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# Does a prostate cancer diagnosis affect management of pre-existing diabetes? Results from PCBaSe Sweden: a nationwide cohort study

Danielle Crawley,[1] Hans Garmo,[1] Sarah Rudman,[2] Pär Stattin,[3] Björn Zethelius,[4,5] Jo Armes,[6] Lars Holmberg,[1] Jan Adolfsson,[6,7] Mieke Van Hemelrijck[1]

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[1]School of Cancer and Pharmaceutical Sciences, Translational Oncology and Urology Research (TOUR), King's College London, London, UK
[2]Comprehensive Biomedical Research Centre, Guy's and St Thomas' NHS Foundation Trust and King's College London's, London, UK
[3]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden
[4]Department of Public Health and Geriatric, Uppsala University, Uppsala, Sweden
[5]Medical Products Agency, Uppsala, Sweden
[6]Florence Nightingale Faculty of Nursing and Midwifery, King's College London, London, UK
[7]Department of Clinical Science, Intervention and Technology, Karolinska Insituet, Stockholm, Sweden

**Correspondence to**
Dr Danielle Crawley;
Danielle.crawley@kcl.ac.uk

## ABSTRACT

**Objectives** Both prostate cancer (PCa) and type 2 diabetes mellitus (T2DM) are increasingly prevalent conditions, which frequently coexist in men. Here, we set out to specifically examine the impact of a PCa diagnosis and its treatment on T2DM treatment.

**Setting** This study uses observational data from Prostate Cancer database Sweden Traject.

**Participants** The study was undertaken in a cohort of 16 778 men with T2DM, of whom 962 were diagnosed with PCa during mean follow-up of 2.5 years.

**Primary and secondary outcome measures** We investigated the association between PCa diagnosis and escalation in T2DM treatment in this cohort. A treatment escalation was defined as a new or change in anti-T2DM prescription, as recorded in the prescribed drug register (ie, change from diet to metformin or sulphonylurea or insulin). We also investigated how PCa diagnosis was associated with two treatment escalations. Multivariate Cox proportional hazards regression with age as a time scale was used while adjusting for educational level and initial T2DM treatment.

**Results** We found no association between PCa diagnosis and risk of a single treatment escalation (HR 0.99, 95% CI 0.87 to 1.13). However, PCa diagnosis was associated with an increased risk of receiving two consecutive T2DM treatment escalations (HR 1.75, 95% CI 1.38 to 2.22). This increase was strongest for men on gonadotropin-releasing hormone (GnRH) agonists (HR 3.08, 95% CI 2.14 to 4.40). The corresponding HR for men with PCa not on hormonal treatment was 1.40 (95% CI 1.03 to 1.92) and for men with PCa on antiandrogens 0.91 (95% CI 0.29 to 2.82).

**Conclusions** Men with T2DM who are diagnosed with PCa, particularly those treated with GnRH agonists, were more likely to have two consecutive escalations in T2DM treatment. This suggests a need for closer monitoring of men with both PCa and T2DM, as coexistence of PCa and its subsequent treatments could potentially worsen T2DM control.

## Strengths and limitations of this study

- ► Large population design of Prostate Cancer (PCa) database.
- ► Large numbers of men with type 2 diabetes (T2DM) included.
- ► Inclusion of a large number of men who subsequently developed PCa (the exposure) as well as information on PCa treatment received.
- ► No serial measurements of haemoglobin A1c were available, so proxy of escalations in pharmacological treatment was used to assess T2DM control.

## INTRODUCTION

There are over 60 million people who have been diagnosed with type 2 diabetes mellitus (T2DM) across Europe, and it is estimated that over 10% of men in Europe have T2DM.[1] Prostate cancer (PCa) is the the most common cancer in men in Europe, with around 417 000 new cases diagnosed in 2012.[2] As a result, these two increasingly prevalent conditions often occur together in the same men. Their relationship has been extensively studied with respect to the effects of T2DM on PCa risk and progression.[3 4] However, conversely the impact of a PCa diagnosis on the treatment of T2DM has received less attention.

