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Journal

Cancer Epidemiology, Biomarkers and Prevention, 32(9)

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Publication Date

2023-09-01

DOI

10.1158/1055-9965.EPI-22-1324

Peer reviewed

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2023 September 01; 32(9): 1208–1216.

doi:10.1158/1055-9965.EPI-22-1324.

Diabetes and prostate cancer outcomes in men with nonmetastatic castrate-resistant prostate cancer: Results from the SEARCH Cohort

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Abstract

Background: The prognosis of diabetic men with advanced prostate cancer (PC) is poorly understood and understudied. Hence, we studied associations between diabetes and progression to metastases, PC-specific mortality (PCSM) and all-cause mortality (ACM) in men with non-metastatic castrate-resistant PC (nmCRPC).

Methods: Data from men diagnosed with nmCRPC between 2000 and 2017 at 8 Veterans Affairs Health Care Centers were analyzed using Cox regression to determine hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between diabetes and outcomes. Men with diabetes were classified according to (i) ICD-9/10 codes only, (ii) two HbA1c values > 6.4% (missing ICD-9/10 codes), and (iii) all diabetic men ((i) and (ii) combined).

Results: Of 976 men (median age: 76 years), 304 (31%) had diabetes at nmCRPC diagnosis, of whom 51% had ICD-9/10 codes. During a median follow-up of 6.5 years, 613 men were diagnosed with metastases, and 482 PCSM and 741 ACM events occurred. In multivariable-adjusted models, ICD-9/10 code-identified diabetes was inversely associated with PCSM (HR= 0.67; 95%CI: 0.48–0.92) while diabetes identified by high HbA1c values (no ICD-9/10 codes) was

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Disclosure of Potential Conflicts of Interest: The authors declare no potential conflicts of interest.

associated with an increase in ACM (HR=1.41; 95%CI: 1.16–1.72). Duration of diabetes, prior to CRPC diagnosis was inversely associated with PCSM among men identified by ICD-9/10 codes and/or HbA1c values (HR=0.93; 95%CI: 0.88–0.98).

Conclusion: In men with late-stage PC, ICD-9/10 code-identified diabetes is associated with better overall survival than 'undiagnosed' diabetes identified by high HbA1c values only.

Impact: Our data suggest that better diabetes detection and management may improve survival in late-stage PC.

Keywords

Diabetes; castration-resistant prostate cancer; metastases; prostate cancer-specific mortality; hemoglobin A1c

Introduction:

Non-metastatic castration-resistant prostate cancer (nmCRPC) is characterized by absence of metastasis on imaging and progressively increasing prostate-specific antigen (PSA) levels despite castrate testosterone levels following continuous treatment with androgen deprivation therapy (ADT) (1). CRPC is a disease with a poor prognosis with a third of patients developing metastases or dying within a median of 2.5 years (2). Though its prevalence is difficult to estimate, it is anticipated to increase in coming years owing to widespread demographic changes that include a growing population of older men (3). As prostate cancer (PC) and diabetes are conditions that commonly co-exist in elderly men, understanding the effect of diabetes on the prognosis of PC is of critical importance in optimizing disease management. Importantly, since men with CRPC are treated with ADT which increases the risk of newly developed diabetes, the prevalence of this metabolic disorder increases even further in patients with CRPC (4).

To date, much of the literature has focused on the effect of diabetes on PC risk and incidence (5,6). While diabetes is associated with an increase in the incidence and poor outcomes for most cancers (7), the evidence is inconclusive for PC risk with several studies and meta-analyses reporting inverse associations (8–12) and some reporting null findings (13–15). Paradoxically, though less well studied, diabetes appears to be associated with worse PC outcomes, particularly in men not optimally treated for diabetes, and those using insulin to control hyperglycemia (16). In a study of men with localized PC treated with radiation, diabetic men not treated for diabetes were more likely to experience biochemical recurrence (BCR) and 4 times as likely to succumb to PC-specific mortality (PCSM) than men without diabetes (16). In another study of men diagnosed with CRPC, men with high levels of hemoglobin A1c (HbA1c: 7.8–11.6 %) were reported to have poor response to treatment with novel antiandrogens (abiraterone and enzalutamide), manifested by reduced progression free survival compared with men with HbA1c <6.0 % (17). In a sub-group of diabetic men undergoing radical prostatectomy (RP) for definitive treatment of localized PC, results from the Shared Equal Access Regional Cancer Hospital (SEARCH) cohort showed that increasing levels of HbA1c were associated with a 21% increase in the risk of metastases and 27% increase in the risk of CRPC (18). As HbA1c is a surrogate marker of

insulin resistance it may also be a marker of high circulating insulin levels which increase in response to persistent hyperglycemia (19). Insulin itself is a mitogen and growth factor with anti-apoptotic properties, and in the presence of elevated circulating levels stimulates liver production of insulin-like growth factor-1 which has similar properties that further promote neoplastic progression (4,20). Hence, frequent bouts of hyperinsulinemia can activate mechanistic pathways in the prostatic tissue to induce PC initiation and progression in the tumor micro-environment (21–23).

