



The association between statin administration and renal cell carcinoma; a systematic review and meta-analysis

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ABSTRACT

Introduction: Renal cell carcinoma (RCC) is the most prevalent renal cancer in adults, with a rising global incidence. There has long been an ambiguity about the effect of statin administration on the incidence of RCC. The present meta-analysis aims to evaluate the relationship between statin usage and RCC.

Materials and Methods: Cochrane, Web of Science, Scopus, and PubMed databases, as well as the Google Scholar search engine, were queried for relevant articles. The data were statistically analyzed by STATA 14 software. The significance level of the tests was considered $P < 0.05$.

Results: In 15 reviewed articles, 46 735 subjects used statin, and 673 752 did not. The odds ratio (OR) between statin usage and the risk incidence of RCC was 0.86 (OR: 0.86; 95% CI: 0.63, 1.17) overall and estimated as 0.94 (OR: 0.94; 95% CI: 0.69, 1.28) in males and 0.92 (OR: 0.92; 95% CI: 0.66, 1.28) in females. The odds ratio of statin administration and the incidence risk of RCC was 0.74 (OR: 0.74; 95% CI: 0.37, 1.49) in case-control and 0.96 (OR: 0.96; 95% CI: 0.79, 1.17) in cohort studies. In addition, the impact of statin usage on overall survival (OS) in RCC was 0.65 (HR: 0.65; 95% CI: 0.53, 0.80), and this relationship was statistically significant. However, the effect of statin usage was 0.68 (HR: 0.68; 95% CI: 0.45, 1.02) on progression-free survival (PFS) and 1.24 (OR: 1.24; 95% CI: 0.66, 2.32) on disease progression (DP), and these relationships were statistically non-significant.

Conclusion: The OS of RCC patients was 35% higher in statin users than in non-users. However, no relationship between statin usage and the incidence risk of RCC was found.

Meta-analysis Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (CRD42023393647).

Implication for health policy/practice/research/medical education:

Our meta-analysis showed that statin administration was not associated with the risk of renal cell carcinoma (RCC) development. Moreover, the patient gender and study type did not affect the relationship between statin administration and the incidence risk of RCC. However, the overall survival in administration was 35% higher in statin users compared to non-users.

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Introduction

Almost 403 000 new cases of renal cancer and 175 000 related deaths occur annually worldwide (1). Renal cell carcinoma (RCC) is the most frequently occurring form of renal cancer, representing approximately 90% of cases (2). It is the sixth most prevalent tumor in men and the tenth most common tumor in women globally, accounting for 5% and 3% of all oncological diagnoses, respectively (3). The incidence of RCC is rising around the globe, with nearly 76 000 new cases estimated in 2021 in the US (4, 5).

Smoking, obesity, and family history are three potential risk factors identified for RCC (6).

Statins or 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors are the most common class of drugs prescribed for lowering plasma cholesterol levels that considerably decrease the risk of cardiovascular events and mortality (7,8). Experimental studies have consistently suggested the antineoplastic effects of statins against several tumor types (9-11). In human observational studies, statin usage has been shown to reduce cancer-

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specific mortality risk in prostate, colorectal, and breast cancers (12-14).

At the cellular level, statins have been related to the halting of cell-cycle progression, apoptosis induction, and inhibition of cell signaling pathways implicated in tumor invasion and metastasis (15). Given the scarcity and inconsistency of the existing epidemiological studies regarding statin administration and RCC risk in humans (16, 17), this study aims to address the possible relationship between statin usage and RCC incidence using a systematic review and meta-analysis approach.

Materials and Methods

Study design

This study designed based on PRISMA reporting guidelines for systematic reviews and meta-analyses, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website (CRD42023393647, <https://www.crd.york.ac.uk/prospero/#recordDetails>).

