Risk of prostate cancer in patients with inflammatory bowel disease: a nationwide cohort study in South Korea

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Abstract

Background: Several studies have suggested an association between inflammatory bowel disease (IBD) and the risk of prostate cancer development. However, these findings are inconsistent, and studies based on Asian populations are limited.

Objectives: We compared the risk of prostate cancer according to IBD status using the Korean National Health Insurance Service database.

Design: A population-based retrospective cohort of age-matched 59,044 non-IBD patients and 14,761 IBD patients between January 2009 and December 2011 was analyzed up to December 2017.

Methods: The risk of prostate cancer was compared between patients with IBD and controls using the Cox proportional hazards regression model and Kaplan-Meier survival analysis.

Results: During a median follow-up of 6 years, the incidence rate of prostate cancer was 264 per 100,000 person-years in non-IBD patients and 242 per 100,000 person-years in patients with IBD. IBD status was not associated with the risk of prostate cancer compared to non-IBD [adjusted hazard ratio (aHR) 0.93, 95% confidence interval (CI): 0.80–1.08, $p = 0.32$]. The cumulative incidence of prostate cancer did not differ by IBD status (non-IBD patients *versus* IBD patients: log-rank $p = 0.27$; non-IBD patients *versus* ulcerative colitis *versus* Crohn's disease: log-rank $p = 0.42$). In multivariate analysis, age was an independent risk factor for the development of prostate cancer (HR 1.03, 95% CI: 1.02–1.03, $p < 0.001$).

Conclusion: In our population-based study, IBD status was not associated with the risk of prostate cancer.

Keywords: inflammatory bowel disease, risk of prostatic cancer

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Introduction

Inflammatory bowel disease (IBD), characterized by ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory disease of the gastrointestinal tract with a rapidly increasing incidence in Asia.[1,2] If disease activity is not properly controlled, its course can progress to bowel damage and disability through repeated acute exacerbations. Therefore, the treatment target has shifted from symptom control to mucosal healing associated with decreased risk of undergoing hospital-based intervention.

The association between chronic inflammation and the increased risk of colorectal cancer has been widely demonstrated in the previous literature; the practice of endoscopic surveillance for colorectal cancer and endoscopic assessment of disease activity in IBD patients has been emphasized.[3,4] Since chronic inflammation of the gastrointestinal tract is thought to play a major role in carcinogenesis,[5] the influence of resolving inflammation through immunomodulators or biologics therapy has been discussed.[6,7] In addition, the association between IBD and risk of extra-colonic

malignancy (especially lymphoma, non-melanoma skin cancer, and melanoma) was observed,[4,8–10] and several studies showed the possibility that it may be associated with the use of immunomodulators or biologics,[8,11] although these findings were not consistent.[12,13] Considering these findings, it is important to be aware of the risk of cancer development, disease course, and therapeutic intervention.

Prostate cancer risk has been suggested among the risk for extra-colonic malignancy in patients with IBD.[14,15] The risk factors of prostate cancer were age, family history, and race, with a higher prevalence in the Western world than in Asia.[16,17] In studies based on Western populations, IBD patients had an increased risk of prostate cancer, especially in cases of UC.[14,15] Recently, this was supported by meta-analyses that showed an increased risk of prostate cancer in UC patients.[18,19] However, in other meta-analyses, the association between IBD patients and the risk of prostate cancer was not identified[20–22]; in another study, the risk of prostate cancer was not found in UC and CD patients, respectively.[23] To date, this matter remains debatable, and there is no data for the association between IBD and prostate cancer compared with matched controls in the Asian population. Therefore, we evaluated the risk of prostate cancer development according to IBD status and concomitant therapies using data from the Korean National Health Insurance Service (KNHIS) database.