Given the accumulating evidence for worse PC outcomes in diabetic men, it is imperative to understand the role of diabetes on the prognosis of men with nmCRPC. We hypothesized that diabetic men with CRPC would have a worse prognosis than non-diabetic men with CRPC. Hence, the primary objective in this study was to examine the relationship between diabetes and risk of metastases in men diagnosed with nmCRPC. Secondary objectives were to study the associations between diabetes and PCSM and all-cause mortality (ACM) in men with nmCRPC. We also examined associations between duration of diabetes and all outcomes among diabetic men. Finally, given the roles that obesity (24) and race (25) may play in modifying these associations, we tested for the interactions between diabetes and obesity and race.

Materials and Methods

Study Population and Data Abstraction

This study was approved by the Durham VA Institutional Review Board with waiver of informed consent and was conducted in accordance with recognized ethical guidelines (e.g., Declaration of Helsinki, CIOMS, Belmont Report, U.S. Common Rule). Following approval, we identified 1676 men who were diagnosed with CRPC without known metastases during the years 2000–2017. We abstracted data from the electronic medical records, at eight Veterans Affairs Medical Centers (Durham and Asheville, NC; Palo Alto, San Francisco, West Los Angeles, and San Diego, CA; Augusta, GA; Portland, OR) in the SEARCH cohort, regardless of mode of primary treatment. Of these, 700 men were excluded from the main analyses due to missing data on race (n=20), body mass index (BMI, n=22), and biopsy grade group (n=646). Men with BMI < 18.5 kg/m^2 who may have been underweight secondary to undiagnosed metastatic PC at CRPC diagnosis (n=12) were excluded, resulting in an analytical dataset of 976 men (Figure 1). We created an additional dataset that included 646 men with missing values for biopsy grade group for the purpose of carrying out a sensitivity analysis.

Identification of Diabetes Status Prior to CRPC Diagnosis

Men were identified as non-diabetic if prior to CRPC diagnosis they did not have electronic medical record documentation of: (i) International Classification of Diseases, Ninth Revision (ICD-9: 250.0–250.9) or Tenth Revision (ICD-10: E10.0-E14.9) codes identifying them as diabetic *or* (ii) two values of documented hemoglobin A1c (HbA1c) > 6.4 % (American Diabetes Association (ADA) Standards of Care in Diabetes) (26). Men without documentation of diabetes comprised the reference group (n=672) in all comparisons with diabetic men. Men were classified as having diabetes using ICD-9/10

and HbA1c documentation as follows: (i) having ICD-9/10 codes only (N=155); (ii) having two values of HbA1c > 6.4 % *and* missing ICD-9/10 codes (N=149); and (iii) all diabetic men identified by either ICD-9/10 codes *or* two values of HbA1c > 6.4 (N=304).

In addition, we determined duration of diabetes as the earliest entry date for ICD-9/10 code; or, in the absence of ICD-9/10 codes, the first of two elevated HbA1c values > 6.4 % prior to CRPC diagnosis.

We also determined the timing of the first documented ICD-9/10 code or elevated HbA1c value in relation to the timing of ADT initiation (first prescription of ADT) and PC diagnosis.

Assessment of Primary and Secondary Outcomes

Time to metastasis was defined as the time from nmCRPC diagnosis to first metastasis determined by bone scan or computer tomography imaging or death from PC, whichever came first. Patients who were metastasis-free at the last contact date, or died due to reasons other than PC were censored.

PCSM was determined through hand-abstraction of patient electronic health records and defined by progressive PC metastases and death without another probable cause. ACM was defined as death from any cause. The date of nmCRPC diagnosis was the index date and August 3rd, 2018, was the date of last follow-up for patient contact with a VA hospital or date of death. Patients who were alive at the last contact date were censored.

We also examined associations between duration of diabetes prior to CRPC diagnosis and risk of metastases, PCSM, and ACM.

Statistical Analysis

Descriptive statistics describe patient demographic and clinical characteristics at nmCRPC diagnosis by diabetes status with median and interquartile ranges (IQR) determined for continuous variables including age, BMI, year of CRPC diagnosis, prostate-specific antigen (PSA), and duration of diabetes. Frequencies and percentages were determined for categorical variables race (Black, White, and other), biopsy grades 1–5, and primary localized treatment received RP+/− radiotherapy (XRT), XRT alone, or no treatment). In sensitivity analyses that included men with missing biopsy grade data, grade groups were classified as 1–5, and missing.

Kruskal-Wallis tests were used to compare differences in baseline demographic and clinic-pathologic characteristics of continuous variables between diabetic and non-diabetic men and Chi-square tests were used to compare differences in categorical variables.

Given that the diabetic categories were not mutually exclusive, two Cox proportional hazard regression models were fit to determine hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between diabetes and risks of metastasis, PCSM and ACM. In the first regression model, the two mutually exclusive diabetic categories comprised the exposure groups: men identified using ICD-9/10 only (n=155) and men identified by HbA1c

(missing ICD-9/10 codes) (n=149), and nondiabetic otherwise. In the second model, diabetic status was identified by ICD-9/10 and/or HbA1c (n=304), and nondiabetic otherwise. For each regression, we performed age-adjusted and multivariable-adjusted models. Fine and Gray competing-risk regression models were applied to estimate the risk of metastasis and PCSM using death from other causes as competing events. Multivariable models were adjusted for continuous variables age, BMI, year of CRPC diagnosis, and log-transformed PSA, and categorical variables race (Black vs. Non-Black), medical center, biopsy grade group, and primary localized treatment modality.

