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Inflammatory Bowel Disease Patients' Risk of Developing Prostate Cancer: A Meta-Analysis

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Abstract: *Background:* Inflammatory bowel disease (IBD) has been linked to an increased risk of prostate cancer (PC) in numerous studies. However, the exact relationship between them remains conflicting. In this meta-analysis, we focus on determining the relationship between PC incidence and IBD. *Methods:* A comprehensive literature search was conducted up until January 2022, selecting 14 studies, comprising 127,323 subjects with IBD, at the beginning of the study, among which 61,985 were patients with ulcerative colitis (UC) and 37,802 were with Crohn's disease (CD). The studies reported the differences between subjects with IBD and controls with regard to the incidence of PC. In order to investigate the relationship between IBD and the prevalence of PC, we estimated the odds ratio (OR) with 95% confidence intervals (CIs). *Results:* IBD significantly increased the incidence of PC (OR, 3.46; 95% CI, 1.40–8.54, $P = 0.007$) compared to controls. UC significantly increased the incidence of PC (OR, 1.43; 95% CI, 1.03–1.98, $P = 0.03$) compared to controls. Yet, no significant difference was observed between CD and controls in relation to PC incidence (OR, 0.89; 95% CI, 0.75–1.06, $P = 0.18$). *Conclusion:* IBD, particularly UC, may increase the risk of developing PC. This relationship prompts us to advocate for increased PC and IBD screening to reduce the risk for possible complications that could occur in these subjects.

Keywords: Prostate cancer; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Retrospective study

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1. Background

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a prevalent chronic inflammatory disorder affecting the small intestine and colon [1]. About five million people in the world are suffering from IBD [2]. Also, according to a recent study, industrialized nations have greater incidence and occurrence rates of IBD [2], and nearly all of new IBD identifies are made in early life [2]. IBD is a difficult and costly disease to treat, posing a significant burden on the healthcare system [3]. Therefore, IBD has surfaced as a progressive global public health issue. Relapsing intestinal inflammation, which compromises the mucosal barrier's ability to mount an immunological defense, is a hallmark of IBD [3]. It has been reported that inflammation is a significant risk factor for the development of cancer [3]. IBD patients have a higher risk of developing gastrointestinal cancers, including colorectal cancer [4] and extraintestinal malignancies [5], such as lymphoma, prostate cancer (PC), and melanoma [6]. There has been extensive research on their risk of developing cancer [3]. However, there is inadequate evidence on PC risk for subjects with IBD [3]. The objective of this meta-analysis was to determine the correlation between PC incidence and IBD.

2. Methods

The present investigation adhered to the meta-analysis of studies in the epidemiology declaration [7] and was carried out in accordance with a predetermined procedure. An Institutional Review Board (IRB) approval was not needed for this work.

2.1. Study selection

Retrospective studies that analyzed the correlation between the prevalence of IBD and PC incidence were included. We considered only human studies in any language. There were no limitations to the type or size of studies that may be included. Studies that did not identify the strength of a connotation were all disregarded. **Figure 1** illustrates the entire course of the study.

