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Metformin use and prostate cancer risk

A meta-analysis of cohort studies

Zhaohan Feng, MSc*, Xiaofeng Zhou, MSc, Naibo Liu, BS, Jianfeng Wang, MSc, Xing Chen, MD, Xin Xu, MSc

Abstract

Background: The relationship between metformin use and the risk of prostate cancer is still inconclusive. Therefore, we performed a systematic review and meta-analysis of all eligible cohort studies to evaluate a potential association of metformin use with prostate cancer risk.

Methods: A comprehensive literature search was performed in PubMed and Web of Science databases through July 2018. A DerSimonian and Laird random-effects model was applied to calculate the pooled relative risk (RR) and its 95% confidence interval (CI).

Results: Eighteen cohort or nested case-control studies were included in this study with a total of 52,328 cases. In a random-effect pooled analysis, metformin use was not significantly associated with the risk of prostate cancer (RR 0.97, 95% CI 0.80–1.16, $P = .711$). Statistically significant heterogeneity was identified among included studies ($P < .001$, $I^2 = 98.1\%$). Sensitivity analysis indicated that no single study dominated the pooled RR.

Conclusion: The present large meta-analysis of cohort studies did not find an association between metformin use and prostate cancer risk.

Abbreviations: CI = confidence interval, NOS = Newcastle–Ottawa scale, RR = relative risk.

Keywords: cohort, meta-analysis, metformin, prostate cancer

1. Introduction

Prostate cancer is the second most common male cancer in the world, with a total of 1,111,700 new cases and 307,500 deaths estimated in 2012.[1] The most well-established risk factors for prostate cancer are age, race/ethnicity, and family history of prostate cancer.[2] Physical activities, coffee consumption, statin use, intake of certain vegetables also have been linked with the prevention of prostate cancer.[3–7] Recently, it was proposed that metformin had additional beneficial anticarcinogenic effects in human cancers,[8,9] including prostate cancer.[10]

Metformin, a biguanide, is the most widely prescribed antidiabetic drug worldwide due to its clinical effectiveness and tolerability.[11] Emerging evidence indicated that metformin might reduce insulin-stimulated cancer growth.[12] Previous large observational studies on commonly diagnosed cancers found inverse associations between metformin use and colon cancer,[8] liver cancer,[13] and lung cancer.[14] However, findings from previous epidemiologic studies on the association of metformin use with prostate cancer risk are inconsistent. Preston et al,[15] Haring et al,[16] and Ruiter et al[17] reported a significant inverse relationship between metformin therapy and the risk of prostate cancer, while many other epidemiological studies failed to find this association.

A few previous meta-analyses[10,18,19] were performed on this topic and indicated a protective effect of metformin use on the risk of prostate cancer. Since then, several new large cohort studies[16,20–22] were published in recent years but the results were still inconsistent. Considering the conflicting findings in the literature, we carried out the present systematic review and meta-analysis of all available cohort studies to summarize evidence on the association of metformin use with the risk of prostate cancer.

2. Materials and methods

2.1. Literature review

We searched for all relevant studies that examined the effects of metformin on the risk of prostate cancer in July 2018 based on PubMed and Web of Science databases with the following search algorithm: ("metformin" or "biguanide" or "dimethylbiguanidine") and ("prostatic neoplasms" or "prostatic cancer" or "prostate neoplasms" or "prostate cancer"). In addition, the cited references of the screened articles and reviews were examined to identify any additional relevant studies. No language or publication date limitation was applied. This systematic review and meta-analysis were designed, performed, and reported in accordance with the standards of quality for reporting meta-analyses.[23] This study was based on previously published studies and did not have original data. Therefore, no ethical approval and patient consent are required.

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The authors declare that there are no conflicts of interest.

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2.2. Study selection criteria

An eligible study must meet all the following criteria:

(1) the exposure of interest was metformin use;
(2) the outcome of interest was prostate cancer risk;
(3) the study design was cohort or nested case-control; and
(4) the risk estimate with its 95% confidence interval (CI) was provided.
(5) If multiple studies used the same population data, the study with the largest sample size was included.

2.3. Study quality assessment

Newcastle–Ottawa scale (NOS, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was adopted to evaluate the study quality by 2 independent reviewers (ZF and XZ). NOS is a 9-star system including the following 3 broad perspectives: selection, comparability, and outcome. The full score is 9 stars and a study with ≥7 awarded stars is regarded as high quality.

2.4. Data extraction

Two reviewers (ZF and XZ) independently collected and recorded the following information: first author's surname, the region where the study was performed, publication year, study design (cohort or nested case–control), age of study population, number of cases and cohorts/controls, fully adjusted risk estimates with their corresponding 95% CIs, and matched or adjusted confounding variables in the study design or statistical analysis. Any discrepancies were resolved by consensus.

