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ORIGINAL PAPER

Risk of bladder cancer in patients with type 2 diabetes mellitus: a retrospective population-based cohort study in Lithuania

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Abstract

Purpose The objective of our study was to evaluate bladder cancer risk among Lithuanian type 2 diabetes mellitus (T2DM) patients and the effect of antihyperglycemic therapy on bladder cancer risk.

Methods We analyzed bladder cancer risk in a cohort of patients who were diagnosed with T2DM between 2001 and 2012 in Lithuania. Bladder cancer risk in four groups of antihyperglycemic medication users (insulin-only, metformin-only, sulfonylurea-only, and pioglitazone ± any other drug) was also assessed. Standardized incidence ratios for bladder cancer were calculated.

Results A total of 76,818 patients (28,762 males and 48,056 females) with T2DM were included in the final cohort. In the whole cohort of diabetic patients, 277 bladder cancer cases were observed, compared to 232.75 expected cases, according to bladder cancer rates in the general population (Standardized Incidence Ratio 1.19; 95% Confidence Interval: 1.06–1.34). Higher risk of bladder cancer was found in both men and women; however, in women the risk increase was not statistically significant. We found higher risk of bladder cancer in patients of both sexes diagnosed with T2DM at the age of 50–79 years and also in all groups of different antihyperglycemic medication users.

Conclusion T2DM was associated with increased risk of bladder cancer.

Keywords Bladder cancer · Type 2 diabetes mellitus · Cohort study · Antihyperglycemic therapy · Cancer risk

Introduction

Bladder cancer with over 570,000 new cases and estimated 212,536 deaths in 2020 worldwide is the tenth most frequently diagnosed cancer. It is about four times more common among men than women. In addition, bladder cancer is the sixth most common cancer and the ninth leading cause of cancer death for males [1].

Tobacco smoking is the most important risk factor for bladder cancer, but many more factors are known or suspected, like occupational carcinogen exposure in the industry (metal, rubber, dye production), environmental factors (arsenic compounds, nitrates), medical conditions (previous radiotherapy, schistosomiasis), and others [2].

In addition to the risk factors mentioned above, there is growing evidence of association between type 2 diabetes mellitus (T2DM) and increased risk for bladder cancer [3], as well as for cancer of other sites, including pancreas, liver, colon, rectum, endometrium, and breast [4, 5]. Although most recent data demonstrate increased risk of

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bladder cancer in patients with T2DM [6], studies showing contradictory results also exist [7, 8]. It is estimated that 537 million adults (1 in 10) worldwide had diabetes in 2021 and numbers are predicted to rise by more than 100 million in the following decade [9].

The pathophysiological link between cancer and diabetes has been explained by metabolic abnormalities observed in diabetes: hyperglycemia-induced chronic inflammation, oxidative stress and DNA damage, insulin resistance, hyperinsulinemia, and insulin/insulin-like growth factor axis activity in metabolic and mitogenic signaling pathways, which may stimulate proliferation, survival, and metastatic potential of tumor cells [4, 10].

As for association of antihyperglycemic medications with cancer risk, the evidence remains conflicting, which may be attributable to methodological issues of existing studies [11]. The use of insulin, sulfonylureas, sodium-glucose co-transporter-2 inhibitors, and metformin does not seem to increase cancer risk [11]. As for bladder cancer specifically, it has been shown that the use of metformin might lower the incidence [12], while pioglitazone is suggested to be increasing the risk according to the recent data [13].

The objective of our study was to evaluate bladder cancer risk among Lithuanian T2DM patients and the effect of antihyperglycemic therapy on bladder cancer risk.

