



Does inflammatory bowel disease increase the risk of lower urinary tract tumors: a meta-analysis

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Background: Inflammatory bowel disease, including ulcerative colitis and Crohn's disease, is characterized by chronic inflammation that could be a risk factor for extraintestinal cancer. The aim of this study is to evaluate whether inflammatory bowel disease is related to the risk of lower urinary tract tumors.

Methods: A systematical research was performed on various medical databases including PubMed, the Cochrane Library, Embase and Web of Science from inception to April 2020. Data were independently extracted by two reviewers. The Newcastle-Ottawa Scale and the Oxford Centre for Evidence-Based Medicine criteria were used to assess the quality of included articles. The analysis was completed by STATA version 14.2.

Results: Six hundred and twelve of records were initially identified and 16 studies were included in the final analysis. In general, inflammatory bowel disease patients were not at increased risk of prostate cancer, bladder cancer and male genital cancer. In the subgroup analysis, Crohn's disease patients seemed to have borderline increased risk of prostate cancer [standardized incidence ratio: 1.05; 95% confidence interval (CI): 0.90–1.21; $I^2=15.1\%$] and bladder cancer (standardized incidence ratio: 1.19; 95% CI: 0.94–1.44; $I^2=0.0\%$), and ulcerative colitis patients seemed to have borderline increased risk of prostate cancer (standardized incidence ratio: 1.13; 95% CI: 0.93–1.33; $I^2=73.5\%$).

Conclusions: Inflammatory bowel disease did not significantly increase the risk of prostate cancer, bladder cancer and male genital cancer. Crohn's disease patients seemed to have a higher risk of prostate cancer and bladder cancer, and ulcerative colitis patients seemed to have a higher risk of prostate cancer. ulcerative colitis patients in East Asian countries have significantly increased prostate cancer risk.

Keywords: Inflammatory bowel disease (IBD); Crohn's disease; prostate cancer (PCa); bladder cancer (BCa); male genital cancer (MGCa)

Submitted Jun 20, 2020. Accepted for publication Oct 16, 2020.

doi: 10.21037/tau-20-1020

View this article at: <http://dx.doi.org/10.21037/tau-20-1020>

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Introduction

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), is characterized by chronic gastrointestinal tract inflammation. In the past decades, a significantly increased incidence of IBD has been observed worldwide, especially in eastern countries (1). IBD has been a great health burden to the society for its high morbidity and tight association with gastrointestinal malignancy (2-4), as well as numerous extraintestinal malignancies (5,6).

Though mechanism underlying IBD and oncogenesis has not been clearly elucidated, it was reported that inflammation not only serves as host's response to malignant tumor but also elicit carcinogenesis (7,8). Moreover, immunosuppressant medications, which are widely used for IBD treatment, are believed to be responsible for elevated risk of cancers like non-Hodgkin lymphoma, acute myeloid leukemia, non-melanoma skin cancers and urinary tract cancers (9-12). From these knowledges, a concept about the interplay between IBD and malignancy could be established, which depicts the inflammation induced immune dysregulation and immunosuppressant medications use as key factors in IBD related malignancies. However, this indirect evidence-based hypothesis may not apply to all kinds of malignant tumors, especially extraintestinal tumors. Direct evidence from studies evaluating the association between certain malignancy and IBD could be of great value in prognosis predicting and providing guidance for cancer surveillance. To our knowledge, no meta-analysis has been performed to evaluating the risk of bladder cancer (BCa) or male genital cancer (MGCa) in IBD patients. A recent study reported an increased risk of prostate cancer (PCa) in IBD patients (13). With the aim of evaluating the risk of lower urinary tract cancers including PCa, BCa and MGCa in IBD patients, we performed this meta-analysis. We presented the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/tau-20-1020>).

Methods

Search strategy

We conducted this meta-analysis according to the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (14). Electronic databases including PubMed, the Cochrane Library,

Embase and Web of Science was initially searched from inception to April 2020 with no language limitation. We used the following Medical Subject Heading (MeSH) terms and related synonyms: "Inflammatory Bowel Diseases", "Urinary Bladder Neoplasms", "Prostatic Neoplasms", and "Genital Neoplasms, Male". The complete search strategy was described in the [Supplementary file](#). We scrutinized all potentially eligible studies, regardless of the primary outcomes or language. Besides, references from related articles were also retrieved manually to ensure a comprehensive search.

Study selection

Studies were regarded as eligible if they satisfied the following inclusion criteria: (I) patients developed with BCa, PCa, or MGCa after being diagnosed with IBD, irrespective of UC or CD; (II) standardized incidence ratio (SIR) or relative risk (RR) with 95% confidence intervals (CIs) were used to evaluate the association between IBD and risk of lower urinary tract tumors (BCa, PCa or MGCa); (III) population-based cohort studies or case-control studies; (IV) the follow-up of included studies should be more than 1 year. If the study population overlapped, we used the most recently published or most informative literature. Exclusion criteria were as follows: (I) any study which did not meet the inclusion criteria; (II) meeting abstracts, review or meta-analysis; (III) data not available. *Figure 1* sketches the PRISMA flow diagram of this meta-analysis.