2.5. Statistical methods

A combined relative risk (RR) with its 95% CI was used to determine the strength of the relationship between metformin use and prostate cancer risk. A DerSimonian and Laird random-effects model,[24] which takes into account both within- and between-study variability, was introduced to calculate the pooled risk estimates. Subgroup analyses were performed by geographical region, study design, study quality, and number of cases. Statistical heterogeneity across studies was evaluated by Cochran Q test with the level of significance set at 0.1.[25] The I^2 score was used to measure the degree of heterogeneity ($I^2<25\%$: no heterogeneity; $I^2=25$–50%: moderate heterogeneity; $I^2>50\%$: large or extreme heterogeneity).[25] Meta-regression analysis was performed to explore the potential source of heterogeneity. Sensitivity analysis was performed by removing each study in turn and recalculating the pooled RR of remainder studies. Potential publication bias was evaluated by funnel plots, Begg test (rank correlation method),[26] and Egger test (linear regression method).[27] All statistical analyses were performed with STATA 11.0 (StataCorp, College Station, TX), using 2-sided P values (set at .05).

3. Results

3.1. Literature search and study main characteristics

Figure 1 shows a flow diagram of the literature review. A total of 18 eligible studies[15–17,20–22,28–39] were ultimately included in our meta-analysis aimed to comprehensively evaluate the association of metformin use with prostate cancer risk. These studies were published between 2011 and 2017, with a total of 52,328 cases. Of the studies included, 15 were cohort studies and 3 were nested case–control studies. These studies were performed in the following geographical regions: Europe (n=9), North America (n=8), and Asia (n=1). Sixteen of the 18 studies analyzed the risk of prostate cancer in patients with diabetes. The study quality was evaluated by the NOS. Scores ranged from 6 to 8, with a mean of 6.78. Table 1 summaries the characteristics of studies analyzed in this meta-analysis.

3.2. Overall analysis and heterogeneity assessment

Multivariable-adjusted RRs with their corresponding 95% CIs for each individual study and for the combination of all included studies are presented in Figure 2. In a random-effects meta-

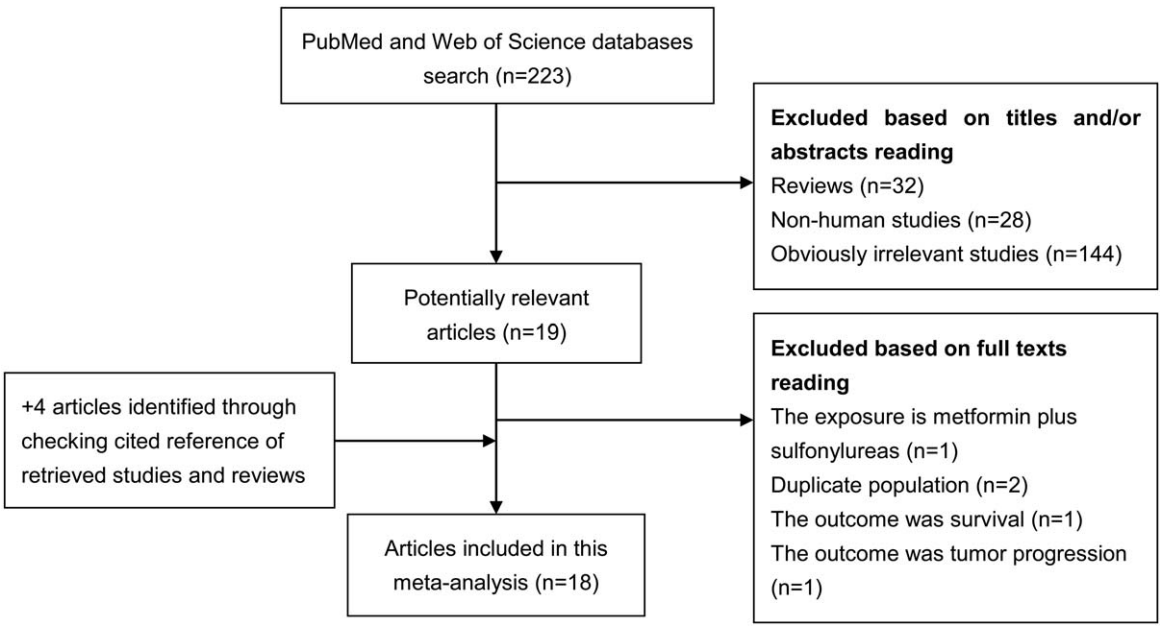

Figure 1. Literature search and study selection.

Table 1

Characteristics of the studies included in this meta-analysis.

