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ARTICLE

Preexisting diabetes, metformin use and long-term survival in patients with prostate cancer

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ABSTRACT

Objective: To assess prostate cancer-specific and overall survival in prostate cancer patients with or without preexisting type 2 diabetes mellitus (T2DM) with regards to metformin use.

Methods: Patients diagnosed with prostate cancer in the Lithuanian population between 2001 and 2005 were identified through the Lithuanian Cancer Registry and followed until 2016, date of death, loss to follow-up or whichever came first. Information regarding the diagnosis of T2DM and antihyperglycemic medications were obtained from the National Health Insurance Fund database. Prostate cancer-specific and overall survival outcomes were analysed using univariate and multivariate Cox proportional hazard models.

Results: Out of 6689 men included, 254 (3.8%) had preexisting T2DM. There were 4807 deaths during follow-up, including 2084 from prostate cancer. No differences were found in prostate cancer-specific survival between men with or without T2DM. The risk of overall mortality was higher (HR = 1.24, 95% CI = 1.07–1.43) in diabetic men. Univariate analysis showed cancer stage at diagnosis and age to be significant predictors of survival. After adjustment for age and stage at diagnosis, there was no difference in prostate-specific survival between non-diabetic patients compared to metformin users or metformin non-users. However, overall survival was lower in T2DM patients, with a higher mortality risk for metformin non-users (HR = 1.63, 95% CI = 1.27–2.10). Prostate cancer-specific mortality risk was insignificantly lower in diabetic men on metformin (HR = 0.74, 95% CI = 0.54–1.02).

Conclusion: There was no difference in long-term prostate cancer-specific survival in patients with or without T2DM. Overall survival was lower in T2DM patients not treated with metformin.

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Diabetes mellitus; metformin; prostate cancer; survival; hazard ratios

Introduction

Diabetes has been associated with an increased risk for several types of cancer, such as liver, pancreas, endometrium, colorectal, breast and bladder [1,2]. Furthermore, studies show that diabetes can also negatively affect the survival of cancer patients, with an all-cause mortality hazard ratio (HR) of 1.41 (95% confidence interval (CI) = 1.28–1.55) [3] or an overall risk of death from cancer HR of 1.26 (95% CI = 1.21–1.31) [4], compared with non-diabetic individuals. Worse cancer prognosis in diabetes patients may be caused by different biological mechanisms related to hyperglycemia, hyperinsulinemia and inflammation which have been implicated in carcinogenesis progression and result in tumor cell proliferation and metastases [5].

Unlike for other cancers, more than one meta-analysis has shown that people with diabetes have a decreased risk of developing prostate cancer (PCa) compared to the general population [6,7]. This raises an interest of the impact of diabetes on PCa prognosis. The results in cohort studies are conflicting [8–13]. A latest meta-analysis of 17 studies by Lee et al. [14] showed that pre-existing diabetes was associated with a 29% increase in PCa-specific mortality (relative risk (RR) = 1.29, 95% CI = 1.22–1.38), and with a 37% increase in all-cause mortality (RR = 1.37, 95% CI = 1.29–1.45). There was, however, significant heterogeneity between studies and type 2 diabetes (T2DM) as a subgroup was analysed only in five of them.

Metformin is the first-line of treatment for people with T2DM [15]. There is growing interest in examining the role of the metformin for its anti-cancer properties in different cancers. Although the precise molecular mechanisms by which metformin affects various cancers have not been fully elucidated, activation of AMPK-dependent and AMPK-independent pathways along with energy metabolism aberration, cell cycle arrest and apoptosis or autophagy induction have emerged as crucial regulators in this process [16].

Whether metformin influences PCa outcomes is still unclear. Previous studies have shown that metformin use could reduce mortality from PCa [17–19], but others did not

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find a protective effect [20–22]. Although the two recent meta-analyses of nine studies each and the latest of 30 studies which analysed the influence of metformin on PCa incidence and outcomes suggest a benefit of metformin use in men with diabetes and prostate cancer, authors agree that further investigation is needed to confirm the findings [23–25].

The aim of this study was to assess long-term PCa-specific and overall survival and the influence of metformin therapy in a cohort of PCa patients with or without preexisting T2DM in a large nationwide population-based study.