Materials and methods

To assess the association between T2DM and bladder cancer risk we conducted a retrospective cohort study. In this study we used individual patient records from Lithuanian Cancer registry and the National Health Insurance fund (NHIF). Lithuanian Cancer Registry is a population-based cancer registry, containing personal and demographic information (place of residence, sex, date of birth, vital status), information on diagnosis (cancer site, date of diagnosis, method of cancer verification), and death (date of death, cause of death) of all cancer patients in Lithuania since 1978, while NHIF gathers data on provided healthcare services, emergency, and hospital admissions and data on prescriptions of reimbursed medications. We identified patients diagnosed with T2DM during 2001–2012 who were 40 years and older at the time of diagnosis. Entries regarding the diagnosis of T2DM (International Classification of Diseases (ICD)-10 code E11), type of antihyperglycemic medication, and number of prescriptions were obtained from the NHIF. Only patients with six and more prescriptions for reimbursed antihyperglycemic medication were included in the study to increase the specificity for T2DM. Bladder cancer cases in the study cohort were identified by linking every individual patient to the Lithuanian Cancer Registry using personal ID. Patients diagnosed with bladder or any other cancer prior to T2DM diagnosis were excluded from the study. Bladder cancer (ICD-10, codes C67) cases diagnosed more than 6 months after T2DM diagnosis were included in the risk analysis. The final cohort comprised 76,818 patients (28,762 males and 48,056 females) with T2DM.

Regarding antihyperglycemic medication exposure, four groups of patients were classified: insulin-only users, metformin-only users, sulfonylurea-only users, and patients who had been prescribed with pioglitazone, either alone or in combination with any other antihyperglycemic drug. We considered a period of 6 months to be the shortest time of exposure required for cumulative effect.

The start of the observation was the date of the T2DM diagnosis reported in NHIF database and the end of observation was defined as either of these events: bladder cancer diagnosis, death, emigration, or end of observation period (31 December 2017). Person-time from the start to the end of observation was calculated.

Standardized incidence ratios (SIRs) for bladder cancer were then calculated as a ratio of bladder cancer number observed in T2DM patient cohort, to the expected number of bladder cancer in the general Lithuanian population. Corresponding population data, by age, sex, and year were available from Statistics Lithuania. Expected numbers were calculated by multiplying the person-years under observation in the cohort by sex-, calendar year- and 5-year age group-specific national bladder cancer incidence rates. 95% confidence intervals (CI) for the SIRs were then calculated, following the assumption that a number of observed bladder cancer cases were Poisson distributed. SIRs were calculated by sex, age at the time of T2DM diagnosis, and by selected groups of antihyperglycemic medication users. All statistical analyses were performed using STATA 15 statistical software (StataCorp. revision 03 Feb. 2020. Stata Statistical Software: Release 15.1. College Station, TX, USA).

Results

A total of 76,818 patients (28,762 males and 48,056 females) with T2DM in Lithuania between 2001 and 2012 were included in the final cohort. In the whole cohort of patients with T2DM, 277 bladder cancer cases were observed, compared to 232.75 expected cases, according to bladder cancer rates in the general population (SIR 1.19; 95% CI 1.06–1.34) (Table 1). Higher risk of bladder cancer was found in both men and women; however, in women the risk increase was not statistically significant.

We found higher risk of bladder cancer in patients of both sexes diagnosed with T2DM at the age of 50–79 years. The risk of bladder cancer was higher than in general population in all groups of antihyperglycemic medication users;

Table 1 Numbers of observed and expected cases of bladder cancer standardized incidence ratios with 95 percent confidence intervals in T2DM patients