Author	Region	Design	Age	Case/cohort or control	Follow	Reference	Cohort name	Population	Matched or adjusted variables	NOS
Azoulay, 2011	UK	NCC	>40 (62.7)	739/7359	3.7 yr (1988–2009)	Never use metformin	UK General Practice Research Database	Diabetes	Age, cohort entry, follow-up, HbA1c, alcohol, obesity, smoking, LUTS, previous cancer, and use of NSAIDs, antihypertensive, statins, and other antidiabetic agents	7
Chen, 2017	Canada	C	≥50 (64)	3557/80,001	9 yr (1994–2012)	No metformin use	British Columbia, Canada's Population Data BC	Diabetes	SES, time-varying physician visits, and other diabetes medications	8
Feng, 2015	US	C	58–70	122/540	4 yr	None antidiabetic medications	REDUCE Study	Diabetes	Age, race, region, PSA, DRE, BMI, prostate volume, family history, CAD, smoking, NSAIDs, statins, aspirin, and treatment group	6
Häggström, 2017	Sweden	C	72 (9)	759/25,238	4 yr (2006–2013)	Not on antidiabetic drugs	Prostate Cancer data Base Sweden 3.0	Diabetes	Age, educational level, CCI, and stratified for county	7
Haring, 2017	Finland	C	55–67	1253/15,578	12 yr (1995–2009)	Users of other oral antidiabetic drugs	Finnish Randomized Study of Screening for Prostate Cancer	Diabetes	Age, trial arm, and use of antihypertensive, cholesterol-lowering drugs, 5-ARIs, a-blockers, NSAIDs, and aspirin	8
Kowall, 2015	Germany and UK	C	30–89	286/44,444	4.8 yr (1995–2013)	Users of sulfonylurea	Disease Analyzer database	Diabetes	Age, sex, country, time of first diabetes drug, obesity, hypertension, hyperlipidemia, microcomplications, Charlson index, use of antihypertensive, antithrombotic agents, aspirin, statins, NSAIDs and contraceptives.	7
Lehman, 2012	US	C	70.2 (9.2)	376/5042	5.2 yr 1999–2005	Sulfonylurea use	Veteran Administration Health Care System	Diabetes	HbA1c, age, diabetes, duration, and race	6
Margel, 2013	Canada	NCC	≥66	5306/26,530	2.9 yr (1994–2008)	Diet-controlled patients	Health-care Administrative databases in Ontario	Diabetes	Age, cohort entry, other antidiabetic drugs, comorbidity, socioeconomic status, rural housing, and previous use of COX-2 inhibitors, statins, and 5-ARIs	7
Morden, 2011	US	C	>68 (77.4)	427/25,660	1.9 yr (2003–2008)	Users of non-glargine	Medicare sample Denominator files	Diabetes	Age, race, diabetes complications, obesity, oral estrogen use, Part D low income subsidy, Charlson comorbidities, and smoking	6
Nordström, 2015	Sweden	C	66.8 (8.8)	7356/18,574	2007–2012	Nonusers	Stockholm County biopsy study cohort	Population	Age, PSA concentration, PSA quotient, Charlson index, education, use of aspirin, statin, and anti-diabetic medication	6
Preston, 2014	Denmark	NCC	71.7	12,226/122,260	1989–2011	No diabetes	Danish Cancer Registry and the Aarhus University Prescription Database	Diabetes	Age, comorbidities, diabetic complications, marital status and use of statins, PPIs, and 5-ARIs	7
Randazzo, 2015	Switzerland	C	55–70 (65.5)	372/4314	7.6 yr	No metformin use	A prospective screening trial (ERSPC Aarau)	Population	Age and baseline PSA	7
Ruiter, 2012	Netherlands	C	52.8–76.0	226/40,131	1998–2008	Sulfonylurea Derivatives	PHARMO Record Linkage System	Diabetes	Age at first OGLD prescription, sex, year in which the first OGLD prescription was dispensed, number of unique drugs used in the year, and number of hospitalizations in the year before the start of the OGLD	6
Tseng, 2014	Taiwan	C	≥40 (59.4)	12,418/395,481	1996–2009	Never-users	National Health Insurance (NHI) database	Diabetes	Age, all variables at baseline, and propensity score derived from the baseline characteristics	7
Tsilidis, 2014	UK	C	35–90	580/53,789	5.1 yr (1987–2010)	Sulfonylurea use	UK Clinical Practice Research Datalink	Diabetes	Smoking, BMI, alcohol, use of aspirin or NSAIDs and statins, diabetes duration, and year of the first antidiabetes prescription	7
Wang, 2016	US	C	67.8 (9.8)	3983/76,733	6.4 yr (2003–2012)	Nonusers of metformin	Veterans Administration Health Care System	Diabetes	Age, Charlson index, and the mean change of BMI, LDL and HbA1c, and the maximum PSA during the study period.	8
Ferrara, 2011	US	C	≥40	2105/252,467	1997–2005	NA	Kaiser Permanente Northern California Diabetes Registry	Diabetes	Age, ever use of other diabetes medications, cohort entry, sex, race, income, current smoking, baseline HbA1c, diabetes duration, new diabetes diagnosis, creatinine, and CHF	6
Onitilo, 2014	US	C	52.3–71.1 (61.7)	237/4956	7.1 yr 1995–2009	NA	Marshfield Clinic	Diabetes	BMI, age, diagnosis date, insurance, comorbidities, smoking, and residence location	6

5-ARIs = 5-alpha-reductase inhibitors, BMI = body mass index, CAD = coronary artery disease, CHF = congestive heart failure, DRE = digital rectal examination, LUTS = lower urinary tract symptoms, NA = not available. No. = number, NOS = Newcastle–Ottawa scale, NSAIDs = nonsteroidal anti-inflammatory drugs, OGLD = oral glucose lowering drugs, PSA = prostate-specific antigen, y = year.

