ARTICLE

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Effect of metformin on incidence, recurrence, and mortality in prostate cancer patients: integrating evidence from real-world studies

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PURPOSE: Metformin has been suggested to reduce the risk of cancer. However, previous studies have been inconsistent regarding the relationship between metformin use and the risk of occurrence of prostate cancer (PCa). The purpose of this study was to assess the effect of metformin on clinical outcomes in patients with PCa in a meta-analysis and to explore the possible dose-response relationship.
METHODS: A systematic literature search was conducted in 10 electronic databases and 4 registries. The combined relative risks (RRs) were calculated using a random-effects model with 95% confidence interval (CIs) to assess the effect of metformin on the risk of PCa. Relevant subgroup analyses and sensitivity analyses were performed.
RESULTS: The across studies results show that metformin use associated with lower incidence of PCa (RR: 0.82, 95% CI: 0.74–0.91). Metformin use was also found to reduce PCa recurrence, but the results were not statistically significant (RR: 0.97, 95% CI: 0.81–1.15). Metformin use was not associated with PCa mortality (RR: 0.94, 95% CI: 0.81–1.09). The results of subgroup analyses indicated that the type of study was a cohort study and the population came from both Asia and Europe showed that taking metformin reduced the incidence of PCa. A linear correlation was found between the duration of metformin use and its protective effect.
CONCLUSIONS: This meta-analysis revealed an independent correlation between metformin use and reduced incidence of PCa. Metformin use was not associated with either PCa recurrence rate or mortality. Furthermore, the effect of metformin on PCa incidence was found to be related to duration.

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INTRODUCTION

Prostate cancer (PCa) is the most frequently diagnosed cancer among men in over half of all countries worldwide and is the second leading cause of cancer deaths in men, after lung cancer [1–5]. PCa remains the third most prevalent cancer globally, with over 1.4 million new cases and 370,000 fatalities reported in 2020 [6]. On the other hand, apart from skin cancer, PCa is the most common cancer among men in the Western world [7]. Frequent urination, urinary weakness, urinary incontinence, blood in the urine, burning and persistent pain in the lower back, and abdominal pain are also clinical symptoms of PCa [8]. Various factors such as age, race, genetic factors, environmental factors, and family history play an important role in the progression of PCa [9, 10]. More than 670,000 PCa patients are diagnosed each year. Of these, 225,000 are in Europe and 240,000 in the United States [11]. The incidence of PCa varies between races. For example, 4–7 per 100,000 in Asian countries and 70–100 per 100,000 in European and North American countries [12, 13]. Metformin has multiple mechanisms for reducing cancer and carcinogenesis: direct action (on tumors and the microenvironment) and indirect action (on hosts that may affect tumors). Metformin is generally connected directly or indirectly through the AKT-Mtor pathway [14–17]. Mechanisms of pathway activation most commonly associated with PCa include deletion of inhibitory PTEN [18], PI3K mutations [19], or activation of growth factor receptors such as insulin [20–22]. The ability of metformin to reduce hyperinsulinemia may also indirectly reduce the risk of PCa [23–25]. In addition, laboratory evidence suggests that hyperinsulinemia regulates insulin receptors in PCa cells and promotes tumor growth [26, 27]. Reducing insulin levels in the blood stream or direct activation of AMP kinase. In this study, we used systematic evaluation and meta-analysis to investigate the relationship between metformin and PCa risk.

METHODS

Study design

This study has been registered (registration number: CRD42023447013) with the PROSPERO database before July 22, 2023 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=447013). We used the Cochrane Handbook for Systematic Reviews of Interventions for the preparation and conduct of this meta-analysis [28]. We reported this

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meta-analysis with reference to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [29].

Search strategy

The literature search was completed before July 22, 2023 for relevant available articles from the following databases: (1) PubMed; (2) Ovid MEDLINE; (3) Scopus; (4) Embase; (5) Cochrane library; (6) Web of Science; (7) Sinomed (CBM); (8) China National Knowledge Infrastructure (CNKI); (9) Wanfang Data Knowledge Service Platform; (10) China Science and Technology Journal VIP Database. The registration search was completed by 22 July 2023 and the relevant data retrieved were from the following registration pools: (1) ClinicalTrials.gov; (2) International Clinical Trials Registry Platform (ICTRP); (3) The EU Clinical Trials Register; (4) Chinese Clinical Trial Registry. The relevant retrieval strategy was as following: ("Metformin" or " Dimethylbiguanidine" or " Dimethylguanylguanidine" or " Glucophage") and ("Prostatic Neoplasms" or " Prostate Neoplasms" or " Prostate Cancer" or "Cancer of Prostate" or " Prostatic Cancers"). Relevant Chinese technical terms for the Chinese databases were used to search for published articles. Furthermore, references of all relevant articles and reviews were retrieved to search for additional eligible studies.

