndrome (defined by the ATPIII criteria – the measured presence of 3 of the following: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol, hypertension or high fasting blood glucose) had a 3.82 times higher risk of high-grade tumors (Gleason ≥7).[40] While both of these analyses demonstrate increased grade tumors in diabetic patients, the methods of defining diabetes are subject to bias or are limited by one-time evaluation, potentially altering the results.

Other studies on the effect of DM on tumor grade report findings more similar to what is seen here – diabetes potentially decreases the odds of high grade prostate tumor development. Gong et al. reported a decreased in the odds of higher-grade tumors in patients with self-reported DM (OR=0.72 (0.55-0.94)), although again the definition of DM in these patients is subject to recall bias. Additionally in Gong's analysis, patients with higher BMI and weight also were found to have an increased odds of high-grade tumor development.[6] Previous studies evaluating the effect of metabolic syndrome have found similar results, independent of the effects of DM and insulin exposure, most likely through

alterations in lipid and androgen metabolism.[58] Farwell et al. recently reported a 10% increase in the risk of high-grade tumors in patients with elevated baseline total cholesterol, while Llaverias et al. found that mice fed high-fat/high-cholesterol diets had increased cellular proliferation and metastatic spread.[59,60] Although the models within this study were unable to account for BMI and weight, hypercholesterolemia was not found to have an effect on tumor grade or progression, contrary to previous analysis. These findings suggest that the interaction between DM, other factors in metabolic syndrome, serum insulin and tumor growth is complex.

Although epidemiologic evidence exists suggesting that the use of antidiabetic therapy may alter the development of prostate tumors, again, no evidence exists that these agents alter tumor grade. In this evaluation, the use of insulin stimulating agents was associated with a slight increase in high grade tumors while non-stimulating agents were associated with a lower grade tumor compared to those without diabetes. While this is not statistically significant, this does provide evidence that perhaps the increase in serum insulin seen may lead to increased mitogenic effects. This study was only able to access data from the Kentucky Medicaid database over a 5 year period. Evaluation in a larger database, such as the Veteran's Administration databases may provide further clarity on the effect of diabetic medication use on the development of high-grade prostate tumors.

Similarly, the difference in the time to tumor progression based on the use of antidiabetic medications has not been previously evaluated in the literature. Overall, this study found a potentially lower risk of tumor progression in those using TZDs, metformin or low-dose insulin compared to non-diabetics and a higher risk of progression in those using sulfonylureas or high-dose insulin compared to non-diabetics. Although this was not statistically significant, this observed phenomena may be due in part to independent anti-tumor affects of metformin and TZDs outside of their effects on serum insulin. Metformin has been shown inhibit in-vitro growth of prostate cell lines through AMPK activation and mTOR inhibiton.[61] Thiazolidinediones have also been shown to have independent anti-tumor activity in vitro. This effect is thought to be primarily through the activation of PPAR-γ, although PPAR-γ independent mechanisms have also been suggested.[62] Although sulfonylureas have not yet been shown to have antitumor effects, it is thought that the effects on increased tumor risk and mortality seen with sulfonylureas may be a statistical abnormality due to the comparison to those with known anti-tumor activity.[63] In this study metformin and TZDs were associated with a potentially decreased time to progression, while sulfonylureas had a slight increase in progression. Since the anti-tumor effects were unable to be accounted for it is difficult to ascertain if the effects seen were a result of the effect on insulin, or a modification of alternate tumorgenic cellular pathways by diabetic medications.

Alternate models found an overall decrease in tumor progression in patients with elevated and physiologic insulin exposure compared to those without DM. Similar to the results of the primary evaluation, this was not statistically significant, but leads to interesting observations on the effect of DM on tumor progression. In addition to potential anti-tumor effects of diabetic medications, the decrease in progression risk in those with elevated exposure may indicated a protective effect of physiologic changes in diabetic patients. Vascular changes are common in diabetics, often leading to numerous complications on end-organs. Post-hoc analysis demonstrated that overall case patients in both groups had a lower incidence of metastatic disease than non-diabetics, indicating that despite potentially higher grade at diagnosis, diabetics may have less metastatic spread due to poor vascularization. This hypothesis could not be evaluated in this analysis, but should continue to be investigated in future studies.