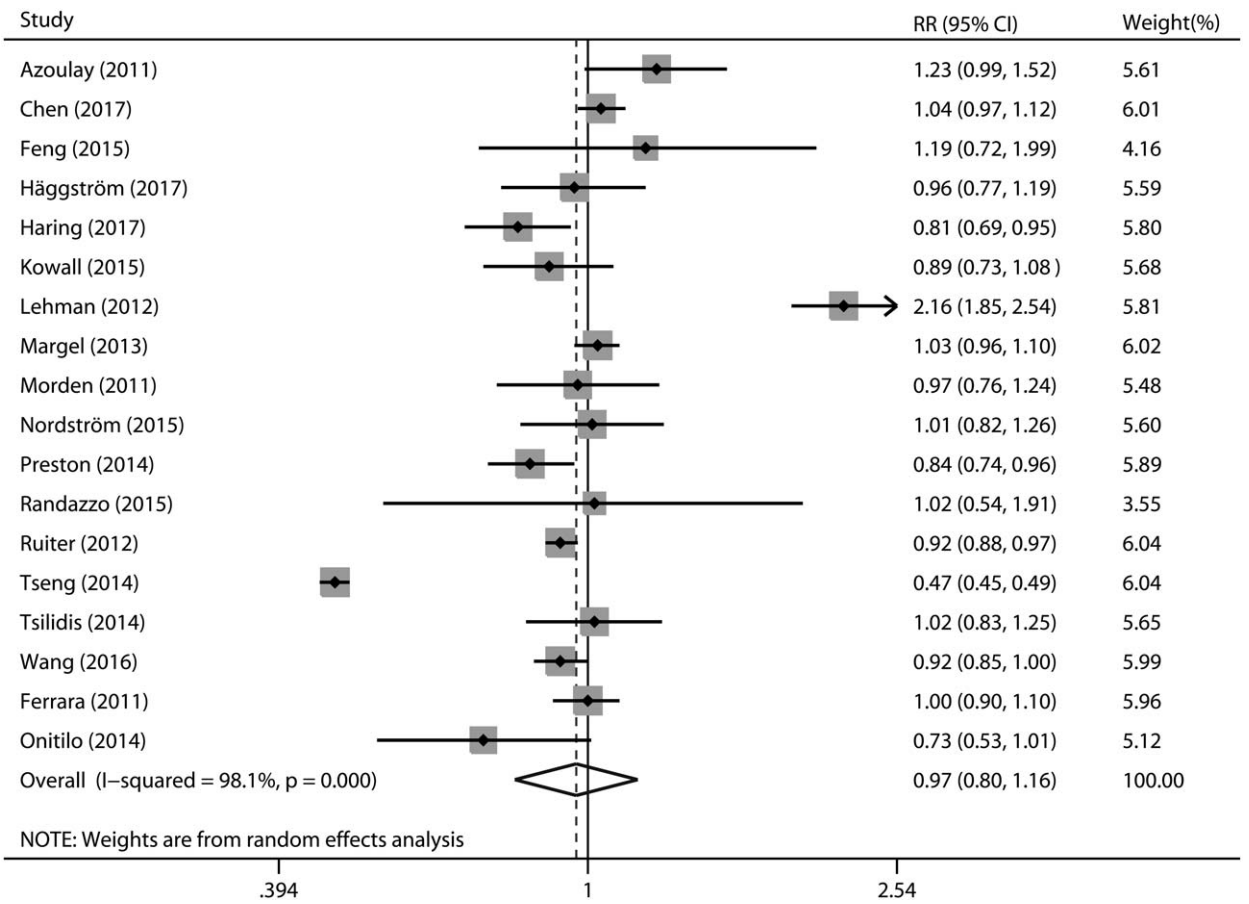

Figure 2. A forest plot showing the relative risk of prostate cancer associated with metformin use. The size of each square is proportional to the study's weight (inverse of variance). Weights are from random effects analysis.

analysis of these studies, metformin use was not significantly associated with the incidence of prostate cancer (RR 0.97, 95% CI 0.80–1.16, $P=.711$). Statistically significant heterogeneity was identified among included studies ($P<.001$ for heterogeneity, $I^2=98.1\%$). We then assessed heterogeneity across studies using meta-regression analysis. As a result, none of the following factors was identified as a possible source of heterogeneity in the pooled analysis: geographical region, study design, study quality, and sample size (all P for interaction $>.05$).