Inclusion and exclusion criteria

Inclusion criteria. This meta-analysis included studies based on the following criteria: (1) participants with no PCa history were selected for the incidence analysis, while those with a PCa history were chosen for recurrence and mortality analyses; (2) metformin was the exposure factor; (3) studies provided relative risks (RRs), odds ratios (ORs), or hazard ratios (HRs) along with 95% confidence intervals (CIs) or data enabling their calculation; (4) in cases of multiple publications from the same population, the study with the larger sample size or more comprehensive data was chosen; and (5) studies were assessed for quality using the Newcastle Ottawa scale (NOS), requiring a score of at least 6 stars.

Exclusion criteria. (1) Antidiabetic drugs which did not include metformin; (2) comments or letters to the editor, case reports, and abstract-only publications; (3) Preprint servers, such as medRxiv/bioRxiv, etc.

Data extraction

After removing duplicates, two reviewers (Y Liu and Q Zhang) independently screened all abstracts and titles to exclude irrelevant articles. Full texts of potentially relevant studies were then downloaded and reviewed, with those meeting the selection criteria included in this systematic review. Two independent investigators (Y Liu and Q Zhang) extracted data from the included articles. The extracted data comprised the first author's name, year of publication, study location, study methods, sample size, metformin usage, primary outcomes, raw data of patient numbers in the trial (metformin) and control groups, and adjusted RRs/ORs/HRs with corresponding 95% CIs.

Quality assessment

Two investigators (Y Liu and Q Zhang) independently evaluated the methodological quality of the included case-control and cohort studies using the nine-star NOS [30]. The assessment considered eight items across four categories: selection of cohort studies, comparability, outcomes, or exposure for case-control studies. Studies were rated as low-, moderate-, or high-quality based on their NOS scores (0–3, 4–6, 7–9, respectively). The certainty of evidence was determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [31].

Statistical analysis

Statistical analyses were conducted using Stata (version 16.0; Stata Corp, College Station, TX) and RevMan (version 5.3; Cochrane Library) software. The pooled RR with 95% CI was calculated from the extracted raw data to assess the association between metformin use and PCa risk. When multiple RRs were available, the effect value controlling for the most confounding factors was chosen. Subgroup analyses were performed to explore the relationship between metformin use and PCa incidence and mortality, considering study region, study design, dosage type, and diagnosis type. HRs were directly considered as RRs [32, 33], and ORs were converted to RRs using the formula: $RR = OR/((1-P_0) + (P_0 \times OR))$, where P_0 represents the incidence of the outcome in the non-exposed group [34]. The standard error (SE) of the converted RR was calculated using $SElog(RR) = SElog(OR) \times log(RR)/log(OR)$. This formula was also applied to determine the upper and lower confidence limits of the CI based on the adjusted odds ratio [35]. To generalize our study results beyond the included studies, a random-effects model was used as it is the most suitable for meta-analysis [36]. Studies reporting data on PC incidence in terms of person-years, number of cases, and metformin dose or duration were included in the dose-response analysis. Restricted cubic splines with three knots at the 10%, 50%, and 90% percentiles of the distribution were used for both linear and non-linear dose-response analyses [37]. The study-specific estimates were then combined using the restricted maximum likelihood method in a multivariate random-effects meta-analysis. Sensitivity analysis was conducted to determine if any single study significantly influenced the results [38]. Publication bias was evaluated qualitatively with funnel plots and quantitatively using Begg's and Egger's tests [39]. A P value of less than 0.05 was considered statistically significant in all analyses.

RESULTS

Study selection and characteristics

A search of databases and registries identified 3950 database records and 82 registry records, and 415 potentially eligible studies were selected after removing duplicate information and screening titles and abstracts. Of the 415 potentially eligible studies, a total of 41 studies met the inclusion criteria, including 34 studies of PCa incidence [15, 40–72], 5 studies of PCa recurrence [73–77], and 5 studies of PCa mortality [52, 55, 75, 78, 79]. Google Scholar and Baidu Scholar were also searched, with 682 records being identified as potentially relevant to this study. However, these records were excluded as they were duplicates to the studies in the databases and the registries. The detailed process of literature screening is shown in Fig. 1.

Finally, forty-one studies with a total of 3,933,414 subjects were included in this meta-analysis. The characteristics of the included studies are shown in Tables 1 and 2.