Data extraction and quality assessment

Two independent authors screened the search results based on title, abstract, and, finally, full text. Disagreements were resolved by discussion or a third party. We prospectively developed a homogeneous form to extract data. Data were independently extracted by two reviewers. The following data were extracted: the first author's name, year of publication, country, study design, period, sample size, cancer types, outcomes (SIRs or RRs).

Two authors independently evaluated the methodological bias of included studies through the Newcastle-Ottawa Scale (NOS) (15). The NOS used a "star system" to assess the quality of study from three perspectives: the selection of the studies, the comparability of studies, and the assessment of outcome. Whenever seven or more of nine stars were received, the study was considered as high quality.

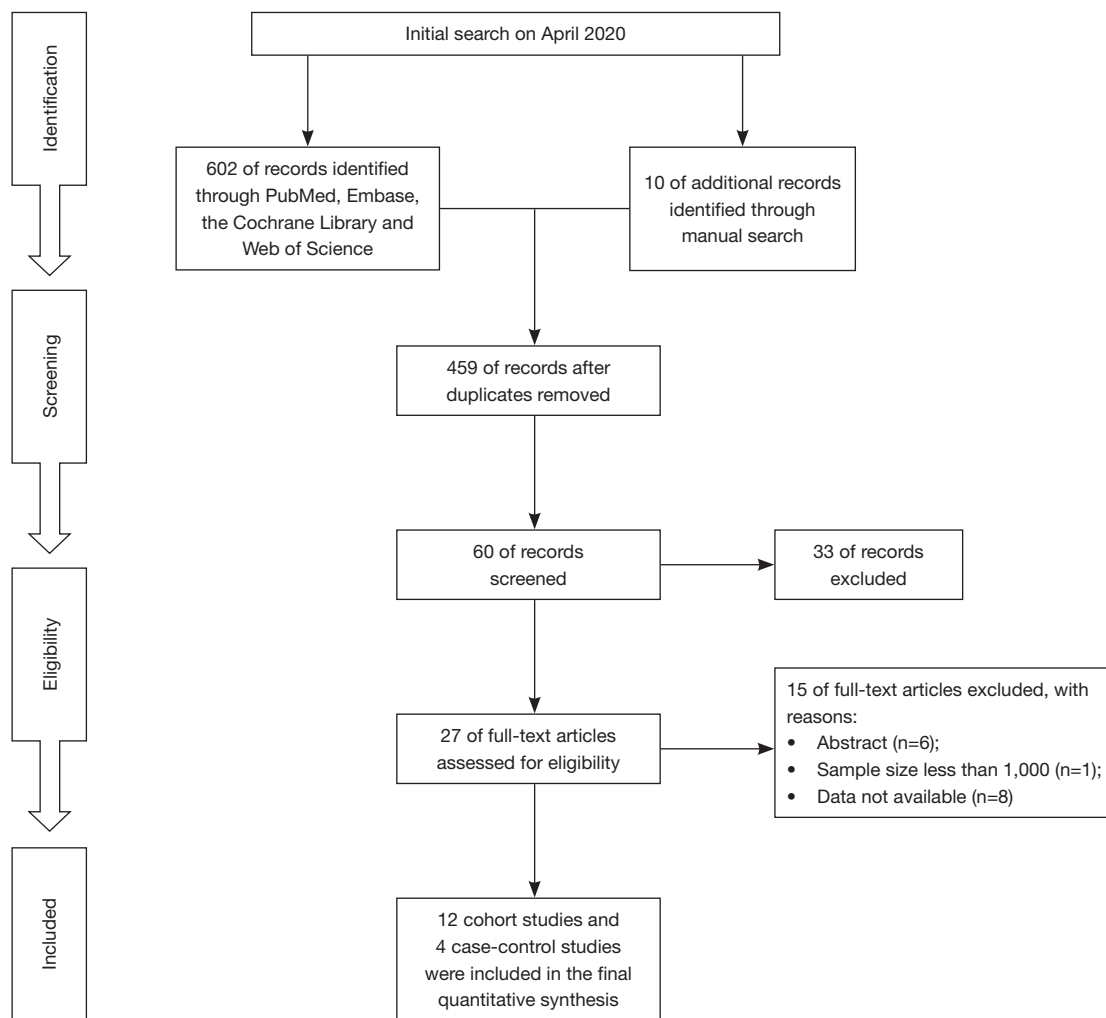


Figure 1 The PRISMA flowchart showing the study selection process of this meta-analysis.

Moreover, two reviewers independently rated the level of evidence of the included articles using the Oxford Centre for Evidence-Based Medicine criteria (16); This scale graded studies from strongest (level 1) to weakest (level 5) strength of evidence on the basis of study design and data quality.