3.3. Stratified analysis

We first analyzed the risk of prostate cancer in terms of geographical region, there was no protective effect of metformin use against prostate cancer in the following geographical populations: North America (RR 1.08, 95% CI 0.93–1.27, $P=.324$) and Europe (RR 0.93, 95% CI 0.87–1.00, $P=.052$). When further subgroup by study design, the analysis of cohort studies yielded a RR of 0.96 (95% CI 0.77–1.19, $P=.681$) and the analysis of nested case-control studies yielded a RR of 1.01 (95% CI 0.84–1.20, $P=.950$). In the stratified analysis by study quality, no significant association was observed either in studies with low quality (RR 1.08, 95% CI 0.86–1.37, $P=.504$) or in studies with high-quality (RR 0.90, 95% CI 0.70–1.16, $P=.424$). Finally, in the stratified analyses by sample size, metformin use was not related with prostate cancer risk in small studies (RR 1.07, 95% CI 0.86–1.32, $P=.327$) as well as in large studies (RR 0.87, 95% CI 0.65–1.16, $P=.544$). The effects of metformin use on prostate cancer risk in subgroup meta-analyses have been shown in Table 2.

3.4. Sensitivity analysis and publication bias

The impact of each individual study on the combined RR was determined by repeating the meta-analysis after omitting each study in turn. As shown in Figure 3, no single study dominated the pooled RR with the 18 study-specific RRs ranging from a low of 0.92 (95% CI 0.77–1.10) to a high of 1.01 (95% CI 0.92–1.11) via removing the study by Lehman et al[36] and the study by Tseng et al,[33] respectively. Finally, significant publication bias was observed in Egger test ($P=.010$), but not in Begg test ($P=.081$). In addition, a certain degree of asymmetry was observed upon visual inspection of the funnel plot (Fig. 4).

4. Discussion

The present systematic review and meta-analysis of relevant cohort studies aimed to evaluate the association of metformin use with the incidence of prostate cancer. A total of 18 eligible cohort studies with 52,328 cases were ultimately included in this study. The results of pooled analysis and subgroup analysis indicated that there was no association between metformin use and the risk of prostate cancer.

Table 2

Subgroup analyses of the association between metformin use and prostate cancer risk.

Subgroup	Included studies	Pooled RR (95% CI)	*P*	Heterogeneity		
				Q	I^2 (%)	*P*
Total	18	0.97 (0.80–1.16)	.711	901.09	98.1	<.001
Study design						
Cohort	15	0.96 (0.77–1.19)	.681	826.28	98.3	<.001
Nested case–control	3	1.01 (0.84–1.20)	.950	11.20	82.1	.004
Geographical region						
North America	8	1.08 (0.93–1.27)	.324	96.01	92.7	<.001
Europe	9	0.93 (0.87–1.00)	.052	13.46	40.6	.097
Asia	1	0.47 (0.45–0.49)	<.001	–	–	–
Study quality						
High (NOS ≥7)	11	0.90 (0.70–1.16)	.424	651.28	98.5	<.001
Low (NOS <7)	7	1.08 (0.86–1.37)	.504	105.49	94.3	<.001
No. of cases						
≥1000	8	0.87 (0.65–1.16)	.544	653.63	98.9	<.001
<1000	10	1.07 (0.86–1.32)	.327	110.65	91.9	<.001

CI = confidence interval, No. = number, NOS = Newcastle–Ottawa scale, RR = relative risk.

Various animal and cell line studies have indicated that metformin is able to inhibit tumor development and progression in prostate cancer. Tong et al[40] reported that metformin suppressed castration-induced EMT in prostate cancer by repressing COX2/PGE2/STAT3 axis. The study by Dirat et al[41] suggested that metformin had antimigratory effects in prostate cancer cells by inhibition of the GTPase Rac1. Akinyeke et al[42] found that metformin targeted c-MYC oncogene to prevent prostate cancer. Recently, Hayashi et al[43] reported that metformin was able to inhibit prostate cancer growth induced by a high-fat diet in Pten-deficient model mice and Liu et al[44] found that metformin inhibited prostate cancer progression by regulating tumor-associated inflammatory infiltration. Additional studies also indicated that metformin could improve the radiosensitivity in prostate cancer cells.[45,46] Zaidi et al[47] reviewed the literature regarding the anticancer potential of metformin on prostate cancer and proposed that metformin may have a future role in the treatment protocol of prostate cancer. However, although the antitumor role of metformin in prostate cancer was supported by few cohort studies, the results of most epidemiological studies, as well as the present meta-analysis, were null.

Previously, 3 meta-analyses have evaluated the role of metformin use in the prevention of prostate cancer. Yu et al[19] reported in 2014 that metformin use was significantly associated with a decreased cancer risk with 14 datasets and 963,991 male subjects. Deng et al study[18] also supported that metformin therapy was associated with a significantly decreased incidence of prostate cancer with 13 studies involving 334,532 participants. Wu et al[10] suggested in 2015 that metformin