Methods

Data source
This retrospective cohort study was conducted using the KNHIS database. Almost all Koreans (>97%) are covered by the mandatory nationwide insurance system. Hence, the KNHIS database contains all relevant health information, including demographic characteristics, inpatient and outpatient usage (diagnosis code, procedure, surgery), prescription records (drug code, prescribed days, dosage), and registration of patients newly diagnosed with cancer. Information on diagnosis is based on the 10th revision of the International Classification of Diseases. In particular, IBD and cancer are registered under the Exempted Calculation of Health Insurance. The patients of these specific categories receive financial support with reduced coinsurance; the statutory coinsurance rate of the national health insurance is 10%

for rare incurable diseases and 5% for cancer. This study was approved by the Institutional Review Board of the Samsung Medical Center, Korea (SMC 2022-01-043; 18 January 2022). The requirement for the acquisition of informed consent was waived according to relevant guidelines because our retrospective design and only de-identified data were collected. The reporting of this study conforms to the STROBE statement.[24]

Study population: Cases, controls, and matching
Between 1 January 2009 and 31 December 2011, we randomly screened 49,531 IBD patients and 1,577,194 non-IBD patients. Patients with IBD (UC: K51.0-51.9 or CD: K50.0-50.9) were registered at least twice, and those prescribed therapies for IBD [5-aminosalicylic acid (5-ASA), steroids, immunomodulators (methotrexate or thiopurines), or anti-tumor necrosis factor (TNF) agent] during the screening period were included as IBD patients. Those who had never been diagnosed with IBD were defined as non-IBD patients. Among these, the following exclusion criteria were applied: follow-up loss ($n=141,286$) or any cancer development ($n=6966$) before the index date (1 January 2012), younger than 40 years ($n=1,220,620$), female ($n=156,363$), and follow-up less than 1 year from the index date ($n=516$). After that, 1:4 matching was performed according to age. Finally, 14,761 patients with IBD and 59,044 non-IBD patients were enrolled (Figure 1).

Outcomes
The primary outcome was a comparison of the incidence of prostate cancer between patients with IBD and controls during follow-up. The occurrence of prostate cancer was identified when the code for prostate cancer (C61) was newly registered. The enrolled patients were followed from the index date (1 January 2012) to the date of prostate cancer development, death, last follow-up date, or the end of the study period (31 December 2017), whichever came first.

Covariates
The IBD status of enrolled patients was divided into non-IBD patients, IBD patients, and IBD subtypes (UC or CD). The following variables were considered to determine potential confounders: age, prior, and concomitant therapies
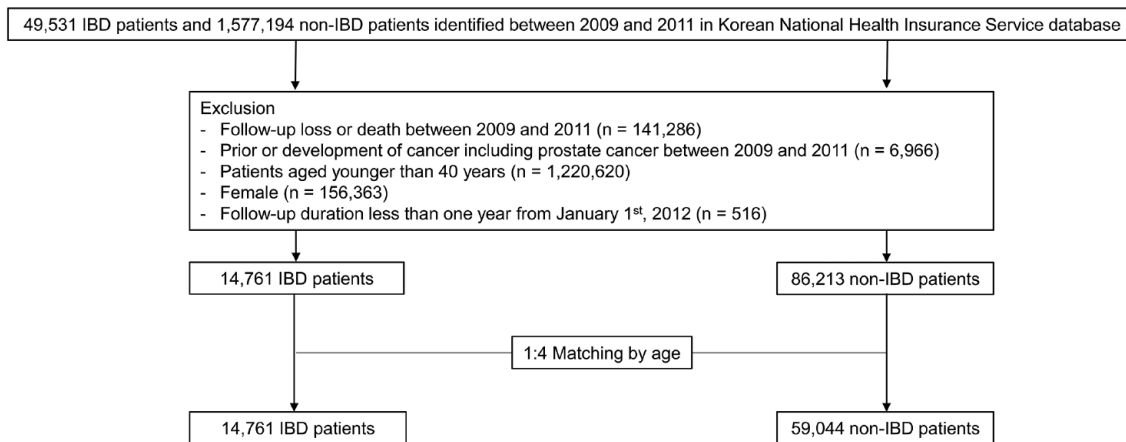
Figure 1. Selection of study population.

(5-ASA, steroid, methotrexate or thiopurines, and anti-TNF agents), history of hospitalization, and Charlson Comorbidity Index (CCI).