Statistical analysis

Data were expressed as SIR or RR with 95% CIs. The Q and I^2 statistics were calculated to estimate the heterogeneity among studies. If $P > 0.1$ or $I^2 \leq 50\%$, we used the fixed-effect models. Otherwise, a random-effect model was used. Besides, we reported the pooled analysis

according to the cancer types and IBD subtype. Funnel plots were used to assess the possibility of publication bias, and the asymmetry of funnel plots was evaluated by Egger's test and Begg's test; We considered significant publication bias as a p value less than 0.1. Furthermore, we conducted sensitivity analyses to evaluate the robustness of the pooled results. Statistical significance was set at $P < 0.05$. This meta-analysis was completed by STATA version 14.2 (StataCorp LP, College Station, TX, USA).

Results

Search results

Six hundred and twelve of records were initially identified

through PubMed, Embase, the Cochrane Library and Web of Science from inception to April 2020, resulting 12 cohort studies (12,17-27) and 4 case-control (28-31) studies included in the final analysis based on title, abstract, and full text (Figure 1). A total of 511,259 participants were included in this population-based study. In the cohort studies, 10 of 12 studies with 174,094 patients reported available data for PCa, 9 of 12 studies with 136,502 patients were available for BCa and 6 of 12 studies were available for MGCa. In the case-control studies, a total of 4 studies containing 335,167 participants reported related outcomes of PCa, and 2 of 4 studies with 285,534 participants were available for BCa. Table 1 details the main characteristics of included studies in this study.

Meta-analysis results

PCa

For cohort studies, the risk of PCa in patients with IBD were of borderline significant increase (SIR: 1.09; 95% CI: 0.95–1.22; $I^2=61.2\%$; Figure 2) when compared with the background population, as was the risk of subgroup of UC (SIR: 1.13; 95% CI: 0.93–1.33; $I^2=73.5\%$; Figure 2) and CD (SIR: 1.05; 95% CI: 0.90–1.21; $I^2=15.1\%$; Figure 2). For case-control studies, the results indicated that there was no significant difference between IBD group and IBD-free group regarding the risk of PCa (RR: 1.70; 95% CI: 0.87–3.33; Figure 2) with great between-study heterogeneity ($I^2=93.5\%$; $P=0.000$; Figure 2). Subgroup analysis revealed that IBD patients in Eastern countries have significantly increased PCa risk (SIR: 2.62; 95% CI: 1.38–3.87; $I^2=13.6\%$; Figure 3), especially for UC patients (SIR: 3.01; 95% CI: 1.75–4.27; $I^2=0.0\%$; Figure 3).

BCa

For cohort studies, no significantly decreased risk of BCa was observed in patients with IBD (SIR: 0.99; 95% CI: 0.87–1.12; $I^2=0.0\%$; Figure 2) and UC subgroup (SIR: 0.92; 95% CI: 0.77–1.06; $I^2=0.0\%$; Figure 2), whereas a trend toward an increased risk of BCa was detected in patients with CD subgroup (SIR: 1.19; 95% CI: 0.94–1.44; $I^2=0.0\%$; Figure 2). Only two case-control studies provided data on BCa in UC and CD combined, revealing that IBD patients seemed to have a higher risk of BCa than IBD-free patients (RR: 1.25; 95% CI: 0.68–2.31; $I^2=37.5\%$; Figure 2).

MGCa

Data from six cohort studies (17,18,21,22,24,26) showed

that IBD or IBD subtype (UC and CD) did not significantly increase the risk of MGCa. The pooled SIRs were 1.30, 1.20 and 1.29 for IBD, UC and CD, respectively (Figure 2).

Publication bias and sensitivity analysis

No significant asymmetry was observed in the present study in terms of PCa and BCa through the corresponding funnel plots (Figure 4). The P values of Egger's test for PCa, BCa and MGCa were 0.234, 0.194 and 0.276, respectively. Furthermore, sensitivity analysis revealed that there was no significant change of the pooled results for all outcomes observed through excluding each study from the meta-analysis sequentially (Figure 4).

Discussion

In this study, we found there was no significant difference between IBD patients and background population regarding the risk of PCa, BCa or MGCa. However, a trend toward higher risk of PCa was suggested in patients with IBD, CD, and UC. For BCa, CD patients seemed to have a higher risk. As was previously reported, lower incidence rate of PCa was observed in East Asian countries when compared with that in other regions (32), we performed a subgroup analysis to evaluate the risk of IBD related PCa in East Asian countries. Different from the general results above, a significantly increased risk of PCa in East Asian IBD patients was detected (SIR: 2.62; 95% CI: 1.38–3.87; $I^2=13.6\%$; Figure 3), especially for UC patients (SIR: 3.01; 95% CI: 1.75–4.27; $I^2=0.0\%$; Figure 3).