In addition to the effects of antidiabetic agents, several covariates were found to alter the time to tumor progression. Patients with longer durations of DM prior to tumor diagnosis were found to have an increased risk of progression, adjusted for use of different diabetic medications. Previous studies have shown a decreased risk of tumor development in those with longer duration of DM, although the effect of this on progression in unknown.[13,14] Future study in this area should adjust for actual serum levels since it appears that there is a disparate effect seen in patients with changing insulin exposures.

Corticosteroid use was consistently found to reduce the risk of progressive disease, a finding that is not well evaluated in the literature. While corticosteroids today are primarily used to reduce the inflammation and pain of metastatic lesions, early studies suggested that they may play a role in inhibiting adrenal-produced testosterones. [64] Short term corticosteroid use may have no effect on testosterone levels, but long term use in older patients has been shown to have a dose-dependent decrease in serum testosterone.[65,66] Within this analysis, steroids were used across all metastatic sites, including some use in those without known metastatic disease. The potential decrease in serum testosterone may have led to delayed progression within these patients, although will need to be further studied.

Although bisphosphonates are typically shown to limit tumor progression, this analysis found that patients using these agents had a significantly increased risk of progression. Bisphosphonates have been shown in numerous cellular studies to inhibit cell signaling pathways that are critical to tumor proliferation, invasion and adhesion.[38,67,68] Conversely, in-vivo mouse models have shown that the use of prophylactic and treatment zoledronic acid were not associated with decreased tumor growth or metastatic spread.[69] Although human studies have demonstrated the effect of bisphosphonates to improve quality of life and reduce skeletal-related events in prostate cancer patients, the use of these agents is typically limited to those with metastatic or highly aggressive disease. The increase risk of progression due to bisphosphonate use may be an artifact of the

correlation of bisphosphonate use to metastatic patients with high tumor burden in bone, a characteristic which could not be discerned in this dataset. Since this effect was not seen until stage was no longer evaluated as a covariate, it is possible that the risk seen is merely a measure of the risk of progression in higher stage disease.

All studies have strength and limitations. This study had several factors that may have limited the ability to detect a difference in tumor grade and progression between users of different antidiabetic medications. First, the sample size was small for the type of large-cohort analysis conducted. Although the trends seen in regards to the effects of insulin exposure on tumor grade support the hypothesis, the lack of power in this analysis leads to inconclusive results. Additionally, changes in endogenous secretion of insulin in patients on anti-diabetic medications could not be accounted for. This lack of quantitation of insulin may have led to unknown misclassification within the exposure groups, potentially skewing the results. Although the duration of DM was accounted for, it was limited to what was observed during the study period – thus any long-term effects of diabetes treatment prior to study initiation is unaccounted for. Further, as discussed above, this study was unable to adjust for potential independent chemotherapeutic effects of anti-diabetic treatments. Finally, analysis using large billing databases is always subject to misclassification, although this was limited through a thorough review of the available data.

SECTION FIVE: CONCLUSION

The use of antidiabetic medications that cause high insulin exposure did not increase the grade of prostate tumor upon diagnosis or decrease the time to tumor progression in this analysis. Although the results were are inconclusive this data provides needed insight into the interactions between diabetes treatments and the development and progression of prostate tumors. While this study was underpowered to provide any conclusive results, the hypothesis remains credible and should continue to be investigated through larger database analyses, as well as potential prospective studies. As seen, there is a multitude of factors that interplay within the proposed mechanism to lead to tumor development and progression. Future analysis should consider an evaluation of serum insulin, weight, BMI, lipids (cholesterol, HDL, LDL, TG), testosterone, and IGFR-1 expression on pathologic samples, along with robust medical histories (including complete antidiabetic and lipid-lowering agents, bisphosphonate use, hormone therapy, and steroid medications histories) in order to fully evaluate the effect of medications on prostate tumors. Through a better characterization of these interactions, future treatment of patients with diabetes and prostate cancer may be optimized and overall health outcomes improved.

