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Meta Analysis

The Association Between Metformin Use and Prostate Cancer Incidence and Mortality: A Systematic Review and Meta-Analysis of Case-Control and Cohort Studies

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Abstract

Background and aims: Prostate cancer (PCa) is the most common cancer among men, and type 2 diabetes mellitus (T2DM) increases the risk of PCa. This meta-analysis aimed to investigate the association between metformin administration, PCa incidence, and mortality rates.

Methods: The inquiry included databases PubMed, Cochrane, Scopus, Web of Science, and Google Scholar search engine and was updated until June 9, 2024. The primary outcome was the effect of metformin on the risk of PCa. Data were analyzed using STATA version 14 software, and statistical significance was determined at $P<0.05$.

Results: The results of 30 studies containing 1 655 591 men showed no significant relationship between metformin use and prostate neoplasm (OR: 0.94; 95% CI: 0.79-1.11). Additionally, the use of metformin in men aged 60 to 69 (OR: 0.97; 95% CI: 0.86-1.09) and men aged 70 to 79 (OR: 1.11; 95% CI: 0.91-1.35) was not associated with the risk of prostate carcinoma. Metformin use was not related to PCa in cohort studies (OR: 0.88; 95% CI: 0.71-1.08) and case-control studies (OR: 1.07; 95% CI: 0.92-1.25). Moreover, no significant relationship was found between metformin use and prostate carcinoma in Asia (OR: 0.78; 95% CI: 0.52-1.17), Europe (OR: 1.13; 95% CI: 0.96-1.32), or America (OR: 0.94; 95% CI: 0.74-1.20). However, metformin use reduced PCa mortality (HR: 0.83; 95% CI: 0.71-0.98).

Conclusion: Although the use of metformin did not reduce the risk of prostate carcinoma, it was associated with a 17% reduction in prostate carcinoma cancer mortality.

Keywords: Metformin, Prostate, Diabetes, Cancer, Neoplasm

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Introduction

Prostate cancer (PCa) is the most common neoplasm among men, and in 2019, it was responsible for 487 000 deaths, ranking among the leading causes of death worldwide.[1] Type 2 diabetes (T2DM) increases the risk of high-grade PCa.[2] After the diagnosis of PCa, diabetes is associated with an increased mortality rate from PCa and other causes.[3]

The first treatment option for patients with T2DM is metformin.[4,5] The effect of metformin on PCa remains unclear, as studies examining the association between PCa and metformin yielded uncertain and sometimes inconsistent results.[6,7] Furthermore, other antidiabetic medications such as sulfonylurea and insulin, may increase the risk of high-grade PCa and the rate of disease progression.[8]

Metformin is mainly prescribed for T2DM and has shown anticancer effects in colon, pancreatic, and breast cancers.[9,10] Several studies have confirmed its efficacy in reducing the risk of neoplasm; however, additional studies and evidence are required for cancers like PCa, including the mortalities related to cancer location.[11-13] A study reported that metformin reduced the risk of PCa,[14] while another study found that metformin increased the risk of

PCa.[6] Given the conflicting results of previous studies, this systematic review and meta-analysis were conducted to examine the association between metformin use and PCa incidence and mortality.

Materials and Methods

Study Design

This study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting systematic reviews and meta-analyses. The protocol was registered on the PROSPERO website (CRD42023389192), which is dedicated to the registration of systematic review and meta-analysis protocols.

Primary outcome: The effect of metformin on the risk of PCa.

Secondary outcome: The effect of metformin on PCa-related mortality.

Search Strategy

Two authors independently conducted the literature search. Sources included the Google Scholar search engine, the Web of Science, Cochrane, Scopus, and PubMed databases were searched using the keywords: "Metformin," "Cancer," "Neoplasm," "Diabetes," and "Prostate," along with their MeSH equivalents and were combined using operators (AND, OR). No language restrictions were applied in the source search phase, and it was updated until June 9, 2024. Search strategy in the PubMed database included ((Cancer[Title/Abstract] OR Neoplasm[Title/Abstract]) AND (Metformin[Title/Abstract])) AND (Prostate[Title/Abstract]).