Statistical analysis
Continuous variables were analyzed by Student's *t*-test, and categorical variables were analyzed using the chi-squared test. Incidence rates of prostate cancer were calculated by IBD status as the number of events per 100,000 person-years. The Cox proportional hazards regression model was used to compare the risk of prostate cancer between the non-IBD patients and IBD patients, and between non-IBD patients and the subtypes of IBD (UC and CD). The cumulative incidence of prostate cancer was analyzed using Kaplan-Meier curves according to IBD status. The risk factors for prostate cancer were identified using logistic regression analysis, and all variables included in the univariate analysis were included in the multivariate analysis. In addition, a sub-analysis was conducted to evaluate whether there was a difference in the risk of prostate cancer development in the age subgroups of those aged 40–64 years and those aged ≥65 years. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using STATA version 14.0 (StataCorp, College Station, TX, USA).

Results

Study population
After matching, 14,761 IBD patients and 59,044 non-IBD patients were analyzed (Figure 1).

Table 1 shows the baseline characteristics of patients with and without IBD and between UC and CD patients. There was no significant difference in age between the non-IBD and IBD groups. Patients with IBD showed a higher proportion of history of hospitalization and slightly lower CCI than non-IBD patients.

When comparing UC and CD patients, UC patients showed older age, lower proportion of history of hospitalization, and lower CCI than CD patients. There were differences in the proportion of prior and concomitant therapy; the proportion of 5-ASA was higher in UC patients than in CD patients, whereas the proportion of steroids, immunomodulators, and anti-TNF was higher in CD patients than in UC patients.

Incidence of prostate cancer
During a median of 6 years of follow-up, 906 (1.5%) non-IBD patients and 207 (1.4%) IBD patients developed prostate cancer. The incidence rate for prostate cancer (incidence per 100,000 person-years) was 264 for non-IBD patients and 242 for IBD patients, with no significant difference between the two groups [adjusted hazard ratio (aHR) 0.93, 95% confidence interval (CI): 0.80–1.08, $p = 0.32$] (Table 2). There was no difference in the risk of prostate cancer between non-IBD, UC, and CD patients (UC: aHR 0.95, 95% CI: 0.81–1.12, $p = 0.52$; CD: aHR 0.83, 95% CI: 0.59–1.17, $p = 0.28$) (Table 2). The cumulative incidence of prostate cancer showed no difference between non-IBD patients, UC, and CD

Table 1. Baseline characteristics of study population.

Characteristics	Non-IBD (n = 59,044)	IBD (n = 14,761)	p Value	UC (n = 12,021)	CD (n = 2740)	p Value
Age, mean (SD), year	55.6 (11.1)	55.6 (11.1)	1.00	55.9 (10.9)	54.2 (12.0)	0.000
Age subgroup (%)			1.00			0.67
40–64	45,668 (77.3)	11,417 (77.3)		9280 (77.2)	2137 (78.0)	
≥65	13,376 (22.7)	3344 (22.7)		2741 (22.8)	603 (22.0)	
Prior and concomitant therapy (%)						
5-ASA		11,218 (76.0)		9482 (78.9)	1736 (63.4)	0.000
Steroid		11,276 (76.4)		9159 (76.2)	2117 (77.3)	0.000
Immunomodulators		1957 (13.3)		1197 (10.0)	760 (27.7)	0.000
Anti-TNF		291 (2.0)		136 (1.1)	155 (5.7)	0.000
Hospitalization (%)	570 (1.0)	219 (1.5)	0.000	162 (1.3)	57 (2.1)	0.000
CCI, mean (SD)	1.64 (1.60)	1.60 (1.58)	0.003	1.58 (1.56)	1.67 (1.68)	0.001

Anti-TNF, anti-tumor necrosis factor; 5-ASA, 5-aminosalicylic acid; BD, inflammatory bowel disease; CCI, Charlson Comorbidity Index; CD, Crohn's disease; SD, standard deviation; UC, ulcerative colitis.

Table 2. Incidence of prostate cancer by IBD status.

