

Association between kidney stones and future risk of kidney cancer: A systematic review and meta-analysis

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ABSTRACT

Introduction: Despite increasing interest in the potential associations between kidney stones and kidney cancer, their relationship remains incompletely characterized. This systematic review and meta-analysis evaluated the association between a history of kidney stones and the future risk of kidney cancer.

Methods: We systematically searched Medline, Embase, and the Cochrane Central Register of Controlled Trials for

observational studies of renal cell carcinoma risk in adults with kidney stones. A random-effects

KEY MESSAGES

- In a systematic review and meta-analysis, a history of kidney stones was associated with a significantly higher risk of developing kidney cancer, potentially warranting increased clinical vigilance in affected patients.
- Healthcare providers should consider informing patients with kidney stones about their potentially increased kidney cancer risk and emphasize the importance of consistent followup care and lifestyle modifications.

meta-analysis was performed to calculate the pooled risk ratio and 95% confidence interval (CI). Subgroup analyses and meta-regression were conducted to assess the associations with study design, data sources, risk of bias, control group type, and sex.

Results: Thirteen studies (five cohort, eight case-control) were included in the meta-analysis. A history of kidney stones was associated with a significantly higher risk of developing kidney cancer (risk ratio 2.36; 95% CI 1.74, 2.98, $p < 0.001$, $I^2 = 94\%$). Subgroup analysis showed a consistently elevated risk of kidney cancer in stone formers across all subgroups. No significant differences were observed between subgroups, except that more recent studies demonstrated significantly stronger associations between stone disease and risk of kidney cancer ($p < 0.001$).

Conclusions: This meta-analysis demonstrates a significant association between kidney stones and increased risk of kidney cancer, with affected individuals having approximately twice the risk of developing kidney cancer. These findings highlight the importance of enhanced cancer surveillance in patients with a history of kidney stones and suggest the need for further research into shared pathophysiologic mechanisms and potential preventative strategies.

INTRODUCTION

Kidney stone disease represents a significant public health burden, affecting approximately 10% of adults during their lifetime.¹ The physiological consequences may extend beyond acute symptomatology, which has prompted investigations into potential associations between kidney stones and other renal pathologies. Epidemiological studies have demonstrated that stone-formers have a significantly higher risk of developing chronic kidney disease²⁻⁴ and urinary tract infections.⁵ These associations highlight the importance of exploring potential connections between kidney stones and other renal conditions, including kidney cancer.

Kidney cancer ranks among the most aggressive urologic malignancies, with a 5-year mortality rate of 22%.⁶ In 2022, there were 434,000 new cases of kidney cancer worldwide, ranking as the 14th leading cause of cancer globally.⁷ Despite increasing interest in the potential mechanistic and clinical associations between nephrolithiasis and kidney cancer, their relationship remains incompletely characterized. A meta-analysis published in 2015 reported a significantly increased risk of kidney cancer among adults with a history of kidney stones.⁸ However, despite the publication of several relevant papers in recent years, no updated meta-analyses on the topic have been conducted. The objective of this systematic review and meta-analysis was to evaluate the association between a history of kidney stones and the subsequent risk of kidney cancer.

METHODS

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Meta-analysis Of

Observational Studies in Epidemiology (MOOSE) guidelines. A protocol was developed and prospectively registered at www.researchregistry.com (reviewregistry1863).

Search strategy and study selection

We systematically searched MEDLINE, EMBASE, and CENTRAL from their inception to December 2024. We performed supplementary searches in the Directory of Open Access Journals and Google Scholar, and manually reviewed reference lists of included papers and relevant systematic reviews. Eligibility criteria for the systematic review included observational case-control or cohort studies reporting risk estimates for the association between kidney stones and kidney cancer. While the search strategy incorporated broad terms for risk factors and kidney cancer without mandating kidney stone-specific terms. This approach was implemented to minimize selection bias towards only the studies that reported kidney stone data in their abstracts, which could potentially overrepresent positive associations between kidney stones and kidney cancer. Further, while this broad search strategy maximized search sensitivity and accounted for inconsistent terminology in the literature, the analysis was restricted to studies of renal cell carcinoma. The complete search strategy is provided in Supplement Table 1. Two investigators (LM, DF) independently screened titles, abstracts, and full texts of potentially eligible studies. Disagreements were resolved through discussion and consensus. We excluded review articles, editorials, commentaries, conference proceedings, grey literature, and papers reporting only upper tract urothelial carcinoma data. No language or publication date restrictions were applied.