PICO Components

- Population: Patients with T2DM
- Intervention: Metformin intake
- Comparison: Non-use of metformin
- Outcomes: Association between metformin intake and PCa incidence or mortality

Two authors also conducted screening of studies based on inclusion and exclusion criteria.

Eligibility Criteria and Study Selection

Inclusion Criteria

- Observational studies
- Studies evaluating the effect of metformin use on PCa

Exclusion Criteria

- Studies lacking sufficient data for analysis
- Descriptive reports on metformin efficacy on PCa
- Articles with unavailable full text
- Studies investigating the effect of two or multiple drugs, including metformin on Pca
- Low-quality studies
- Conference abstracts and conventions
- Review articles, systematic reviews, and meta-analyses

Quality Assessment

The quality of the included studies was assessed using the Newcastle Ottawa Scale (NOS). This tool covers nine items, and each item is assigned a score ranging from 0 to 10, with 0 indicating the lowest quality and 10 implying the highest quality. The NOS's cut point was 6, where research with a score of 6 or more was regarded as high-quality.[15] If two researchers disagreed about the quality of an article, a third researcher resolved the disagreement.

Data Extraction

Two researchers independently designed a form using SPSS version 19 to collect information. The form collects information on the author's name, country, continent, study design, year, sample size, mean age, study quality, odds ratio (OR) between metformin use and PCa incidence, and OR or hazard ratio (HR) between metformin use and mortality.

Statistical Analysis

The OR index was used to evaluate the effect of metformin intake on PCa incidence. The studies were combined using OR logarithm. The I^2 statistic and the Q-Cochrane test were also used to check the heterogeneity of studies. The data were analyzed using STATA version 14 software, with significance set at $P < 0.05$. Meta-regression analysis was conducted to investigate the relationship between the efficacy of metformin intake on PCa and variables such as sample size and year of publication. Egger's test was used to check publication bias.

Results

Initially, 863 studies were identified. After removing 398 duplicates, 465 articles remained for abstract screening. Of these, 45 articles were removed due to lack of access to full-text manuscripts. The remaining 430 were reviewed, and 400 were excluded due to other exclusion criteria. Finally, 30 articles were included in the meta-analysis (Figure 1).

The reviewed articles were cohort and case-control studies published from 2009 to 2024. Table 1 lists some of the most important information from these articles.

The total sample population across all 30 reviewed studies was 1 655 591 men. Among these, 25 studies investigated the association between metformin use and PCa incidence in T2DM patients, 11 studies examined the effect of metformin on mortality from PCa, and several studies investigated both outcomes. Figure 2 indicates no significant relationship between metformin use and PCa (OR: 0.94, 95% CI: 0.79-1.11).

Figure 3 indicates that metformin administration significantly reduced mortality from PCa in patients with T2DM. In other words, patients who used metformin had a 17% lower mortality risk than non-users (HR: 0.83; 95% CI: 0.71-0.98)].