Search strategy

International databases, including Scopus, PubMed, Cochrane, Web of Science, as well as the Google scholar search engine, were searched without time restriction in this meta-analysis. The search process was performed using the following keywords: “Renal cell carcinoma,” “Renal cell cancer,” “Renal cell adenocarcinoma,” “Statin,” and “Hydroxymethyl glutaryl coenzyme A reductase inhibitors”. The literature search was updated until January 2023. For an advanced query, the mentioned databases were searched using a combination of keywords with Boolean operators “AND” and “OR”. The search strategy for the PubMed database is provided as follows; (Renal Cell Carcinoma[Title/Abstract] OR Renal Cell Cancer[Title/Abstract] OR Renal Cell Adenocarcinoma[Title/Abstract]) AND (Statin[Title/Abstract] OR Hydroxymethylglutaryl-CoA Reductase Inhibitors[Title/Abstract] OR Statins[Title/Abstract] OR Atorvastatin[Title/Abstract] OR Cerivastatin[Title/Abstract] OR Fluvastatin[Title/Abstract] OR Lovastatin[Title/Abstract] OR Pravastatin[Title/Abstract] OR Rosuvastatin[Title/Abstract] OR Simvastatin[Title/Abstract])

PICO components

Population: Studies related to patients with hypercholesterolemia. Intervention: statin usage. Comparison: those not on statin therapy. Outcome: the incidence risk of RCC. Studies evaluating the effect of statin usage on overall survival (OS), disease progression (DP), and progression-free survival (PFS) in RCC patients were examined as the secondary outcome.

Inclusion criteria

This meta-analysis included all case-control and cohort

studies investigating the impact of statin usage on RCC incidence.

Exclusion criteria

The studies that met the following criteria were excluded from the study; lacking the required information for data analysis; duplicate studies; case-report studies; studies that examined the effect of statin in combination with another medication on RCC incidence; studies with poor quality according to Newcastle Ottawa Scale (NOS) checklist; studies that explored the effect of stain on tumors other than RCC.

Qualitative assessment

Two researchers performed the quality assessment separately using the NOS (18). Each study was scored ranging from zero to nine, with higher scores indicating higher study quality. The cut-off point of the checklist was set at five in this study. Articles with scores below five were excluded from the study. However, all articles in this meta-analysis were of acceptable quality. A third researcher resolved any potential discrepancies between the two researchers regarding the quality assessment.

Data extraction

To minimize data collection errors, the same two researchers independently extracted the data from the eligible articles and entered them into a checklist containing the author’s name, the number of patients, average age, country, publication year, study type, and the odds ratio (hazard ratio) between statin usage and the incidence risk of RCC.

Statistical analysis

The odds ratio (OR) or hazard ratio (HR) was utilized to establish the relationship between statin usage and RCC occurrence. Logarithmic OR (HR) was considered in all studies to pool their results. The heterogeneity of the studies was assessed using the I^2 index. Random effects model was adopted, given the high heterogeneity of the studies ($I^2=92.4%$). With the help of STATA 14 software, the data were statistically analyzed. The significance level of the tests was considered $P < 0.05$.

Results

Initially, 521 studies were retrieved by searching in databases and the Google Scholar search engine. After checking the titles, 189 duplicates were removed, and the abstracts of 332 studies were screened. At this stage, 85 articles were excluded due to irrelevancy, incomplete abstracts, and unavailable full text. The remaining 247 were assessed for potential inclusion. After applying the other exclusion criteria, ultimately, 15 articles with high quality entered the systematic review and meta-analysis process (Figure 1). A part of the information of the reviewed articles is given in Table 1.