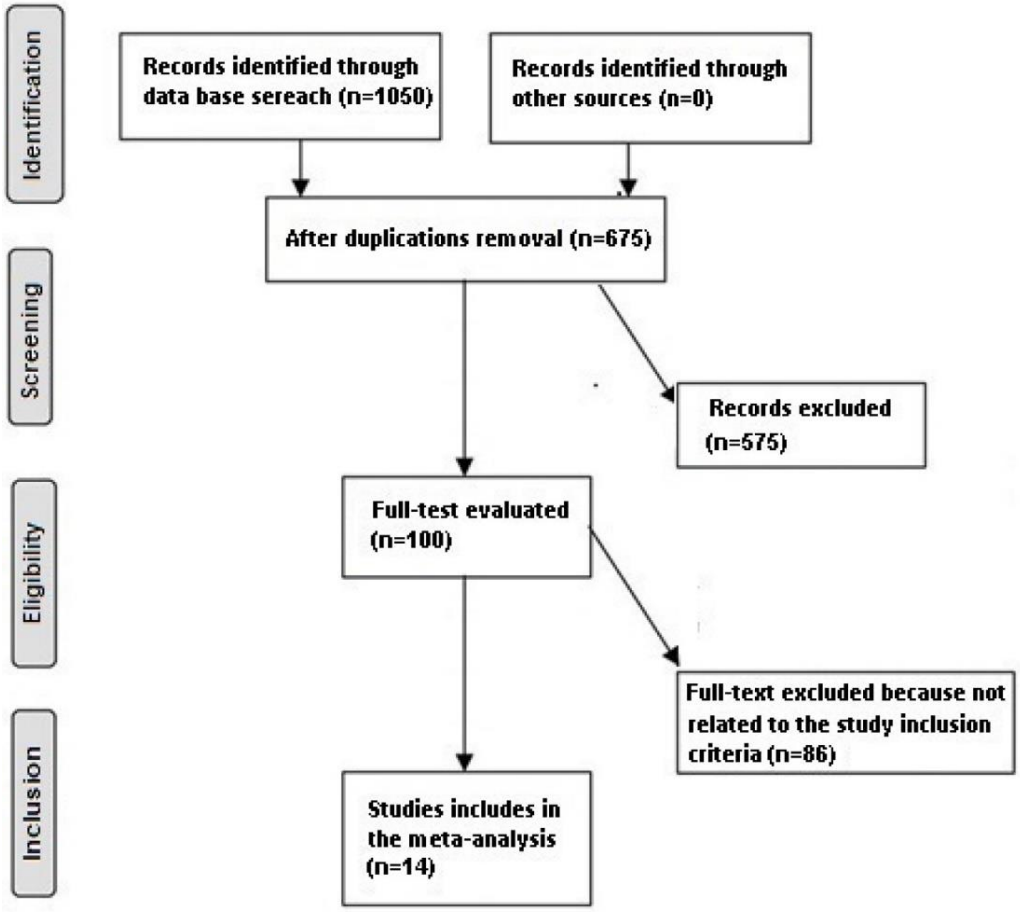

Figure 1. Schematic illustration of the study method

Articles were taken into consideration for meta-analysis when the following inclusion criteria were met: (i) the research was retrospective in nature; (ii) people with IBD in the target demographic; (iii) the intervention program was based on the correlation between the incidence of PC and IBD, UC, and CD; (iv) the study comprised findings from the control and IBD (UC and CD) groups.

2.2. Identification

On the basis of PICOS principle, a protocol for search plans was established [7]. Those with IBD make up the population (P); PC incidence is affected by the following factors: UC, CD, and IBD (I [intervention/exposure]); C (comparison): IBD (UC, CD, and control group results); O (outcome): PC occurs; S (study design): no limitations [8].

First, we conducted a systematic search of Google Scholar, OVID, Embase, PubMed, and Cochrane Library up until January 2022 using a combination of keywords and linked words for inflammatory bowel disease, ulcerative colitis, Crohn's disease, prostate cancer, and retrospective study, as in **Table 1**. A single EndNote file was created from all of the selected papers, duplicates were deleted, and studies that failed to find a link between IBD and the risk of developing PC were excluded.

Table 1. Search strategy for each database

Database	Search strategy
PubMed	#1 "inflammatory bowel disease" [MeSH Terms] OR "Ulcerative colitis" [All Fields] OR "Crohn's disease" [All Fields] OR "Prostate cancer" [All Fields] #2 "retrospective study" [MeSH Terms] OR "inflammatory bowel disease" [All Fields] #3 #1 AND #2
Embase	"inflammatory bowel disease"/exp OR "Ulcerative colitis"/exp OR "Crohn's disease"/exp OR "Prostate cancer" #2 "retrospective study"/exp #3 #1 AND #2
Cochrane library	(inflammatory bowel disease):ti,ab,kw (Ulcerative colitis):ti,ab,kw OR (Crohn's disease):ti,ab,kw (word variations have been searched) #2 (Prostate cancer):ti,ab,kw OR (retrospective study):ti,ab,kw (word variations have been searched) #3 #1 AND #2

2.3. Screening

Data were condensed into a standardized form, founded on subject and study connections: first author's last name, duration of study, year of publication, country, scope of study, population, number of participants, demographic information, management and clinical characteristics, classifications, qualitative and quantitative assessment methods, source of the data, result evaluation, and statistical analysis [9]. According to the aforementioned criteria, data were extracted independently by two authors if a study was deemed appropriate for inclusion. With any disagreements, the corresponding author made the final decision. In order to estimate the risk of bias in each study, the methodological quality of the selected studies was evaluated independently by two authors using RoB 2 (a revised Cochrane risk-of-bias tool for randomized trials) [10].