Duration of diabetes in years was determined for all diabetic men and studied for each of three classifications of diabetes using methods described above to estimate risk of metastasis, PCSM and ACM.

Interactions between diabetic status and BMI and race were tested in fully adjusted regression models. Two-sided *P*-values from the maximum likelihood tests were reported. In sensitivity analyses including the 646 with missing biopsy grade data, all main analyses were repeated.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC). Two-sided *P*-values were reported with $P \leq 0.05$ considered statistically significant except in testing for interactions where $P \leq 0.10$ was used as the criterion considered statistically significant.

Data Availability

The data that support the findings of this study are available from the corresponding authors upon reasonable request within guidelines of VA rules and data sharing policies.

Results

Main Analysis

Among 976 men, the median age was 76 years (IQR 68–82), 68% were White, 29% were Black, and 3% were of other races, 21% underwent RP+/−XRT, 31% underwent XRT alone, and 48% did not receive primary treatment for localized PC. Compared to nondiabetic men, diabetic men within each classification of diabetes had higher BMI (30 vs 28 kg/m^2). Men identified by ICD-9/10 codes were diagnosed with CRPC more recently than men missing ICD-9/10 codes (median year of CRPC diagnosis: 2012 vs 2008) and had lower PSA levels compared to nondiabetic men and men missing ICD-9/10 codes (median PSA: 3.86 vs 4.59 ng/ml and 4.70 ng/ml). The median duration of diabetes prior to CRPC diagnosis was longer for men identified by ICD-9/10 (78 months [IQR 36–132]) than for men identified by HbA1c and missing ICD-9/10 code (51 months [IQR 30–81]). About ~60% and ~40% of men in each diabetes group had documented diabetes onset prior to ADT initiation and PC diagnosis respectively (Table 1).

During a median follow-up of 6.5 years, 613 men were diagnosed with metastases, and 482 PCSM and 741 ACM events occurred. On multivariable analysis, diabetic men identified by ICD-9/10 codes had an HR below 1 for metastases compared with nondiabetic men;

however, statistical significance was not achieved (HR=0.85, 95% CI: 0.66–1.09) (Table 2). On multivariable analysis, HRs for diabetes identified by HbA1c (missing ICD-9/10 codes) and combined HbA1c and/or ICD-9/10 code were not associated with risk for metastases.

Diabetes identified by ICD-9/10 code was associated with a decreased risk of PCSM compared with nondiabetic men (HR=0.54, 95% CI: 0.40–0.73 and HR=0.67, 95% CI: 0.48–0.92, in age- and multivariable adjusted regression models, respectively) (Table 2). Diabetes identified by HbA1c and/or ICD-9/10 codes was associated with a reduced risk of PCSM in the age-adjusted regression model (HR=0.79, 95% CI: 0.65–0.95) but this was not statistically significant in the multivariable adjusted model (HR=0.93, 95% CI: 0.76–1.15). Diabetes identified by HbA1c (missing ICD-9/10 codes) was not associated with PCSM.

Diabetes identified by ICD-9/10 code was associated with a reduced risk of ACM in the age-adjusted (HR=0.69, 95% CI: 0.55–0.87) and multivariable-adjusted models (HR=0.81, 95% CI: 0.63–1.03), though statistical significance was not achieved in the latter. In contrast, diabetes identified by HbA1c (missing ICD-9/10 codes) was associated with an increase in ACM in age-adjusted (HR=1.29, 95% CI: 1.06–1.56) and multivariable adjusted regression models (HR=1.41, 95% CI: 1.16–1.72). Diabetes identified by HbA1c and/or ICD-9/10 code was not associated with ACM (Table 2).

Duration of diabetes was not associated with metastases in any regression model regardless of classifications of diabetes (Table 3). Duration of diabetes was inversely associated with PCSM in diabetic men identified by HbA1c and/or ICD-9/10 code, such that with each year increase in duration of diabetes there was a 7% decrease in the risk of dying from PC (multivariable adjusted HR=0.93, 95% CI 0.88–0.98). Duration of diabetes was not associated with ACM regardless of classification of diabetes (Table 3).

The interactions for diabetes and BMI and diabetes and race were not statistically significant in any of the models at alpha P-value <0.10.

Sensitivity Analysis

Overall compared with men in the main analyses (n=976), men with missing biopsy grade group (n=646) were older (median age 79 vs 76 years), more likely to be non-diabetic (74% vs 69%), diagnosed with CRPC in the more distant past (median year: 2006 vs 2008), with diabetic men having shorter duration from time of diabetes diagnosis to CRPC (median duration 53 vs 64 months), and they were more likely to undergo a RP+/− XRT (28% vs 21%) (Supplementary Table 1.).