Subgroup Analysis

Analysis based on study types revealed that metformin

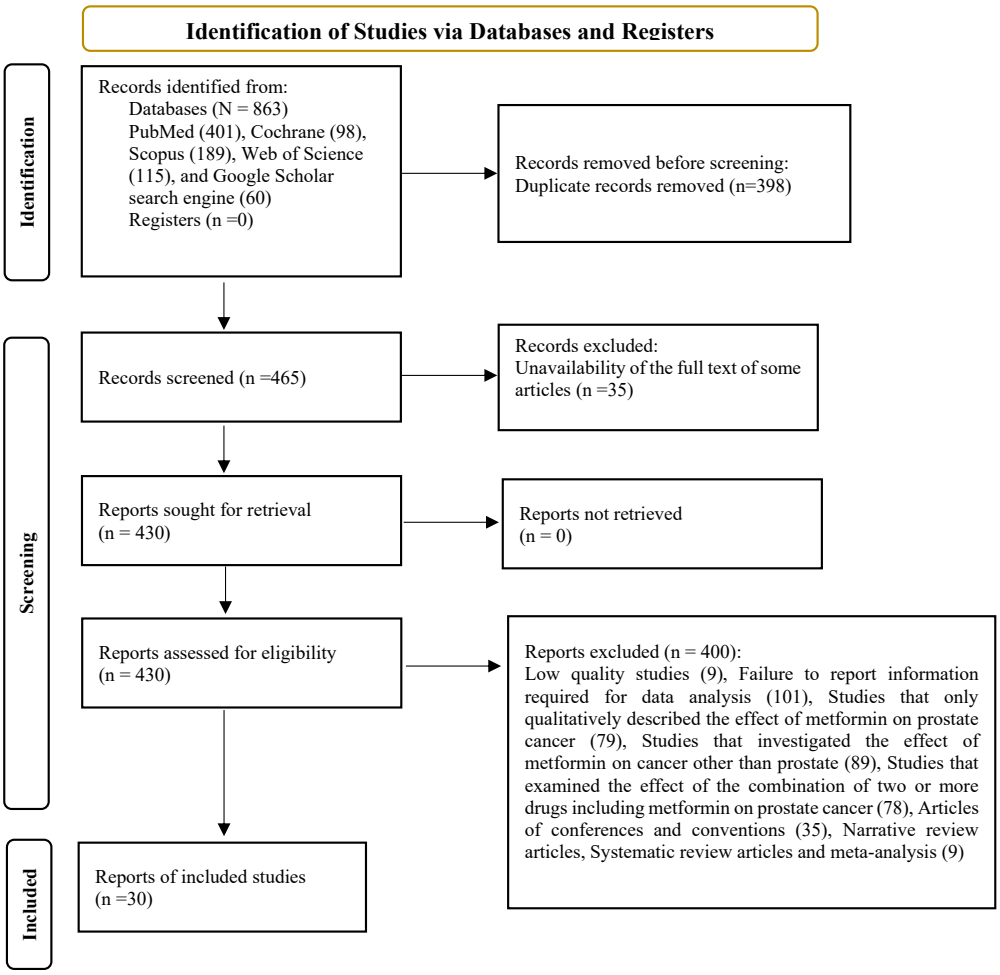

Figure 1. PRISMA Flowchart

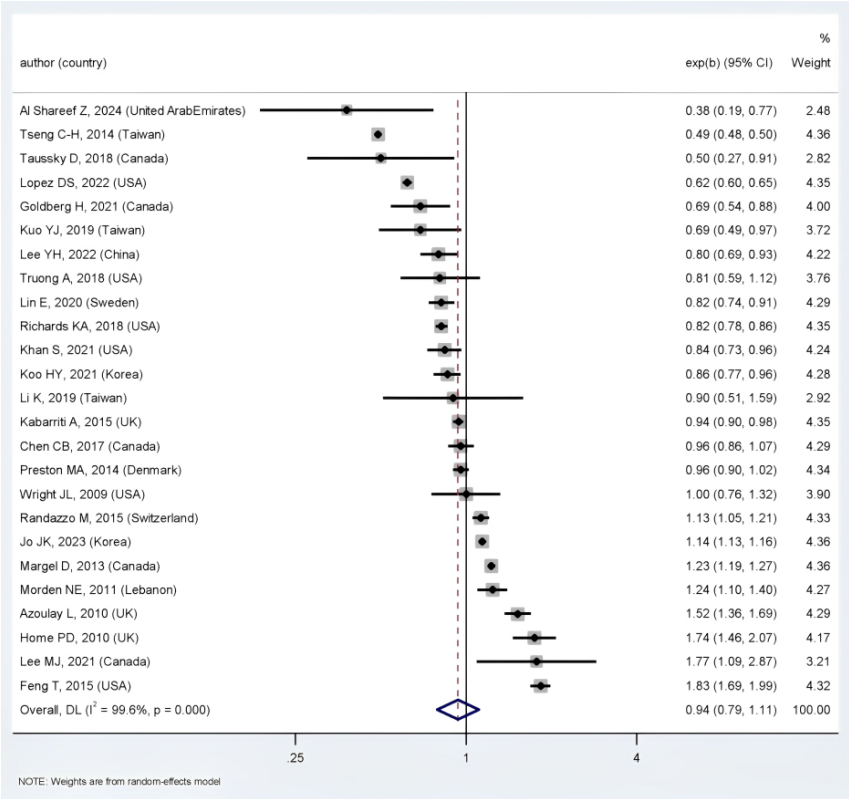

Figure 2. Forest Plot Showing the Effect of Metformin Use on PCa Incidence

Table 1. Key Characteristics of Included Studies

First Author, Year of Publication	Continent	Country	Design	Mean Age (year)	Follow-up (year)	Sample Size	OR (Association Between Metformin Intake and PCa)	CI		Quality Level
Chen, 2017[16]	America	Canada	Cohort	64	≥5	80001	0.96	0.64	0.79	High
Kabarriti, 2015[17]	Europe	UK	Case-Control	NR	NR	132552	0.94	0.79	0.86	High
Margel, 2013[18]	America	Canada	Cohort	76	<5	31836	1.23	1.08	1.15	Moderate
Randazzo, 2015[19]	Europe	Switzerland	Cohort	65.5	≥5	4314	1.13	0.95	1.09	Moderate
Preston, 2014[7]	Europe	Denmark	Case-Control	71.7	<5	134486	0.96	0.74	0.84	High
Tseng, 2014[20]	Asia	Taiwan	Cohort	NR	<5	395481	0.49	0.45	0.47	High
Feng, 2015[21]	America	USA	Cohort	50-75	<5	540	1.83	1.01	1.19	Moderate
Wright, 2009[22]	America	USA	Case-Control	NR	NR	1943	1.00	0.32	0.56	High
Azoulay, 2010[23]	Europe	UK	Cohort	74.1	≥5	8098	1.52	0.99	1.23	High
Morden, 2011[24]	Asia	Lebanon	Cohort	77.4	<5	81681	1.24	0.76	0.97	High
Home, 2010[25]	Europe	UK	Case-Control	NR	NR	6126	1.74	0.86	1.22	Moderate