Great improvement has been made in understanding the interaction between inflammation and carcinogenesis. Current knowledge about the mechanism underlying inflammation related carcinogenesis mainly depicts inflammation induced epigenetic alterations and DNA damage as the key factors in carcinogenesis (33). IBD related malignancy has been the hot point for researchers in the past decades and agreement has been achieved on the increased risk of IBD related colorectal cancer (34). As discussed above, it is widely accepted that the chronic local inflammation in bowel is involved in the carcinogenesis of colorectal cancer (35). For extraintestinal cancers, previous epidemiological studies revealed a tight association between IBD and increased risk of numerous cancers like hematologic cancer, lung cancer and non-Hodgkin lymphoma (26,36). However, studies about the association between IBD and lower urinary tract cancers including

Table 1 the main characteristics of included studies in this meta-analysis

Study	Country	Design	Period	Population	Cancer type	Outcomes	NOS	LoE
Hemminki <i>et al.</i> 2009	Sweden	Cohort	1964–2004	21,788 CD	BCa, PCa and MGCa	SIR	9	2b
Jung <i>et al.</i> 2017	Korea	Cohort	2011–2014	5,825 UC and 3,918 CD	BCa and PCa	SIR	8	2b
Jussila <i>et al.</i> 2013	Finland	Cohort	2000–2010	16,649 UC and 5,315 CD	BCa and PCa	SIR	7	2b
Kappelman <i>et al.</i> 2014	Denmark	Cohort	1978–2010	13,756 CD and 35,152 UC	BCa and PCa	SIR	9	2b
Loo <i>et al.</i> 2019	Canada	Cohort	1998–2015	20,644 CD, 14,000 UC and 1,341 unspecified	PCa	SIR	9	2b
Ekbohm <i>et al.</i> 1991	Sweden	Cohort	1965–1983	1,655 CD and 3,121 UC	BCa, PCa and MGCa	SIR	7	2b
Hemminki <i>et al.</i> 2008	Sweden	Cohort	1964–2004	27,606 UC	BCa, PCa and MGCa	SIR	9	2b
Jess <i>et al.</i> 2013	Denmark	Cohort	1978–2010	1,515 UC and 810 CD	MGCa and PCa	SIR	8	2b
So <i>et al.</i> 2017	China	Cohort	1990–2016	1,603 UC and 1,018 CD	PCa	SIR	7	2b
Karlén <i>et al.</i> 1999	Sweden	Cohort	1955–1989	1,547 UC	BCa, PCa and MGCa	SIR	8	2b
Bourrier <i>et al.</i> 2016	France	Cohort	2004–2005	11,759 CD and 7,727 UC	BCa	SIR	9	2b
Persson <i>et al.</i> 1994	Sweden	Cohort	1955–1989	1,251 CD	BCa and MGCa	SIR	7	2b
Mosher <i>et al.</i> 2018	USA	Case-control	1996–2015	2,080 IBD and 271,898 IBD-free	BCa and PCa	RR	7	3b
Wilson <i>et al.</i> 2016	UK	Case-control	1995–2012	19,647 IBD and 19,647 IBD-free	PCa	HR	8	3b
Burns <i>et al.</i> 2019	USA	Case-control	1996–2017	1,033 IBD and 9,306 IBD-free	PCa	HR	9	3b
Bernstein <i>et al.</i> 2001	Canada	Case-control	1984–1997	6,027 IBD and 5,529 IBD-free	BCa	IRR	9	3b

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; BCa, bladder cancer; PCa, prostate cancer; MGCa, male genital cancer; SIR, standardized incidence ratio; RR, relative risk; HR, hazard ratio; IRR, incidence rate ratio; NOS, Newcastle-Ottawa Scale; LoE, level of evidence.