In analyses including men with missing biopsy grade group data (n=1622), associations between diabetes and PC outcomes were similar to the main analysis; however, inverse associations were stronger for all outcomes for men identified by ICD-9/10 codes and HRs attained statistical significance for metastases (multivariable adjusted HR=0.73, 95% CI: 0.59–0.90) and ACM (multivariable-adjusted HR=0.74, 95% CI: 0.61–0.91) (Table 4).

Similarly, results for associations between duration of diabetes and PC outcomes were largely the same as in the main analyses. (Table 5).

Discussion

In this study, using ICD-9/10 codes and high HbA1c values to determine diabetic status in men diagnosed with nmCRPC, we identified distinct subgroups of men varying in PC prognosis. Diabetic men identified by ICD codes, had a lower risk of PCSM compared with non-diabetic men. In contrast, men who were not identified by ICD code in electronic medical records but who met the criteria for diabetes according to HbA1c levels, had an increased risk for ACM compared with non-diabetic men. When outcomes for all diabetic men, identified by HbA1c levels and/or ICD-9/10 code were compared to non-diabetic men the results were null for all outcomes. Results for duration of diabetes and outcomes were null except for a statistically significant inverse association in the better powered analysis between duration and PCSM among all diabetic men combined. In sensitivity analyses with the inclusion of men with missing biopsy grade scores, the inverse associations between ICD-9/10 code identified diabetes and all outcomes were strengthened owing to an increase in statistical power with the larger sample size. We hypothesize that diabetic men who do not have ICD-9/10 codes but who meet the HbA1c criteria for diabetes reflect “undiagnosed” and thus untreated diabetes resulting in worse overall survival. As such, these men may benefit from better diabetes detection and management.

While 31% of the cohort met the criteria for diabetes, only 16% were identified by ICD-9/10 codes and an additional 15% of men met the ADA criteria for diabetes according to HbA1c levels. Under the assumption that only ICD-9/10 codes represent physician diagnosed conditions – this latter group of diabetic men remained ‘undiagnosed’. The differences in clinical profiles of men represented by these classifications, warrant examination as it may provide insight into circumstances that underpin the variations in PC outcomes.

It is noteworthy that men with documented high levels of HbA1c without ICD-9/10 codes had a somewhat shorter duration of time from first record of high HbA1c to CRPC diagnosis compared with men with documented ICD-9/10 codes (median months: 51 vs 78) and had higher PSA levels (median ng/mL: 4.70 vs 3.86), suggesting a more rapid progression of their PC. In addition, these men missing ICD-9/10 codes were diagnosed with CRPC at an earlier time (median year of CRPC diagnosis: 2008 vs 2012). We can only speculate as to why these men remained ‘undiagnosed’ for diabetes – however, it is interesting to note that the Food and Drug Administration (FDA) only added risk of diabetes to the label of gonadotropin-releasing hormone (GnRH), the predominant type of ADT prescribed in the US, in 2010 (27). Despite clear therapeutic benefits (4), ADT side-effects include insulin resistance, hyperglycemia and risk of diabetes (28–30). The pathophysiology underpinning ADT-induced diabetes is not fully understood; however, low circulating levels of testosterone are thought to play a role. The testosterone-insulin resistance theory is supported by a link between low levels of testosterone and insulin resistance even in cancer-free men (31) and improvement in insulin sensitivity with testosterone replacement in hypogonadal men has been shown (32). Other adverse effects of ADT include an increase in adiposity which can further exacerbate insulin resistance and lead to hyperglycemia that may be more difficult to manage without administration of insulin (33). While not all men undergoing ADT develop diabetes, prolonged treatment increases the risk of diabetes peaking at 3 years of use (34). Most of the men with ‘undiagnosed’ diabetes would have

undergone ADT prior to the FDA diabetes risk alert when treating physicians may have been less mindful of diabetes risk. As such, elevated HbA1c levels may have been viewed as ‘transient’ adverse responses to ADT, not warranting ICD-9/10 code documentation. On the other hand, most men with ICD-9/10 codes, who were diagnosed with diabetes after ADT initiation (38%), would have undergone ADT following the FDA alert (median year of CRPC diagnosis 2012), when physicians may have been more vigilant in monitoring and diagnosing diabetes.

The finding that ACM is increased by 41% in men with high HbA1c levels (missing ICD-9/10 codes) compared with non-diabetic men, is consistent with results reporting that untreated diabetes is associated with ACM (16); although ADT itself (specifically GnRH), has been shown to increase the risks of cardiovascular diseases, such as myocardial infarction, stroke and sudden cardiac death (35,36). However, ADT alone cannot explain the increase in ACM since all men diagnosed with CRPC have undergone ADT. Poorly controlled diabetes exacerbated by ADT could, however, increase the risk of ACM from cardiovascular comorbidities. Details pertaining to non-PC deaths are not available; however, of the ~35% of deaths not attributed to PC, a substantial portion could have been related to cardiovascular disease, reported to be the leading competing cause of non-PC mortality in elderly men with PC (37,38). As such, our findings underscore the need for increased vigilance in diagnosing and treating diabetes to improve overall survival in men with CRPC.