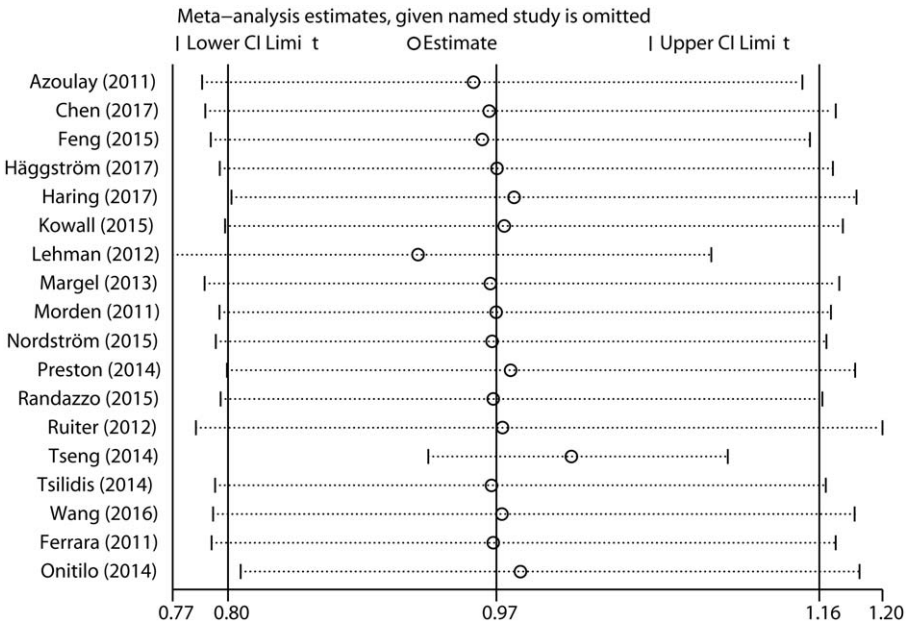

Figure 3. Sensitivity analysis was performed whereby each study was omitted in turn and the pooled relative risks were recalculated to determine the influence of each study.

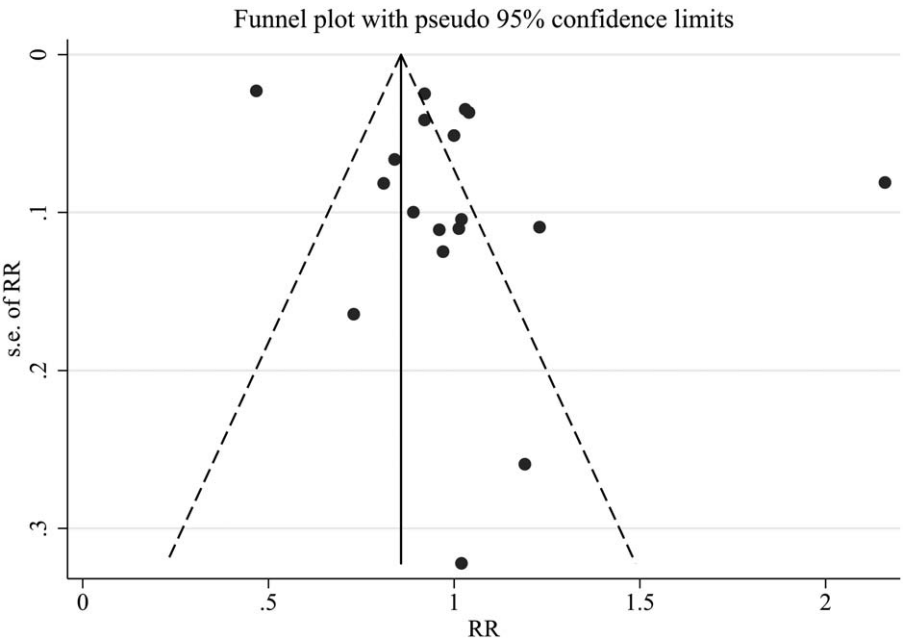

Figure 4. Publication bias was evaluated by the funnel plot.

therapy was associated with a significant reduced risk of prostate cancer among cohort studies rather than among case–control studies.

During the peer review process of this manuscript, Ghiasi et al[48] also summarized the relationship between prostate cancer and metformin consumption but only included 11 observational studies. Compared with these previous studies, our meta-analysis only included cohort and nested case–control studies and the results indicated that metformin use was not related with the incidence of prostate cancer. Metformin therapy has been associated with a reduced risk of endometrial cancer,[49] liver cancer,[13] lung cancer,[14] pancreatic cancer,[9] and colorectal cancer,[8] but not related with breast cancer.[50] Our meta-analysis indicated that there was no association of metformin use with prostate cancer risk, which further enriched the knowledge of relationship between metformin therapy and cancer development.

Our study had several important strengths. First, this meta-analysis only included cohort/nested case–control studies, which had the advantage of being less subject to potential selection and recall bias than case-control studies. Second, our meta-analysis included a total of 18 published studies with 52,328 prostate cancer cases, which might improve statistical power. Third, various stratified analyses, sensitivity analysis, and publication bias analysis were performed to comprehensively evaluate the robustness of the combined effect size estimate. Finally, the results of our study were not consistent with the previous meta-analysis on same topics, which had important implications for future studies.

