Prostate Cancer Risk in Pre-Diabetic Men: A Matched Cohort Study

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Background: Diagnosis and duration of type 2 diabetes mellitus (DM) appear to be associated with decreased prostate cancer risk. Limitations of previous studies include methods of subject selection and accurate definition of DM diagnosis. We examined the temporal relationship between DM and prostate cancer risk exploring the period of greatest risk starting from the prediabetic to the post-diabetic period using clinical and administrative data to accurately define the date of DM diagnosis.

Methods: We identified 5,813 men who developed DM between January 1, 1995 and December 31, 2009 (reference date, date of DM onset or matched date for non-diabetic cohort) and 28,019 non-diabetic men matched by age, smoking history, residence, and reference date. Prostate cancer incidence before and after the reference date was assessed using Cox regression modeling adjusted for matching variables, body mass index, insurance status, and comorbidities. Primary outcomes included hazard ratio (HR) and number needed to be exposed to DM for one additional person to be harmed (NNEH) or benefit (NNEB) with respect to prostate cancer risk.

Results: After full adjustment, the HR for prostate cancer before DM diagnosis was 0.96 (95% CI 0.85–1.08; \( P = 0.4752 \)), and the NNEB was 974 at DM diagnosis. After the reference date, the fully-adjusted HR for prostate cancer in diabetic men was 0.84 (95% CI 0.72–0.97, \( P = 0.0167 \)), and the NNEB 3 years after DM onset was 425. The NNEB continued to decrease over time, reaching 63 at 15 years after DM onset, suggesting an increasing protective effect of DM on prostate cancer risk over time. No significant difference between the diabetic and non-diabetic cohort was found prior to reference date.

Conclusion: Prostate cancer risk is not reduced in pre-diabetic men but decreases after DM diagnosis and the protective effect of DM onset on prostate cancer risk increases with DM duration.

Keywords: Type 2 diabetes mellitus; NNEH/NNEB; Prostatic neoplasms/epidemiology; Risk factors

Although type 2 diabetes mellitus (DM) appears to be associated with increased risk of many types of cancer, a notable exception is prostate cancer. Several studies have demonstrated a reduced risk of prostate cancer in men with DM. A 2012 meta-analysis of 45 studies of prostate cancer and diabetes published between 1970 and 2011 demonstrated a 14% reduction in the risk of prostate cancer in men with DM compared to non-diabetic men. The mechanism by which DM is associated with a reduced risk of prostate cancer is currently unknown, but it is thought to likely be related to testosterone levels. Evidence suggests that metabolic factors associated with DM impact on the hypothalamic-pituitary-testicular axis, and there is a clear inverse relationship between testosterone levels and DM. Since testosterone also plays an important role in the development and progression of prostate cancer, lower
levels of testosterone in diabetic patients may lessen the risk for prostate cancer.\(^1\)

The problem, however, is that DM is a progressive disease associated with a number of physiological changes that start before its clinical onset (figure 1). DM-associated physiological changes and exposures with the potential to influence cancer risk evolve over time, and while studies have looked at risk post-DM onset, none have examined risk during the pre-diabetes phase. Of studies that have examined temporal relationships, it has usually been DM duration and risk, with the majority reporting an inverse relationship, whereby risk of prostate cancer is reduced with increased DM duration;\(^3,9-13\) although there are discrepant reports.\(^14-16\) Data regarding the pre-diabetic state are lacking, and in the present study, we used an extensive electronic database to pinpoint the date of clinical DM onset to examine the temporal relationship between DM and prostate cancer in clearly delineated time periods pre- and post-DM onset.