Our results showing a decreased risk of PCSM among men identified by ICD-9/10 diabetic codes contrasts with the increase in ACM and otherwise null effects associated with the group identified by high HbA1c values only. As might be expected – among ICD-9/10 identified diabetes ‘diagnosed’ men, about two thirds (103 of 155 men) also had laboratory monitoring indicating elevated HbA1c levels at some point. Importantly, once diagnosed, they may have had better diabetic control (through multiple modes of management, including lifestyle) reducing the need for subsequent treatment with insulin, and improving PC prognosis (16,18,33). We also note that more men with ICD-9/10 had undergone RP +/− XRT for primary treatment of PC than nondiabetic men (though differences were not statistically significant: p=0.066 for ICD-9/10 group vs nondiabetics) and men missing ICD-9/10 codes, potentially contributing to better outcomes; however, we controlled for primary treatment and PSA levels in analyses. Nonetheless, as men with ICD-9/10 codes were diagnosed with CRPC more recently, they may have been treated with newer therapies to improve their PC prognosis (e.g., novel antiandrogens) which we cannot account for in the current study.

Our results for ICD-9/10 identified diabetic men are more aligned with inverse associations reported for diabetes and PC risk. While the evidence is conflicting, long-standing diabetes has been reported to have protective effects for PC through proposed mechanisms that include ß-cell exhaustion resulting in insulin depletion, and lower circulating testosterone and insulin-like growth factor-1 levels (4). This is supported by evidence from observational studies reporting a reduced risk for both low and high-grade PC among diabetic men compared with nondiabetic men (8) and progressively decreasing PC risk with increasing duration of diabetes (39). However, it has also been argued that few type 2 diabetics

experience the hypoinsulinemia that is characteristic of type 1 diabetes, highlighting the need for additional investigation of mechanistic pathways (40).

In contrast to our results and those for PC risk, diabetes has been associated with worse prognosis in men with PC (41,42). A meta-analysis of 17 cohort studies reported that pre-existing diabetes was associated with a 29% increase in PCSM and a 37% increase in ACM (41). In a subgroup analysis of five studies that included only pre-existing type 2 diabetes, ACM was twice as high amongst diabetic men compared with non-diabetic men, but the association with PCSM was null. Importantly, the authors noted significant heterogeneity between studies (41). Duration of diabetes in relation to PC outcomes has also been understudied, however, one large population-based cohort analysis of patients found that PCSM increased with duration of diabetes in the two lowest tertiles of duration but declined to the null in the 3rd tertile (≥7.9 years) compared with non-diabetic men (42). As such, questions remain with respect to the link between diabetes and PC prognosis. As an additional note, previous studies generally enrolled men at the time of PC diagnosis. Here we report results for men enrolled at CRPC diagnosis. Furthermore, a substantial proportion (~60%) of men had newly diagnosed diabetes after PC diagnosis. Given the paucity of studies examining the prognosis of diabetic men with CRPC, we can only speculate that the associations between diabetes and PC prognosis may differ from men with newly diagnosed with PC.

Our study has limitations that need to be acknowledged. First, treatment-related aspects may play a role in our findings; however, we did not have information on antidiabetic medications. Poor outcomes in PC patients treated with insulin have been reported (16), whereas better outcomes, reduced PC death and increases in overall survival have been associated with metformin in some (43–45), but not all studies (46,47). The better PC prognosis with metformin may be linked to its antidiabetic action whereby it increases insulin sensitivity to lower plasma glucose levels rather than stimulating insulin secretion. Moreover, a Finnish study reported that post-RP metformin users had a 25% lower risk of being initiated on ADT compared with nonusers, while insulin users had a 25% higher risk of being initiated on ADT which increased with intensity of insulin use (33). In addition, post diagnostic insulin use was associated with an increase in PC death, while metformin was associated with a decrease in death compared with nonusers.

Second, our diabetic classifications are only surrogates of subgroups of diabetic men with CRPC who appear to differ in PC prognosis – we did not have information on the true definition of ‘diabetes’. In a validation study of algorithms used to identify diabetic status at the VA, a combination of data sources that included Medicare and VA antidiabetic medications optimized estimates of diabetes prevalence such that it was 15% higher with their inclusion (48). As that study was in the general population of VA enrollees prior to 2000, it is unclear how relevant the findings are to the current study, but it is an important question to address in future studies.

Third, we did not have data pertaining to smoking behavior – a risk factor for diabetes (49,50) and also associated with increases in PCSM (51–53) and ACM. As such, the prevalence of smoking may have been higher amongst diabetic men than amongst controls,

potentially obscuring the associations between diabetes and PC outcomes. Importantly, compared with ICD-9/10 confirmed diabetes, we speculate that 'undiagnosed' diabetic men (without ICD-9/10 codes) would have been less likely to have been counselled to quit smoking, and hence, the association between diabetes and ACM in this group could have been overestimated. While it is possible that among ICD-9/10 confirmed diabetic men, the inverse association between diabetes and PCSM could have been underestimated (given the increased risk of PCSM associated with smoking), we expect this scenario to be less likely as they would have been more likely to receive counselling to quit smoking once diagnosed with diabetes. As the impact of smoking history on the link between diabetes and PC outcomes is complex, studies with detailed smoking history data are needed. On a final note, as our analysis is limited to veterans our results may not be generalizable to non-veteran populations.

