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ORIGINAL ARTICLE



Reduced risk of prostate cancer in a cohort of Lithuanian diabetes mellitus patients

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ABSTRACT

Background: During the past decade, a huge interest was devoted to the type-2 diabetes mellitus and their associations with prostate cancer development.

Objectives: The aim of this study was to determine whether type 2 diabetes mellitus and treatment with metformin is associated with prostate cancer risk.

Materials and methods: The cohort was composed of diabetic male patients identified in the National Health Insurance Fund database during 2000–2016 and cancer cases in national Cancer Registry. We calculated standardized incidence ratios (SIR) for prostate cancers as a ratio of observed number of cancer case in people with diagnosis of diabetes to the expected number of cancer cases in the underlying general population.

Results: 2754 prostate cancers were observed versus 3111.26 expected within the period of observation entailing an SIR of 0.89 (95% CI: 0.85–0.92). Significantly lower risk of prostate cancer was found in diabetes patients in all age groups, also was in metformin-users and never-users' groups, with higher risk reduction in metformin-users (SIR 0.71, 95% CI: 0.68–0.75) than in diabetes patients never-users (SIR 0.88, 95% CI: 0.80–0.96).

Conclusion: In this large population-based study, we found a significantly decreased risk of prostate cancer among men with diabetes and metformin-users.

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Introduction

Prostate cancer is a leading cancer in the male patient population across the Western world [1]. Approximately 450,000 men in Europe are diagnosed with prostate cancer and 107,000 died from this disease in 2018 [2]. It is estimated that by 2040 more than 2 million new prostate cancer cases and 740,000 prostate cancer deaths, due to aging population [3]. It is thought that such epidemiology in Western countries in part might be associated with changing lifestyle, environment and development of various chronic diseases. During the past decade, a huge amount of interest was devoted to the metabolic syndrome and, especially, type 2 diabetes mellitus (T2DM) and their associations with prostate cancer development [4,5]. However, results from published studies that analyse T2DM association with prostate cancer are conflicting. Some have found that T2DM reduces

prostate cancer incidence risk by 11–44% [6–8]. Pooled analysis of 45 studies showed that patients with T2DM were associated with an estimated reduction of 14% in the risk of developing prostate cancer as compared with those without diabetes [9]. Conversely, some other studies lack significant association [10–12]. However, it has been shown, that diabetes could be independent predictor of high-risk prostate cancer [13].

Metformin is the most widely used in the treatment of T2DM and reduces insulin resistance and diabetes-related morbidity and mortality. Population-based studies show that metformin treatment is associated with a dose-dependent reduction in cancer risk [14]. Data on the influence of metformin on prostate cancer risk, incidence, growth, and aggressiveness and survival rate are still conflicting and controversial. Some epidemiological studies indicate that metformin

Table 1. Numbers of observed (Obs) cases of prostate cancers, standardized incidence ratios (SIR) with 95% confidence intervals (CI) in diabetes patients.

	Obs	Exp	SIR	95% CI		p Value ^b
All diabetes patients	2751	3106.54	0.89	0.85	0.92	<0.001
Age, years						
<50	149	171.02	0.87	0.74	1.02	0.092
50–59	783	901.25	0.87	0.81	0.93	<0.001
60–69	1177	1348.92	0.87	0.82	0.92	<0.001
70–79	574	607.82	0.94	0.87	1.02	0.170
>80	68	77.52	0.88	0.69	1.11	0.300
Follow up, years ^a						
<5	1108	1325.43	0.84	0.79	0.89	<0.001
5–9	736	805.68	0.91	0.85	0.98	0.014
10 +	204	251.71	0.81	0.71	0.93	0.003

^aPrevalent cases not included.^bFor Chi-square.

decreases prostate cancer incidence [15,16], while other authors do not report any beneficial effect [17,18]. A recently published meta-analysis by Soranna et al. found no association between metformin use and prostate cancer risk in T2DM patients [19]. Therefore, it is still difficult to characterize the exact role of metformin in prostate cancer chemoprevention.

The aim of this analysis was to evaluate whether T2DM and metformin use could be associated with decreased prostate cancer risk in Lithuanian male patients with T2DM.

Materials and methods

Dataset

The National Health Insurance Fund (NHIF) database was created in 1999, seeking to reimburse healthcare institutions for the healthcare services provided from the NHIF. The system is used for the management, storage, exchange, analysis and reporting of all the services provided by healthcare institutions. The national database contains demographic data and entries on the primary and secondary healthcare services provided, emergency and hospital admissions, and prescriptions of reimbursed medications.

Study design and population

This study was approved by the Vilnius Regional Bioethics Committee, No. 158200-17-913-423. A retrospective cohort design was used to examine the relationship between diabetes and prostate cancer risk. The cohort was composed of patients (informed consent of study subject is not required for a record-linkage studies) identified in the NHIF database with the diagnosis of T2DM. Male patients with a diagnosis of diabetes during 2000–2016 were identified for the

study. Patients with a first diabetes diagnosis in the NHIF database in 2000 include prevalent cases of diabetes diagnosed before NHIF database establishment. Because the diagnoses of admission are registered by healthcare providers into the database, to increase the sensitivity of case definition for diabetes, only patients who had received prescriptions for reimbursed antidiabetic drugs were included.