2.4. Eligibility

The major finding was centered on a summary of the evaluation of the relationship between the incidence of PC and IBD.

2.5. Inclusion

Sensitivity analyses were only allowed for studies that demonstrated a correlation between the incidence of PC and IBD when compared to controls.

We compared the frequency of PC in IBD, UC, CD, and control groups for subgroup and sensitivity analyses.

2.6. Statistical analysis

We estimated the odds ratio (OR), mean difference (MD), and 95% confidence interval (CI) with a random- or fixed-effects model using a dichotomous or continuous method. The I^2 index ranged from 0% to 100%. A calculated I^2 index of 0%, 25%, 50%, and 75% indicated no, low, moderate, and high heterogeneity,

respectively. We stratified the initial computation based on the previously defined result groups to perform subgroup analysis [11]. A *P*-value of 0.05 indicated that the differences between the subgroups were statistically significant. By examining the funnel plots of the logarithm of odds ratios against study results, the quality of the studies was evaluated [7].

3. Results

We found 1,050 different studies in total, 14 of which from 2001 to 2020 met the inclusion criteria and were included in the analysis [3, 12-24]. The data of these studies are summarized in **Table 2**.

Table 2. Characteristics of the selected studies for meta-analysis

Study	Country	Total inflammatory bowel disease	Ulcerative colitis	Crohn's disease	Years
Bernstein, 2001 [20]	Canada	5,529	2857	2,672	1984–1997
Hemminki, 2008 [21]	Sweden	27,606	27,606		1964–2004
Hemminki, 2009 [22]	Sweden	21,788		21,788	1964–2004
Jussila, 2013 [23]	Finland	21,964	16,649	5,315	2000–2007
Jess, 2013 [6]	Denmark	1,878	1437	441	1978–2002
Wilson, 2016 [24]	Switzerland	19,647			1995–2012
Mosher, 2016 [25]	USA	2,080			1996–2015
Hovde, 2017 [26]	Norway	756	519	237	1990–2013
Jung, 2017 [27]	Korea	15,644	10,049	5,595	2011–2014
So, 2017 [28]	China	2,621	1,603	1,108	1990–2016
Kundu, 2018 [29]	USA	1,033			1996–2017
Mosher, 2018 [30]	USA	2,080			1996–2015
Burns, 2019 [31]	USA	1,033			1996–2017
Taborelli, 2020 [32]	Italy	3,664	1,265	646	1995–2013
	Total	**127,323**	**61,985**	**37,802**	

From the 14 studies, 127,323 participants had IBD at the start of the research, among which 37,802 had CD and 61,985 had UC.

At the start of the investigation, there were a total of 756–27,606 patients with IBD in the selected trials. With regard to PC incidence, 5 studies conducted data-stratified comparisons between the overall prevalence of IBD and controls, 8 between the prevalence of UC and controls, and 8 between the prevalence of CD and controls.

IBD significantly increased the incidence of PC (OR, 3.46; 95% CI, 1.40–8.54, $P = 0.007$) with high heterogeneity ($I^2 = 96\%$) compared to controls, as shown in **Figure 2**. UC significantly increased the incidence of PC (OR, 1.43; 95% CI, 1.03–1.98, $P = 0.03$) with high heterogeneity ($I^2 = 84\%$) compared to controls, as shown in **Figure 3**. However, no significant difference was observed between CD and controls in relation to the incidence of PC (OR, 0.89; 95% CI, 0.75–1.06, $P = 0.18$) with low heterogeneity ($I^2 = 32\%$), as shown in **Figure 4**.

Since none of the studies mentioned or made adjustments for ethnicity and age, a stratified analysis for nominated papers was not performed.