Appendix

Appendix Table 1: NDC Codes used to determine medication classifications

Drug	Insulin Exposure Group	Medication Class	NDC
Acarbose	Excluded	Antidiabetic	26286148, 26286151, 26286251, 26286351, 16250000000
Chlorpropamide	Elevated Insulin Exposure	Antidiabetic	50110000000
Exenatide	Excluded	Antidiabetic	66780000000
Glimepiride	Elevated Insulin Exposure	Antidiabetic	39022110, 39022210, 39022211, 39022310, 39022311, 55110000000, 63300000000, 66990000000
Glipizide	Elevated Insulin Exposure	Antidiabetic	49155066, 49155073, 49156066, 49156073, 49162030, 172400000, 378100000, 591000000, 591100000, 781100000, 51080000000, 51290000000, 52540000000, 59760000000, 60510000000, 62040000000
Glyburide	Elevated Insulin Exposure	Antidiabetic	9017105, 9035204, 9344903, 39005210, 93803501, 93834301, 93834305, 93834310, 93834401, 93834405, 93834410, 93936401, 93936405, 93936410, 93943301, 93943305, 93947753, 378100000, 781100000, 38250000000, 38250000000, 51080000000, 55370000000, 55950000000, 59760000000, 59760000000, 67250000000

Glyburide/metformin	Elevated Insulin Exposure	Antidiabetic	87607211, 87607311, 87607411, 93571201, 93571205, 172600000, 228300000, 781500000, 49880000000
Insulin	Elevated Insulin Exposure if avgqty >20mL Q30days (determined on avg supply since such variation in day supply. This is based on 0.8units*85kg =68units/day; 100 units/mL= ~20mL/month) Physiologic Insulin Exposure if avgqty <20mL Q30days	Antidiabetic	2751001, 2751101, 2821501, 2831001, 2831501, 2861501, 2871501, 2872559, 2873059, 2877059, 2879459, 69005053, 88222033, 88222060, 169000000, 169200000, 169200000, 169200000, 169200000, 169200000, 169200000, 169300000, 169300000, 169400000, 169600000, 169800000, 59060000000
Metformin	Physiologic Insulin Exposure	Antidiabetic	87606005, 87606010, 87606313, 87607005, 87607010, 87607111, 87607112, 93104801, 93104805, 93104810, 93104901, 93104905, 93721401, 93721405, 93726701, 93726710, 172400000, 172400000, 185000000, 185400000, 228300000, 378000000, 555000000, 591200000, 591300000, 781500000, 904600000, 49880000000, 49880000000, 51080000000, 53490000000, 57660000000,

			60510000000, 60510000000, 62020000000, 62040000000, 62040000000, 62580000000, 62760000000, 63300000000, 65860000000, 68380000000
Miglitol	Excluded	Antidiabetic	9501201, 9501301, 9501401
Nateglinide	Excluded	Antidiabetic	78035105, 78035205
Pioglitazone	Physiologic Insulin Exposure	Antidiabetic	64760000000
Pioglitazone/ metformin	Physiologic Insulin Exposure	Antidiabetic	64760000000
Repaglinide	Excluded	Antidiabetic	169000000
Rosiglitazone	Physiologic Insulin Exposure	Antidiabetic	29315818, 29315913, 29315918, 29315920, 29316013, 29316020
Rosiglitazone/ metformin	Physiologic Insulin Exposure	Antidiabetic	7316418, 7316718, 7316720, 7316818, 7316820
Sitagliptin	Excluded	Antidiabetic	6027731
Troglitazone	Physiologic Insulin Exposure	Antidiabetic	71035223, 71035315, 71035323, 71035720
Bicalutamide		Antiandrogen/ GNRH agonist	93022056, 310100000
Flutamide		Antiandrogen/ GNRH agonist	85052506, 93712086, 172500000, 555100000
Ketoconazole		Antiandrogen/ GNRH agonist	93090001, 51670000000
Nilutamide		Antiandrogen/ GNRH agonist	88111035, 88111114
Goserelin		Antiandrogen/ GNRH agonist	310100000
Leuprolide		Antiandrogen/ GNRH agonist	300200000, 300300000, 300400000
Alendronate		Bisphosphonate	6003121, 6003144, 6007744, 6092531, 6093628, 6093631, 6093658, 93517120,