Lee, 2022[26]	Asia	China	Cohort	65	≥5	25695	0.80	0.69	0.93	Moderate
Lopez, 2022[27]	America	USA	Cohort	>65	≥5	6960	0.62	0.60	0.65	Moderate
Lee, 2022[28]	Asia	China	Cohort	76	<5	1971	NR	NR	NR	High
Koo, 2021[14]	Asia	Korea	Cohort	40-80	≥5	388760	0.86	0.77	0.96	High
Lee, 2021[6]	America	Canada	Case-Control	64	NR	3481	1.77	1.10	2.90	High
Khan, 2021[29]	America	USA	Cohort	68	NR	4572	0.84	0.73	0.96	Moderate
Vihervuori, 2021[30]	Europe	Finland	Cohort	55-67	≥5	1603	NR	NR	NR	Moderate
Joentausta, 2021[31]	Europe	Finland	Cohort	63	NR	14424	NR	NR	NR	High
Goldberg, 2021[32]	America	Canada	Cohort	66	≥5	2332	0.69	0.54	.88	Moderate
Tan, 2020[11]	America	USA	Cohort	>65	<5	5003	NR	NR	NR	Moderate
Linkeviciute-Ulinskiene, 2020[33]	Europe	Lithuania	Cohort	70	NR	6689	NR	NR	NR	Moderate
Kuo, 2019	Asia	Taiwan	Cohort	>50	≥5	2906	0.69	0.49	0.96	High
Li, 2019[35]	Asia	Taiwan	Cohort	72	≥5	59	0.90	0.51	1.59	High
Richards, 2018[36]	America	USA	Cohort	71	≥5	87344	0.82	0.78	0.86	High
Taussky, 2018[37]	America	Canada	Cohort	NR	<5	382	0.50	0.26	0.86	Moderate
Truong, 2018[38]	America	USA	Cohort	NR	NR	87344	0.81	0.59	1.13	High
Al Shareef, 2024[39]	Asia	United Arab Emirates	Cohort	NR	≥5	2377	0.38	0.19	0.78	High
Jo, 2023[40]	Asia	Korea	Cohort	69	≥5	105216	1.14	1.12	1.15	High
Lin, 2020[41]	Europe	Sweden	Case-Control	NR	<5	31415	0.82	0.74	0.91	High