Materials and methods

Study population

Patients diagnosed with PCa (ICD-10-AM code C61) in the entire Lithuanian male population between 1 January 2001 and 31 December 2005 were identified through the Lithuanian Cancer registry. The database contains personal and demographic information, as well as information on the diagnosis of all people diagnosed with cancer in Lithuania since 1978. The Lithuanian Cancer Registry data has been published in the International Association of Cancer Registries publications 'Cancer Incidence on Five Continents', which are submitted to systematic quality control [26]. From this database, we obtained information regarding age at the day of diagnosis, date of diagnosis, tumor stage classified by TNM Classification of Malignant Tumors, cause and date of death. Identified patients were followed until 31 December 2016, date of death or loss to follow-up, whichever came first.

Similarly to other European countries, Lithuania has a compulsory health insurance system, which means that residents of Lithuania are obliged to obtain health insurance coverage (i.e. pay compulsory health insurance contributions). The State therefore guarantees healthcare services compensated by the National Health Insurance Fund (NHIF). Information regarding the diagnosis of T2DM (ICD-10-AM code E11) and information on antihyperglycemic medications were obtained from the NHIF database. This database contains demographic data and entries on the primary and secondary healthcare services provided, emergency and hospital admissions and prescriptions of reimbursed medications. An assessment performed by independent European experts in 2019 identified NHIF data as high quality [27].

Exclusion criteria

Patients with less than 6 months of follow-up after prostate cancer diagnosis, patients with T2DM diagnosis after PCa and patients with a recorded T2DM diagnosis, but without prescribed antihyperglycemic medications, where excluded from the analysis. The latter exclusion was necessary to increase the sensitivity of case definition for diabetes.

Cohort patients were divided into three groups: prostate cancer patients without T2DM as 'non-diabetic patients', prostate cancer patients with T2DM (diabetic patients) who had ever been prescribed metformin were defined as 'metformin users', and the third group – prostate cancer patients with T2DM (diabetic patients) who had used other than metformin antihyperglycemic medications (sulfonylureas or insulin) as 'metformin non-users' (Figure 1).

Outcome measures

Survival outcomes were compared between diabetic and non-diabetic patients with PCa and between the three groups of patients – non-diabetic patients, metformin users and metformin non-users. PCa-specific survival was the primary outcome, measured from the date of PCa diagnosis to date of death due to PCa, or last known date alive. Patients who were not deceased or who died of causes other than PCa were censored at the last known date alive or date of death, respectively. Overall survival was analyzed as a secondary outcome, and defined as the period from the date of diagnosis of PCa to the date of death or last known date alive. For this secondary outcome, only those patients who were not deceased were censored at the last known date alive.

Statistical analysis

Patient demographic and clinical characteristics were compared between the three groups using the Chi-square analysis for categorical variables. Kaplan-Meier survival analyses stratified by exposure group were used to generate median survival curves for both PCa-specific and overall survival. Univariate Cox proportional hazard models were used to estimate hazard ratios and their 95% confidence intervals to compare PCa-specific and overall survival differences by known prognostic factors. These included age at diagnosis, spread of disease (localized vs. regional and distant), and metformin use (yes/no). Unadjusted and multivariate adjusted Cox proportional hazards models including age and stage at diagnosis were also conducted to estimate the effect of diabetes status on PCa-specific and overall survival. Multivariate Cox proportional hazard models for PCa-specific and overall survival were built that included prognostic factors which had a significant impact on survival as determined by a univariate hazard ratio (HR) with a p-value < 0.2.

All statistical analyses were carried out using STATA 11 statistical software (StataCorp. 2009. Stata Statistical Software: Release 11.0. College Station, TX). This study was approved by the Vilnius Regional Biomedical Research Ethics Committee (Nr. 158200-17-913-423).

Results

After excluding those with less than 6 months of follow-up after PCa diagnosis, patients with T2DM diagnosis after PCa and patients with recorded a T2DM diagnosis without antihyperglycemic medication prescriptions, there were 6689 men who met eligibility criteria for this analysis, including 254 (3.8%) with pre-existing T2DM and 6345 without T2DM (Figure 1). During follow-up there were 4807 deaths, including 2084 from PCa.