Data extraction and quality assessment

Two investigators (LM, DF) independently retrieved data using a piloted standardized form. The extracted information included study metadata, study design, sample size, participant characteristics, definitions of exposure and outcome, risk estimates, and confounding variables accounted for in the analysis. We selected the most fully adjusted model for studies reporting multiple renal cell carcinoma risk estimates to minimize potential confounding effects. Study quality was assessed using the Newcastle-Ottawa Scale for cohort and case-control studies.⁹ For case-control studies, we evaluated the adequacy of case definition, representativeness of cases, selection of controls, definition of controls, comparability of cases and controls, ascertainment of exposure, same method of ascertainment for cases and controls, and nonresponse rate. For cohort studies, we evaluated the representativeness of exposed cohort, selection of nonexposed cohort, ascertainment of exposure, outcome of interest not present at the start of the study, comparability of cohorts, assessment of outcome, follow-up duration, and adequacy of follow-up of cohorts.

Statistical analysis

A biostatistician performed a meta-analysis using a random-effects model with restricted maximum likelihood to calculate pooled risk ratios (RRs) and their corresponding 95% confidence intervals (CIs) for the association between kidney stones and renal cell carcinoma

risk. Random-effects models were selected *a priori* to account for anticipated heterogeneity among studies. The meta-analyses incorporated odds ratios, hazard ratios, and relative risks as approximations of each other based on the rare disease assumption. This approach is widely accepted in epidemiology research when the outcome is uncommon, as with kidney cancer.¹⁰⁻¹² Publication bias was investigated by visually examining funnel plots and using Egger's regression test. One-study removed sensitivity analyses were conducted to evaluate the influence of individual studies on the pooled risk estimates. Statistical heterogeneity was quantified using the I^2 statistic, with values of 25%, 50%, and 75% indicative of low, moderate, and high heterogeneity, respectively. Subgroup analyses were performed to examine potential sources of heterogeneity, including study design, geographic region, sex distribution, data source, type of control group, and publication year. All statistical tests were two-sided, with a significance threshold of $p < 0.05$. Analyses were performed using Stata version 18.5 (StataCorp, College Station, TX, USA).

RESULTS

The systematic search yielded 875 potentially relevant articles. Following the removal of duplicates and the screening of titles and abstracts, 127 full-text articles were assessed for eligibility. Ultimately, 13 studies met the inclusion criteria and were included in the meta-analysis.¹³⁻²⁵ The PRISMA flow diagram illustrating the study identification and selection process is presented in Supplement Figure 1. Ten studies^{14, 16-21, 23-25} included individual controls while three studies^{13, 15, 22} used population-based controls to compare kidney cancer cases to expected rates in the general population. The study participants were predominantly male, ranging from 48% to 68% across studies, with mean ages ranging from 49 to 65 years. The meta-analysis included five cohort and eight case-control studies conducted across eight countries in Asia, Europe, North America, and Australia (Table 1). Ten studies were deemed low risk of bias, three had an intermediate risk, and none had a high risk. Retrospective patient enrollment and inadequate statistical adjustment for baseline comorbidities were the most common bias sources (Supplement Table 2).

A history of kidney stones was statistically associated with an increased risk of kidney cancer in 11 of the 13 studies. The pooled RR in the meta-analysis was 2.36 (95% CI: 1.74, 2.98; $p < 0.001$), which indicates that a history of kidney stones was associated with approximately twice the risk of developing kidney cancer compared to those without kidney stones (Figure 1). The funnel plot demonstrated no asymmetry and Egger's test indicated no evidence of significant publication bias ($p = 0.22$). The one-study removed sensitivity analysis demonstrated that no single study significantly influenced the meta-analysis results, with the RR ranging from 2.18 to 2.49 (all $p < 0.001$) following the iterative removal of each study.