Note. OR: Odds ratio; CI: Confidence interval; NR: Not reported; PCa, prostate cancer.

use was not significantly associated with PCa risk in either cohort studies (OR: 0.88; 95% CI: 0.71-1.08) or case-control studies (OR: 1.07; 95% CI: 0.92-1.25). Moreover, metformin use in men aged 60 to 69 (OR: 0.97; 95% CI: 0.86-1.09) and men aged 70 to 79 (OR: 1.11; 95% CI: 0.91-1.35) was not related to PCa risk. In addition, no significant relationship was observed between metformin use and PCa risk in Asia (OR: 0.78; 95% CI: 0.52-1.17), Europe (OR: 1.13; 95% CI: 0.96-1.32), and America (OR: 0.94; 95% CI: 0.74-1.20).

However, at the country level, metformin use in the United Arab Emirates (62%), Taiwan (38%), China (20%), and Sweden (18%) reduced the risk of PCa and prevented PCa. In contrast, no significant relationship was observed between metformin use and PCa in Canada, America, Korea, England, and Denmark. On the other hand, metformin use increased the risk of PCa in Switzerland (OR: 1.13; 95% CI: 1.05-1.21) and Lebanon (OR: 1.24; 95% CI: 1.10-1.40).

Regarding the follow-up period, studies were classified into two groups: those with follow-up periods of < 5 years and those with follow-up periods of ≥ 5 years. In both groups, there was no statistically significant relationship between metformin use and PCa risk (Table 2).

A detailed analysis was also conducted to assess the efficacy of metformin administration on mortality due to PCa. It must be noted that all studies included in this analysis were cohort studies, so no classification according to study design was required. Regarding age, metformin use demonstrated a statistically significant reduction in PCa mortality among men aged 60-69 years, with a 24% decrease in mortality risk. However, no statistically

Table 2. Relationship Between Metformin Intake and PCa Mortality in T2DM Patients by Subgroups

Outcomes	Subgroups		OR/HR	Low	Up	I^2 (%)	*P* Value
Association between metformin use and PCa risk	Study type	Cohort	0.88	0.71	1.08	99.7	<0.001
		Case-Control	1.07	0.92	1.25	91.7	<0.001
	Mean age (y)	60-69	0.97	0.86	1.09	91.2	<0.001
		70-79	1.11	0.91	1.35	97.9	<0.001
	Follow-up Duration (y)	<5	0.93	0.59	1.46	99.8	<0.001
		≥5	0.87	0.72	1.05	98.9	<0.001
	Continent	Asia	0.78	0.52	1.17	99.8	<0.001
		America	0.94	0.74	1.20	99	<0.001
		Europe	1.13	0.96	1.32	96.2	<0.001
	Country	United Arab Emirates	0.38	0.19	0.77	0	-
		Taiwan	0.62	0.44	0.88	76	0.16
		Canada	0.97	0.76	1.24	92	<0.001
		USA	0.93	0.66	1.31	99.1	<0.001
		China	0.80	0.69	0.93	0	-
		Sweden	0.82	0.74	0.91	0	-
		Korea	1	0.76	1.31	96	<0.001
		UK	1.35	0.89	2.03	98	<0.001
		Denmark	0.96	0.90	1.02	0	-
		Switzerland	1.13	1.05	1.21	0	-
		Lebanon	1.24	1.10	1.40	0	-
Association between metformin use and PCa mortality	Mean age	60-69 years	0.76	0.60	0.96	79.7	0.007
		70-79 years	0.81	0.53	1.22	88.9	<0.001
	Follow-up duration	<5 year	0.59	0.39	0.90	76	0.041
		≥5 year	1.02	0.84	1.24	90.5	<0.001
	Continent	Asia	1.03	0.65	1.62	93.4	<0.001
		America	0.80	0.62	1.03	89.8	<0.001
		Europe	0.79	0.45	1.38	85.7	0.001
	Country	Finland	0.80	0.29	2.22	92.2	<0.001
		China	0.67	0.37	1.20	96.3	<0.001
		USA	0.80	0.62	1.03	89.8	<0.001
		Lithuania	0.74	0.54	1.02	0	-
		Korea	1.15	0.86	1.54	0	-
		Taiwan	6.78	2.45	18.77	0	-