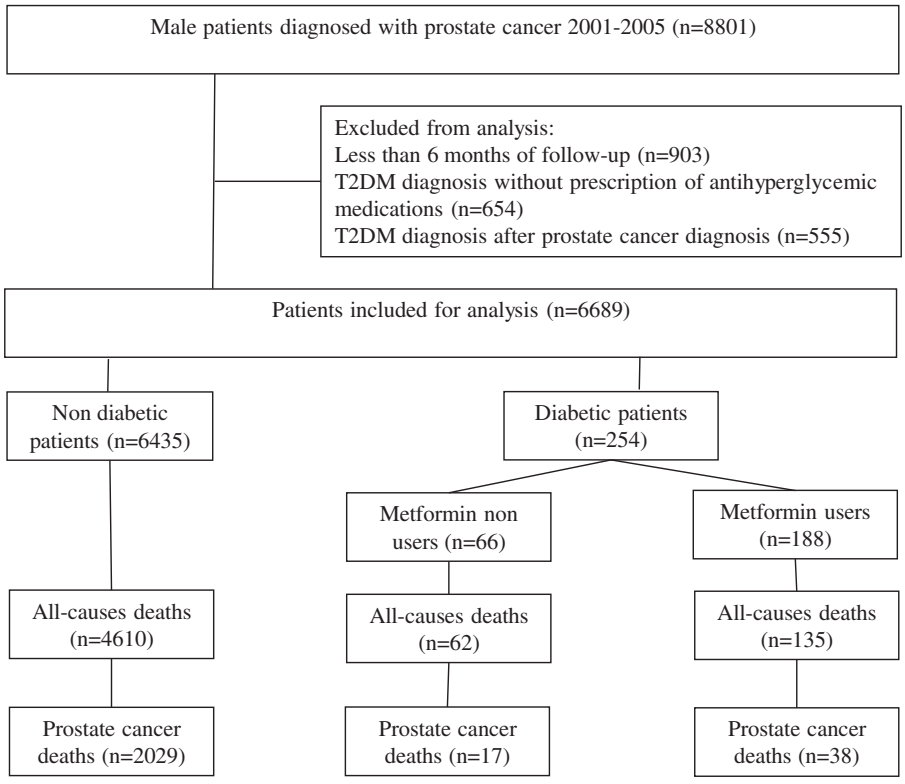

Figure 1. Study flow chart of male prostate cancer patients. T2DM, type 2 diabetes mellitus.

Table 1. Demographic and clinical characteristics of men with prostate cancer, according to diabetes and metformin status.

	Non-diabetic patients		Diabetic patients				
			Metformin users		Metformin non-users		
	n	%	*n*	%	*n*	%	*p*-value
Total	6435		188		66		
Age at diagnosis, years							
Mean (SD)	71.3 (8.3)		69.9 (6.7)		74.4 (7.2)		
<60	551	8.6	12	6.4	1	1.5	0.002
60–69	1994	31.0	69	36.7	15	22.7	
70–79	2936	45.6	95	50.5	37	56.1	
80+	954	14.8	12	6.4	13	19.7	
Stage							
Localized	2474	38.4	94	50.0	30	45.5	0.005
Regional	2748	42.7	61	32.4	29	43.9	
Distant	667	10.4	12	6.4	4	6.1	
Unknown	546	8.5	21	11.2	3	4.5	

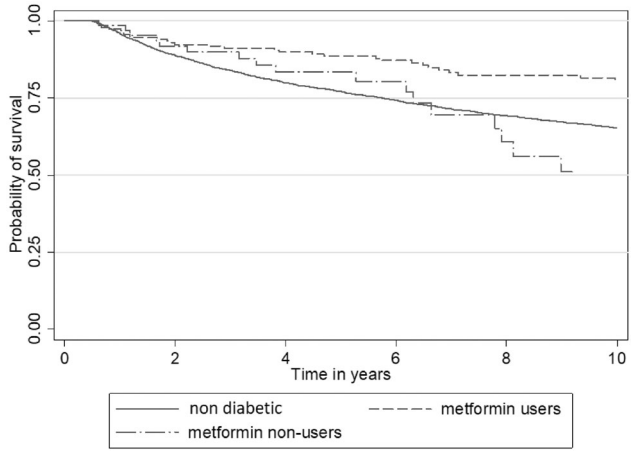

Figure 2. Kaplan-Meier survival curve comparing prostate cancer-specific survival between non-diabetic patients, diabetic patients who used metformin (metformin users) and diabetic patients who used other than metformin antihyperglycemic medications (metformin non-users).