4.1. Limitations

Several limitations should be acknowledged for this meta-analysis. First, obvious heterogeneity was observed across studies ($P < .001$ for heterogeneity, $I^2 = 98.1\%$), which was attributed to the variation in study design, study population, the methods of exposure and outcome assessment, and so on. Second, Egger test indicated the existence of some publication bias, which was inevitable as studies with small sample size and null results were less likely to be published. Third, the quality of a systematic review and meta-analysis depended on each individual study, which usually was not able to adjust for all confounding factors and thus might bias the risk estimate.

4.2. Future directions

Numerous biological studies have indicated the anticancer potential of metformin on prostate cancer. However, many epidemiological studies, as well as our meta-analysis, did not support that metformin had a protective effect against prostate cancer. Therefore, further large well-designed cohort studies are still warranted to examine the potential role of metformin on progression and mortality of prostate cancer.

5. Conclusion

In summary, this large meta-analysis of cohort studies did not find an association between metformin use and risk of prostate cancer.

Author contributions

Conceptualization: Zhaohan Feng, Xiaofeng Zhou, Jianfeng Wang, Xin Xu.
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Software: Zhaohan Feng, Naibo Liu.
Supervision: Zhaohan Feng, Xiaofeng Zhou, Naibo Liu.

Validation: Zhaohan Feng, Naibo Liu.
Visualization: Zhaohan Feng, Xiaofeng Zhou, Naibo Liu.
Writing – original draft: Zhaohan Feng, Xiaofeng Zhou, Naibo Liu, Xin Xu.
Writing – review and editing: Zhaohan Feng.