T2DM is associated with increased risk of several solid malignancies.[5] However, for men with T2DM there has been a consistent decrease in risk of PCa in several meta-analysis,[3 6 7] as compared with not having T2DM. T2DM is, however, also included in the cluster of disorders which comprise the metabolic syndrome (MetS).[8] During the last decade, several studies have investigated if MetS is involved in the aetiology of PCa.[9–11] A meta-analysis of risk of PCa related to MetS found a pooled relative risk of 1.54 (95% CI 1.23 to 1.94).[12] Hence, the relationship between PCa and T2DM is not fully understood. Finally, the gold standard treatment for advanced PCa is androgen deprivation therapy (ADT), which has been

shown to increase the risk of T2DM.[13 14] The risk is highest in men on gonadotropin-releasing hormone (GnRH) agonists.[13]

A recent meta-analysis of glycaemic control in subjects with T2DM during and after cancer treatment found mixed results, with four studies reporting no increase in haemoglobin A1c (HbA1c) and three studies reporting an increase in HbA1c after cancer treatment.[15] Of those three studies where glycaemic control worsened, two were in patients with PCa who had received ADT.[16 17] The largest study was by Keating *et al*, and it showed an increase in HbA1c at 1 and 2 years despite a 20% increased risk of receiving additional T2DM medications in men with PCa on GnRH agonists.[16] With the recent emergence of novel treatments that increase survival in men with advanced PCa, there is an increasing need to understand how PCa treatment affects T2DM control. Here, we aimed to further investigate the impact of a PCa treatment on the management of T2DM.

## METHODS

### Study population and data collection

Prostate Cancer database (PCBaSe) Sweden 3.0 is based on the National Prostate Cancer Register (NPCR) of Sweden, which became nationwide in 1998 and covers 98% of all newly diagnosed cases of PCa, as compared with the Swedish Cancer Register.[15 16] NPCR includes information on date of diagnosis, age at diagnosis, tumour stage and differentiation, serum levels of prostate-specific antigen at time of diagnosis. Using the Swedish personal identity number, five PCa-free men from the general population in Sweden were randomly selected within sets of men who matched the index case on birth year and county of residence and included in a PCa-free control cohort.[15] Both men with PCa and those in the control cohort were subsequently linked to a series of national health-care registers and demographic databases, including the National Diabetes Register (NDR) and the Prescribed Drug Register (PDR). PCBaSe Traject includes all data in

**Table 1** Baseline characteristics of all patients and divided by those later diagnosed with PCa and those who were not

| | All men | | No PCa | | PCa | |
|---|---|---|---|---|---|---|
| | N=16 778 | | N=15 816 | | N=962 | |
| Age onset of DM (median) | | Q1–Q3 | | Q1– Q3 | | Q1– Q3 |
| | 71.1 | (65.5–77.2) | 71.2 | (65.6–77.3) | 69 | (63.1–75.5) |
| Follow-up years (median) | | Q1–Q3 | | Q1–Q3 | | Q1–Q3 |
| | 2.5 | (1.1–4.3) | 2.5 | (1.1–4.3) | 3.2 | (1.5–5.2) |
| Initial DM treatment | | % | | % | | % |
| Diet | 9692 | 57.8 | 9126 | 57.7 | 566 | 58.8 |
| Metformin | 6373 | 38 | 6020 | 38.1 | 353 | 36.7 |
| Metformin+SU | 79 | 0.5 | 75 | 0.5 | 4 | 0.4 |
| SU | 634 | 3.8 | 595 | 3.8 | 39 | 4.1 |
| HbA1c at DM onset (%) | | Q1–Q3 | | Q1–Q3 | | Q1–Q3 |
| | 48 | 43–56 | 48 | 43–56 | 48 | 43–55 |
| Missing HbA1c (N) | | % | | % | | % |
| | 2310 | 13.8 | 2208 | 14 | 102 | 10.6 |
| BMI[2] median (kg/m$^2$) | | Q1–Q3 | | Q1–Q3 | | Q1–Q3 |
| | 28.7 | 26–31.6 | 28.6 | 26–31.6 | 28.7 | 26.2–31.4 |
| Missing BMI[2] (N) | | % | | % | | % |
| | 4540 | 27.1 | 4305 | 27.2 | 235 | 24.4 |
| Education status | | % | | % | | % |
| Low | 7402 | 44.1 | 6998 | 44.2 | 404 | 42 |
| Middle | 6336 | 37.8 | 5976 | 37.8 | 360 | 37.4 |
| High | 2810 | 16.7 | 2623 | 16.6 | 187 | 19.4 |
| Missing | 230 | 1.4 | 219 | 1.4 | 11 | 1.1 |
| Civil status | | % | | % | | % |
| Not married | 5649 | 33.7 | 5317 | 33.6 | 332 | 34.5 |
| Married | 11 129 | 66.3 | 10 499 | 66.4 | 630 | 65.5 |