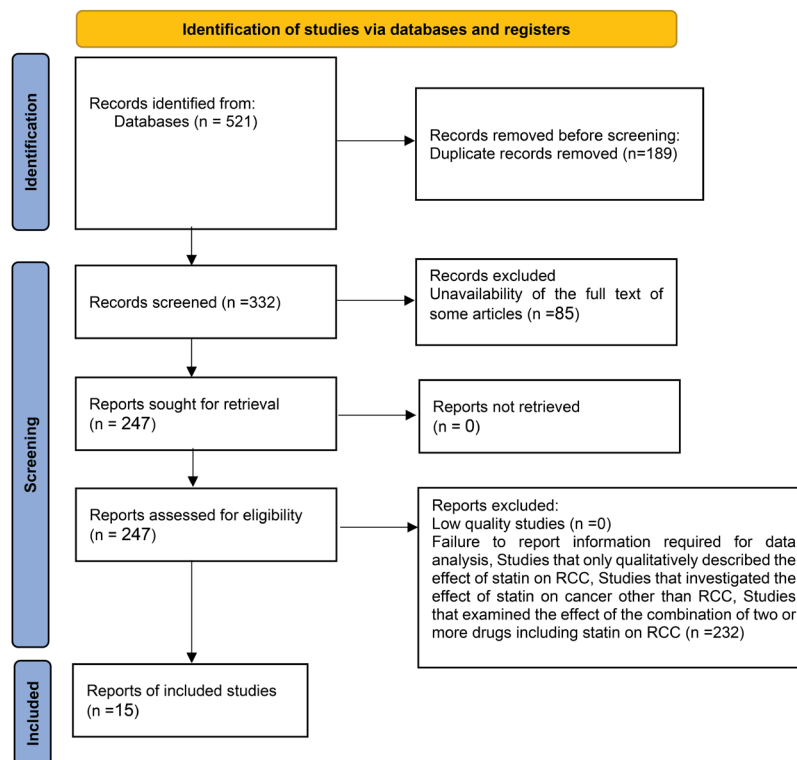


Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Of 15 identified studies, two were case-control, and 13 were cohort studies. Overall, 46735 patients used statin, and 673752 did not. The odds ratio of statin and the incidence risk of RCC was 0.86 (OR: 0.86; 95% CI: 0.63, 1.17, $P=0.000$, $I^2 = 92.4\%$), and this relationship was not statistically significant (Figure 2).

Sub-group analysis

The estimated odds ratio between statin usage and the incidence risk of RCC was 0.019 (OR: 0.94; 95% CI: 0.69, 1.28, $P=0.019$, $I^2 = 69.9\%$) in men compared to 0.92 (OR: 0.92; 95% CI: 0.66, 1.28, $P=0.010$, $I^2 = 73.7\%$) in women. Likewise, the odds ratio of statin treatment and the incidence risk of RCC was 0.74 (OR: 0.74; 95% CI: 0.37, 1.49, $P=0.000$, $I^2 = 98.2\%$) in case-control and 0.96 (OR: 0.96; 95% CI: 0.79, 1.17, $P=0.183$, $I^2 = 38.2\%$) in cohort studies. These relationships showed no statistical significance.

Evaluation of secondary outcomes

The impact of statin usage on OS in RCC was 0.65 (HR: 0.65; 95% CI: 0.53, 0.80, $P=0.114$, $I^2 = 43.6\%$). This relationship was statistically significant, with statin usage improving the overall cancer survival in RCC patients (Figure 3).

The effect of statin usage on PFS was 0.68 (HR: 0.68; 95% CI: 0.45, 1.02, $P=0.000$, $I^2 = 81\%$), and this relationship was statistically insignificant (Figure 4).

Besides, the odds ratio for the effect of statin usage on RCC progression was 1.24 (OR: 1.24 (95% CI: 0.66,

2.32), $P=0.000$, $I^2 = 90.1\%$), which was statistically non-significant (Figure 5).

Discussion

By screening 15 articles in this meta-analysis, we found that the OS rate for RCC patients was 35% higher in statin users than in non-users. Nevertheless, no relationship between statin usage and the risk of RCC incidence, RCC progression, and PFS was observed. However, the obtained results might have been drastically different if it was possible to stratify the identified studies by statin dose and duration.