Demographic and staging (as localized, regional, distant or unknown) information for the three exposure cohorts is presented in Table 1. The mean age at diagnosis was slightly higher in men with T2DM who did not use metformin. The groups also differed in stage of disease and age at diagnosis.

There were significant differences in PCa-specific survival and overall survival between groups in the Kaplan-Meier survival analysis (Figures 2 and 3). Univariate analysis showed that cancer stage at diagnosis and age were significant predictors of both PCa-specific and overall survival. After adjustment for age and stage at diagnosis, we found no differences in PCa-specific survival between men with and without T2DM, but higher risk of overall mortality (HR = 1.24, 95% CI = 1.07–1.43) in men with T2DM (Table 2). There was also no difference in PCa-specific survival between men without T2DM compared to men with T2DM who were metformin users or non-users (Table 3). Overall survival was significantly lower in diabetes patients with a higher mortality risk for metformin non-users (HR = 1.63, 95% CI = 1.27–2.10). Prostate cancer mortality risk was insignificantly lower in diabetic men on metformin (HR = 0.74, 95% CI = 0.54–1.02).

Discussion

Our national PCa patient cohort study showed that patients with PCa and T2DM had a significantly higher risk of overall mortality, but PCa-specific survival did not differ significantly between diabetes and non-diabetes patient groups,

regardless of their treatment with metformin. However, there was a trend towards increased PCa-specific survival in metformin users. Furthermore, overall survival of diabetic metformin users did not differ from the non-diabetic population, but was significantly decreased in diabetes patients who did not use metformin.

Evidence regarding the beneficial effect of metformin in PCa are conflicting. Experimental research reports that metformin exhibits advantages in PCa treatment *in vitro*. The Cyclin D1 pathway is related to PCa cell cycle progression and androgen-dependent transcription [28]. Metformin inhibits PCa cell proliferation by reducing cyclin D1 activity [29]. Metformin also reduces PCa cell viability and enhances apoptosis by downregulating androgen receptors in both androgen-dependent and androgen-independent PCa [30]. Given that mTOR is overexpressed in PCa, metformin reduces PCa growth by inhibiting mTOR signalling [31].

In clinical research, the effect of metformin is not that clear. The interpretation of the effect of metformin therapy is complicated due to heterogeneity between various study populations. To our knowledge, there are at least 12 retrospective studies [17,18,21,32–40] analysing the effect of metformin therapy on overall survival and seven [17,18,21,32,33,35,41] studies analysing metformin therapy and PCa-specific survival to date.

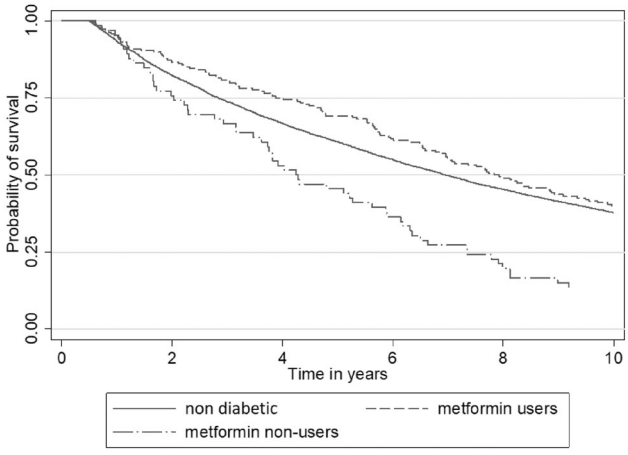

Figure 3. Kaplan-Meier survival curve comparing overall survival between non-diabetic patients, diabetic patients who used metformin (metformin users) and diabetic patients who used other than metformin antihyperglycemic medications (metformin non-users).