Importantly, this study also has several strengths. CRPC patients were identified using detailed data collected from VA chart reviews to confirm CRPC status, a condition not typically captured in claims data. Quality control checks of data abstraction are routinely conducted to minimize errors. In addition, the VA health-care system promotes equal access to medical coverage for all members; hence, minimizing access to care obstacles.

To conclude, diabetes identified by ICD-9/10 codes only was associated with a decrease in PCSM in men with nmCRPC compared with nondiabetic men. While similar trends were seen with metastases and ACM, statistical significance was only attained in sensitivity analyses. In contrast diabetes identified by high HbA1c values with missing ICD-9/10 codes, was associated with an increase in ACM. Our results suggest that better diabetes detection and management may improve survival in men with late-stage PC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial Support:

Supported by National Institutes of Health 1R01CA231219-01 (WJA).

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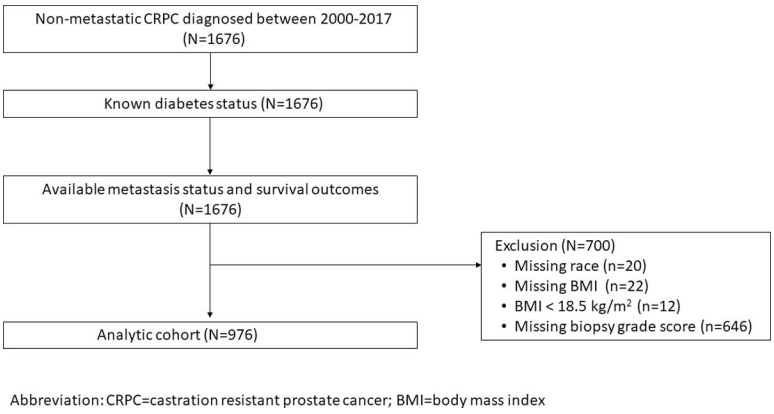

Figure 1:

Inclusion and exclusion of analytic cohort. This figure shows the sample size of the non-metastatic CRPC cohort before and after exclusion of men with missing data.

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Table 1.

Demographic and disease characteristics of patients at CRPC diagnosis by diabetic status (976 men with non-missing data)

Characteristics	All Men (N=976)	Diabetics			Nondiabetics (N=672)	P [τ]		
		ICD-9/10 only (N=155)	HbA1c/no ICD-9/10 (N=149)	HbA1c and/or ICD-9/10 (All diabetic men combined) (N=304)		P*	P**	P***
Age, Median (IQR)	76 (68, 82)	76 (68, 82)	74 (66, 81)	75 (67, 81)	76 (68, 82)	0.790	0.059	0.165
Race, n (%)						0.234	0.113	0.052
White	662 (68)	98 (63)	92 (62)	190 (63)	472 (70)			
Black	281 (29)	51 (33)	52 (35)	103 (34)	178 (26)			
Other	33 (3)	6 (4)	5 (3)	11 (4)	22 (3)			
BMI (kg/m2), Median (IQR)	28 (25, 32)	30 (26, 34)	30 (27, 34)	30 (26, 34)	28 (25, 31)	<.001	<.001	<.001
Year of CRPC, Median (IQR)	2008 (2004, 2012)	2012 (2007, 2014)	2008 (2005, 2009)	2009 (2006, 2012)	2007 (2003, 2011)	<.001	0.976	<.001
Biopsy grade, n (%)						0.351	0.726	0.560
1	242 (25)	38 (25)	41 (28)	79 (26)	163 (24)			
2	175 (18)	20 (13)	26 (17)	46 (15)	129 (19)			
3	126 (13)	22 (14)	15 (10)	37 (12)	89 (13)			
4	196 (20)	30 (19)	33 (22)	63 (21)	133 (20)			
5	237 (24)	45 (29)	34 (23)	79 (26)	158 (24)			
PSA (ng/ml), Median (IQR)	4.50 (3.01, 8.53)	3.86 (2.80, 7.57)	4.70 (3.07, 9.90)	4.25 (2.97, 8.61)	4.59 (3.10, 8.46)	0.040	0.740	0.254
Primary localized treatment, n (%)						0.066	0.998	0.291
RP +/− XRT	208 (21)	44 (28)	30 (20)	74 (24)	134 (20)			
XRT alone	302 (31)	42 (27)	47 (32)	89 (29)	213 (32)			
None	466 (48)	69 (45)	72 (48)	141 (46)	325 (48)			
Months from diabetes diagnosis to CRPC, Median (IQR)	--	78 (36, 132)	51 (30, 81)	64 (33, 103)	--	--	--	--
Diabetes onset prior to ADT initiation, n (%)		96 (62)	90 (60)	186 (61)				
Diabetes onset prior to PC diagnosis, n (%)		67 (43)	60 (40)	127 (42)				

[τ] Kruskal-Wallis tests for continuous variables and Chi-squared tests for categorical variables;

[*] p-value compares diabetics defined as ICD-9/10 only vs nondiabetics

[**] p-value compares diabetics defined by HbA1c/no ICD-9/10 vs nondiabetics

*** p-value compares diabetics defined by ICD-9/10 and/or HbA1c vs nondiabetics

Abbreviation: CRPC=castration resistant prostate cancer; BMI=body mass index; IQR=interquartile range; PSA=prostate-specific antigen; RP=radical prostatectomy; XRT=radiotherapy

Table 2.