The finding of a 2014 meta-analysis by Zhang et al, including 12 studies, indicated no statistically significant relationship between statin usage and the risk of renal tumor (RR = 0.92, 95% CI 0.71, 1.19) (32). In 2013, Zhang et al conducted a meta-analysis of 13 studies to establish the relationship between statin usage and the risk of bladder tumor. Their findings could not reveal any statistically significant effect of statin usage on increasing the incidence of bladder tumor (RR = 1.07, 95% CI (0.95, 1.21)) (33). A recent meta-analysis by Xu et al in 2022 evaluated the effect of statin usage on the overall incidence of prostate tumor. The pooled results of 6 randomized control trials (RCTs) and 26 cohort studies indicated a non-significant relationship between statins and prostate cancer occurrence (RR = 0.94, 95% CI: 0.82 to 1.08). Similar results were also achieved from nine case-control studies (OR = 1.03, 95% CI: 0.99 to 1.07) (34). Our results corroborate those of the above meta-analysis, suggesting

Table 1. Summary of the information available in the reviewed articles

First author, year of publication	Type of Study	Place	Mean age in statin group (years)	Mean age in compare group (years)	Compared with	Mean follow-up time (month)	Statin group			Never user statin group		
							Total number	No. of females	No. of males	Total number	No. of females	No. of males
Santoni, 2022 (19)	Cohort	Italy, Spain, USA	65	-	Never users	35.8	304	80	224	-	-	-
McKay, 2016 (20)	Cohort	USA	-	-	Never users	-	511	133	378	4225	1235	2990
Nayan, 2016 (21)	Cohort	Canada	66	57	Never users	47	259	72	187	634	247	387
Haddad, 2015 (22)	Cohort	USA	62	55	Never users	25	342	143	199	508	217	291
Kaffenberger, 2015 (23)	Cohort	USA	60.8	60.8	Never users	42.5	270	77	193	646	245	401
Lin-Tsai, 2013 (24)	Cohort	USA	-	-	Never users	42.9	294	-	-	672	-	-
Berquist, 2017 (25)	Cohort	USA	57.5	57.6	Never users	68	180	66	114	103	28	75
Viers, 2015(26)	Cohort	USA	66	61	Never users	-	630	182	448	1727	597	1130
Hamilton, 2014 (27)	Cohort	USA	66	59	Never users	36	708	226	482	1900	691	1209
Chou, 2020 (16)	Cohort	Taiwan	50.4	50.4	Never users	-	14067	6938	7228	56268	27356	28912
Wilson, 2018 (17)	Cohort	USA	-	-	Never users	-	661	-	-	-	-	-
Pottegard, 2016 (28)	Case-Control	Denmark	64	64	Never users	-	4606	1554	3052	46060	15540	30520
Chery, 2012 (29)	Cohort	USA	50-76	-	Never users	-	249	-	-	-	-	-
Liu, 2012 (30)	Cohort	USA	68	65	Never users	-	22208	15341	6867	78722	55711	23011
Khurana, 2008(31)	Case-Control	USA	67	61.22	Never users	-	1446	38	1408	482287	40128	442159

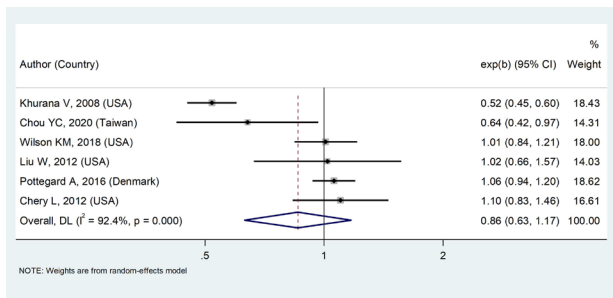


Figure 2. Graph of the effect of statin use on risk of RCC and its 95% CI.

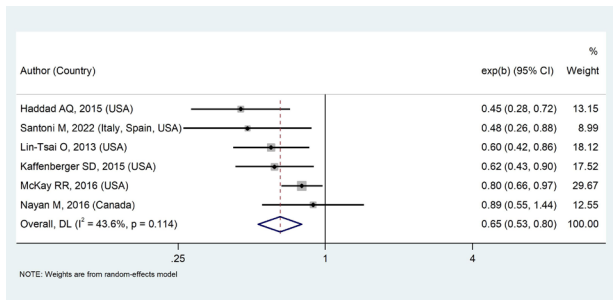


Figure 3. Graph of the effect of statin on overall survival (OS) and its 95% CI in RCC patients.