**Materials and Methods**

Prostate cancer risk was assessed before and after DM diagnosis in a retrospective, matched, cohort study of male subjects at Marshfield Clinic. Marshfield Clinic is a large, multi-specialty healthcare system located in Wisconsin, USA. Data sources included the combined medical record of Marshfield Clinic and affiliated hospitals (CMR) and the Marshfield Clinic/St. Joseph’s Hospital Cancer Registry (MC/SJH-CR). The MC/SJH-CR was started in 1960, is approved by the American College of Surgeons Commission on Cancer, and meets the standards of the Association of Community Cancer Center for cancer programs. Cancer registry data is submitted to the National Cancer Database and State of Wisconsin cancer reporting system. The registry has a 93.4% 5-year follow-up rate, and overall follow-up rate of 89.9%. To assure quality data, 10% of analytical records are audited by the registrars and physician group.

The CMR provides an extensive archive of medical information dating back to the early 1990s; several enhanced clinical registries; files of all procedures, insurance claims, and laboratory results available retrospectively to 1985; and a file of more than 124 million patient diagnoses dating back to 1960.\(^17\) The CMR integrates data from all MC facilities and affiliated hospitals and provides access to all textual documentation for events and encounters, diagnostic and procedural codes, medication history and alerts, as well as access to over a decade of laboratory and radiology results.\(^17\) Data were collected electronically from the Marshfield Clinic electronic medical record (EMR) and cancer registry, with manual validation of a subset of data for diagnosis and dates of diagnosis. Marshfield Clinic’s Institutional Review Board approved the study protocol and granted a waiver of informed subject consent.

The study period included January 1, 1995 through December 31, 2009. All potential subjects were required to be 30 years of age or older by the end of the study period and could not have any diagnosis of DM as documented by International Classification of Disease (ICD) code before the study period began. The pool of potential subjects was then divided into two cohorts based on whether or not they had any ICD diagnostic codes (250.X0, 250.X2) for type 2 DM in the medical record during the study period. Additional inclusion and exclusion criteria were then applied to further refine
Figure 2. Subject selection and matching. Study subjects were selected based on whether or not they were diagnosed with type 2 diabetes mellitus (DM) between January 1, 1995 and December 31, 2009. Diabetic and non-diabetic subjects were matched at an approximately 5:1 ratio based on gender, birth date, smoking, residency in the Marshfield Epidemiologic Study Area (MESA), and study period.
DM-status in the two cohorts, as shown in figure 2. Diabetic subjects were required to have at least one ICD diagnostic code for DM and at least two elevated glucose and/or hemoglobin A1c (HbA1c) test results meeting American Diabetes Association (ADA) criteria for DM. The reference date for the diabetic cohort was the date of DM diagnosis, which was defined as the earliest of the first DM diagnosis by diagnostic code or the second high glucose and/or HbA1c value. The non-diabetic cohort was defined by the absence of DM diagnosis, with a requirement for at least one normal HbA1c or glucose test during the study period.

Based on the need for extensive follow-up information, subjects were required to have received sufficient care through the Marshfield Clinic system so that diagnosis dates for DM and prostate cancer could be determined with reasonable accuracy. All subjects were required to have at least one non-diabetes diagnosis or electronic code documenting a clinic visit from a Marshfield Clinic provider in at least one of the three calendar years before the reference date. Observation times were censored before any large gap in at least one of the three calendar years before the reference date extended as far back as 20 years before the reference date.20 Analyses were performed using SAS® and cancer-free at a specified time interval (CI). The number needed to be exposed to DM for one additional person to be harmed (i.e., develop prostate cancer) (NNEH) or benefit (i.e. prevent prostate cancer) (NNEB) was calculated as follows:

\[
NNEH = \frac{1}{S_2(t) - S_1(t)} \quad \text{and} \quad NNEB = -NNEH,
\]

where \(S_1(t)\) is the probability of a non-diabetic subject being alive and cancer-free at a specified time \(t\), with respect to the reference date.20 Analyses were performed using SAS® version 9.2 statistical software.