Some of the earliest clinical studies showed a positive effect of metformin on prostate cancer survival. Margel et al. [18] evaluated the association between cumulative duration of metformin use after PCa diagnosis and all-cause and PCa-specific mortality among patients with diabetes. The cohort consisted of 3837 patients. Cumulative duration of metformin treatment after PCa diagnosis was associated with a significant decreased risk of PCa-specific and all-cause mortality in a dose-dependent fashion. Adjusted HR for PCa-specific mortality was 0.76 (95% CI = 0.64–0.89) for each additional 6 months of metformin use. The association with all-cause mortality was also significant, but declined from an HR of 0.76 in the first 6 months to 0.93 between 24 and 30 months. Spratt et al. [17] evaluated the effect of metformin in localized PCa treated with external-beam radiation therapy. After adjustment for prostate specific antigen, tumor stage, Gleason score, age, diabetic status, and use of androgen-deprivation therapy, metformin use independently predicted improvement in all outcomes compared with the diabetic metformin non-user group: PSA-recurrence free survival, HR = 1.99, 95% CI = 1.24–3.18; $p = 0.004$), distant metastases-free survival (adjusted HR = 3.68, 95% CI = 1.78–7.62; $p < 0.001$), and PCa-specific mortality (HR = 5.15, 95% CI = 1.53–17.35; $p = 0.008$).

A recent large study by Richards et al. [35] included 87,344 patients from a US Veterans Affairs databases, including 61% without T2DM, 22% metformin non-users with T2DM, and 17% metformin users with T2DM. All men diagnosed with PCa were treated with androgen deprivation therapy (ADT). Overall survival was improved in men with T2DM who were metformin users (HR = 0.82, 95% CI = 0.78–0.86) compared to those with T2DM who were

Table 2. Prostate cancer-specific and overall survival according to diabetes status.

	Unadjusted HR (95% CI)	*p*-value	Multivariate-adjusted* HR (95% CI)	*p*-value
Prostate cancer specific survival				
Non-diabetic patients	1.00	Ref.	1.00	Ref.
Diabetic patients	0.70 (0.54–0.92)	0.01	0.81 (0.62–1.06)	0.12
Overall survival				
Non-diabetic patients	1.00	Ref.	1.00	Ref.
Diabetic patients	1.13 (0.98–1.31)	0.09	1.24 (1.07–1.43)	0.003

*Adjusted for age (as a continuous variable) and stage at diagnosis.

Table 3. Prostate cancer-specific and overall survival according to diabetes status and metformin use.

	Unadjusted HR (95% CI)	*p*-value	Multivariate-adjusted* HR (95% CI)	*p*-value
Prostate cancer-specific survival				
Non-diabetic patients	1.00	Ref.	1.00	Ref.
Diabetic metformin users	0.61 (0.44–0.84)	0.003	0.74 (0.54–1.02)	0.07
Diabetic metformin non-users	1.05 (0.66–1.71)	0.82	1.03 (0.64–1.66)	0.91
Overall survival				
Non-diabetic patients	1.00	Ref.	1.00	Ref.
Diabetic metformin users	0.96 (0.81–1.14)	0.81	1.12 (0.94–1.33)	0.20
Diabetic metformin non-users	1.86 (1.45–2.39)	<0.001	1.63 (1.27–2.10)	<0.001

*Adjusted for age (as a continuous variable) and stage at diagnosis.

metformin non-users (HR = 1.03, 95% CI = 0.99–1.08). Furthermore, PCa-specific survival was also improved in men with T2DM who were metformin users (HR = 0.70, 95% CI = 0.64–0.77) vs metformin non-users (HR = 0.93, 95% CI = 0.85–1.00). The reference group was men without T2DM.

However, other studies did not seem to find such a benefit of treatment with metformin. Mayer et al. [32] analysed survival in 2832 men diagnosed with metastatic castration resistant PCa, treated with docetaxel. Patents were stratified into groups based on diabetes status and use of antihyperglycemic medications. Metformin use during docetaxel chemotherapy did not improve PCa-specific or overall survival in diabetic patients with metastatic castration resistant PCa. Zaorsky et al. [33] performed a retrospective review of 3217 patients receiving radiation treatment for PCa and divided them into five subgroups according to diabetes status and diabetes treatment. Only the group of T2DM patients not receiving any medication differed significantly and had increased overall mortality (subdistribution hazard ratio (sHR) = 2.1; 95% CI = 0.66–1.54) and cause-specific mortality (sHR = 3.87, 95% CI = 1.31–11). A nested case–control study by Bensimon et al. [21] of a cohort of 935 men newly diagnosed with non-metastatic PCa with a history of treated T2DM showed that the post-diagnostic use of metformin was not associated with a decreased risk of PCa-specific mortality (rate ratio (RR) = 1.09, 95% CI = 0.51–2.33) or all-cause mortality (RR = 0.79, 95% CI = 0.50–1.23).