			93517144
Ibandronate		Bisphosphonate	4018682
Pamidronate		Bisphosphonate	83260901, 55390000000
Risedronate		Bisphosphonate	149000000
Zoledronic acid		Bisphosphonate	78035084, 78038725
Dexamethasone		Steroids	54317763, 54418025, 54418125, 54418325, 54418425, 54817525, 95008651, 402100000, 517500000, 603300000, 641000000, 703400000, 904000000, 49880000000, 60430000000, 63320000000
Fludrocortisone		Steroids	3042950, 115700000, 555100000
Hydrocortisone		Steroids	6061968, 9001201, 9003101, 9082501, 143100000, 536400000, 574200000, 677000000, 39820000000
Methylprednisolone		Steroids	9019009, 9019016, 9030602, 9307301, 9307303, 9347501, 74568502, 182100000, 254400000, 527100000, 536400000, 555000000, 591100000, 603500000, 677100000, 781500000, 49880000000, 51290000000, 52540000000, 59750000000, 59760000000, 62270000000, 63300000000
Prednisolone		Steroids	58180000000, 59200000000, 60430000000, 65580000000
Prednisone		Steroids	9004501, 9004502, 9004516, 9016501, 9016502, 9019301, 9019302, 9038801, 54001720, 54001725, 54001729, 54001820,

			54001825, 54001829, 54472825, 54472831, 54472925, 54472929, 54473025, 54473029, 54473325, 54474125, 54872425, 54872525, 54872625, 54874025, 143100000, 182100000, 254500000, 259000000, 364000000, 536400000, 591500000, 603500000, 677000000, 677100000, 904200000, 51080000000, 52540000000, 53490000000

Appendix Table 2: Multivariate Analysis of Odds of Developing High Gleason Score Based on Insulin Exposure (n=236; eliminating Charlson score as a covariate)

	Odds Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	0.68	(0.31-1.50)	0.338
Rural	0.93	(0.49-1.73)	0.808
Corticosteroid Use (before dx)			
No	Reference		
Yes	1.27	(0.21-7.75)	0.798
Diabetes Group			
No Diabetes	Reference		
Elevated insulin exposure	0.98	(0.48-1.97)	0.946
Physiologic insulin exposure	0.56	(0.21-1.49)	0.245
Physiologic compared to elevated	0.56	(0.22-1.48)	0.244

Appendix Table 3: Multivariate Analysis of Odds of Developing High Gleason Score Based on Insulin Exposure (n=236; uses presence of hypertension and hypercholesterolemia as a measure of comorbid disease)

	Odds Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	0.67	(0.30-1.48)	0.318
Rural	0.90	(0.46-1.73)	0.741
Presence of HTN			
No	Reference		
Yes	0.67	(0.31-1.45)	0.306
Presence of Hypercholesterolemia			
No	Reference		
Yes	1.12	(0.61-2.04)	0.715
Corticosteroid Use (before dx)			
No	Reference		
Yes	1.17	(0.19-7.26)	0.867
Diabetes Group			
No Diabetes	Reference		
Elevated insulin exposure	1.00	(0.49-2.08)	0.988
Physiologic insulin exposure	0.59	(0.22-1.60)	0.304
Physiologic compared to elevated	0.59	(0.22-1.57)	0.293

Appendix Table 4: Multivariate Analysis of Odds of Developing High Gleason Score Based on Insulin Exposure (n=61; includes measure of duration of DM diagnosis prior to prostate cancer)

	Odds Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	0.76	(0.13-4.48)	0.762
Rural	0.34	(0.05-2.29)	0.267
Presence of HTN			
No	Reference		
Yes	Dropped – all those without HTN (#2) did not have a high Gleason		
Presence of Hypercholesterolemia			
No	Reference		
Yes	2.54	(0.43-14.94)	0.302
Corticosteroid Use (before dx)			
No	Reference		
Yes	2.04	(0.10-41.4)	0.641
Diabetes Group			
No Diabetes	Reference		
Elevated insulin exposure	N/A	N/A	N/A
Physiologic insulin exposure	0.49	(0.15-1.65)	0.250
Physiologic compared to elevated	N/A	N/A	N/A
Duration of DM diagnosis prior to PCa(yr)	0.87	(0.58-1.33)	0.528