Cancer cases were identified by record linkage with the Lithuanian Cancer Registry which is a nationwide population-based cancer registry that contains personal and demographic information, as well as information on diagnosis of all people diagnosed with cancer in Lithuania since 1978.

Only patients with the diagnosis of T2DM aged 40 or more years were included. We excluded 9 records because of incorrect date of diagnosis or death, 1938 records with prostate cancer diagnosis before diabetes diagnosis and 482 with prostate cancer diagnosis less than 1 year after diabetes diagnosis. We finally had 64,000 males with a previous diabetes diagnosis in our analysis.

Statistical methods

The person-time of observation was computed from the date of the first recorded diabetes mellitus diagnosis in the NHIF database until diagnosis of prostate cancer, emigration or end of the observation period (December 31 2016), whichever came first.

We calculated standardized incidence ratios (SIRs) for prostate cancers as a ratio of observed number of cancer cases in people with diabetes diagnosis to the expected number of cancer cases in the underlying general population. Expected numbers were calculated as multiplication of the exact person-years under observation in the cohort by calendar year- and 5-year-age-groups-specific national incidence rates. The 95% confidence intervals for the SIRs were estimated assuming number of observed cases follows Poisson distribution.

We computed SIRs by age of diabetes diagnosis, duration of follow-up until occurrence of prostate cancer and use of metformin. Patients with a first diabetes diagnosis in 2000 also included prevalent cases; therefore, they were excluded from analysis by duration of follow-up. Patients who had never been prescribed metformin after entry were defined as never-users; ever-users were defined as those who had been prescribed metformin more than 6 times and first prescription more than 1 year before prostate cancer

Table 2. Numbers of observed (Obs) cases of prostate cancers, standardized incidence ratios (SIR) with 95% confidence intervals (CI) in diabetes patients by metformin use.

Metformin	Obs	Exp	SIR	95% CI		<i>p</i> value ^a
Never-users	464	529.68	0.88	0.80	0.96	0.004
Users	1482	2078.16	0.71	0.68	0.75	<0.001
Cumulative dose (mg)						
<846000	195	346.71	0.56	0.49	0.65	<0.001
846,000–163,200	280	431.36	0.65	0.58	0.73	<0.001
1,635,000–3,060,000	424	552.64	0.77	0.70	0.84	<0.001
>3060000	583	747.45	0.78	0.72	0.85	<0.001

^aFor Chi-square.

diagnosis. To evaluate dose–response relationship, we calculated cumulative dose from the NHIF database.

All statistical analyses were carried out using STATA 11 statistical software (StataCorp. 2009. Stata Statistical Software: Release 11.0., College Station, TX).

Results

Overall, 64,000 males diagnosed with T2DM in Lithuania between 2000 and 2016 were included in the final cohort. They contributed 490,187.88 person-years of follow-up to the study.

Table 1 presents observed number of cases, SIRs of prostate cancer together with 95% confidence intervals by age, by time since T2DM diagnosis and duration of follow-up. Overall, 2751 prostate cancer cases were observed versus 3106.54 expected within a period of observation entailing a SIR of 0.89 (95% CI: 0.85–0.92). Significantly lower risk of prostate cancer was found among men with T2DM in all age groups, there were no differences in prostate cancer risk according to T2DM duration. Significantly lower prostate cancer risk was found in both metformin users and never-users T2DM groups, with lower risk of prostate cancer in ever-users (SIR 0.71, 95% CI: 0.68–0.75) in comparison with never-users (SIR 0.88, 95% CI: 0.80–0.96) (Table 2). However, there was no clear trend in the SIRs according to the cumulative dose of metformin.

Discussion

In this analysis involving 64,000 men with more than 1 years' duration of T2DM, we found an 11% reduction in the risk of developing prostate cancer compared to the general population. Our findings were in accordance with the results of a meta-analysis by Bansal et al. which covered forty five studies involving approximately 8 million participants with 132 thousand prostate cancer cases detected and showed that T2DM lowers the risk of prostate by 14% (95% CI 0.8–0.9, $p < 0.01$) [9].