BMI, body mass index; DM, diabetes mellitus; HbA1c, haemoglobin A1c; PCa, prostate cancer; Q1, quartile 1; Q3, quartile 3.

Table 2 Single treatment changes and event numbers

| One treatment change | Event number |
|---|---|
| No change | 10573 |
| Diet ->metformin | 3495 |
| Diet ->SU | 389 |
| Metformin ->insulin | 695 |
| Metformin ->SU | 770 |
| Metformin+SU ->insulin | 79 |
| SU ->insulin | 129 |
| SU ->metformin | 212 |
| Diet ->metformin+SU | 19 |
| Diet ->insulin | 417 |

SU, sulphonylurea.

PCBaSe 3.0 but has additional linkages. It focuses specifically on men diagnosed with PCa between 1992 and 2012 with information available on their complete treatment trajectory.[16]

Using PCBaSe Traject, we included all men with a diagnosis of T2DM without a pre-existing PCa diagnosis, taken either from the NDR or those receiving antidiabetic medications within the PDR between 2005 and 2014. The Research Ethics Board at Umeå University approved this study.

The main outcome variable in this study was an escalation in T2DM treatment (ie, change from diet control to metformin or sulphonylurea or insulin). Information on filled prescriptions of metformin, sulphonylurea and insulin were obtained from the PDR using Anatomical Therapeutic Chemical (ATC) codes (insulin-ANA, metformin-A10BA/BD, sulphonylurea- A10BB).[18] The initial T2DM treatment was defined using filled drug prescriptions for antidiabetic drugs entered during a 6-month run-in period following the date of registration of T2DM in the NDR. If the same drug was used in two consecutive 90-day periods, it was deemed to be the initial T2DM treatment. Follow-up started after the run-in and if no drug prescriptions had been filled during that period, then diet control was deemed to be the initial treatment. All men who received insulin as initial treatment were excluded from the study, since escalation of insulin doses could not be assessed due to an absence of data on dose.

The main exposure variable in this study was a diagnosis of PCa in PCBaSe Traject. We also examined PCa treatments, divided into no ADT, antiandrogens (AA) monotherapy and GnRH agonists. We specifically focused on ADT because it has consistently been found to increase the risk of T2DM.[13 14] Exposure to these treatments was taken from the PDR. If a man received more than one of these treatments, they contributed exposure time to each category for the duration of that therapy, that is, a man could have contributed person-time to the no ADT group

Table 3 Two consecutive treatment changes and event numbers

| Two treatment changes | Event numbers |
|---|---|
| No changes | 10573 |
| One change* | 1320 |
| SU ->metformin ->insulin | 66 |
| SU ->metformin+SU ->insulin | 8 |
| Diet ->metformin ->insulin | 314 |
| Diet ->metformin ->SU | 450 |
| Diet ->SU ->insulin | 60 |
| Diet ->SU ->metformin | 96 |
| Metformin ->SU ->insulin | 197 |

*These numbers reflect those who only underwent one change.
SU, sulphonylurea.

Table 4 HRs and 95% CI for a single change of T2DM treatment by PCa diagnosis and PCa treatments

| | | Multivariate analysis* | |
|---|---|---|---|
| | | HR | 95% CI |
| PCa diagnosis | No PCa | 1 | (Ref) |
| | PCa | 0.99 | 0.87 to 1.13 |
| PCa treatment | No PCa | 1 | (Ref) |
| | No ADT | 0.97 | 0.83 to 1.14 |
| | AA | 0.80 | 0.48 to 1.36 |
| | GnRH | 1.12 | 0.86 to 1.47 |

*Multivariate analysis with age as time scale and adjusted for education status and initial diabetes treatment.
AA, antiandrogen; ADT, androgen deprivation therapy; GnRH, gonadotropin-releasing hormone agonist; PCa, prostate cancer; T2DM, type 2 diabetes mellitus.