Overall meta-analysis of metformin use on PCa risk

The results showed that metformin use was associated with a lower incidence of PCa (RR: 0.82, 95% CI: 0.74–0.91, $P < 0.001$, $I^2 = 97\%$, Fig. 2), and the random effects model was adopted. Meanwhile, metformin use was found to be associated with reduced recurrence (RR: 0.97, 95% CI: 0.81–1.15, $P = 0.71$, $I^2 = 0\%$, Fig. 3) and mortality (RR: 0.94, 95% CI: 0.81–1.09, $P = 0.42$, $I^2 = 75\%$, Fig. 4) in PCa with a random effects model, but the results were not statistically significant.

Subgroup analysis of metformin use on PCa risk

The results of subgroup analyses based on the study design showed that metformin administration was associated with a reduced incidence of PCa in the cohort study subgroup (RR: 0.81, 95% CI: 0.73–0.90, $P < 0.001$, $I^2 = 97\%$), and that metformin administration did not increase the risk of recurrence (RR: 0.93, 95% CI: 0.81–1.18, $P = 0.77$, $I^2 = 0\%$) and mortality (RR: 0.94, 95% CI: 0.81–1.09, $P = 0.42$, $I^2 = 75\%$,) from PCa. Meanwhile, the results of the case-control study suggested that metformin was not associated with either PCa incidence (RR: 0.90, 95% CI: 0.78–0.91, $P = 0.16$, $I^2 = 81\%$).

Subgroup analysis by study area showed that metformin was found to be associated with a reduced incidence of PCa in Asia (RR: 0.67, 95% CI: 0.56–0.79, $P < 0.001$, $I^2 = 96\%$) and Europe (RR: 0.89, 95% CI: 0.81–0.97, $P = 0.01$, $I^2 = 83\%$). In the North American study, metformin use was also found to reduce the risk of PCa, but the difference was not statistically significant (RR: 0.83, 95% CI: 0.66–1.05, $P = 0.11$, $I^2 = 97\%$). Meanwhile, in the North American study, metformin use was found to reduce the risk of mortality from PCa, but the difference was not statistically significant (RR: 0.91, 95% CI: 0.77–1.07, $P = 0.24$, $I^2 = 78\%$).

The results of all subgroup analyses are shown in Table 3.