Hypothesized mechanisms for decreased prostate cancer risk among diabetics include decreased levels of hormones and other cancer-related growth factors among diabetics and protective effects of diabetes medications [20]. Inverse association between T2DM and prostate cancer can be explained by the changes in insulin levels in men with diabetes. Initially many of them are hyperinsulinemic, but as the disease progresses, the level of insulin may decline and thus have growth inhibitory effect on cancer cell development [21]. Prolonged hyperglycaemia, hyperinsulinemia and insulin resistance have been reported to cause destruction of the Leydig cells, causing lower testosterone levels [22,23]. Our analysis, similar to the data published by Turner et al. did not show any association between T2DM duration and risk of prostate cancer [24]. Xu et al. in meta-analysis of 29 studies didn't find statistically significant associations between length of T2DM duration and prostate cancer risk ($p = 0.338$) as well [25]. On the other hand, US investigators have reported that the strength of diabetes and prostate cancer inverse association differed significantly by time since diagnosis of diabetes and increases with longer duration of diabetes; risk of prostate cancer was slightly increased during the first 3 years after diagnosis of diabetes, but was reduced among men diagnosed 4 or more years before [26]. Another study showed that prostate cancer risk was not reduced in the first year after diabetes diagnosis, was lower for men diagnosed for 1–6 years, and was even lower for men who had been diagnosed for more than 6 years after diabetes diagnosis [27]. In our study, the first year of follow-up was excluded from the analysis.

It was previously published that younger patients have lower risk of prostate cancer. Two studies both revealed that patients diagnosed with diabetes mellitus before 30 might have a relatively lower risk of prostate cancer than those diagnosed with diabetes after age 30 [27,28]. However, these studies included all types of diabetes mellitus and very young patients, therefore knowing that prostate cancer is predominantly a disease of the elderly, it is possible that studying a younger cohort and with shorter follow up these results could be inaccurate. Our T2DM cohort data demonstrated that prostate cancer risk was reduced similarly through all age groups starting from 40 years of age.

Studies with hypogonadal men and testosterone substitution therapies showed that testosterone level plays crucial role in the development of prostate cancer [29,30]. As testosterone deprivation is main

element of multimodal treatment of prostate cancer, it makes a large impact for outcomes for patients with diabetes, by increasing pro-inflammatory cytokines, worsening glycaemic control, lowering bone density and increasing risk of cardiovascular events [31–34]. Euglycaemic state of disease ensures fat loss and muscle-mass building, by activating metabolic processes. In contrary, testosterone loss disrupts glycaemic control, in some cases leading even to remission of type 2 diabetes [35,36]. Testosterone replacement therapy and monitoring of testosterone levels could lead to detection of prostate cancer at earlier stage of disease [37,38]. Testosterone levels at the day of diabetes diagnosis and during the treatment undoubtedly would be helpful for patients of our national diabetic patients' cohort to evaluate confounding factors for development of prostate cancer.

Metformin as the most common medication used in the management of T2DM and has also been suggested to decrease overall risk of prostate cancer [8]. We found a slightly lower risk of prostate cancer in patients who have used metformin compared to never users, 29% versus 12% respectively. Data from a Taiwanese study suggest that the longer T2DM is controlled and the higher the cumulative metformin dose, the more pronounced metformin protective effect against prostate cancer can be seen [15]. Recent data coming from Finland confirm that patients with T2DM and a normo-glycaemic status have a lower risk for developing prostate cancer, supporting the risk lowering effect of this antidiabetic drug [39]. However, in a study from Sweden, men with T2DM on metformin had no decrease risk compared to men with T2DM not on anti-diabetic drugs [18]. Therefore, more clinical prospective randomized trials are needed to consider it for everyday use as a prostate cancer chemopreventive drug.

The relationship between diabetes and metformin use and prostate cancer may be suspected to be causal due to evidence of decreasing prostate cancer risk with increasing diabetes duration and longer duration of metformin use, or higher cumulative dose. Our study failed to show dose–response relationship between duration of diabetes and cumulative dose of metformin.

The strength of this study is in its population-based nature, enabling comparisons with the same population from which the cases were obtained and avoiding selection bias of the control group. Unfortunately, the registry-based studies are unable to control for the individual level confounders other than age, which limits the strength of the inferences. T2DM is a chronic

disease and patients, probably after being diagnosed, can be thought to adjust their dietary habits, alcohol consumption or increase physical activity. However, it is not possible to control and measure these changes and account that they are crucial in reducing prostate cancer risk in T2DM patients. Also, other limitations of this study should be emphasized. Patients with T2DM are under increased surveillance and the possibility to discover prostate cancer might be higher, patients have more frequent visits to the doctors and are more likely to undergo additional medical examinations including PSA testing. If such bias exists, it would imply that in our study the reduction of prostate cancer risk among T2DM is under-estimated. On the other hand, men with diabetes have been found to have lower PSA levels compared to men without diabetes [40], while lower PSA levels could also contribute to reduced detection of prostate cancer in men with diabetes and they had significantly more advanced tumours with higher PSA levels [41]. Another limitation of this study lack of information on grading and staging of prostate cancer, therefore, we were not able to analyse risk by aggressiveness of prostate cancer.

In summary, in this large population-based study, we found significantly decreased risk of prostate cancer among men with T2DM. The risk of prostate cancer seemed not be influenced by patients age and increasing time since T2DM diagnosis. Significantly lower risk also was found in both metformin users and never-users groups, with lower risk of prostate cancer in ever-users, however, there was no clear trend in the risk according cumulative dose.

Disclosure statement

Authors have no conflict of interest to disclose.

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