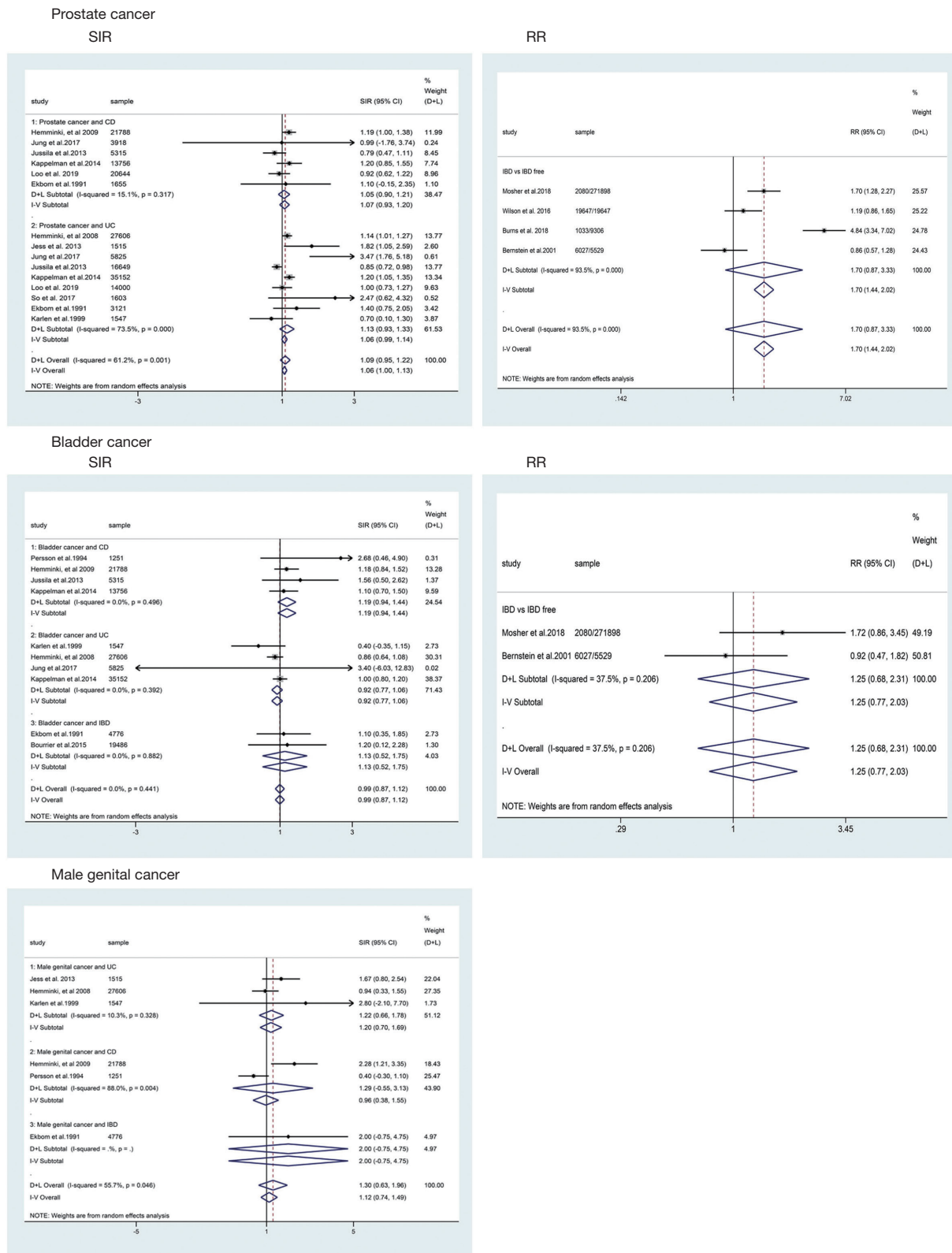


Figure 2 The pooled results of this meta-analysis. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; SIR, standardized incidence ratio; RR, relative risk; CI, confidence interval; D+L, DerSimonian-Laird; I-V, inverse-variance.