A few studies collected data on metformin use prospectively. Jarrard et al. [42] identified patients with metastatic PCa who underwent either ADT alone or ADT and docetaxel chemotherapy. Comparison of ADT + docetaxel + metformin ($n = 39$) to ADT + docetaxel ($n = 357$) and ADT + metformin ($n = 29$) to ADT alone ($n = 363$) revealed similar clinicopathologic characteristics. Cause of death was PCa in 13 (81%) of ADT + docetaxel + metformin, 72 (85%) ADT + docetaxel, 9 (82%) ADT + metformin and 105 (84%) ADT alone groups. Baseline metformin did not improve prostate cancer outcomes. Furthermore, metformin use was associated with a trend for worse overall survival (HR = 1.47, 95% CI = 0.95–2.26; $p = 0.08$) with adjustment for the treatment arm and prior local therapy. Randazzo et al. [39] followed up PCa patients for an average of 7.6 years and found that all-cause mortality was significantly higher among those on metformin, compared to metformin non-users (adjusted odds ratio = 2.50, 95% CI = 1.59–3.82; $p = 0.0001$). A relatively small number of men using metformin (68 and 150) is a limitation of these studies.

Finally, the latest meta-analysis by He et al. [25] on metformin therapy and PCa incidence and survival, which included 30 studies, showed that metformin treatment improves overall survival, cancer-specific survival and recurrence-free survival in PCa compared with non-metformin treatment. Moreover, PCa patients with metformin therapy accepting radical radiotherapy exhibited more dramatic effects on overall survival, cancer-specific and even recurrence-free survival. However, further randomized controlled trials are needed to confirm the association of PCa and metformin usage [25].

A possible antineoplastic effect of metformin for locally advanced and metastatic prostate, treated with androgen deprivation medication in combination with radiation therapy is currently evaluated by multi-arm and multi-stage trial STAMPEDE (Arm K) investigators [43].

Our population-based cohort study has several strengths. First, we used real-world data on prescriptions and diagnoses both in primary and secondary care practices where most patients with T2DM are treated. Second, we could study a large number of PCa cases in a longitudinal, well-established, validated database and did not rely on self-reports. Third, men with PCa from the whole Lithuanian population were followed up for a long period of time.

There are some limitations of our study as well. First, we did not assess the potential confounders such as BMI, smoking and alcohol status, glycemia and diabetes control, comorbidities, other medications used by the patients or cancer treatments. Patients with T2DM tend to have more comorbidities, such as hypertension, coronary heart disease, or metabolic syndrome. These, diabetes related, conditions may also contribute to a higher non-cancer-specific mortality rate. However, the confounders could not be extracted from our database. Since this was a retrospective study, we included only those patients that had a documented T2DM diagnosis, therefore, there is a probability that some patients who could have had undiagnosed T2DM were left out of the study population. Also, we did not have information about specific treatments that the individual patients had received. Prostate cancer treatment is organised according to the EAU (European Association of Urology) guidelines with minor country-specific limitations of systemic prostate cancer treatment due to unavailability of medications on the market. Therefore, prostate cancer treatment patterns are similar to other European countries. Furthermore, users of metformin were compared with never users of metformin. This makes it difficult to interpret results because both groups are heterogeneous. In ever-users, metformin is often but not always used as first-line therapy, can be used in different doses and might be combined with other antihyperglycemic medications, whereas never users comprise patients who use a combination of any other antihyperglycemic medication except metformin.

Conclusion

In conclusion, this large observational study showed that there was no difference in long-term prostate cancer-specific survival in patients with or without type 2 diabetes mellitus. However, overall survival was lower in type 2 diabetes mellitus patients who were not treated with metformin.

Ethical approval

The study was approved by the Vilnius Regional Biomedical Research Ethics Committee.

Informed consent

Due to the design of the study, informed consent of individuals was not obtained.