We identified significant heterogeneity among the included studies ($I^2 = 94\%$, $p < 0.001$). Subgroup analysis showed a consistently elevated risk of kidney cancer across all subgroups. Study characteristics including design, data sources, risk of bias, control group type, and sex did not significantly influence the observed association between kidney stones and kidney cancer

risk. Notably, the association between kidney stones and kidney cancer risk was significantly stronger in more recent studies compared to older studies (RR=3.08 vs. 1.35; $p<0.001$) (Table 2). Meta-regression corroborated this trend, demonstrating a significant association between publication year and the strength of the association between kidney stones and kidney cancer risk (Figure 2).

DISCUSSION

This systematic review and meta-analysis identified a significant association between a history of kidney stones and the risk of kidney cancer. Our findings indicate that individuals with a history of kidney stones have approximately twice the risk of developing kidney cancer compared to those without kidney stones. Our meta-analysis builds upon the work of Cheungpasitporn et al.⁸ by incorporating 13 studies compared to their 7, and yielding a higher pooled RR of 2.36 compared to their reported RR of 1.76. Cheungpasitporn et al. observed increased risk only in males, whereas our analysis demonstrated elevated cancer risk in both males and females. This discrepancy may be attributed to our increased statistical power from including more studies as well as the inclusion of more recent studies, which showed stronger associations between kidney stone history and kidney cancer risk. These results suggest that a history of kidney stones may serve as an important risk factor for kidney cancer, potentially warranting increased clinical vigilance in affected patients.

Our findings align with other reviews that have reported an increased risk of various cancers in patients with kidney stones, with a particularly elevated risk for urinary tract malignancies.¹⁵ Notably, Yu et al.²⁶ noted almost twice the risk of bladder cancer in individuals with a history of kidney stones (odds ratio=1.87, $p<0.001$). Additionally, kidney stones have been associated with upper tract urothelial carcinomas.²⁷ Theories have been proposed which suggest dual mechanisms of cancer promotion in stone formers. First, the higher risk of bladder cancers and upper tract urothelial carcinomas suggests a localized effect. This local mechanism may involve chronic inflammation, irritation, and cellular damage caused by stone formation and passage, creating a microenvironment conducive to cancer development within the urinary tract. The chronic inflammatory state may be further exacerbated by recurrent urinary tract infections, which are common in stone formers. However, the biological mechanism leading to an increased risk of renal cell carcinoma is less clear. It has been suggested that systemic factors such as shared metabolic abnormalities or environmental exposures may contribute to both stone formation and carcinogenesis.²⁸ Notably, we found comparable cancer risk between men and women despite the higher prevalence of kidney stones and kidney cancer in males,¹⁴ suggesting that the underlying mechanisms may be independent of sex-specific factors.

Our analysis identified a stronger association between kidney stones and kidney cancer risk in more recent publications. We hypothesize that this temporal trend may reflect changes in diagnostic practices, particularly the widespread adoption of computed tomography (CT). Over the past two decades, CT has become the gold standard for diagnosing and monitoring kidney stones, replacing less sensitive imaging modalities. The high sensitivity of CT in detecting small

renal lesions may have led to increased incidental discovery of kidney cancers in stone formers. This hypothesis is supported by the fact that most kidney cancers are diagnosed incidentally, and actively surveilled kidney stone patients undergo CT scans 10 times more frequently than those without stones.²⁹ Hemminki and colleagues¹⁵ also reported smaller tumor sizes in patients with kidney stones, supporting this surveillance bias hypothesis. Consequently, the observed strengthening of the association between kidney stones and kidney cancer risk over time may reflect enhanced detection capabilities rather than a true increase in cancer risk among stone formers. Another possible explanation is cumulative radiation exposure from diagnostic imaging. Because ionizing radiation is a well-recognized carcinogen, increased exposure from repeated CT scans may partially account for the higher observed risk of kidney cancer. These hypotheses warrants further investigation to separate the contributions of diagnostic imaging from potential underlying biological mechanisms.

The clinical implications of this meta-analysis are significant. The increased risk of kidney cancer in patients with a history of kidney stones suggests the potential benefit of enhanced surveillance protocols for this population. While current guidelines do not advocate routine screening for kidney cancer in the general public,³⁰ targeted screening of high-risk groups, including stone formers, may be justified. Moreover, the association between kidney stones and kidney cancer highlights the importance of kidney stone prevention and management strategies. The shared risk factors between these conditions such as obesity, smoking, and certain dietary habits²⁸ suggest that interventions targeting these conditions could potentially reduce the risk of both conditions simultaneously. Healthcare providers should consider informing patients with kidney stones about their potentially increased kidney cancer risk and emphasize the importance of consistent follow-up care and lifestyle modifications. This approach could potentially improve patient engagement in long-term urological health management and overall health outcomes.