Note. PCa: Prostate cancer; T2DM: Type 2 diabetes mellitus; OR: Odds ratio; HR; Hazard ratio; Low: Low limit; Up: Up limit.

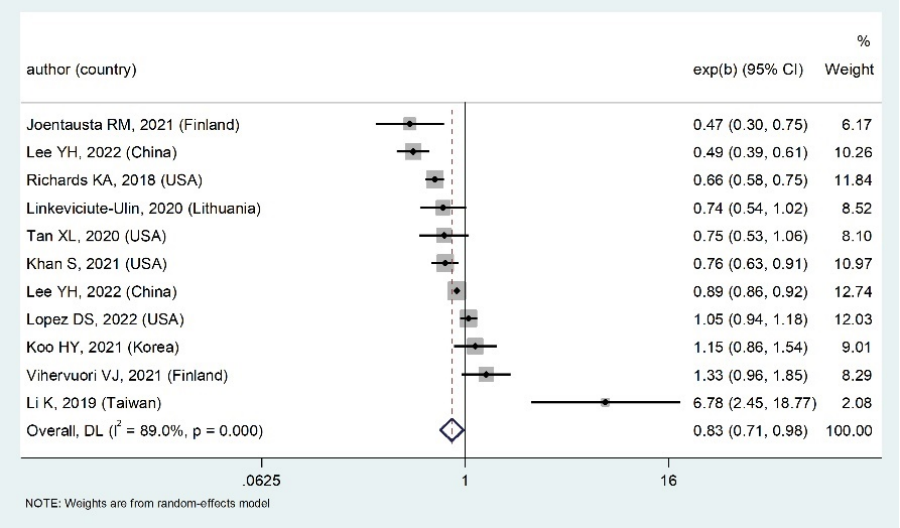

Figure 3. Forest Plot Showing the Effect of Metformin Use on Mortality

significant relationship was observed between metformin use and PCa mortality in men aged 70-79 years, suggesting that the death of some cases in this group may be influenced by factors such as senescence.

In terms of follow-up duration, metformin administration in the group with a follow-up period of < 5 years significantly reduced the mortality due to PCa (HR: 0.59; 95% CI: 0.39-0.90). However, this relationship was not statistically significant in patients with a follow-up period of ≥ 5 years.

When the results were analyzed by continent, there was no statistically significant relationship between metformin use and PCa mortality in Asia, America, or Europe. Similarly, at the country level, no statistically significant relationship was found in Finland, China, America, Lithuania, and Korea; however, the use of metformin in Taiwan significantly increased the risk of Pca mortality (OR: 6.78; 95% CI: 2.45-18.77), as depicted in Table 2.