Author contributions

Study conception and design: G. Smailyte, L. Zabuliene, D. Linkeviciute-Ulinskiene, A. Patasius. Data Analysis and Interpretation: Giedre Smailyte, A. Patasius, M. Kincius. Manuscript writing: D. Linkeviciute-Ulinskiene, A. Patasius, G. Smailyte. Project management: G. Smailyte. All authors reviewed, edited and approved the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

[1] Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010;33(7):1674–1685.
[2] Onitilo AA, Engel JM, Glurich I, et al. Diabetes and cancer I: risk, survival, and implications for screening. Cancer Causes Control. 2012;23(6):967–981.
[3] Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA. 2008;300(23):2754–2764. Dec 17
[4] Chen Y, Wu F, Saito E, et al. Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia Cohort Consortium. Diabetologia. 2017;60(6):1022–1032.
[5] Sciacca L, Vigneri R, Tumminia A, et al. Clinical and molecular mechanisms favoring cancer initiation and progression in diabetic patients. Nutr Metab Cardiovasc Dis. 2013;23(9):808–815.
[6] Jian Gang P, Mo L, Lu Y, et al. Diabetes mellitus and the risk of prostate cancer: an update and cumulative meta-analysis. Endocr Res. 2015;40(1):54–61.
[7] Bansal D, Bhansali A, Kapil G, et al. Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies. Prostate Cancer Prostatic Dis. 2013;16(2):151–158.
[8] Bensimon L, Yin H, Suissa S, et al. Type 2 diabetes and the risk of mortality among patients with prostate cancer. Cancer Causes Control. 2014;25(3):329–338.
[9] Liu X, Ji J, Sundquist K, et al. The impact of type 2 diabetes mellitus on cancer-specific survival: a follow-up study in Sweden. Cancer. 2012;118(5):1353–1361.
[10] D'Amico AV, Braccioforte MH, Moran BJ, et al. Causes of death in men with prevalent diabetes and newly diagnosed high- versus favorable-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2010;77(5):1329–1337.
[11] Batty GD, Kivimaki M, Clarke R, et al. Modifiable risk factors for prostate cancer mortality in London: forty years of follow-up in the Whitehall study. Cancer Causes Control. 2011;22(2):311–318.
[12] Chiou WK, Hwang JS, Hsu KH, et al. Diabetes mellitus increased mortality rates more in gender-specific than in nongender-specific cancer patients: a retrospective study of 149,491 patients. Exp Diabetes Res. 2012;2012:701643.
[13] Smith MR, Bae K, Efstathiou JA, et al. Diabetes and mortality in men with locally advanced prostate cancer: RTOG 92-02. J Cin Oncol. 2008;26(26):4333–4339.
[14] Lee J, Giovannucci E, Jeon JY. Diabetes and mortality in patients with prostate cancer: a meta-analysis. Springerplus. 2016;5(1):1548.
[15] American Diabetes Associaton. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S90–S102.
[16] Sui X, Xu Y, Wang X, et al. Metformin: a novel but controversial drug in cancer prevention and treatment. Mol Pharm. 2015;12(11):3783–3791.
[17] Spratt DE, Zhang C, Zumsteg ZS, et al. Metformin and prostate cancer: reduced development of castration-resistant disease and prostate cancer mortality. Eur Urol. 2013;63(4):709–716.
[18] Margel D, Urbach DR, Lipscombe LL, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. J Clin Oncol. 2013;31(25):3069–3075.
[19] He XX, Tu SM, Lee MH, et al. Thiazolidinediones and metformin associated with improved survival of diabetic prostate cancer patients. Ann Oncol. 2011;22(12):2640–2645.
[20] Kaushik D, Karnes RJ, Eisenberg MS, et al. Effect of metformin on prostate cancer outcomes after radical prostatectomy. Urol Oncol. 2014;32(1):43 e1.
[21] Bensimon L, Yin H, Suissa S, et al. The use of metformin in patients with prostate cancer and the risk of death. Cancer Epidemiol Biomarkers Prev. 2014;23(10):2111–2118.
[22] Currie CJ, Poole CD, Jenkins-Jones S, et al. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care. 2012;35(2):299–304.
[23] Raval AD, Thakker D, Vyas A, et al. Impact of metformin on clinical outcomes among men with prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2015;18(2):110–121.
[24] Stopsack KH, Ziehr DR, Rider JR, et al. Metformin and prostate cancer mortality: a meta-analysis. Cancer Causes Control. 2016;27(1):105–113.
[25] He K, Hu H, Ye S, et al. The effect of metformin therapy on incidence and prognosis in prostate cancer: a systematic review and meta-analysis. Sci Rep. 2019;9(1):2218.
[26] Bray F, Ferlay J, Laversanne M, et al. Cancer incidence in five continents: inclusion criteria, highlights from Volume X and the global status of cancer registration. Int J Cancer. 2015;137(9):2060–2071.
[27] Gurevicius R. An international assessment of the state and possibilities of Lithuanian health statistics. Visuomenes sveikata. 2019;2(85):7.
[28] Comstock CE, Revelo MP, Buncher CR, et al. Impact of differential cyclin D1 expression and localisation in prostate cancer. Br J Cancer. 2007;96(6):970–979.
[29] Ben Sahra I, Laurent K, Loubat A, et al. The antidiabetic drug metformin exerts an antitumoral effect in vitro and in vivo through a decrease of cyclin D1 level. Oncogene. 2008;27(25):3576–3586.
[30] Wang Y, Liu G, Tong D, et al. Metformin represses androgen-dependent and androgen-independent prostate cancers by targeting androgen receptor. Prostate. 2015;75(11):1187–1196.
[31] Dowling RJ, Zakikhani M, Fantus IG, et al. Metformin inhibits mammalian target of rapamycin-dependent translation initiation in breast cancer cells. Cancer Res. 2007;67(22):10804–10812.
[32] Mayer MJ, Klotz LH, Venkateswaran V. The effect of metformin use during docetaxel chemotherapy on prostate cancer specific and overall survival of diabetic patients with castration resistant prostate cancer. J Urol. 2017;197(4):1068–1075.
[33] Zaorsky NG, Shaikh T, Ruth K, et al. Prostate cancer patients with unmanaged diabetes or receiving insulin experience inferior outcomes and toxicities after treatment with radiation therapy. Clin Genitourin Cancer. 2017;15(2):326–335 e3.
[34] Taussky D, Preisser F, Karakiewicz PI, et al. Impact of diabetes and metformin use on prostate cancer outcome of patients treated with radiation therapy: results from a large institutional database. Can J Urol. 2018;25(5):9509–9515.