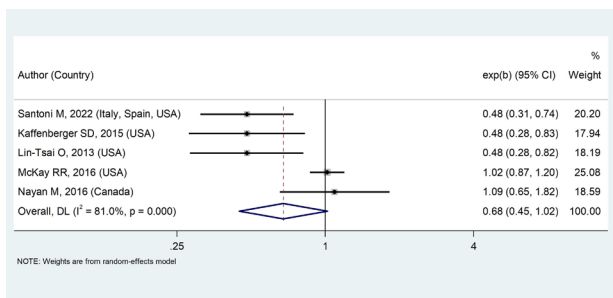


Figure 4. Graph of the effect of statin on progression-free survival (PFS) and its 95% CI in RCC patients.

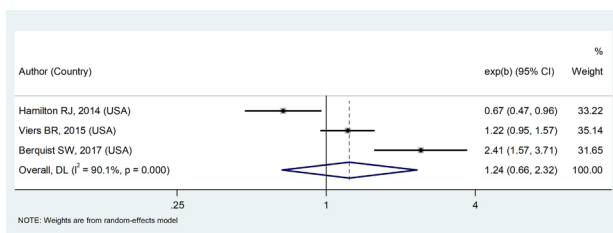


Figure 5. Graph of the effect of statin on disease progression (DP) and its 95% CI in RCC patients.

a lack of a statistically significant relationship between statin usage and cancer development, including prostate, bladder, and renal cancers.

A previous meta-analysis by Wu et al (2020), comprising five studies and 5299 patients, assessed the relationship between statin usage and OS in RCC patients. Based on

their findings, statin administration did not affect the OS of RCC patients compared to the control groups (OR = 1.07, 95% CI: 0.77, 1.49, P = 0.68) (35), which contradicts the results of the present meta-analysis. The observed discrepancy can be due to the higher number of reviewed articles and the larger sample size in our meta-analysis compared to the study by Wu et al. However, given the comprehensiveness of this meta-analysis, which covers a total of 15 studies, it is likely to yield more generalizable results (35).

In another meta-analysis of 12 studies with a sample size of 18105 patients, Nayan et al aimed to determine the effect of statin therapy on renal cancer survival outcomes. The authors reported no significant relationship between statin usage and recurrence-free survival (HR 0.97, 95% CI 0.89 to 1.06) or PFS (HR 0.92, 95% CI 0.51 to 1.65). Conversely, statin usage considerably improved the OS (HR 0.74, 95% CI 0.63 to 0.88) (36), which was in line with the results of our study. One reason for the consistency between our results and those of the Nayan et al study may be that RCC is the most common subtype of renal cancer.

Conclusion

Our results suggested that statin usage was not associated with the risk of RCC development. Moreover, the patient gender and study type did not affect the relationship between statin usage and the incidence risk of RCC. However, the OS in RCC was 35% higher in statin users compared to non-users. Nonetheless, statin usage did not influence DP and PFS in RCC patients. Given the limitations of this study, further clinical trials in this area are essential.

Limitations of the study

This study faced limitations, including the limited number of studies and not stratifying the outcomes by statin dose, type, and duration.

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Authors' contribution

- Conceptualization: MKH and PR.
- Methodology: MKH and PR.
- Data curation: MKH and PR.
- Validation: MKH and PR.
- Formal analysis: MKH and PR.
- Investigation: MKH and PR.
- Visualization: MKH and PR.
- Supervision: MKH and PR.
- Project administration: MKH and PR.
- Writing—original draft preparation: MKH and PR.
- Writing—review and editing: MKH and PR.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website (CRD42023393647, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023393647). Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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