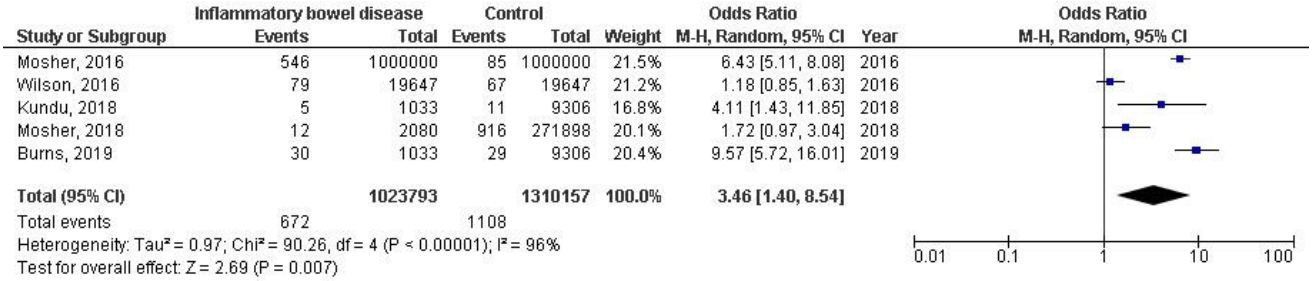

Figure 2. A forest plot of the effect of inflammatory bowel disease on the incidence of prostate cancer

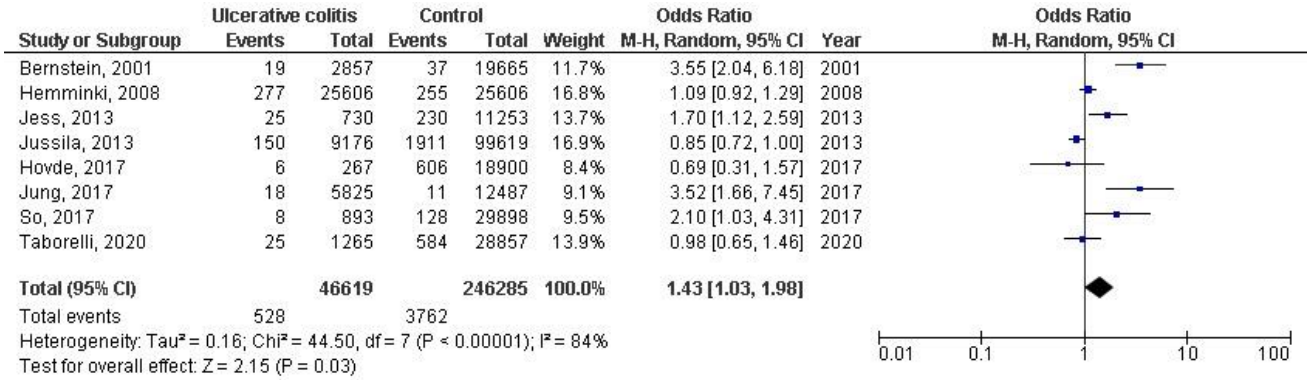

Figure 3. A forest plot of the effect of ulcerative colitis on the incidence of prostate cancer

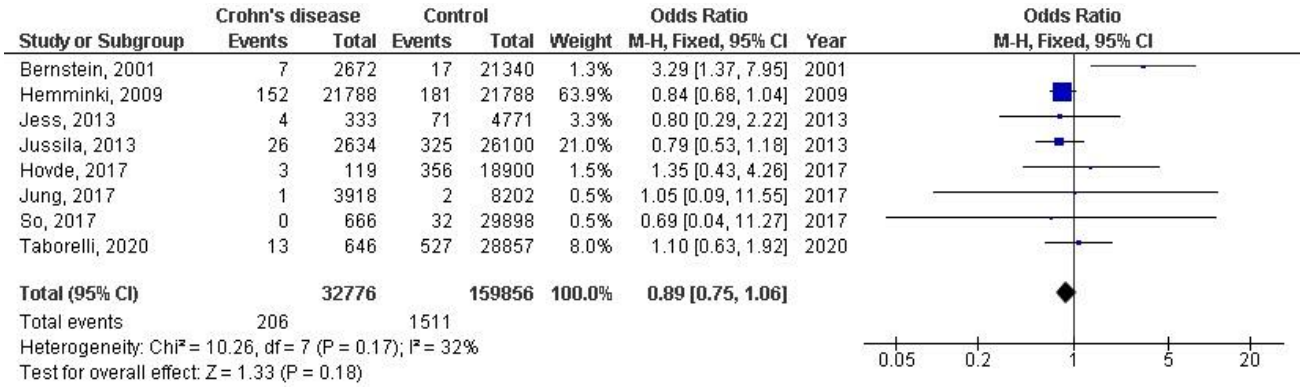

Figure 4. A forest plot of the effect of Crohn's disease on the incidence of prostate cancer

4. Discussion

This meta-analysis was founded on 14 studies, comprising 127,323 subjects with IBD, at the baseline of the study, among which 61,985 had UC and 37,802 had CD [3, 12-24]. In comparison to the control group, patients with UC and IBD had a considerably increased incidence of PC [6, 20-32]. However, with regard to the prevalence of PC, there was no discernible difference between CD and the control group. This finding suggests that IBD, especially UC, may increase the risk of incidence of PC compared to controls. The explanations for these results are multifactorial [3, 12-24].