	N	Person-years	Number of PC	Incidence/ 100,000 PYs	Crude HR (95% CI)	p Value	Adjusted HR (95% CI)[a]	p Value
Non-IBD	59,044	343,120	906	264	1.00 (reference)		1.00 (reference)	
IBD	14,761	85,415	207	242	0.92 (0.79–1.07)	0.30	0.93 (0.80–1.08)	0.32
UC	12,021	69,654	173	248	0.94 (0.80–1.11)	0.48	0.95 (0.81–1.12)	0.52
CD	2740	15,761	34	216	0.82 (0.58–1.15)	0.25	0.83 (0.59–1.17)	0.28

[a]Adjusted for age and Charlson Comorbidity Index.
CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; PC, prostate cancer; PYs, person-years; UC, ulcerative colitis.

patients (*p* = 0.42) as well as between non-IBD patients and IBD patients (*p* = 0.27) (Figure 2).

Additionally, we evaluated the association between IBD status and the risk of prostate cancer in different age subgroups; no differences in the incidence rates of prostate cancer were observed between non-IBD patients and IBD patients in the 40–64 years old subgroup (aHR 0.84, 95% CI: 0.66–1.05) or in the ≥65 years old subgroup (aHR 1.01, 95% CI: 0.83–1.24) (Supplemental Table S1). There was no difference in the cumulative incidence of prostate cancer by IBD status in the

subgroup of patients aged 40–64 years (between non-IBD and IBD patients: *p* = 0.10; between non-IBD, UC, and CD patients: *p* = 0.07) or in the subgroup of patients aged ≥65 years (between non-IBD and IBD patients: *p* = 0.90; between non-IBD, UC, and CD patients: *p* = 0.80) (Supplemental Figure S1).

Risk factors for prostate cancer among IBD patients

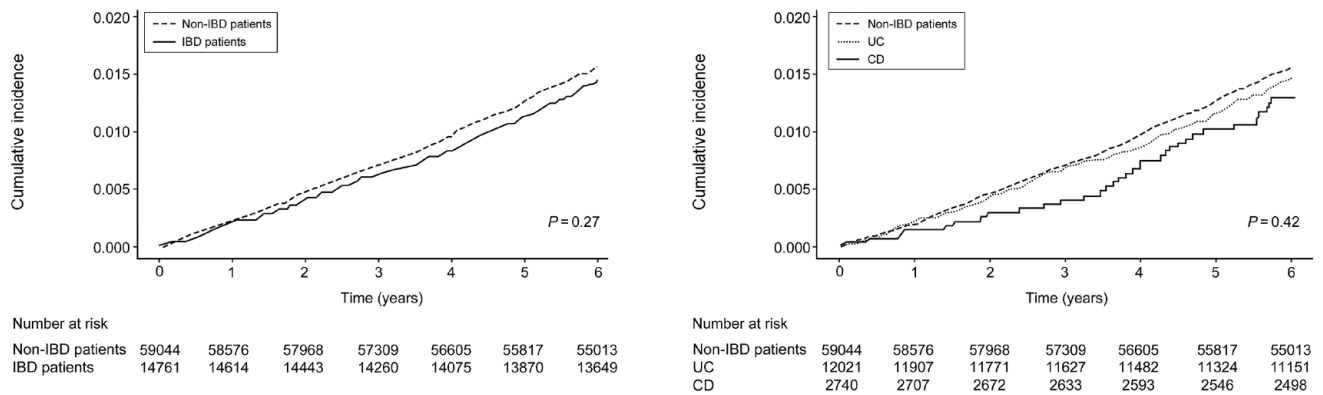Multivariate analysis of IBD patients showed that age was an independent risk factor for prostate

Figure 2. Kaplan-Meier analysis for cumulative incidence of prostatic cancer by inflammatory bowel disease (IBD) status.

cancer (odds ratio 1.03, 95% CI: 1.02–1.03, $p < 0.001$). The subtypes of IBD and therapies were not associated with an increased risk of prostate cancer (Table 3).

Discussion

This study showed that IBD status was not associated with an increased risk of prostate cancer compared to non-IBD status, and this finding was consistent among UC and CD patients. Age was an independent risk factor associated with prostate cancer development. However, when patients were grouped into those aged less than 65 years and those aged 65 years or more, there was no difference in the risk of prostate cancer between IBD patients and non-IBD patients. In addition, neither immunomodulators nor anti-TNF antibodies were associated with the risk of prostate cancer.