Additional Analysis

Meta-regression revealed a statistically significant association between the efficacy of metformin on PCa risk and the year of publication ($P = 0.016$). However, no significant relationship was found between PCa risk and the studies' sample size ($P = 0.146$). The publication bias diagram was not statistically significant, indicating this meta-analysis is unlikely to be affected by publication bias. This suggests that studies were included regardless of their negative or positive results and that all relevant studies were covered during the search stage ($P = 0.950$), as illustrated in Figures 4-6.

Discussion

The current meta-analysis showed no statistically significant relationship between metformin use and PCa risk in men in all studies and the investigated subgroups. However, metformin use was associated with a 17% reduction in PCa mortality, which reached 24% in men aged 60 to 69. Furthermore, in studies with a follow-up period of less than 5 years, metformin use reduced PCa-related mortality by 31%. The significant heterogeneity in the results may be attributed to the differences in participant age, study design, evaluation methods, and participant ethnicity across studies.

A previous meta-analysis indicated that metformin, compared to sulfonylurea, reduced PCa risk in patients with T2DM.[42] This finding is contrary to the current research, which did not find any statistically significant relationship between metformin use and PCa risk. The number of studies and sample size in the current meta-analysis are larger than those of the previous meta-analysis, incorporating published articles from 2020 to 2024 that were not included in earlier reviews. In addition to the relationship between metformin use and PCa, the relationship between metformin use and mortality has also been investigated in the current meta-analysis. Therefore, the results of the current research are more up-to-date and comprehensive.

Ghiasi and colleagues' meta-analysis of 11 studies involving 877058 individuals reported that metformin administration did not increase the incidence of PCa (OR: 0.89; 95% CI: 0.67-1.17).[43] In a meta-analysis by Want et al comprising 2009504 male patients with T2DM, metformin administration did not increase the risk of PCa in case-control (0.97; 95% CI: 0.84–1.12) and cohort (0.94; 95% CI: 0.79–1.12) studies.[42] In a cohort of 52,328, Feng et al also found that metformin administration was not significantly associated with PCa (RR: 0.97; 95% CI: 0.80–

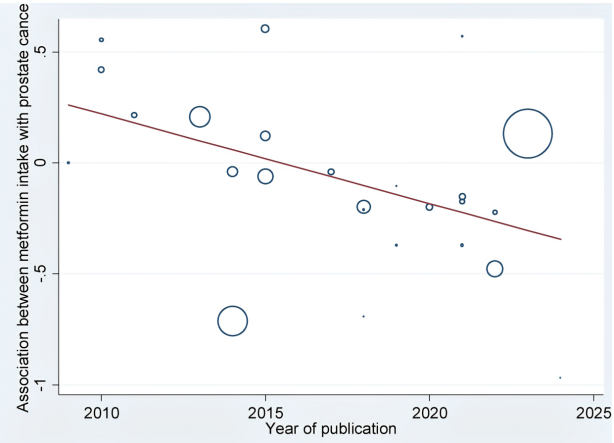

Figure 4. Meta-regression of the Association Between Metformin Use and Prostate Cancer Incidence by Year of Publication

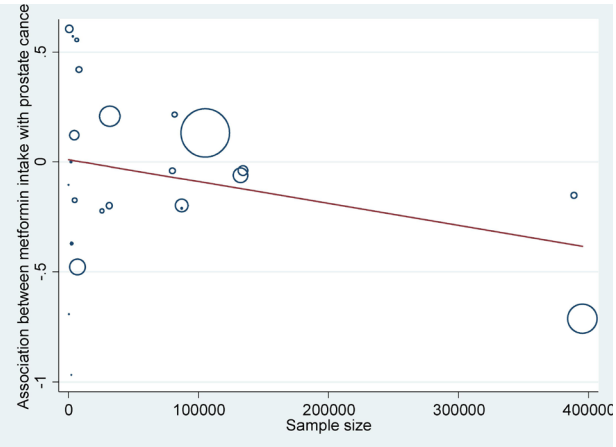

Figure 5. Meta-regression of the Association Between Metformin Use and Prostate Cancer Incidence by Study Sample Size