Limitations

Several limitations of this meta-analysis warrant consideration. First, the observational nature of the included studies limited our ability to establish a causal relationship between kidney stones and kidney cancer. Second, the high heterogeneity among studies was only partially explained by the temporal trends in risk estimates. However, the consistent direction of effects across various populations and study methodologies demonstrates the robustness of the association between kidney stones and kidney cancer. Third, while several studies adjusted their results for specific covariates, residual confounding cannot be ruled out, particularly regarding factors such as dietary habits or genetic predisposition that may influence both kidney stone formation and kidney cancer development. Finally, the observed temporal trend of increasing relative risks of kidney cancer associated with kidney stones remains incompletely explained and warrants further investigation to identify contributing factors such as improved detection with CT and distinguish between actual risk increase and enhanced diagnostic capabilities.

CONCLUSIONS

This meta-analysis demonstrates a significant association between kidney stones and increased risk of kidney cancer, with affected individuals having approximately twice the risk of developing kidney cancer. These findings highlight the importance of enhanced cancer surveillance in patients with a history of kidney stones and suggest the need for further research into shared pathophysiological mechanisms and potential preventative strategies.

DRAFT

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Conflict of interest

Dr. Bhojani reports consultancy with Boston Scientific. Dr. Miller reports consultancy with Boston Scientific. Dr. Bhattacharyya reports employment with Boston Scientific. Dr. Chew reports consultancy with Boston Scientific.

FIGURES AND TABLES

Figure 1. Forest plot of the risk of kidney cancer in adults with a history of kidney stones. The odds ratio (OR) and 95% confidence interval (CI) are plotted for each study. The pooled risk ratio (diamond apex) and 95% CI (diamond width) are calculated using a random effects model.

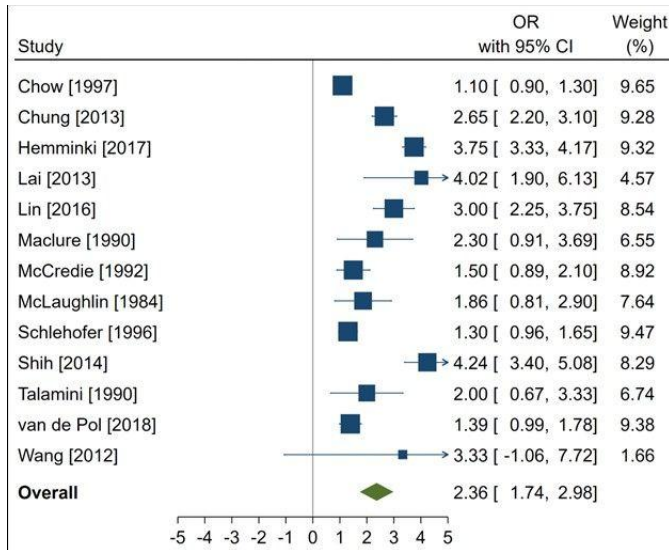


Figure 2. Meta-regression of the relationship between the publication year of each study and the risk of kidney cancer in patients with kidney stones. Markers are proportional to the weight of each study in the meta-analysis. logRR: log risk ratio.