However, due to the small number of studies included in this meta-analysis (14 studies), consequence analysis should be performed with caution. More studies should be conducted to either approve of these findings or, more likely, significantly reduce the confidence in the result computation.

The careful management of subjects with IBD, *e.g.*, biopsies for cancer screening and other prophylactic therapy, might be of benefit to these patients in reducing the risk of developing cancer [13]. Subjects with IBD have been proven to have a high risk of intestinal cancer [19]. Herrinton *et al.* have

reported that subjects with IBD had a 60% higher incidence of colorectal cancer [16]. IBD has also been found to be related to the increased risk of extra-intestinal cancer, *e.g*., hematologic cancer, lung cancer, and non-Hodgkin lymphoma [25,26]. Former trials have investigated the association between IBD and the risk of PC, but the consequence of IBD on the incidence of PC remains conflicting [20,27]. With about 1.5 million new cases and a death rate of 27%, PC is the most common cancer among males [3]. PC may develop as a result of persistent prostatic inflammation [8]. Proliferative inflammatory atrophy, which is seen as a PC lesion, is associated with inflammation. Additionally, inflammation may cause epigenetic changes that led to neoplastic transformation and drive prostatic mutagenesis via oxidative stress [28]. However, the mechanism that links IBD with PC remains unclear. Several studies have indicated that the ecological community of commensal, symbiotic, and pathogenic gut microorganisms (microbiota) plays a fundamental role in the development of IBD [29]. It has been demonstrated that the microbiome can influence PC-related inflammation [14]. A new trial has shown that pathogenic microorganisms related to IBD can move to the prostate through the circulatory system, causing cancer-stimulating prostatic inflammation [13]. Moreover, immunosuppressive treatment for subjects with IBD has been linked to a higher risk of extraintestinal cancer [25,30,31]. This may lead to a difference in PC risk between UC and CD [31]. Genomic alterations of CD have also been observed to be different from those of UC patients [32]. However, the moderately small sample size of subjects with CD in each of the selected studies might have led to the dissimilarity in PC risk between UC and CD. Hence, further studies are needed to understand this difference. This meta-analysis shows the association between IBD and the incidence of PC. Nonetheless, more research is needed to verify the observed potential relationships, inspect the characteristics of both UC and CD, as well as to demonstrate a difference that is clinically significant in the results. Other than that, more homogeneous samples are obligatory for these studies. This has also been suggested by a prior study that used a similar meta-analysis method and found that IBD has a comparable influence on the probability of developing PC [30,33]. These findings have not been well-explained, thus demanding additional investigations and clarification. In order to analyze these influences, which include a mixture of different ages and ethnicities, well-designed studies are essential. This is necessary in view of the limitation of this meta-analysis in determining the correlation of these factors with the results. The data in this analysis indicate that PC risk may increase as a result of IBD, particularly UC. In order to decrease the likelihood of problems in these patients, we advise additional screening for IBD in conjunction with PC based on the present study.

In our study, there were some limitations. The fact that many studies were excluded from our meta-analysis suggests that there might have been selection bias in this study although the studies that were eliminated did not meet the inclusion criteria. Moreover, we were unable to control whether or not the results were influenced by age, gender, or ethnicity. Other than that, the findings about the relationship between the incidence of PC and IBD may have been biased as a result of the lack of complete data from earlier research.

Only 3 of the 14 retrospective studies that comprised the risk assessment of cancers were solely focused on PC. Other likely bias-inducing characteristics were the subjects' age, gender, compliance, ethnicity, and nutritional status. The aggregated outcome could also be biased as a result of unpublished research and missing data.

5. Conclusion

UC and other IBDs may increase the risk of developing PC. However, the study showed no appreciable difference in the incidence of PC between those with CD and those in the control group. In view of these associations, we recommend more screening efforts for PC and IBD to reduce the likelihood of possible complications occurring in these patients.

Disclosure statement

The authors declare no conflict of interest

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