References

[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[2] Attard G, Parker C, Eeles RA, et al. Prostate cancer. Lancet 2016; 387:70–82.
[3] Xu X, Cheng Y, Li S, et al. Dietary carrot consumption and the risk of prostate cancer. Eur J Nutr 2014;53:1615–23.
[4] Liu Y, Hu F, Li D, et al. Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. Eur Urol 2011;60:1029–44.
[5] Liu B, Mao Q, Cao M, et al. Cruciferous vegetables intake and risk of prostate cancer: a meta-analysis. Int J Urol 2012;19:134–41.
[6] Liu H, Hu GH, Wang XC, et al. Coffee consumption and prostate cancer risk: a meta-analysis of cohort studies. Nutr Cancer 2015;67:392–400.
[7] Bansal D, Undela K, D'Cruz S, et al. Statin use and risk of prostate cancer: a meta-analysis of observational studies. PLoS One 2012;7:e46691.
[8] Liu F, Yan L, Wang Z, et al. Metformin therapy and risk of colorectal adenomas and colorectal cancer in type 2 diabetes mellitus patients: a systematic review and meta-analysis. Oncotarget 2017;8:16017–26.
[9] Wang Z, Lai ST, Xie L, et al. Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Res Clin Pract 2014;106:19–26.
[10] Wu GF, Zhang XL, Luo ZG, et al. Metformin therapy and prostate cancer risk: a meta-analysis of observational studies. Int J Clin Exp Med 2015;8:13089–98.
[11] Alexander GC, Sehgal NL, Moloney RM, et al. National trends in treatment of type 2 diabetes mellitus, 1994-2007. Arch Intern Med 2008;168:2088–94.
[12] Zakikhani M, Dowling RJ, Sonenberg N, et al. The effects of adiponectin and metformin on prostate and colon neoplasia involve activation of AMP-activated protein kinase. Cancer Prev Res (Phila) 2008;1:369–75.
[13] Ma S, Zheng Y, Xiao Y, et al. Meta-analysis of studies using metformin as a reducer for liver cancer risk in diabetic patients. Medicine (Baltimore) 2017;96:e6888.
[14] Zhu N, Zhang Y, Gong YI, et al. Metformin and lung cancer risk of patients with type 2 diabetes mellitus: a meta-analysis. Biomed Rep 2015;3:235–41.
[15] Preston MA, Riis AH, Ehrenstein V, et al. Metformin use and prostate cancer risk. Eur Urol 2014;66:1012–20.
[16] Haring A, Murtola TJ, Talala K, et al. Antidiabetic drug use and prostate cancer risk in the Finnish Randomized Study of Screening for Prostate Cancer. Scand J Urol 2017;51:5–12.
[17] Ruiter R, Visser LE, van Herk-Sukel MP, et al. Lower risk of cancer in patients on metformin in comparison with those on sulfonylurea derivatives: results from a large population-based follow-up study. Diabetes Care 2012;35:119–24.
[18] Deng D, Yang Y, Tang X, et al. Association between metformin therapy and incidence, recurrence and mortality of prostate cancer: evidence from a meta-analysis. Diabetes Metab Res Rev 2015;31:595–602.
[19] Yu H, Yin L, Jiang X, et al. Effect of metformin on cancer risk and treatment outcome of prostate cancer: a meta-analysis of epidemiological observational studies. PLoS One 2014;9:e116327.
[20] Haggstrom C, Van Hemelrijck M, Zethelius B, et al. Prospective study of Type 2 diabetes mellitus, anti-diabetic drugs and risk of prostate cancer. Int J Cancer 2017;140:611–7.
[21] Chen CB, Eurich DT, Majumdar SR, et al. Metformin and the risk of prostate cancer across racial/ethnic groups: a population-based cohort study. Prostate Cancer Prostatic Dis 2017;20:122–6.
[22] Wang CP, Lehman DM, Lam YF, et al. Metformin for reducing racial/ethnic difference in prostate cancer incidence for men with type II diabetes. Cancer Prev Res (Phila) 2016;9:779–87.
[23] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9.
[24] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[25] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
[26] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[27] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[28] 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;33:1189–96.
[29] Nordstrom T, Clements M, Karlsson R, et al. The risk of prostate cancer for men on aspirin, statin or antidiabetic medications. Eur J Cancer 2015;51:725–33.
[30] Kowall B, Stang A, Rathmann W, et al. No reduced risk of overall, colorectal, lung, breast, and prostate cancer with metformin therapy in diabetic patients: database analyses from Germany and the UK. Pharmacoepidemiol Drug Saf 2015;24:865–74.
[31] Feng T, Sun X, Howard LE, et al. Metformin use and risk of prostate cancer: results from the REDUCE study. Cancer Prev Res (Phila) 2015;8:1055–60.
[32] Tsilidis KK, Capothanassi D, Allen NE, et al. Metformin does not affect cancer risk: a cohort study in the U.K. Clinical Practice Research Datalink analyzed like an intention-to-treat trial. Diabetes Care 2014;37:2522–32.
[33] Tseng CH. Metformin significantly reduces incident prostate cancer risk in Taiwanese men with type 2 diabetes mellitus. Eur J Cancer 2014;50:2831–7.
[34] Onitilo AA, Stankowski RV, Berg RL, et al. Type 2 diabetes mellitus, glycemic control, and cancer risk. Eur J Cancer Prev 2014;23:134–40.
[35] Margel D, Urbach D, Lipscombe LL, et al. Association between metformin use and risk of prostate cancer and its grade. J Natl Cancer Inst 2013;105:1123–31.
[36] Lehman DM, Lorenzo C, Hernandez J, et al. Statin use as a moderator of metformin effect on risk for prostate cancer among type 2 diabetic patients. Diabetes Care 2012;35:1002–7.
[37] Morden NE, Liu SK, Smith J, et al. Further exploration of the relationship between insulin glargine and incident cancer: a retrospective cohort study of older medicare patients. Diabetes Care 2011;34:1965–71.
[38] Ferrara A, Lewis JD, Quesenberry CPJr, et al. Cohort study of pioglitazone and cancer incidence in patients with diabetes. Diabetes Care 2011;34:923–9.
[39] Azoulay L, Dell'Aniello S, Gagnon B, et al. Metformin and the incidence of prostate cancer in patients with type 2 diabetes. Cancer Epidemiol Biomarkers Prev 2011;20:337–44.
[40] Tong D, Liu Q, Liu G, et al. Metformin inhibits castration-induced EMT in prostate cancer by repressing COX2/PGE2/STAT3 axis. Cancer Lett 2017;389:23–32.
[41] Dirat B, Ader I, Golzio M, et al. Inhibition of the GTPase Rac1 mediates the antimigratory effects of metformin in prostate cancer cells. Mol Cancer Ther 2015;14:586–96.
[42] Akinyeke T, Matsumura S, Wang X, et al. Metformin targets c-MYC oncogene to prevent prostate cancer. Carcinogenesis 2013;34:2823–32.
[43] Hayashi T, Fujita K, Matsushita M, et al. Metformin inhibits prostate cancer growth induced by a high-fat diet in Pten-deficient model mice. Int J Urol 2019;26:307–9.
[44] Liu Q, Tong D, Liu G, et al. Metformin inhibits prostate cancer progression by targeting tumor-associated inflammatory infiltration. Clin Cancer Res 2018;24:5622–34.
[45] Gonnissen A, Isebaert S, McKee CM, et al. The effect of metformin and GANT61 combinations on the radiosensitivity of prostate cancer cells. Int J Mol Sci 2017;18:399.
[46] Zhang T, Zhang L, Fan J, et al. Metformin sensitizes prostate cancer cells to radiation through EGFR/p-DNA-PKCS in vitro and in vivo. Radiat Res 2014;181:641–9.
[47] Zaidi S, Gandhi J, Joshi G, et al. The anticancer potential of metformin on prostate cancer. Prostate Cancer Prostatic Dis 2019;doi: 10.1038/s41391-018-0085-2. Epub ahead of print.
[48] Ghiasi B, Sarokhani D, Najafi F, et al. The relationship between prostate cancer and metformin consumption: a systematic review and meta-analysis study. Curr Pharm Des 2019;doi: 10.2174/1381612825666190215123759. Epub ahead of print.
[49] Meireles CG, Pereira SA, Valadares LP, et al. Effects of metformin on endometrial cancer: systematic review and meta-analysis. Gynecol Oncol 2017;147:167–80.
[50] Yang T, Yang Y, Liu S. Association between metformin therapy and breast cancer incidence and mortality: evidence from a meta-analysis. J Breast Cancer 2015;18:264–70.