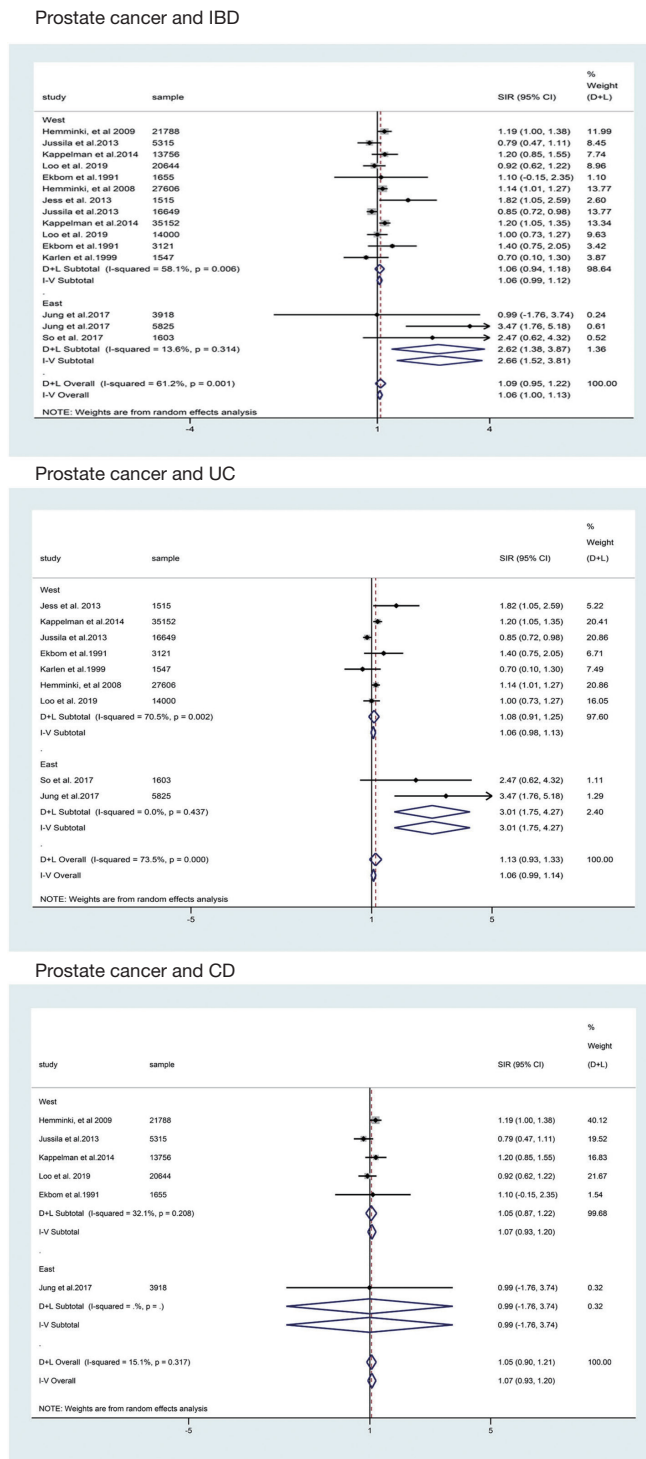


Figure 3 The funnel plots and sensitivity analyses of outcomes in this meta-analysis. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn’s disease; SIR, standardized incidence ratio; CI, confidence interval; D+L, DerSimonian-Laird; I-V, inverse-variance.

BCa and MGCa are limited and no conclusive results are available. A previous meta-analysis evaluating the risk of extraintestinal cancers in IBD patients reported an increased risk of BCa (6). However, only 2 eligible studies were included in their pool analysis for risk of BCa, which could weaken the strength of their conclusion. For the risk of PCa in IBD patients, controversies still remain. Some studies reported that there was an association between increased risk of PCa and IBD (23,26,31). In contrast, in a previous meta-analysis of population-based studies, they found there was no increased incidence of PCa among IBD patients (6).

Though mechanism underlying increased risk of PCa among IBD patients in East Asian countries remains elusive, the findings of our study could still be of value in providing guidance for PCa surveillance in IBD patients, especially for those in East Asian countries. Meanwhile, as the risk of BCa was not statistically different between IBD patients and background population, we detected from the results a trend toward higher risk in IBD group. We believed that this might be due to the lack of data from Eastern countries in the included studies. These findings could be inconsistent with previous meta-analysis (6) and more qualitative studies are needed to yield a conclusive result in the future. Besides, although chronic inflammation was thought to be an important risk factor for extraintestinal cancer in IBD patients, mechanism for IBD related colorectal cancer and extraintestinal cancer might be different. Instead, immunosuppression medications that are widely used for IBD treatment have been demonstrated to be related to increased risk of numerous malignancies including non-Hodgkin lymphoma, acute myeloid leukemia and myelodysplastic syndromes, non-melanoma skin cancers and urinary tract cancers (9-12). Concerned the large range of immunosuppression agents currently available for IBD treatment and insufficient data from studies evaluating their effect on carcinogenesis in IBD patients, we were unable to perform a subgroup analysis to evaluate the effect of immunosuppression agents on the risk of cancer in IBD. Future studies conducted on this topic could be of great value in providing guidance in immunosuppression agent option for IBD treatment.

Conclusions

IBD did not significantly increase the risk of PCa, BCa and MGCa. CD patients seemed to have a higher risk of PCa and BCa, and UC patients seemed to have a higher risk of PCa. However, IBD patients, especially for UC patients, in