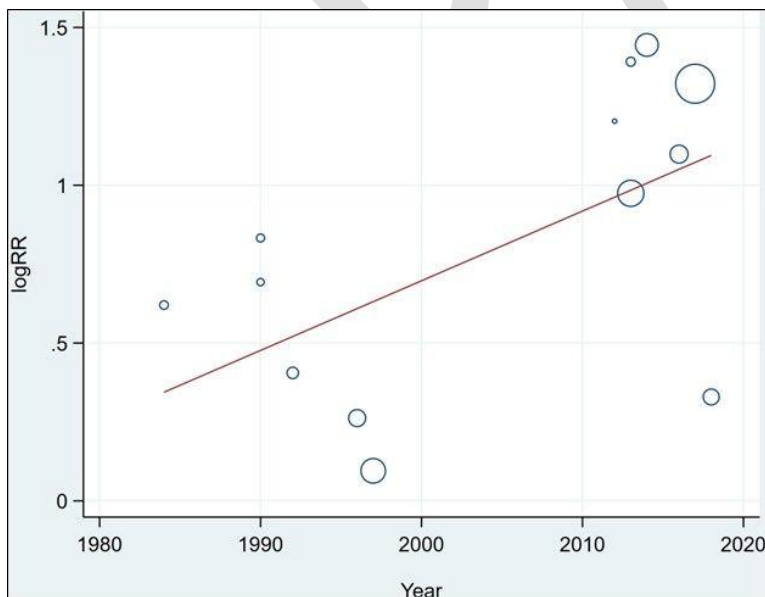


Table 1. Study and patient characteristics								
Study	Design	Country	Cases	Controls	Male sex	Mean age	Data source	Confounder adjustments
Chow, 1997 ¹³	Retrospective cohort	Sweden	61 144	Population	68%	65	Diagnosis codes	None
Chung, 2013 ¹⁴	Case-control	Taiwan	1308	6540	52%	65	Diagnosis codes	HTN, DM, CKD, obesity, smoking, alcohol, geography, income
Hemminki, 2017 ¹⁵	Retrospective cohort	Sweden	211 718	Population	¾	¾	Diagnosis codes	None
Lai, 2013 ¹⁶	Case-control	Taiwan	116	464	59%	62	Diagnosis codes	Age, sex, DM, HTN, kidney infection, CKD, cystic kidney disease,
Lin, 2016 ¹⁷	Retrospective cohort	Taiwan	2652	253,740	65%	[58]	Diagnosis codes	Age, sex, DM, coronary heart disease, CKD, tobacco use, obesity, alcohol, hydronephrosis, urinary stricture, interstitial cystitis, schistosomiasis, urinary tract infection, geography, urbanization, income, occupation

Maclure, 1990 ¹⁸	Case-control	U.S.	203	227	68%	[65]	Medical records	Cardiovascular disease, income, education, occupation
McCredie, 1992 ¹⁹	Case-control	Australia	636	523	52%	¾	Diagnosis codes	Age, sex, smoking, method of interview
McLaughli, 1984 ²⁰	Case-control	U.S.	495	697	62%	[65]	Medical records	Age, smoking
Schlehofer, 1996 ²¹	Case-control	Australia Denmark Sweden, U.S.	1732	2309	61%	¾	Diagnosis codes	Age, sex, BMI, smoking
Shih, 2014 ²²	Retrospective cohort	Taiwan	106	Population	65%	49	Diagnosis codes	None
Talamini, 1990 ²³	Case-control	Italy	240	665	66%	58	Diagnosis codes	Age, sex, education, geography
van de Pol, 2018 ²⁴	Prospective cohort	Netherlands	544	3808	48%	62	Medical records	Age, BMI
Wang, 2012 ²⁵	Case-control	China	250	299	60%	[54]	Medical records	Age, sex

BMI: body mass index; CKD: chronic kidney disease; DM: diabetes mellitus; HTN: hypertension.

Table 2. Subgroup analysis of patient and study-related factors on the risk of kidney cancer in patients with kidney stones

Variable	Subgroup	Risk ratio	95% CI	p (within-group)	p (between-group)
Publication year	1984–1997	1.35	1.07, 1.63	<0.001	<0.001
	2013–2018	3.08	2.22, 3.94	<0.001	
Data source	Medical records	1.61	1.11, 2.11	<0.001	0.054
	Diagnosis codes	2.53	1.74, 3.33	<0.001	
Control group	Individual	2.06	1.56, 2.56	<0.001	0.35
	Population	3.00	1.08, 4.93	<0.001	
Study design	Case-control	2.02	1.48, 2.56	<0.001	0.35
	Cohort	2.67	1.43, 3.90	<0.001	
Risk of bias	Low	2.06	1.56, 2.56	<0.001	0.35
	Intermediate	3.00	1.08, 4.93	<0.001	
Male sex	≤61%	1.92	1.23, 2.60	<0.001	0.41
	>62%	2.41	1.46, 3.35	<0.001	