	Men				Women				Both sexes			
	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
Overall	200	164.26	1.22	1.06–1.34	77	68.49	1.12	0.89–1.41	277	232.75	1.19	1.06–1.34
Age at diagnosis												
40–49	8	7.97	1.00	0.50–2.01	0	1.51	0.00	–	8	9.48	0.84	0.42–1.69
50–59	47	35.12	1.34	1.06–1.78	12	9.41	1.28	0.72–2.25	59	44.53	1.32	1.03–1.71
60–69	82	62.96	1.30	1.05–1.62	20	21.43	0.93	0.60–1.45	102	84.39	1.21	0.99–1.47
70–79	55	48.51	1.13	0.87–1.48	37	28.06	1.32	0.96–1.82	92	76.57	1.20	0.98–1.47
80 +	8	9.71	0.82	0.41–1.65	8	8.08	0.99	0.49–1.98	16	17.79	0.90	0.55–1.47
Antihyperglycemic medication												
Metformin-only	55	45.72	1.20	0.92–1.57	26	20.76	1.25	0.85–1.84	81	66.48	1.22	0.98–1.51
Sulfonylurea-only	22	18.09	1.22	0.80–1.85	11	7.78	1.41	0.78–2.55	33	25.87	1.28	0.91–1.79
Insulin-only	8	4.02	1.99	0.99–3.98	0	0.93	0.00	–	8	4.95	1.62	0.81–3.23
Pioglitazone ± other	12	8.96	1.34	0.76–2.36	4	3.88	1.03	0.39–2.75	16	12.84	1.25	0.76–2.03
Other	103	87.47	1.18	0.97–1.43	36	35.14	1.02	0.74–1.42	139	122.61	1.13	0.96–1.34

T2DM Type 2 diabetes mellitus; *Obs* observed number of cases; *Exp* expected number of cases; *SIR* standardized incidence ratio; *CI* confidence interval

however, risk estimates in insulin-only and pioglitazone users were based on small number of cases.

Detailed characteristics (stage and morphology) of bladder cancer diagnosed in diabetic patients are presented in Supplementary Table 2.

Discussion

In our cohort study, we found that the risk of bladder cancer was increased in T2DM patients compared to the general population (SIR 1.19; 95% CI 1.06–1.34). These results are compatible with the data from recent meta-analyses of observational studies, showing the association of diabetes with increased risk of bladder cancer [6, 14–20]. We found that bladder cancer risk was significantly higher only among male T2DM patients (SIR 1.22; 95% CI 1.06–1.40). These findings are supported by several meta-analyses, which also found increased bladder cancer risk only among males [15, 16, 20]. On the contrary, a meta-analysis by Fang et al. observed a positive association between diabetes and bladder cancer risk only in women (RR 1.23; 95% CI 1.02–1.49) [18], while the most contemporary meta-analysis by Ahmadinezhad et al. found that diabetes was associated with increased risk of bladder cancer in both women (RR 1.23; 95% CI 1.12–1.34) and men (RR 1.19; 95% CI 1.09–1.30) [6].

In our study, we found higher risk of bladder cancer in patients of both sexes diagnosed with T2DM at the age of 50–79 years. In comparison, cohort study by Chen et al. suggested that only men more than 65 years of age experienced a significantly increased risk of bladder cancer [21]. A Swedish nationwide cohort study by Hemminki et al. revealed that bladder cancer risk was significantly higher in 60–74-year-old T2DM patients, but lower in the other age groups [22].

We did not find any differences in bladder cancer risk between the antihyperglycemic medication groups (insulin-only, metformin-only, sulfonylurea-only or pioglitazone users). In all groups the risk of bladder cancer was increased, but the results were not statistically significant and risk estimates in insulin-only and pioglitazone users were based on small number of cases. The evidence regarding association of antihyperglycemic medications with bladder cancer risk remains conflicting. Hu et al. performed a meta-analysis on the association between metformin use and bladder cancer risk. They found that metformin intake was not associated with a decreased incidence of bladder cancer (HR 0.82; 95% CI 0.61–1.09) [23], while more recent work by Liu et al. criticized the previous study for methodological issues and showed that the use of metformin could decrease the incidence of bladder cancer (OR 0.45; 95% CI 0.37–0.56; $p < 0.01$) [12]. In addition, Mamtani et al. found no difference in the incidence of bladder cancer among new users of metformin compared to new users of sulfonylurea [24]. Use of thiazolidinedione pioglitazone has been shown to increase the risk of bladder cancer by randomized control trials and observational studies in time- and dose-dependent manner [13]; however, Ripamonti et al. noted that a number of studies regarding pioglitazone use and risk of bladder cancer are affected by different types of bias and are widely

heterogeneous so the evidence should be considered with caution [25].