Cancer Diagnosis, Comorbidities, and Clinical Risk Factors

The EMR was interrogated for ICD diagnostic codes for prostate cancer (185, 198.82, 233.4). The first date an ICD code for prostate cancer was documented was used as the date of cancer diagnosis and verified using the diagnosis dates in the cancer registry. Several covariates with the potential to impact on cancer risk, including comorbidities and clinical risk factors, were also examined. Comorbidities of interest included myocardial infarction, coronary heart disease, peripheral vascular disease, cardiovascular disease, chronic pulmonary disease, rheumatic heart disease, and renal insufficiency/renal failure, which were summarized using a modified Charlson score (excluding cancer and diabetes). Comorbidities were electronically abstracted from the EMR by ICD diagnostic code, using a rule of two, requiring a minimum documentation of same diagnosis on two separate service dates. The EMR was also interrogated for body mass index (BMI) at the reference date, smoking history (ever/never), and insurance status at the reference date (yes/no), as well as frequency of healthcare visits for 5 years before and after the reference date.

Statistical Analysis

For risk analyses, the time periods before and after the reference date were examined separately to delineate the temporal relationship between prostate cancer risk and progression from pre-diabetes to diabetes. To determine prostate cancer risk before clinical onset of DM, subject records were examined for prostate cancer diagnoses before the reference date (year 0), and cumulative incidence is reported starting at 15 years before the reference date (year -15). Subjects who developed prostate cancer more than 15 years before the reference date were included in the analysis of prostate cancer risk before DM onset. Consequently, baseline incidence at year -15 is not zero. Cumulative prostate cancer incidence after the reference date starts over at zero by exclusion of subjects with a history of prostate cancer.

Subject characteristics were summarized using standard descriptive statistics. Prostate cancer risk was assessed by calculating hazard ratios (HRs) before and after DM onset. Cox regression analysis was used to assess differences between diabetic and non-diabetic subjects with respect to development of prostate cancer before and after the reference date. Models were adjusted for all matching variables in addition to insurance status, BMI, and comorbidities. Model results were summarized with HR and 95% confidence interval (CI). The number needed to be exposed to DM for one additional person to be harmed (i.e., develop prostate cancer) (NNEH) or benefit (i.e. prevent prostate cancer) (NNEB) was calculated as follows:

\[
NNEH = \frac{1}{S_2(t) - S_1(t)} \quad \text{and} \quad NNEB = -NNEH,
\]

where \(S_1(t)\) is the probability of a non-diabetic subject being alive and cancer-free at a specified time \(t\), with respect to the reference date.20 Analyses were performed using SAS® statistical software.

Results

Application of inclusion and exclusion criteria to the data obtained from the EMR, as shown in figure 2, resulted in 5,813 male diabetic subjects who were matched with non-diabetic subjects in the 60 strata created by all possible combinations of the four matching variables. Reference dates were assigned to 28,019 potential non-diabetic subjects. Losses in the matching process resulted in a final matched cohort with a ratio of non-diabetic to diabetic subjects of 4.82

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to 1. Here we report prostate cancer incidence in the 33,832 men included in these cohorts.

Table 1 shows the descriptive characteristics of diabetic and non-diabetic male subjects included in the study. Mean observation time in the EMR was approximately 16 years before the reference date in both groups. After the reference date, mean observation time in the EMR was 7.2 years for diabetic subjects and 5.9 years for non-diabetic subjects. Matching variables were similar between diabetic and non-diabetic subjects, but as expected, diabetic subjects had a higher BMI and greater visit frequency than non-diabetic subjects. Information regarding androgen deprivation therapy (ADT) use was available only for subjects found in the Cancer Registry, but was not significantly different in diabetic and non-diabetic subjects in this subset.