Associations of diabetes and the risk of metastases progression, PCSM, and ACM in CRPC patients (976 men with non-missing data)

			Age adjusted		Multivariable adjusted [□]		*p* (interaction) [T]	
PC outcome	**Diabetic status**	**# Event/Total**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**BMI**	**Race**
Metastases	Nondiabetics	427/672	Reference		Reference			
	ICD-9/10 only [*]	85/155	0.83 (0.66–1.05)	0.119	0.85 (0.66–1.09)	0.192	0.266	0.705
	HbA1c/no ICD-9/10 [*]	101/149	1.00 (0.81–1.23)	0.981	1.07 (0.86–1.33)	0.528	0.276	0.590
	HbA1c and/or ICD-9/10 [**]	186/304	0.91 (0.77–1.08)	0.295	0.96 (0.80–1.15)	0.674	0.207	0.946
PCSM	Nondiabetics	347/672	Reference		Reference			
	ICD-9/10 only [*]	46/155	0.54 (0.40–0.73)	<.001	0.67 (0.48–0.92)	0.014	0.194	0.872
	HbA1c/no ICD-9/10 [*]	89/149	1.03 (0.83–1.29)	0.760	1.15 (0.91–1.44)	0.238	0.157	0.147
	HbA1c and/or ICD-9/10 [**]	135/304	0.79 (0.65–0.95)	0.014	0.93 (0.76–1.15)	0.516	0.157	0.170
ACM	Nondiabetics	517/672	Reference		Reference			
	ICD-9/10 only [*]	87/155	0.69 (0.55–0.87)	0.002	0.81 (0.63–1.03)	0.081	0.576	0.599
	HbA1c/no ICD-9/10 [*]	137/149	1.29 (1.06–1.56)	0.009	1.41 (1.16–1.72)	<.001	0.977	0.692
	HbA1c and/or ICD-9/10 [**]	224/304	0.96 (0.82–1.13)	0.640	1.11 (0.93–1.31)	0.242	0.667	0.508

[□] Adjusted for age (continuous), race, BMI (continuous), year of CRPC diagnosis, medical center, biopsy grades 1–5, log-transformed PSA, and primary localized treatment.

[*] Cox PH modeling with 2 levels of diabetes identified by ICD-9/10 and by HbA1c/no ICD-9/10 vs. nondiabetic men otherwise.

[**] Cox PH modeling with dichotomy of diabetes - diabetic men were identified by HbA1c and/or ICD-9/10 vs. nondiabetic men otherwise.

[T] Maximum likelihood test 2-sided p-value of interaction of diabetes with BMI and race.

Abbreviation: ACM=all-cause mortality; BMI=body mass index; CRPC=castration resistant prostate cancer; PCSM=prostate cancer-specific mortality.

Table 3.

Associations of duration of diabetes prior to CRPC diagnosis and risk of metastases progression, PCSM, and ACM in CRPC patients (976 men with non-missing data)

PC outcome	# Event/Total	Age adjusted		Multivariable adjusted [α]		p-int [τ]	
		HR (95% CI) (unit=12 months)	p	HR (95% CI) (unit=12 months)	p	BMI	Race
Metastases							
ICD-9/10 only	85/155	0.97 (0.93–1.02)	0.292	0.95 (0.89–1.00)	0.070	0.405	0.149
HbA1c /no ICD-9/10	101/149	1.01 (0.94–1.08)	0.885	1.00 (0.91–1.10)	0.996	0.288	0.316
HbA1c and/or ICD-9/10	186/304	0.98 (0.94–1.02)	0.276	0.96 (0.91–1.00)	0.077	0.271	0.161
PCSM							
ICD-9/10 only	46/155	0.93 (0.87–0.99)	0.019	0.93 (0.86–1.01)	0.073	0.889	0.125
HbA1c /no ICD-9/10	89/149	0.95 (0.87–1.04)	0.281	0.95 (0.87–1.05)	0.302	0.848	0.833
HbA1c and/or ICD-9/10	135/304	0.93 (0.89–0.97)	0.002	0.93 (0.88–0.98)	0.008	0.541	0.124
ACM							
ICD-9/10 only	87/155	0.99 (0.94–1.04)	0.780	0.98 (0.93–1.05)	0.622	0.494	0.834
HbA1c /no ICD-9/10	137/149	1.02 (0.96–1.09)	0.457	0.98 (0.91–1.05)	0.598	0.114	0.300
HbA1c and/or ICD-9/10	224/304	0.98 (0.95–1.02)	0.320	0.97 (0.93–1.01)	0.161	0.187	0.673

[α] Adjusted for age (continuous), race, BMI (continuous), year of CRPC diagnosis, medical center, biopsy grade, log-transformed PSA, and primary localized treatment.

[τ] Maximum likelihood test 2-sided p-value of interaction of duration of diabetes with BMI and Race.

Abbreviation: ACM=all-cause mortality; BMI=body mass index; CRPC=castration resistant prostate cancer; PCSM=prostate cancer-specific mortality.