Smoking is considered the main risk factor for bladder cancer. Cumberbatch et al. found the cumulative relative risk of bladder cancer to be 3.47 (95% confidence interval [CI] 3.07–3.91) for current smokers and 2.04 (95% CI 1.85–2.25) for former smokers, compared with never smokers [26]. One of the major limitations of our study was the inability to adjust for tobacco use, because the data on smoking status were unavailable. This residual confounder could potentially account, to some extent, for the observed association between T2DM and bladder cancer. On the other hand, the prevalence of smoking has been shown to be comparable in diabetic patients and nondiabetic population [27], so it is debatable if the increased bladder cancer risk in diabetic patients could be attributed for tobacco exposure only. Several meta-analyses report a statistically significant relationship between T2DM and bladder cancer when the analysis is restricted to the studies that adjusted for smoking [14–20].

Although data on the exact relationship between diabetes and cancer are yet inconclusive, metabolic abnormalities observed in diabetes may have a critical role on the initiation and progression of carcinogenesis [28]. Insulin resistance, being a major feature of T2DM and subsequent chronic hyperinsulinemia is considered to be one of possible pathogenetic mechanisms linking T2DM to cancer by initiating and promoting tumorigenesis [29]. Increased insulin concentrations reduce the level of insulin-like growth factor (IGF)-binding protein, thus increasing the amount of bioactive IGF-1, which has mitogenic and anti-apoptotic activity and could act as a stimulus for tumor cell growth [18]. It has been shown that patients with bladder cancer have higher plasma levels of IGF-1 [30]. Hyperglycemia is another common metabolic abnormality in diabetes mellitus, which has been estimated to increase cancer risk in both men and women [31]. The phenomenon, known as the 'Warburg effect,' describes a switch of energy source to glucose-dependent glycolytic pathway in tumor cells and is recognized in virtually all types of cancer [10]. Thus, increased requirement of glucose uptake in tumor cells might be satisfied by increased level of blood glucose in diabetic patients. Finally, hyperglycemia is accounted for the induction of oxidative stress, DNA damage, and chronic inflammation, which create an environment supporting the neoplastic process [10].

We would like to acknowledge the strengths and limitations of our study. To begin with, our cohort study had a large sample size. We used data from Lithuanian Cancer Registry linked with the National Health Insurance Fund (NHIF) database, which relies on medical records rather than self-reports and represents the entire Lithuanian population. Using the data retrieved from the total national population minimized selection bias. Additionally, we analyzed the association between antihyperglycemic medication exposure and risk of bladder cancer using real-world data.

Unfortunately, we were unable to adjust our analysis for confounding factors, like body mass index, obesity, carcinogen exposure, and most important smoking, as this data was unavailable in Lithuanian Cancer Registry or the National Health Insurance Fund database. In addition, we analyzed the effect of different antihyperglycemic medication use in groups of insulin-only, metformin-only, sulfonylurea-only, and pioglitazone in any combination users; however, many patients with T2DM are prescribed more than one antihyperglycemic medication during their lifetime. Also, we used the total population as a control, which might have affected the accuracy of the selection of the nonexposed cohort. Finally, the number of bladder cancer cases in some groups was small; therefore, results should be interpreted with caution.

Conclusion

In conclusion, the risk of bladder cancer was increased in Lithuanian cohort of T2DM patients. Higher risk was found in patients of both sexes diagnosed with T2DM at the age of 50–79 years, also in all groups of different antihyperglycemic medication users.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10552-024-01911-2.

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Data Availability Data are available upon reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical Approval The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Vilnius Regional Biomedical Research Ethics Committee (No. 158200-17-913-423).

Consent to Participate Not applicable.

Consent to Publish Not Applicable.

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