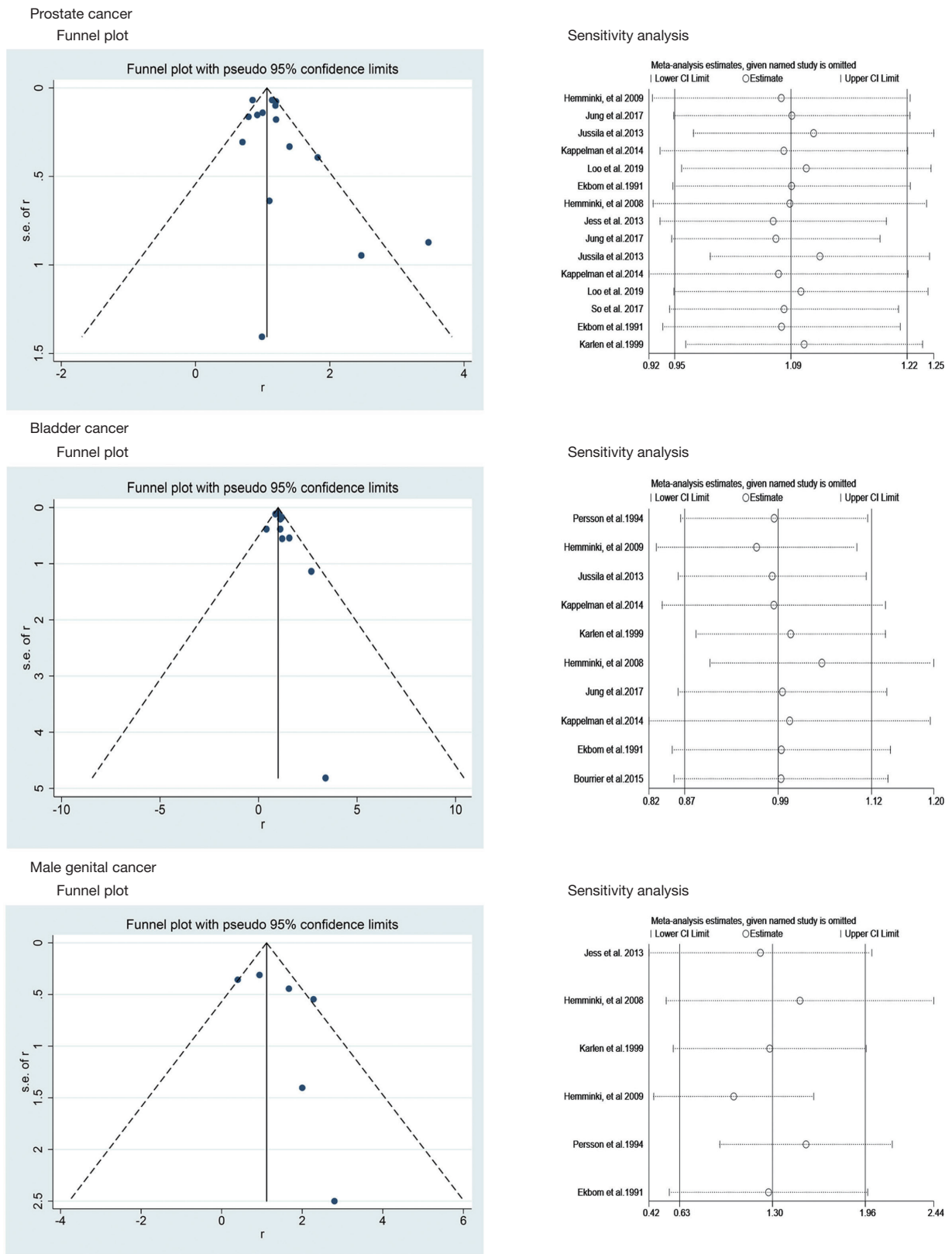


Figure 4 The subgroup analysis of prostate cancer according to geographical region. CI, confidence interval.

Eastern countries have significantly increased PCa risk.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <http://dx.doi.org/10.21037/tau-20-1020>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tau-20-1020>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Zhang C, Liu S, Peng L, Wu J, Zeng X, Lu Y, Shen H, Luo D. Does inflammatory bowel disease increase the risk of lower urinary tract tumors: a meta-analysis. *Transl Androl Urol* 2021;10(1):164-173. doi: 10.21037/tau-20-1020

Inflammatory bowel diseases and bladder cancer

PubMed

(((((Inflammatory Bowel Diseases[Title/Abstract] OR Inflammatory Bowel Disease[Title/Abstract]) OR Bowel Diseases, Inflammatory[Title/Abstract])) AND (((((((((((((((Urinary Bladder Neoplasms[Title/Abstract] OR Neoplasm, Urinary Bladder[Title/Abstract] OR Urinary Bladder Neoplasm[Title/Abstract] OR Neoplasms, Bladder[Title/Abstract] OR Bladder Neoplasms[Title/Abstract] OR Bladder Neoplasm[Title/Abstract] OR Neoplasm, Bladder[Title/Abstract] OR Bladder Tumors[Title/Abstract] OR Bladder Tumor[Title/Abstract] OR Tumor, Bladder[Title/Abstract] OR Tumors, Bladder[Title/Abstract] OR Urinary Bladder Cancer[Title/Abstract] OR Cancer, Urinary Bladder[Title/Abstract] OR Malignant Tumor of Urinary Bladder[Title/Abstract] OR Cancer of the Bladder[Title/Abstract] OR Bladder Cancer[Title/Abstract] OR Bladder Cancers[Title/Abstract] OR Cancer, Bladder[Title/Abstract] OR Cancer of Bladder[Title/Abstract]))))))))))))

44 records

Web of Science

#1 TOPIC: (Inflammatory Bowel Diseases) OR TOPIC: (Inflammatory Bowel Disease) OR TOPIC: (Bowel Diseases, Inflammatory)

#2 TOPIC: (Urinary Bladder Neoplasms) OR TOPIC: (Neoplasm, Urinary Bladder) OR TOPIC: (Urinary Bladder Neoplasm) OR TOPIC: (Neoplasms, Bladder) OR TOPIC: (Bladder Neoplasms) OR TOPIC: (Bladder Neoplasm) OR TOPIC: (Neoplasm, Bladder) OR TOPIC: (Bladder Tumors) OR TOPIC: (Bladder Tumor) OR TOPIC: (Tumor, Bladder) OR TOPIC: (Tumors, Bladder) OR TOPIC: (Urinary Bladder Cancer) OR TOPIC: (Cancer, Urinary Bladder) OR TOPIC: (Malignant Tumor of Urinary Bladder) OR TOPIC: (Cancer of the Bladder) OR TOPIC: (Bladder Cancer) OR TOPIC: (Bladder Cancers) OR TOPIC: (Cancer, Bladder) OR TOPIC: (Cancer of Bladder)

#3 #1 and #2 115 records

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#1 (Inflammatory Bowel Diseases or Inflammatory Bowel Disease or Bowel Diseases, Inflammatory).kw.