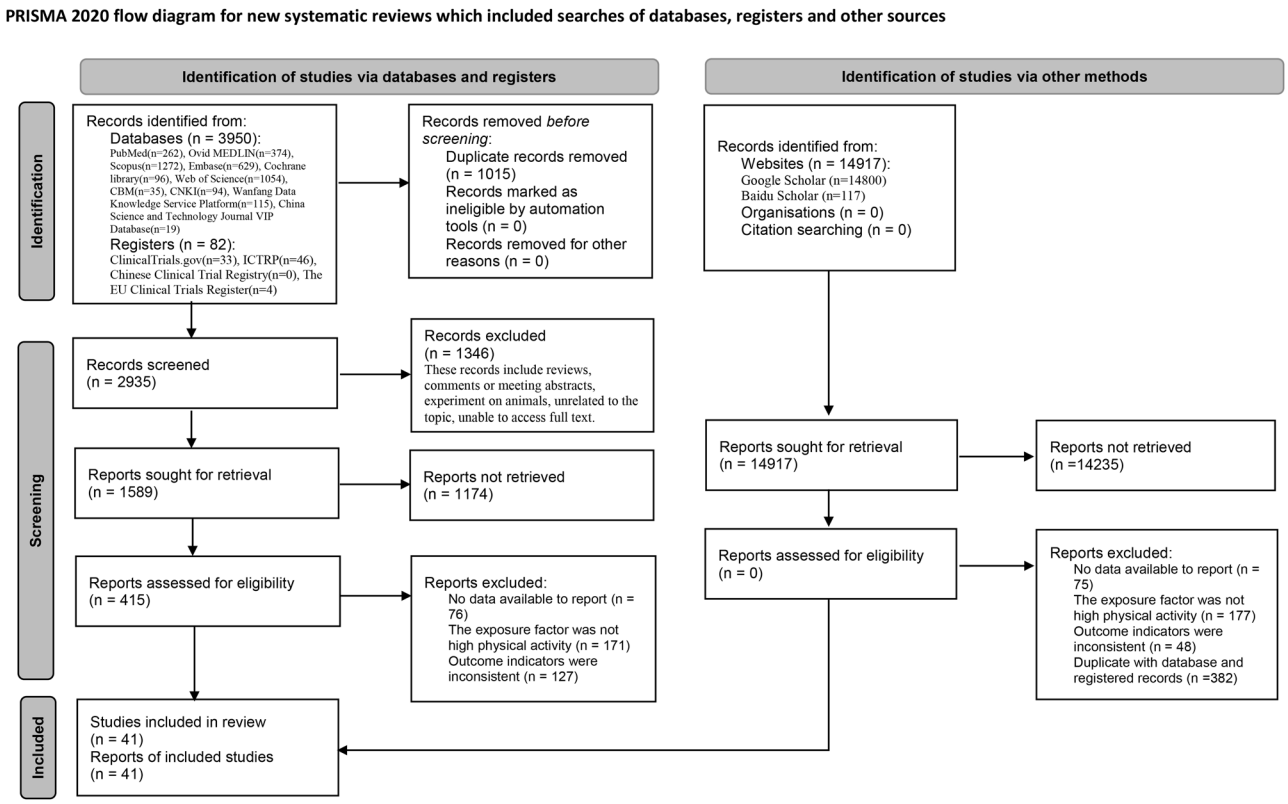

Fig. 1 PRISMA flow diagram of search strategy. Flow diagram of the study search and selection process.

Dose-response meta-analysis

Three studies with a total of 515,615 participants were included in a dose-response analysis of incidence [49, 66, 69]. Among these studies, metformin exposure was expressed as duration of exposure.

Linear dose-response models showed a significant negative association between duration of metformin exposure and risk of PCa (exb(b): 0.980, $P < 0.001$). Furthermore, nonlinear dose-response analysis showed a similar association ($Coef_1 = -0.299$, $P_1 < 0.001$, $Coef_2 = 0.325$, $P_2 < 0.001$). Each 1-year increment in metformin exposure was associated with a 22% reduction in the risk of PCa (RR: 0.78, 95% CI: 0.77–0.79, $p < 0.001$, Fig. 5).

Study quality assessment and risk of bias

All included observational studies were considered to be above moderate quality studies, as depicted by NOS ≥ 6. The NOS-based assessment indicated a low to moderate risk of bias, while the GRADE assessment revealed low certainty in the evidence supporting metformin's ability to reduce PCa incidence, recurrence and mortality. This is mainly due to the retrospective nature of the studies and potential selection and publication biases (See Supplementary Information: Fig. S1). In addition, Begg's test and Egger's test found publication bias in some studies. In this study, for PCa incidence, *P* value of Begg's test was 0.047, and *P* value of Egger's test was 0.004. For PCa recurrence, *P* value of Begg's test was 0.806, and *P* value of Egger's test was 0.182. For PCa mortality, *P* value of Begg's test was 0.825, and *P* value of Egger's test was 0.573. Some of the funnel plots were shown to be unsymmetrical (Fig. S2).

Sensitivity analysis

For incidence, recurrence, and mortality, conclusions were unchanged after excluding individual papers and calculating heterogeneity and effect sizes (Fig. S3).

DISCUSSION

In this study, we synthesized evidence from cohort and case-control studies involving 3,933,414 participants in 15 countries and regions. Our findings suggest a potential chemoprotective effect of metformin on PCa incidence, recurrence, and mortality. We reported the effect of metformin use on PCa risk in different types of studies and regions. In addition, our study explored a possible dose-response relationship between metformin use and PCa incidence based on exposure time. Finally, the main findings of this study support the mechanistic hypothesis that metformin use is negatively associated with the risk of PCa incidence, recurrence, and mortality.

The relationship between metformin use and cancer has been widely debated. Several studies have explored metformin's potential chemopreventive effects on various tumors, including breast [80], brain [81], and melanoma [82]. This meta-analysis, with a larger participant pool than previous ones [83, 84], further substantiates metformin's protective effect against PCa.

Several studies suggest that metformin's antitumor effects may involve multiple mechanisms. It has been reported as an indirect activator of AMP-activated protein kinase (AMPK), inhibiting the growth of PCa cells [85] and being selectively toxic to p53-deficient tumor cells [86]. However, metformin also inhibits the proliferation of most breast cancer cells, regardless of p53 status [87]. Ben Sahra et al. [16] showed that metformin decreases the level of cell cycle protein D1, exerting antitumor effects both in vivo and ex vivo. Huang et al. [18] demonstrated that metformin inhibition might trigger a signaling pathway that effectively inhibits cellular growth.

Existing studies have demonstrated that insulin and insulin-like growth factors are crucial in regulating cellular energy and growth. These hormones and their associated signaling networks significantly contribute to tumor formation [88]. Epidemiological studies have found that insulin-like growth factor-1 (IGF-1) promotes the proliferation of various cancer cells, including breast and prostate cancers. Additionally, it has been demonstrated that

Table 1. General characteristics of eligible case-control studies.