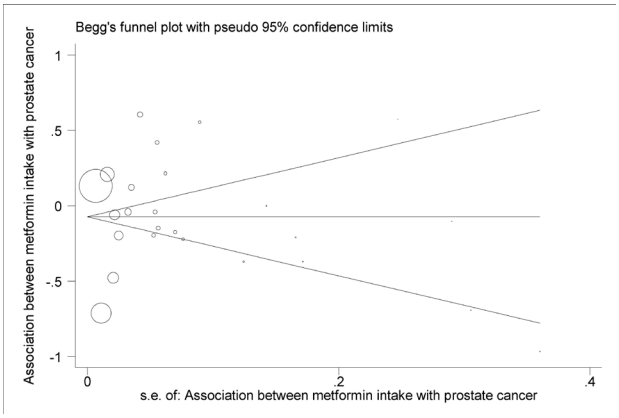

Figure 6. Diagram of Publication Bias

1.16).[44] Similarly, Chen and colleagues' review of 26 studies comprising 1 572 307 patients revealed no significant association between PCa and metformin use. Their findings were consistent with clinical trials in Western countries (RR: 1.38; 95% CI: 0.72-2.64) and observational studies (RR: 1.03; 95% CI: 0.94-1.13).[16] These studies support the results of the current research, which similarly indicated no significant association between metformin administration and PCa incidence in patients with T2DM.

On the other hand, a meta-analysis by Stopsack et al, which included nine retrospective cohort studies with 9186 patients, indicated that metformin administration was associated with improved overall survival (HR: 0.88; 95% CI: 0.86–0.90) and decreased the risk of biochemical recurrence (HR: 0.79; 95% CI: 0.63–1).[45] A meta-analysis by He et al on 1660795 individuals indicated that metformin treatment improved overall survival (HR: 0.72; 95% CI: 0.59–0.88), cancer-specific survival (HR: 0.78; 95% CI: 0.64–0.94), and recurrence-free survival (HR: 0.60; 95% CI: 0.42–0.87) o compared with alternative metformin treatments.[44] These results are consistent with the current study's conclusion that metformin administration reduces PCa mortality rate, thereby improving patient survival. However, the results of a meta-analysis by Raval et al involving 9 cohort and case-control studies indicated no significant association between metformin administration and all-cause mortality (pHR: 0.86; 95% CI: 0.65, 1.1) or PCa-specific mortality (pHR: 1.22; 95% CI: 0.58, 2.56).[46] This is consistent with the results of the current meta-analysis, where metformin use in patients aged 60 to 69 years was associated with a significant reduction in the risk of death of patients. However, in patients aged 70 to 79 years, there was no significant relationship between metformin intake and mortality. No study yet identified metformin as a risk factor influencing PCa mortality. It is likely that the increasing age and underlying diseases in patients over 70 years old may contribute to their death, and that is why metformin use in this age group did not reduce their mortality risk. This appears to be unrelated to the prescription of metformin itself.

Limitations

The study's limitations included the lack of access to full-text versions in some studies, failure to mention the administered metformin dosage in some studies, inability to categorize some studies into specific age groups, and failure to mention other influential background diseases affecting PCa incidence and patient mortality.

Conclusion

Although the use of metformin did not significantly reduce the risk of PCa, it was associated with a 17% reduction in PCa-related mortality, which reached 24% in men aged 60 to 69 years. Additionally, metformin use in patients with a follow-up period of less than 5 years reduced the risk of death from PCa by 31%. Therefore, it is recommended that future studies investigate the effects of different metformin doses on the risk of PCa, addressing the current study's limitations.

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Competing Interests

The authors declare no conflict of interests regarding the contents of this article.

Ethical Approval

This study was approved by the Research and Technology Deputy of the Kermanshah University of Medical Sciences (IR.KUMS.MED.REC.1402.087) and was conducted according to the World Medical Association Declaration of Helsinki. The authors have completely observed ethical issues, including avoidance of plagiarism, data fabrication, and double publication.

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