#2 (Urinary Bladder Neoplasms or Neoplasm, Urinary Bladder or Urinary Bladder Neoplasm or Neoplasms, Bladder or Bladder Neoplasms or Bladder Neoplasm or Neoplasm, Bladder or Bladder Tumors or Bladder Tumor or Tumor, Bladder or Tumors, Bladder or Urinary Bladder Cancer or Cancer, Urinary Bladder or Malignant Tumor of Urinary Bladder or Cancer of the Bladder or Bladder Cancer or Bladder Cancers or Cancer, Bladder or Cancer of Bladder).kw.

#3 #1 and #2 3 records

Inflammatory bowel diseases and prostate cancer

PubMed

((((((((((((((((((Prostatic Neoplasms[Title/Abstract] OR Prostate Neoplasms[Title/Abstract] OR Neoplasms, Prostate[Title/Abstract] OR Neoplasm, Prostate[Title/Abstract] OR Prostate Neoplasm[Title/Abstract] OR Neoplasms, Prostatic[Title/Abstract] OR Neoplasm, Prostatic[Title/Abstract] OR Prostatic Neoplasm[Title/Abstract] OR Prostate Cancer[Title/Abstract] OR Cancer, Prostate[Title/Abstract] OR Cancers, Prostate[Title/Abstract] OR Prostate Cancers[Title/Abstract] OR Cancer of the Prostate[Title/Abstract] OR Prostatic Cancer[Title/Abstract] OR Cancer, Prostatic[Title/Abstract] OR Cancers, Prostatic[Title/Abstract] OR Prostatic Cancers[Title/Abstract] OR Cancer of Prostate[Title/Abstract])))))))))))) AND (((Inflammatory Bowel Diseases[Title/Abstract] OR Inflammatory Bowel Disease[Title/Abstract]) OR Bowel Diseases, Inflammatory[Title/Abstract])) 109 records

Web of Science

TOPIC: (((((((((((((((((((Prostatic Neoplasms) OR Prostate Neoplasms) OR Neoplasms, Prostate) OR Neoplasm, Prostate) OR Prostate Neoplasm) OR Neoplasms, Prostatic) OR Neoplasm, Prostatic) OR Prostatic Neoplasm) OR Prostate Cancer) OR Cancer, Prostate) OR Cancers, Prostate) OR Prostate Cancers) OR Cancer of the Prostate) OR Prostatic Cancer) OR Cancer, Prostatic) OR Cancers, Prostatic) OR Prostatic Cancers) OR Cancer of Prostate)) AND (((Inflammatory Bowel Diseases) OR Inflammatory Bowel Disease) OR Bowel Diseases, Inflammatory)) 305 records

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#1 (Prostatic Neoplasms or Prostate Neoplasms or Neoplasms, Prostate or Neoplasm, Prostate or Prostate Neoplasm or Neoplasms, Prostatic or Neoplasm, Prostatic or Prostatic Neoplasm or Prostate Cancer or Cancer, Prostate or Cancers, Prostate or Prostate Cancers or Cancer of the Prostate or Prostatic Cancer or Cancer, Prostatic or Cancers, Prostatic or Prostatic Cancers or Cancer of Prostate).kw.
#2 (Inflammatory Bowel Diseases or Inflammatory Bowel Disease or Bowel Diseases, Inflammatory).kw.
#3 1 and 2 22 records

Inflammatory bowel disease and male genital cancer

PubMed

((((((((Genital Neoplasms, Male[Title/Abstract]) OR Neoplasms, Male Genital[Title/Abstract]) OR Male Genital Neoplasms[Title/Abstract]) OR Genital Neoplasm, Male[Title/Abstract]) OR Male Genital Neoplasm[Title/Abstract]) OR Neoplasm, Male Genital[Title/Abstract])) AND (((Inflammatory Bowel Diseases[Title/Abstract]) OR Inflammatory Bowel Disease[Title/Abstract]) OR Bowel Diseases, Inflammatory[Title/Abstract]) 3 records

Web

((((((((Genital Neoplasms, Male) OR Neoplasms, Male Genital) OR Male Genital Neoplasms) OR Genital Neoplasm, Male) OR Male Genital Neoplasm) OR Neoplasm, Male Genital)) AND (((Inflammatory Bowel Diseases) OR Inflammatory Bowel Disease) OR Bowel Diseases, Inflammatory)) 1 records

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0 records