Study	Study region	Study design	Primary outcome	Number of cases	Number of controls	Percentage of males (%)	Age of participants (range or mean)	RR (95% CI)	Covariate adjustment	Dataset sources	NOS quality score
Azoulay L [40]	UK	Nested case-control study	PCa incidence	793	7359	100	74.1 years	1.23 (0.99–1.52)	HbA1c, excessive alcohol use, obesity, smoking, lower urinary tract symptoms, previous cancer, and use of NSAIDs, antihypertensive drugs, statins, and other antidiabetic agents.	UK General Practice Research Database	7
Margel D [15]	Canada	Nested case-control study	PCa incidence	5306	26,530	100	66 years	0.964 (0.889–1.048)	Use of other antidiabetic drugs, weighted adjusted clinical groups comorbidity index, socioeconomic status, rural/urban, and use of cyclooxygenase 2, statins and 5-alpha reductase inhibitors.	The Ontario Cancer Registry (OCR), a computerized database of Ontario residents newly diagnosed with cancer	7
Murtola TJ [58]	Finland	Case-control study	PCa incidence	24,723	24,723	100	20–96 years	OR 0.80 (0.73–0.88)	Age, place of residence, and simultaneous use of other medications.	the Finnish Cancer Registry	8
Patel T [76]	USA	Nested case-control study	PCa recurrence	200	409	100	62.2 years	0.94 (0.60–1.50)	Age, diabetes, preoperative PSA, pathologic Gleason sum, surgical margin, pathologic stage, race/ethnicity.	the Columbia University Urologic Oncology Database	7
Preston MA [62]	Danish	Nested case-control study	PCa incidence	12,226	122,260	100	71.7 years	OR 0.84 (0.74–0.96)	Comorbidities, diabetic complications, marital status, and use of statins, PPIs, and 5-ARIs.	Health-related services are recorded using the unique civil personal registration (CPR) number assigned to all Danish citizens	8
Wright JL [72]	USA	Case-control study	PCa incidence	1001	942	100	35–74 years	OR 0.56 (0.32–1.00)	Age, other diabetic treatments, aspirin and NSAIDs usage, BMI, PSA tests in preceding 5 years and family history of prostate cancer	Data were derived from the SEER-Medicare linked database	8

HbA1c Hemoglobin A1c, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PPIs* proton pump inhibitors, *5-ARIs* 5α-reductase inhibitors, *PSA* prostate specific antigen, *BMI* body mass index.

Table 2. General characteristics of eligible cohort studies.

Study	Study region	Study design	Primary outcome	Cohort Size	Cases in cohort	Percentage of males (%)	Age of participants (range or mean)	RR (95% CI)	Covariate adjustment	Dataset sources	NOS quality score
Allott EH [73]	USA	retrospective cohort	PCa recurrence	371	134	100	61.9 years	0.93 (0.61–1.41)	Age at surgery, year of surgery, BMI, race, pre-operative PSA, surgical center, biopsy Gleason score and clinical stage.	the Shared Equal Access Regional Cancer Hospital (SEARCH) database	8
Aminsharifi A [74]	USA	retrospective cohort	PCa recurrence	843	266	100	63 years	0.88 (0.53–1.47)	Age, race, body mass index, prostate-specific antigen, year of surgery, surgical center, pathologic Gleason score, positive surgical margins, seminal vesicle invasion, extracapsular extension, positive lymph nodes, and time-dependent postsurgical metformin and statin receipt.	the Shared Equal Access Regional Cancer Hospital (SEARCH) database	9
But A [41]	Finland	cohort	PCa incidence	23,394	226	57.8	61.1 years	0.84 (0.43–1.64)	Age, BMI, Smoking, alcohol consumption, metformin exposure duration.	Data are available from Statistics Finland, with National FINRISK study.	8
Chen CB [42]	Canada	cohort	PCa incidence	80,001	3560	100	64 years	0.740 (0.657–0.843)	Age, socioeconomic class, number of physician visits and use of other diabetes medications.	Canadian National Diabetes Surveillance System	8
Currie CJ [43]	UK	retrospective cohort	PCa incidence	62,809	301	53.7	62 years	0.93 (0.67–1.30)	Age, smoked, prior solid tumor cancer and different treatment regimens.	The Health Information Network (THIN)	7
Currie CJ [78]	UK	retrospective cohort	PCa mortality	112,408	16,641	48.1	69.6 years	0.850 (0.775–0.933)	Age, smoking status, year of cancer diagnosis, and Charlson comorbidity index.	Data compiled from >350 primary care practices in the U.K.	8
Ferrara A [44]	USA	cohort	PCa incidence	252,467	2015	53.4	≥40 years	1.0 (0.9–1.1)	Age, ever use of other diabetes medications, year of cohort entry, sex, race/ethnicity, income, current smoking, baseline HbA1c, diabetes duration, new diabetes diagnosis, creatinine, and congestive heart failure.	the Kaiser Permanente Northern California Diabetes Registry	9