The crude incidence of prostate cancer before the reference date was 101.0 per 100,000 person-years and 100.7 per 100,000 person-years in non-diabetic and diabetic subjects. After the reference date, incidence rose to 763.0 per 100,000 person-years in non-diabetic subjects and 664.8 per 100,000 person-years in diabetic subjects. Figure 3 shows cumulative prostate cancer incidence in diabetic and non-diabetic subjects in the time periods before and after the reference date. After full covariate adjustment, the HR for prostate cancer in pre-diabetic men was 0.96 (95% CI 0.85–1.08, \(P=0.4752\)) (Table 2), and the NNEB was 974 at DM onset (Table 3). After the reference date, the fully adjusted HR for prostate cancer in diabetic men was 0.84 (95% CI 0.72–0.97, \(P=0.0167\)) (Table 2), and the NNEB 3 years after DM onset was 425 (Table 3). At 15 years after DM onset, the NNEB decreased to 63, suggesting that the protective effect of DM on prostate cancer risk increased over time in diabetic men compared to their non-diabetic counterparts (Table 3).

For men diagnosed with prostate cancer before the reference date, median time from cancer diagnosis to reference date in diabetic and non-diabetic subjects was 11.4 and 11.6 years, respectively. After the reference date, median time to prostate cancer diagnosis was 3.9 vs. 4.4 years in diabetic and non-diabetic subjects, respectively.

**Discussion**

The diabetic state appears to be protective for prostate cancer in men in a carefully defined cohort of diabetic men and matched non-diabetic controls. By defining the date of clinical DM onset, we were able to assess the temporal relationship between DM and prostate cancer risk and found that risk was similar in both groups before DM onset, but that risk of prostate cancer decreased shortly after onset and continued to decrease throughout the following 15 years. Although DM clearly carries more health risks than benefits, we have delineated for the first time that this protective period is indeed post onset of diabetes and excludes the pre-diabetic phase. This is important, because it suggests that the mechanism of the post-DM protection is also working in the pre-DM phase and prevents the expected increase in risks for this period followed by decreased risk in the post-DM period, when the protective effect takes off. The mechanism of the pre-DM protection that prevents the expected increase in risks for this period could be testosterone level related, because studies reveal an age related decrease in testosterone levels in metabolic syndrome.21

The specific mechanism by which onset of DM further reduces prostate cancer risk (apart from the progressive decline in hyperinsulinemia) is not well-understood, but it is likely related to the further drop in testosterone levels precipitated by onset of hyperglycemia. The latter is thought to happen via downregulation of kisspeptin, a peptide crucial for normal gonadotropin-releasing hormone pulsatility.22 It is reported that 44% of men with DM have low total testosterone levels and, more importantly, that 57% had low calculated free testosterone levels, which is a more accurate measure of bioavailable testosterone.23 In a similar study, Kasper et al24 found that an initial decrease in testosterone after DM diagnosis resulted in levels that were significantly lower than

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**Figure 3.** Cancer incidence before and after onset of type 2 diabetes mellitus (DM). Cumulative incidence of prostate cancer in men (A) before DM onset and (B) after DM onset. Diabetic subjects are indicated by the solid line and non-diabetic subjects are indicated by the dashed line.
Table 1. Descriptive characteristics and matching variables in diabetic and non-diabetic subjects.