Appendix Table 5: Multivariate Analysis of Hazard of Prostate Cancer Progression (n=294; eliminating Charlson score as a covariate)

	Hazard Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	0.79	(0.40-1.55)	0.496
Rural	0.80	(0.47-1.36)	0.416
Stage			
Localized	Reference		
Regional	0.94	(0.36-2.41)	0.890
Distant Metastases	0.95	(0.47-1.90)	0.881
Unknown/unstageable	0.77	(0.28-2.15)	0.623
Corticosteroid Use (prior to recurrence)			
No	Reference		
Yes	0.53	(0.27-1.03)	0.060
Bisphosphonate Use (prior to recurrence)			
No	Reference		
Yes	2.36	(1.21-4.59)	0.012
Antiandrogen/GNRH agonist (prior to recurrence)			
No	Reference		
Yes	1.02	(0.61-1.70)	0.950
Diabetes Group			
No Diabetes	Reference		
Elevated insulin exposure	0.95	(0.54-1.68)	0.872
Physiologic insulin exposure	0.59	(0.23-1.51)	0.272
Physiologic compared to elevated	0.60	(0.24-1.51)	0.278

Appendix Table 6: Multivariate Analysis of Hazard of Prostate Cancer Progression (n=491; eliminating Charlson score and stage as a covariate)

	Hazard Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	1.14	(0.68-1.91)	0.622
Rural	0.85	(0.56-1.30)	0.464
Corticosteroid Use (prior to recurrence)			
No	Reference		
Yes	0.56	(0.34-0.93)	0.025
Bisphosphonate Use (prior to recurrence)			
No	Reference		
Yes	2.44	(1.46-4.06)	0.001
Antiandrogen/GNRH agonist use (prior to recurrence)			
No	Reference		
Yes	1.20	(0.79-1.83)	0.390
Diabetes Group			
No Diabetes	Reference		
Elevated insulin exposure	0.75	(0.46-1.20)	0.231
Physiologic insulin exposure	0.53	(0.26-1.10)	0.086
Physiologic compared to elevated	0.56	(0.27-1.16)	0.117

Appendix Table 7: Multivariate Analysis of Hazard of Prostate Cancer Progression (n=491; uses presence of hypertension and hypercholesterolemia as a measure of comorbid disease)

Variable	Hazard Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	1.10	(0.65-1.85)	0.728
Rural	0.79	(0.51-1.23)	0.300
Presence of HTN			
No	Reference		
Yes	0.87	(0.52-1.48)	0.618
Presence of Hypercholesterolemia			
No	Reference		
Yes	1.35	(0.92-1.98)	0.127
Presence of metastases at diagnosis			
No	Reference		
Yes	0.93	(0.48-1.81)	0.840
Corticosteroid Use (prior to recurrence)			
No	Reference		
Yes	0.58	(0.35-0.97)	0.037
Bisphosphonate Use (prior to recurrence)			
No	Reference		
Yes	2.41	(1.44-4.04)	0.001
Antiandrogen/GNRH agonist (prior to recurrence)			
No	Reference		
Yes	1.25	(0.81-1.91)	0.311
Diabetes Group			
No Diabetes	Reference		
Elevated insulin exposure	0.73	(0.45-1.18)	0.198
Physiologic insulin exposure	0.50	(0.24-1.06)	0.070
Physiologic compared to elevated	0.55	(0.26-1.14)	0.106

Appendix Table 8: Multivariate Analysis of Hazard of Prostate Cancer Progression (n=153; includes measure of duration of DM diagnosis prior to prostate cancer)