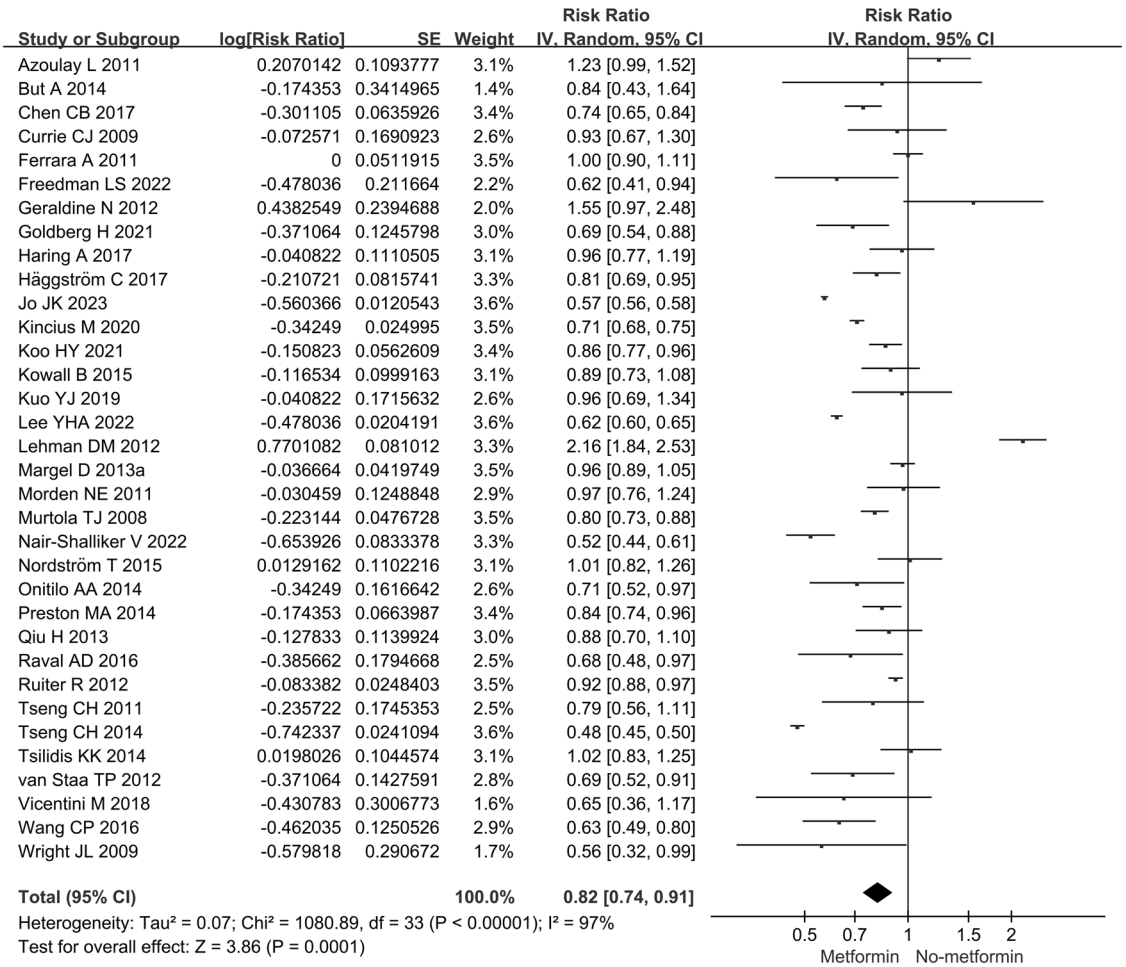

Fig. 2 Metformin use on PCa risk of incidence. Results of a meta-analysis of metformin use on PCa risk of incidence.

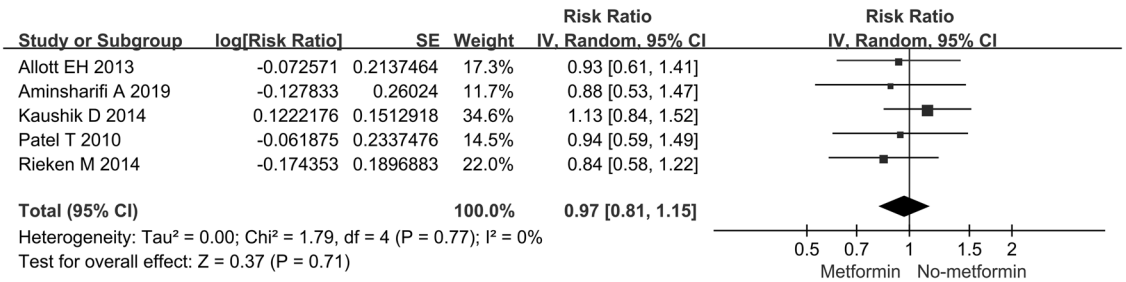

Fig. 3 Metformin use on PCa risk of recurrence. Results of a meta-analysis of metformin use on PCa risk of recurrence.