| Matching Variables                  | Diabetic (N = 5,813) | Non-Diabetic (N = 28,019) |
|-------------------------------------|----------------------|---------------------------|
|                                     | N (%)                | N (%)                     |
| Mean age (IQR)                      | 62.3 (53-71)         | 62.5 (53-72)              |
| Age group                           |                      |                           |
| 30–49 years                         | 1041 (17.9)          | 5205 (18.6)               |
| 50–59 years                         | 1436 (24.7)          | 6854 (24.5)               |
| 60–69 years                         | 1642 (28.2)          | 7615 (27.2)               |
| 70–79 years                         | 1207 (20.8)          | 5376 (19.2)               |
| ≥ 80 years                          | 487 (8.4)            | 2969 (10.6)               |
| Birth year                          |                      |                           |
| 1929 and prior                      | 1324 (22.8)          | 6430 (22.9)               |
| 1930–1939                           | 1488 (25.6)          | 7089 (25.3)               |
| 1940–1949                           | 1472 (25.3)          | 7208 (25.7)               |
| 1950–1959                           | 1028 (17.7)          | 5033 (18.0)               |
| 1960 and later                      | 501 (8.6)            | 2259 (8.1)                |
| Smoking status                      |                      |                           |
| Ever                                | 4477 (77.0)          | 21457 (76.6)              |
| Never                               | 1336 (23.0)          | 6562 (23.4)               |
| DM diagnosis period                 |                      |                           |
| 1995–1999                           | 1263 (21.7)          | 6137 (21.9)               |
| 2000–2004                           | 2401 (41.3)          | 11640 (41.5)              |
| 2005–2009                           | 2149 (37.0)          | 10242 (36.6)              |
| MESA residency                      |                      |                           |
| No                                  | 4672 (80.4)          | 22645 (80.8)              |
| Yes                                 | 1141 (19.6)          | 5374 (19.2)               |
| Other Variables                     |                      |                           |
| Mean BMI (IQR) (kg/m²)              | 33.1 (29-39)         | 29.2 (27-30)              |
| Have insurance (yes)                | 4545 (78.2)          | 20809 (74.3)              |
| Visit frequency before DM<sup>a</sup> |                      |                           |
| 5 or less                           | 1335 (23.0)          | 9168 (32.7)               |
| 6–10                                | 1302 (22.4)          | 6704 (23.9)               |
| 11–20                               | 1575 (27.1)          | 6755 (24.1)               |
| >20                                 | 1601 (27.5)          | 5392 (19.2)               |
| Visit frequency after DM<sup>b</sup> |                      |                           |
| 5 or less                           | 700 (12.0)           | 12345 (44.1)              |
| 6–10                                | 869 (14.9)           | 5142 (18.4)               |
| 11–20                               | 1723 (29.6)          | 5271 (18.8)               |
| > 20                                | 2521 (43.4)          | 5261 (18.8)               |
| Mean observation time (IQR)         |                      |                           |
| Years Before DM Onset               | 16.1 (5.7-25.5)      | 15.8 (5.2-25.6)           |
| Years After DM Onset                | 7.2 (4.2-9.9)        | 5.9 (2.6-8.5)             |
| Comorbidities                       |                      |                           |
| Myocardial infarction               | 142 (2.4)            | 408 (1.5)                 |
| Coronary heart disease              | 355 (6.1)            | 798 (2.8)                 |
| Peripheral vascular disease         | 186 (3.2)            | 645 (2.3)                 |
| Cardiovascular disease              | 206 (3.5)            | 742 (2.6)                 |
| Chronic pulmonary disease           | 553 (9.5)            | 1695 (6.0)                |
| Rheumatic heart disease             | 65 (1.1)             | 326 (1.2)                 |
| Renal disease                       | 122 (2.1)            | 395 (1.4)                 |
| Prostate Cancer Treatment<sup>c</sup> |                      |                           |
| Androgen Deprivation Therapy        |                      |                           |
| No                                  | 275 (95.8)           | 1180 (94.7)               |
| Yes                                 | 12 (4.2)             | 66 (5.3)                  |

DM, type 2 diabetes mellitus; IQR, interquartile range; MESA, Marshfield Epidemiologic Study Area; BMI, body mass index

<sup>a</sup>Number of visits in 5 years before or after reference date.
<sup>b</sup>Treatment data only available for subjects in cancer registry (N = 287 diabetic and 1246 non-diabetic subjects).
levels in non-diabetic subjects. Testosterone levels later increased slightly with duration of DM, but the ratio of testosterone to sex hormone binding globulin decreased, suggesting that despite improvement in overall testosterone levels, less may be bioavailable.24 Reduced levels of cancer promoting factors such as insulin and testosterone may create a hormonal environment that is protective against prostate cancer, accounting for the reduced risk observed in men post-onset of DM.1 This effect seems to be ongoing in this study which is in keeping with other reports also demonstrating that the protective effect of DM on prostate cancer risk increases with DM duration.9,14,15,25