Table 4.

Associations of diabetes and the risk of metastases progression, PCSM, and ACM in CRPC patients (976 men with non-missing data and 646 men with missing biopsy grade group classification)

			Age adjusted		Multivariable adjusted [□]		p (interaction) [T]	
PC outcome	**Diabetic status**	**# Event/Total**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**BMI**	**Race**
Metastases	Nondiabetics	721/1148	Reference		Reference			
	ICD-9/10 only [*]	109/226	0.71 (0.58–0.87)	0.001	0.73 (0.59–0.90)	0.004	0.725	0.971
	HbA1c/no ICD-9/10 [*]	163/248	1.01 (0.86–1.19)	0.917	1.06 (0.89–1.27)	0.515	0.750	0.761
	HbA1c and/or ICD-9/10 [**]	272/474	0.86 (0.75–0.99)	0.037	0.90 (0.77–1.05)	0.176	0.660	0.901
PCSM	Nondiabetics	596/1148	Reference		Reference			
	ICD-9/10 only [*]	59/226	0.47 (0.36–0.62)	<.001	0.56 (0.42–0.74)	<.001	0.899	0.313
	HbA1c/no ICD-9/10 [*]	138/248	0.97 (0.82–1.16)	0.757	1.05 (0.87–1.27)	0.577	0.419	0.361
	HbA1c and/or ICD-9/10 [**]	197/474	0.74 (0.63–0.87)	<.001	0.84 (0.71–0.99)	0.044	0.490	0.295
ACM	Nondiabetics	903/1148	Reference		Reference			
	ICD-9/10 only [*]	126/226	0.68 (0.56–0.82)	<.001	0.74 (0.61–0.91)	0.003	0.580	0.972
	HbA1c/no ICD-9/10 [*]	220/248	1.18 (1.01–1.36)	0.031	1.25 (1.07–1.46)	0.004	0.483	0.859
	HbA1c and/or ICD-9/10 [**]	346/474	0.93 (0.82–1.05)	0.231	1.01 (0.88–1.15)	0.880	0.865	0.841

[□] Adjusted for age (continuous), race, BMI (continuous), year of CRPC diagnosis, center, biopsy grade (1,2,3,4,5, and missing), log-transformed PSA, and primary localized treatment.

[*] Cox PH modeling with 2 levels of diabetes identified by ICD-9/10 and by HbA1c/no ICD-9/10 vs. nondiabetic men otherwise.

[**] Cox PH modeling with dichotomy of diabetes - diabetic men were identified by HbA1c and/or ICD-9/10 vs. nondiabetic men otherwise.

[T] p-value of interaction of diabetes with BMI and race (Maximum likelihood test).

Abbreviation: ACM=all-cause mortality; BMI=body mass index; CRPC=castration resistant prostate cancer; PCSM=prostate cancer-specific mortality.

Table 5.

Associations of duration of diabetes prior to CRPC diagnosis and risk of metastases progression, PCSM, and ACM in CRPC patients (sensitivity analysis)

PC outcome	# Event/Total	Age adjusted		Multivariable adjusted [α]		p-int [τ]	
		HR (95% CI) (unit=12 months)	p	HR (95% CI) (unit=12 months)	p	BMI	Race
Metastases							
ICD-9/10 only	109/226	0.98 (0.94–1.03)	0.446	0.96 (0.91–1.01)	0.110	0.137	0.092
HbA1c /no ICD-9/10	163/248	0.99 (0.93–1.05)	0.657	0.94 (0.88–1.01)	0.077	0.905	0.127
HbA1c and/or ICD-9/10	272/474	0.98 (0.95–1.01)	0.153	0.96 (0.92–0.99)	0.027	0.286	0.164
PCSM							
ICD-9/10 only	59/226	0.94 (0.89–1.00)	0.043	0.96 (0.90–1.03)	0.299	0.845	0.093
HbA1c /no ICD-9/10	138/248	0.97 (0.90–1.04)	0.361	0.95 (0.88–1.02)	0.180	0.939	0.444
HbA1c and/or ICD-9/10	197/474	0.94 (0.91–0.98)	0.005	0.95 (0.91–1.00)	0.040	0.645	0.145
ACM							
ICD-9/10 only	126/226	0.99 (0.95–1.03)	0.586	1.00 (0.95–1.05)	0.922	0.985	0.118
HbA1c /no ICD-9/10	220/248	1.06 (1.01–1.12)	0.019	1.04 (0.98–1.10)	0.156	0.180	0.472
HbA1c and/or ICD-9/10	346/474	0.99 (0.96–1.02)	0.688	1.00 (0.96–1.03)	0.842	0.170	0.465

[α] Adjusted for age (continuous), race, BMI (continuous), year of CRPC diagnosis, center, biopsy grade (1,2,3,4,5,and missing), log-transformed PSA, and primary localized treatment.

[τ] p-value of interaction of duration of diabetes with BMI and Race (Maximum likelihood test).

Abbreviation: ACM=all-cause mortality; BMI=body mass index; CRPC=castration resistant prostate cancer; PCSM=prostate cancer-specific mortality.

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2024 March 01.