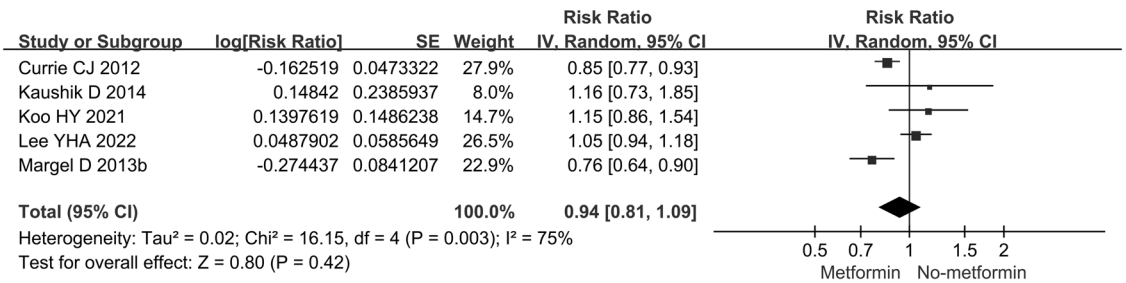

Fig. 4 Metformin use on PCa risk of mortality. Results of a meta-analysis of metformin use on PCa risk of mortality.

Table 3. Subgroup analysis of metformin use on PCa risk.

Subgroup	Incidence					Recurrence					Mortality				
	Number of studies	I^2(%)	RR	95%CI	*P*	Number of studies	I^2(%)	RR	95%CI	*P*	Number of studies	I^2(%)	RR	95%CI	*P*
Overall	34	97	**0.82**	**0.74–0.91**	<0.001	5	0	0.97	0.81–1.15	0.71	5	75	0.94	0.81–1.09	0.42
Study design															
Cohort	29	97	**0.81**	**0.73–0.90**	<0.001	4	0	0.93	0.81–1.18	0.77	5	75	0.94	0.81–1.09	0.42
Case-control study	5	81	0.90	0.78–1.04	0.16	1	NA	0.94	0.60–1.49	0.79		–	–	–	–
Region															
Asia	6	96	**0.67**	**0.56–0.79**	<0.001	0	–	–	–	–	1	NA	1.15	0.86–1.54	0.38
Europe	16	83	**0.89**	**0.81–0.97**	0.01	1	NA	0.84	0.58–1.22	0.36	0	–	–	–	–
North America	11	97	0.83	0.66–1.05	0.11	4	0	1.01	0.83-1.23	0.94	4	78	0.91	0.77-1.07	0.24
Oceania	1	NA	**0.52**	**0.44–0.61**	<0.001	0	–	–	–	–	0	–	–	–	–

RR relative risks, *95%CI* 95% confidence interval, *NA* not available, Boldface denotes statistically significant associations.

Fig. 5 Dose-response analysis of duration of metformin use and risk of PCa. Dose-response analysis of restricted cubic splines in multivariate random-effects dose-response models for the relationship between duration of metformin use and risk of PCa.

insulin can regulate the activity of the IGF-1 receptor [89]. IGF-1 is present in normal cells, but in cells with malignant growth characteristics, it exerts strong mitogenic and anti-apoptotic effects. Thus, the level of IGF-1 in the human body influences tumorigenesis. Tumor cells can produce IGF-1 through autocrine or paracrine secretion, promoting their differentiation and proliferation. When IGF-1 binds to its receptor, it initiates the mitogen-activated protein kinase 2 signaling pathway and the phosphatidylinositol 3-kinase/Akt signaling pathway, which, when activated, promotes cell proliferation and inhibits apoptosis in tumor cells [90]. The mammalian target of rapamycin (mTOR) is a serine/threonine kinase of the phosphatidylinositol 3-kinase-related enzyme family, regulated by intracellular and extracellular signals, including nutrients like glucose and amino acids, as well as growth factors such as insulin and insulin-like growth factors. These factors regulate cell growth. When metformin is used, it reduces glucose and insulin levels in the body, thereby affecting mTOR activity and inhibiting cell growth.