There are conflicting reports in the literature, and one report from researchers in Taiwan using a National Health Insurance database to capture administrative claims data related to diabetes care found that the risk for prostate cancer in diabetic men was increased (RR 1.56; 95% CI 1.19–2.04, P = 0.0013) after adjusting for age, hypertension, dyslipidemia, and gout.26 This discrepancy may be the result of confounding by BMI, which was not adjusted for, as well as a significant increase in the risk of prostate cancer in Asian populations compared to Western populations. A recent meta-analysis also seemed to confirm their findings of increased post-DM risk,27 but suffered from poor quality data by including several studies that relied on self-report to determine DM status, as well as studies with minimal adjustment for confounding. Additionally, the latter meta-analysis did not distinguish between odds ratios, HRs, and RRs for pooling, possibly resulting in considerable bias. Nevertheless, differences in distributions of genes associated with prostate cancer risk in Asian populations cannot be ruled out.2

Despite the many strengths of our study, we still experienced limitations inherent to any retrospective study in that data was limited to what was available in the medical record which

Table 2. Prostate cancer risk before and after DM onset.

|                        | Before DM Onset | P value | After DM Onset | P value |
|------------------------|-----------------|---------|----------------|---------|
|                        | N (%)a          | HR (95% CI) | N (%)a          | HR (95% CI) |
| Diabetes status        |                 |          |                 |          |
| Yes                    | 363 (6.2)       | 0.96 (0.947–1.320) | 0.4752 | 237 (4.8) | 0.84 (0.72–0.97) | 0.0167 |
| No                     | 1759 (6.3)      | 1.00 (ref) | 1073 (4.5)    | 1.00 (ref) |
| Smoking                |                 |          |                 |          |
| Yes                    | 1678 (6.5)      | 1.00 (ref) | 921 (4.3)     | 1.00 (ref) |
| No                     | 444 (5.6)       | 1.09 (0.844–1.172) | 0.1255 | 389 (5.6) | 1.20 (1.06–1.35) | 0.0036 |
| MESA residency         |                 |          |                 |          |
| Yes                    | 374 (5.7)       | 1.00 (ref) | 273 (4.9)     | 1.00 (ref) |
| No                     | 1748 (6.4)      | 0.94 (0.833-1.048) | 0.2483 | 1037 (4.5) | 1.00 (0.87–1.15) | 0.9893 |
| Birth year             |                 |          |                 |          |
| 1929 and prior         | 1124 (14.5)     | 56.5 (39.9–79.9) | < 0.0001 | 513 (9.5) | 91.2 (22.6–366.9) | < 0.0001 |
| 1930–1939              | 696 (8.1)       | 26.4 (18.6–37.3) | < 0.0001 | 528 (7.6) | 87.8 (21.9–352.0) | < 0.0001 |
| 1940–1949              | 268 (3.1)       | 8.79 (6.15–12.6) | < 0.0001 | 362 (4.6) | 52.3 (13.0–209.9) | < 0.0001 |
| 1950–1959              | 34 (0.6)        | 1.00 (ref)b | 105 (1.8)     | 21.0 (5.2–85.1) | < 0.0001 |
| 1960 and later         | 0 (0.0)         |          | 2 (0.1)       | 1.00 (ref) |
| DM diagnosis period    |                 |          |                 |          |
| 1995–1999              | 504 (6.8)       | 0.52 (0.46–0.59) | < 0.0001 | 450 (7.3) | 0.52 (0.43–0.62) | < 0.0001 |
| 2000–2004              | 870 (6.2)       | 0.69 (0.62–0.76) | < 0.0001 | 564 (4.8) | 0.65 (0.56–0.75) | < 0.0001 |
| 2005–2009              | 748 (6.0)       | 1.00 (ref) | 296 (2.8)     | 1.00 (ref) |
| BMI (kg/m²)            |                 |          |                 |          |
| < 25                   | 248 (7.0)       | 1.00 (ref) | 145 (5.1)     | 1.00 (ref) |
| 25–29.9                | 1318 (6.6)      | 0.99 (0.86–1.138) | 0.8530 | 770 (4.6) | 0.85 (0.71–1.02) | 0.0743 |
| ≥ 30                   | 556 (5.4)       | 1.19 (1.02–1.39) | 0.0293 | 395 (4.3) | 0.93 (0.76–1.13) | 0.4540 |
| Insurance              |                 |          |                 |          |
| Yes                    | 1750 (6.9)      | 1.00 (ref) | 909 (4.3)     | 1.00 (ref) |
| No                     | 372 (4.4)       | 0.83 (0.73–0.93) | 0.0020 | 401 (5.5) | 0.88 (0.77–1.01) | 0.0672 |
| Comorbidity            |                 |          |                 |          |
| ≥ 1                    | 486 (9.5)       | 1.00 (ref) | 168 (4.4)     | 1.00 (ref) |
| < 1                    | 1636 (5.7)      | 0.99 (0.90–1.10) | 0.9082 | 1142 (4.6) | 0.97 (0.82–1.14) | 0.7097 |