Variable	Hazard Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	2.19	(0.79-6.08)	0.133
Rural	0.57	(0.20-1.66)	0.303
Presence of HTN			
No	Reference		
Yes	1.17	(0.14-9.63)	0.880
Presence of Hypercholesterolemia			
No	Reference		
Yes	1.37	(0.59-3.20)	0.466
Presence of metastases at diagnosis			
No	Reference		
Yes	1.07	(0.13-8.58)	0.947
Corticosteroid Use (prior to recurrence)			
No	Reference		
Yes	0.31	(0.08-1.12)	0.073
Bisphosphonate Use (prior to recurrence)			
No	Reference		
Yes	4.16	(1.28-13.5)	0.017
Antiandrogen/GNRH agonist use (prior to recurrence)			
No	Reference		
Yes	1.04	(0.43-2.53)	0.925
Diabetes Group			
No Diabetes	Reference		
Elevated insulin exposure	N/A	N/A	N/A
Physiologic insulin exposure	0.58	(0.24-1.41)	0.230
Physiologic compared to elevated	N/A	N/A	N/A
Duration of DM diagnosis prior to PCa (years)	1.26	(1.02-1.55)	0.031

Appendix Table 9: Multivariate Analysis of Odds of Developing High Gleason Score Based on Presence of Diabetes (n=133)

	Odds Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	0.52	(0.17-1.57)	0.249
Rural	0.75	(0.31-1.83)	0.532
Charlson score	1.09	(0.81-1.46)	0.573
Corticosteroid Use (before dx)			
No	Reference		
Yes	1.44	(0.23-9.11)	0.699
Presence of DM			
No	Reference		
Yes	0.84	(0.41-1.75)	0.648

Appendix Table 10: Multivariate Analysis of Odds of Developing High Gleason Score Based on Presence of Diabetes (n=236; eliminating Charlson score as a covariate)

	Odds Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	0.68	(0.31-1.51)	0.347
Rural	0.93	(0.50-1.74)	0.819
Corticosteroid Use (before dx)			
No	Reference		
Yes	1.21	(0.20-7.39)	0.835
Presence of DM			
No	Reference		
Yes	0.81	(0.44-1.49)	0.501

Appendix Table 11: Multivariate Analysis of Odds of Developing High Gleason Score Based on Presence of Diabetes (n=236; uses presence of hypertension and hypercholesterolemia as a measure of comorbid disease)

	Odds Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	0.67	(0.30-1.49)	0.324
Rural	0.90	(0.46-1.73)	0.742
Presence of Hypertension			
No	Reference		
Yes	0.66	(0.30-1.43)	0.288
Presence of Hypercholesterolemia			
No	Reference		
Yes	1.31	(0.62-2.06)	0.687
Corticosteroid Use (before dx)			
No	Reference		
Yes	1.12	(0.18-6.92)	0.905
Presence of DM			
No	Reference		
Yes	0.84	(0.45-1.59)	0.601

Appendix Table 12: Multivariate Analysis of Hazard of Prostate Cancer Progression Based on Presence of Diabetes (n=168)

	Hazard Ratio	**95% Confidence Interval**	**p-value**
Rurality			
Urban	Reference		
Suburban	0.83	(0.32-2.17)	0.706
Rural	0.73	(0.33-1.62)	0.439
Charlson score	0.86	(0.63-1.18)	0.342
Stage			
Localized	Reference		
Regional	1.07	(0.32-3.65)	0.910
Distant Metastases	0.97	(0.37-2.57)	0.952
Unknown/unstageable	1.76	(0.40-7.67)	0.452
Corticosteroid Use (prior to recurrence)			
No	Reference		
Yes	0.34	(0.13-0.86)	0.024
Bisphosphonate Use (prior to recurrence)			
No	Reference		
Yes	2.07	(0.65-6.55)	0.217
Antiandrogen/GNRH agonist use (prior to recurrence)			
No	Reference		
Yes	0.90	(0.43-1.90)	0.784
Presence of Diabetes			
No	Reference		
Yes	0.96	(0.49-1.87)	0.907

Appendix Table 13: Multivariate Analysis of Hazard of Prostate Cancer Progression Based on Presence of Diabetes (n=294; eliminating Charlson score as a covariate)