Additionally, confounding mechanisms might explain the link between metformin use and reduced PCa incidence. Type 2 diabetes is a known risk factor for PCa [91]. Metformin users are often obese and have type 2 diabetes, both conditions associated with a lower risk of PCa [92, 93]. Metformin, a common antidiabetic drug, helps control hyperglycemia in type 2 diabetes patients by affecting mitochondrial respiration, leading to energy deficiency and molecular changes [94, 95]. One proposed mechanism for metformin's antitumor effects is the inhibition of mitochondrial respiratory complex I. This inhibition reduces ATP production, activating AMPK in an LKB1-dependent manner, which then inhibits mTOR, leading to anticancer effects [95]. Additionally, new diabetes treatments, such as GLP-1 inhibitors, have been found to inhibit PCa growth, reducing the risk of PCa [96]. We hypothesize that treating diabetes can further lower the incidence of PCa.

In addition to the mechanisms described above, this may be due to lower testosterone levels in diabetic men than in non-diabetic men [97].

Based on the potential antitumor mechanism of metformin, numerous reports have explored its relationship with PCa risk, but the quality and findings of these studies vary. This article reviews and analyzes 41 studies, encompassing 3,933,414 participants, and finds that metformin use reduces the risk of PCa recurrence and death. However, the results show no significant difference and exhibit high heterogeneity. This variability may stem from differences in study design, such as drug use in control groups, drug combinations, sequential drug use, dosages, follow-up periods, control of confounding factors, duration of drug use,

and variations in study populations' age, occupation, ethnicity, and geographic area. In the subgroup analyses of this study, metformin administration was found to reduce the risk of PCa in Asian and European populations. However, no significant correlation was observed between metformin use and PCa incidence, recurrence, and mortality in North American populations. This may be due to the limited number of studies conducted in North America and the focus of current research on Asia and Europe. Additionally, significant genetic differences and susceptibility loci for PCa between Asian, European, and American populations may influence metformin's effectiveness in preventing PCa [98–100].

Although this meta-analysis showed a potential benefit of metformin for PCa treatment and a better risk-benefit ratio, this study has several limitations. First, there are limitations in that the inclusion of so many retrospective studies does not lead to a reasonable and unbiased conclusion and is prone to bias. Second, in studies examining the association between metformin and PCa recurrence and mortality, there was a trend toward lower risk, but it did not reach statistical significance. Further randomized controlled trials and real-world studies are needed to explore potential dose-response relationships. Third, subgroup analyses of PCa types were not performed in this study; therefore, it was not possible to examine the effect of metformin on different types of PCa. Finally, although some confounders were corrected for in the analysis, there is no guarantee that all potential confounders were considered. Other unreported and unanalyzed confounders may have been present in the original study. However, future randomized, double-blind controlled trials with adequate sample sizes and validated study protocols are still needed to assess and confirm the potential benefits of metformin for PCa prevention and to determine the optimal dose of metformin with a favorable risk-benefit ratio.

CONCLUSIONS

This meta-analysis showed that metformin use was independently associated with a reduction in PCa incidence. A duration-dependent relationship was found between metformin and PCa incidence, suggesting that prolonged metformin use is associated with a lower risk of developing PCa. Meanwhile, this study may provide guidance to clinicians to improve the prognosis of PCa patients. In the future, larger prospective cohort studies or even randomized controlled as well as longer follow-up trials are needed to confirm the relationship between metformin use and PCa.

DATA AVAILABILITY

The data utilized in this study was sourced exclusively from published RWS, all of which are comprehensively presented within this article (including its supplementary information files).

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AUTHOR CONTRIBUTIONS

Yuchen Liu and Xuan Huang designed research; Yuchen Liu, Qingfang Zhang, and Xuan Huang conducted literature search; Yuchen Liu participated and assisted in literature search and data collection; Yuchen Liu and Qingfang Zhang analyzed and interpreted data; and Yuchen Liu wrote the paper. Xuan Huang and Qingfang Zhang provided critical opinion. Yuchen Liu, Qingfang Zhang, and Xuan Huang revised the paper. Yuchen Liu had primary responsibility for final content. Xuan Huang is the corresponding authors. All authors read and approved the final manuscript. Guarantor of the article: Xuan Huang. The authors are responsible for the reported research, and have participated in the concept and design, analysis and interpretation of data, drafting or revising of the manuscript, and have approved the manuscript as submitted.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors. We did not use individual data but published data. These data have been widely utilized in research and are generally available. Therefore, we confirm that any aspect of the work covered in this manuscript has been conducted with ethical approval. And this study has been registered (registration number: CRD42023447013) with the PROSPERO (International Prospective Register of Systematic Reviews) and was conducted according to the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) statement.

CONSENT FOR PUBLICATION

All individuals gave written informed consent for publication.

ADDITIONAL INFORMATION

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