DM, type 2 diabetes mellitus; HR, hazard ratio; CI, confidence interval; MESA, Marshfield Epidemiologic Study Area; BMI, body mass index

aNumber of subjects with prostate cancer over total number of subjects in each group. bThere were no cases of prostate cancer in men born in 1960 or later before DM onset; men born in 1950 or later were considered the referent group.

Despite the many strengths of our study, we still experienced limitations inherent to any retrospective study in that data was limited to what was available in the medical record which
was collected as part of routine clinical care. Baseline information about patients was collected at the reference date, so we were not able to account for changes over time. We also did not collect information about other possible risk factors, such as diabetes medication use, or cancer specifics such as tumor grade. Additionally, we were unable to capture cancer treatment data for the majority of patients. Many men receive adjuvant ADT during treatment for prostate cancer, which has been shown to increase the risk of DM. We were only able to assess ADT use in 4% to 5% of subjects, but found usage to be relatively low. Of the subjects with available treatment data, 4.2% of diabetic and 5.3% of non-diabetic subjects received ADT, suggesting that ADT-related DM was unlikely to be an issue in the present study. We also acknowledge the possible impact of immortal time bias if patients with an aggressive rapidly progressive cancer who could have developed DM instead died before DM diagnosis. These patients may have been either excluded from analysis or might have been classified in the non-DM group. If the pre-diabetic or diabetic state results in a more aggressive prostate cancer, then immortality bias might contribute to why we did not find a significant increase risk of prostate cancer in the pre-diabetic period. However, we do not believe immortality bias is a major bias in our study, since most patients with prostate cancer survive beyond 10 years, allowing for enough time to develop DM and be appropriately classified.

**Conclusion**

We demonstrate that onset of DM was associated with a reduction in prostate cancer risk by approximately 16%, while risk was similar in both groups before DM onset. The risk of prostate cancer decreased shortly after onset and continued to decrease throughout the following 15 years. Although DM clearly carries more health risks than benefits, we have delineated for the first time that this protective period excludes the pre-diabetic phase. However, given our demonstration of increased risk of other cancers in the prediabetes phase, the absence of a similar increase for prostate cancer may be explained by the presence of hyperinsulinemia and the pre-prediabetic cancer promoting milieu counteracting the otherwise protective effect seen from lower testosterone levels in both the pre- and post-diabetic periods, although it is only post-DM when both insulin and testosterone levels are low. In addition, onset of hyperglycemia is an extra protective factor post-DM onset, because it lowers testosterone levels further. It is likely that dietary and other weight control strategies for pre-diabetics can have beneficial effects in terms of prostate cancer prevention, and such strategies need to be explored further in prospective studies.

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