[35] Richards KA, Liou JI, Cryns VL, et al. Metformin use is associated with improved survival for patients with advanced prostate cancer on androgen deprivation therapy. J Urol. 2018;200(6): 1256–1263.
[36] Chong RW, Vasudevan V, Zuber J, et al. Metformin has a positive therapeutic effect on prostate cancer in patients with type 2 diabetes mellitus. Am J Med Sci. 2016;351(4):416–419.
[37] Joentausta RM, Kujala PM, Visakorpi T, et al. Tumor features and survival after radical prostatectomy among antidiabetic drug users. Prostate Cancer Prostatic Dis. 2016;19(4):367–373.
[38] Xu H, Aldrich MC, Chen Q, et al. Validating drug repurposing signals using electronic health records: a case study of metformin associated with reduced cancer mortality. J Am Med Inform Assoc. 2015;22(1):179–191.
[39] Randazzo M, Beatrice J, Huber A, et al. Influence of metformin use on PSA values, free-to-total PSA, prostate cancer incidence and grade and overall survival in a prospective screening trial (ERSPC Aarau). World J Urol. 2015;33(8):1189–1196.
[40] Taira AV, Merrick GS, Galbreath RW, et al. Metformin is not associated with improved biochemical free survival or cause-specific survival in men with prostate cancer treated with permanent interstitial brachytherapy. J Contemp Brachyther. 2014;6(3): 254–261.
[41] Lu-Yao GL, Lin Y, Moore D, et al. Combination statin/metformin and prostate cancer specific mortality: a population-based study. J Cin Oncol. 2015;33(15_suppl):5018–5018.
[42] Jarrard DF, Chen Y-H, Liu G, et al. Impact of metformin on prostate cancer (PC) outcomes in the E3805 CHAARTED trial. J Cin Oncol. 2017;35(6_suppl):181–181.
[43] Gillessen S, Gilson C, James N, et al. Repurposing metformin as therapy for prostate cancer within the STAMPEDE trial platform. Eur Urol. 2016;70(6):906–908.