Table 5 HRs and 95% CI for two consecutive changes of DM treatment by PCa diagnosis and PCa treatments

| | | Multivariate analysis* | |
|---|---|---|---|
| | | HR | 95% CI |
| PCa diagnosis | No PCa | 1.00 | (Ref) |
| | PCa | 1.75 | 1.38 to 2.22 |
| PCa treatment | No PCa | 1.00 | (Ref) |
| | No ADT | 1.40 | 1.03 to 1.92 |
| | AA | 0.91 | 0.29 to 2.82 |
| | GnRH | 3.08 | 2.14 to 4.44 |
| PCa diagnosis in relation to prior change in T2DM treatment | No PCa | 1.00 | (Ref) |
| | PCa prior to one change | 1.09 | 0.78 to 1.54 |
| | PCa after one change | 3.59 | 2.61 to 4.93 |

*Multivariate analysis with age as time scale and adjusted for education status and initial diabetes treatment.
AA, antiandrogen; ADT,androgen deprivation therapy; GnRH, gonadotropin-releasing hormone agonist; PCa, prostate cancer; T2DM, type 2 diabetes mellitus.

initially and then later to the GnRH agonist or AA exposure group after conversion to hormonal therapy.

### Analysis

Multivariate cox proportional hazards regression was used to calculate HRs and 95% CI for one and two T2DM treatment escalations in men who had and had not been diagnosed with PCa. Age was used as a time scale and all models were adjusted for educational level and initial T2DM treatment. We performed a further analysis in which the exposure was defined as type of PCa treatment (as defined above). We also performed an analysis examining the risk of consecutive treatment escalations in patients whose PCa diagnosis came before and after the first treatment change.

All data management was performed with SAS V.9.3 (SAS Institute) and all data analysis was conducted with R V.2.13.2 (R Foundation for Statistical Computing).

## RESULTS

A total of 16 778 men with T2DM were included in the study of whom 962 were diagnosed with PCa during follow-up, median of 2.5 years (IQR 1.3 1.1–4.3) (table 1). Initially treated with diet control were 9692 men (57%) and 6373 (38%) received metformin as initial T2DM treatment (table 1). All baseline characteristics were similar between men who later were and were not diagnosed PCa. Table 2 shows the single treatment escalations captured and the event numbers for each change for all men. About 6205 treatment changes were seen, the most common change was from diet control to metformin (3495). Those who had two consecutive treatment escalations (table 3) were 1191 men.

There was no association between PCa diagnosis and risk of a single treatment escalation (HR 0.99, 95% CI 0.87 to 1.13) (table 4). Neither was there any association with the type of PCa treatment (no ADT HR 0.97, 95% CI 0.83 to 1.14, AA HR 0.80, 95% CI 0.48 to 1.36, GnRH agonists HR 1.12, 95% CI 0.86 to 1.47) (table 4).

PCa diagnosis was associated with an increased risk of two consecutive T2DM treatment escalations (HR 1.75, 95% CI 1.38 to 2.22) (table 5). This increase was strongest in men on GnRH agonists (HR 3.08, 95% CI 2.14 to 4.40). The corresponding HR for men with PCa not on ADT was 1.40 (95% CI 1.03 to 1.92) and for men on AA was 0.91 (95% CI 0.29 to 2.82) (table 5). The increased risk was seen only in men who were diagnosed with PCa after a change of T2DM treatment, that is, who were treated with a drug (HR 3.59, 95% CI 2.61 to 4.93), compared with those who were diagnosed with PCa prior to any change in T2DM treatment (HR 1.09, 95% CI 0.78 to 1.54).

## DISCUSSION

In this population-based cohort study, PCa diagnosis was associated with an increased risk of two consecutive T2DM treatment escalations. The association was strongest in men treated with GnRH agonists and was only observed in men who were receiving pharmacological treatment for their T2DM.