	Hazard Ratio	**95% Confidence Interval**	**p-value**
Rurality			
Urban	Reference		
Suburban	0.76	(0.39-1.49)	0.427
Rural	0.81	(0.48-1.37)	0.435
Stage			
Localized	Reference		
Regional	0.98	(0.38-2.51)	0.960
Distant Metastases	0.95	(0.48-1.91)	0.894
Unknown/unstageable	0.80	(0.29-2.20)	0.661
Corticosteroid Use (prior to recurrence)			
No	Reference		
Yes	0.53	(0.27-1.05)	0.068
Bisphosphonate Use (prior to recurrence)			
No	Reference		
Yes	2.38	(1.22-4.64)	0.011
Antiandrogen/GNRH agonist use (prior to recurrence)			
No	Reference		
Yes	1.01	(0.60-1.69)	0.973
Presence of Diabetes			
No	Reference		
Yes	0.84	(0.50-1.39)	0.493

Appendix Table 14: Multivariate Analysis of Hazard of Prostate Cancer Progression Based on Presence of Diabetes (n=491; eliminating Charlson score and stage as a covariate)

	Hazard Ratio	**95% Confidence Interval**	**p-value**
Rurality			
Urban	Reference		
Suburban	1.11	(0.66-1.85)	0.694
Rural	0.85	(0.56-1.30)	0.451
Corticosteroid Use (prior to recurrence)			
No	Reference		
Yes	0.57	(0.34-0.94)	0.028
Bisphosphonate Use (prior to recurrence)			
No	Reference		
Yes	2.45	(1.47-4.08)	0.001
Antiandrogen/GNRH agonist use (prior to recurrence)			
No	Reference		
Yes	1.20	(0.79-1.83)	0.390
Presence of Diabetes			
No	Reference		
Yes	0.67	(0.44-1.02)	0.062

Appendix Table 15: Multivariate Analysis of Hazard of Prostate Cancer Progression Based on Presence of Diabetes (n=491; uses presence of hypertension and hypercholesterolemia as a measure of comorbid disease)

Variable	Hazard Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	1.07	(0.64-1.79)	0.807
Rural	0.79	(0.51-1.23)	0.292
Presence of HTN			
No	Reference		
Yes	0.87	(0.51-1.47)	0.598
Presence of Hypercholesterolemia			
No	Reference		
Yes	1.34	(0.91-1.97)	0.135
Presence of metastases at diagnosis			
No	Reference		
Yes	0.94	(0.49-1.82)	0.853
Corticosteroid Use (prior to recurrence)			
No	Reference		
Yes	0.59	(0.35-0.98)	0.042
Bisphosphonate Use (prior to recurrence)			
No	Reference		
Yes	2.43	(1.45-4.07)	0.001
Antiandrogen/GNRH agonist (prior to recurrence)			
No	Reference		
Yes	1.25	(0.81-1.91)	0.311
Presence of Diabetes			
No	Reference		
Yes	0.65	(0.42-1.00)	0.051

Appendix Table 16: Multivariate Analysis of Hazard of Prostate Cancer Progression Based on Presence of Diabetes (n=153; includes measure of duration of DM diagnosis prior to prostate cancer)

Variable	Hazard Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	1.90	(0.70-5.12)	0.206
Rural	0.59	(0.21-1.67)	0.319
Presence of HTN			
No	Reference		
Yes	0.93	(0.12-7.30)	0.945
Presence of Hypercholesterolemia			
No	Reference		
Yes	1.31	(0.57-3.02)	0.520
Presence of metastases at diagnosis			
No	Reference		
Yes	1.11	(0.14-8.87)	0.924
Corticosteroid Use (prior to recurrence)			
No	Reference		
Yes	0.34	(0.10-1.22)	0.099
Bisphosphonate Use (prior to recurrence)			
No	Reference		
Yes	4.09	(1.27-13.2)	0.018
Antiandrogen/GNRH agonist (prior to recurrence)			
No	Reference		
Yes	1.03	(0.42-2.53)	0.942
Presence of Diabetes			
No	Reference		
Yes	Dropped due to collinearity with DM time variables		
Duration of DM diagnosis prior to PCa (years)	1.28	(1.04-1.57)	0.018

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