Prior to this study, all studies examining worsening of glycaemic control and T2DM treatments following a PCa diagnosis have focused solely on men on ADT. In a small study of 29 patients with advanced PCa and insulin dependent T2DM on ADT, Haidar *et al* showed a worsening in HbA1c and increasing insulin requirements.[17] In a similar US study of 77 patients with T2DM and PCa on ADT, 15 (19.5%) men had a >10% increase in HbA1c.[18] However, there were no control men in either of these small single institution studies. The largest study to date used the Veterans Affairs observational cohort to study 2237 pairs of propensity matched men with PCa and T2DM who were or were not treated with GnRH agonists.[16] They showed an increase in HbA1c at 1 and 2 years despite a 20% increased risk of receiving additional T2DM medications in those receiving GnRH agonists. Most recently a case–control study showed no impact of PCa diagnosis on mean HbA1c or glucose.[19] However, over 70% of patients in this study underwent prostatectomy and therefore did not receive ADT.

These studies are in line with the findings of our study that a diagnosis of PCa worsens glycaemic control in men with pre-existing T2DM when looking at the proxy of escalating pharmacological treatment. Worsening of glycaemic control was strongest in men on GnRH agonists compared with other forms of ADT such as AA. This mirrors what has previously been seen with the increased risk of T2DM in non-diabetics treated with ADT.[13] However, we also show an increased risk of two consecutive treatment escalations in those who are not receiving any form of ADT. Current literature has focused only on those receiving ADT, so this is a new finding. This may suggest that there is a true disease effect of PCa on glycaemic control, not just as a result of treatments received.

We showed no increased risk of a single treatment escalation. The risk was highest in those who already had one escalation of treatment prior to the diagnosis of PCa. As nearly 60% of our population was initially treated with dietary modification, this suggests those who are already receiving a pharmacological treatment for T2DM are at highest risk of further escalations following a PCa diagnosis. This is in concordance with previous studies. Keating *et al* looked specifically at initiation or addition of insulin therapy and found a higher rate in men on ADT versus men not on ADT (94.5 men per 1000 person-years vs 81.2) as a marker of intensification of antidiabetes management.[16]

Use of GnRH agonists decreases insulin sensitivity and increases body fat. These physiological effects have been shown to occur early after treatment initiation[20] and although it has not been directly studied it can be hypothesised that similar physiological changes would occur in patients with pre-existing diabetes leading to a worsening of glycaemic control and the need for escalating pharmacological management.

Strengths of our study include the large population design of PCBaSe and the large number of men with T2DM included in this study, meaning it has good external validity. The design of the study allows for inclusion of a large number of men who subsequently developed PCa. The linkage to both the NDR and PDR allowed detailed data on the initial and subsequent T2DM treatments to be accessed. Unlike previous studies, we had detailed data on the type of PCa treatment being received and were able to examine GnRH agonists individually, not only in combination with other forms of ADT. Weaknesses include the lack of repeated measures of HbA1c, so although we are able to present median HbA1c at T2DM diagnosis, there are insufficient data available to examine changes following a PCa diagnosis. However, using change in T2DM treatments as a proxy of worsening glycaemic control is a clinically relevant outcome. Patients who had insulin-dependent T2DM at diagnosis were excluded from the study, as we were unable to capture change in insulin doses from the available data. However, it is unusual for a person with newly diagnosed T2DM to require insulin as first-line treatment. By using a 6-month run in window, with consecutive 90-day periods, to determine initial T2DM treatment, we were still able to include any patients who needed a one-off period of insulin to rapidly achieve glycaemic control at presentation before moving on to different forms of maintenance treatment. Hence, the numbers lost because of this exclusion were small.

## CONCLUSION

Men with T2DM who are diagnosed with PCa, particularly those treated with GnRH agonists, were more likely to have two consecutive escalations in T2DM treatment. This suggests a need for closer monitoring of men with both PCa and T2DM, as coexistence of PCa and its subsequent treatments could potentially worsen T2DM control.

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**Competing interests** None declared.

**Patient consent** Not required.

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