To the best of our knowledge, our study is the first to compare the risk of prostate cancer in IBD patients with age and sex-matched non-IBD patients in a population-derived Asian cohort. The strengths of this study are that we had a sufficient sample size using a national database, provided a clear definition of IBD for inclusion in this study, and tried to identify the relationship between the IBD therapy used and the risk of prostate cancer. In South Korea, IBD and cancer are registered as specific codes with the Exempted Calculation of Health Insurance; hence, the diagnosis of these diseases is highly reliable. In addition, we present a prolonged follow-up period with near-complete data.

Two recent meta-analyses suggested an association between IBD and prostate cancer; however, these studies showed high heterogeneity, included a study with inadequate quality, and analyzed a relatively small number of studies.[18,19] To compensate for the limitations of these reports, another meta-analysis was published, in which no association between the risk of prostate cancer development, CD, and UC was found.[23] Also, in the two most recently published meta-analyses, the risk of prostate cancer in IBD patients was not significantly different compared with the general population or non-IBD patients. However, a sub-analysis of Eastern countries showed an increased risk of prostate cancer in UC patients, although this analysis only included two studies.[20,21] These two studies conducted in South Korea using nationwide data and in Hong Kong using a regional registry found the association between UC and increased risk of prostate cancer.[10,25] But, these two studies were interpreted with caution due to the difference of methodology compared with our study. First, they designed a comparative group as general population using incidence statistics like the expected number of cancers from the data of cancer registry, although these registries were not the group in which IBD patients were excluded strictly. We structured an age- and sex-matched control group excluding IBD from the KNHIS database. Second, in the previous studies, the expected number of cancers calculated by multiplying sex- and age-specific cancer incidence rates by the person-years of the UC or CD cohort needs attention to the reliability of the computed value; in terms of characteristics of prostate cancer occurring in older men and

Table 3. Risk factors for prostate cancer in IBD patients.

	Univariate		Multivariate	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Subtype of IBD				
UC	1.00 (reference)		1.00 (reference)	
CD	1.00 (0.99–1.00)	0.43	1.00 (0.99–1.00)	0.60
Age				
40–64	1.00 (reference)		1.00 (reference)	
⩾65	1.03 (1.02–1.03)	<0.001	1.03 (1.02–1.03)	<0.001
Prior and concomitant therapy				
5-ASA	0.99 (0.99–0.99)	<0.001	1.00 (1.00–1.01)	0.08
Corticosteroids	1.01 (1.00–1.01)	0.001	1.00 (1.00–1.01)	0.10
Immunomodulators	0.99 (0.99–1.00)	<0.001	1.00 (0.99–1.00)	0.12
Anti-TNF therapy	0.99 (0.97–1.00)	0.040	0.99 (0.98–1.01)	0.39
Hospitalization (frequency)				
<1/year	1.00 (reference)		1.00 (reference)	
⩾1/year	1.00 (0.99–1.02)	0.59	1.00 (0.98–1.02)	0.91

Analyzed by multivariate logistic regression analysis.
anti-TNF, anti-tumor necrosis factor; 5-ASA, 5-aminosalicylic acid; CD, Crohn's disease; CI confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; UC, ulcerative colitis.

unclear explanation for the denominator. Third, our study contains time-to-event analyses, whereas they analyzed the incidence for a certain period without consideration of time variable. In addition, the total 4-year period between enrollment and observation in the Korean study was relatively short to demonstrate causation, and the Hong Kong study had a relatively small sample size. Our study is meaningful in that it was a well-designed cohort study that addressed the limitations of previous reports to identify whether there is an association between IBD and prostate cancer.

Previous studies have supported the hypothesis that localized or systemic chronic inflammation is associated with an increased risk of prostate cancer in IBD patients.[14,15] However, those were conducted in Western countries and could not explain the mechanism behind the relationship between chronic gut inflammation and prostate carcinogenesis. Recent studies have proposed the role of human microbiota and the microbiome in the process of prostate cancer development[26–28]; however, this literature has mainly focused on the urinary microbiome.[28] The mechanism behind the abundant microbiota in patients with prostate cancer and the microbiota in patients with IBD has yet not been elucidated. In addition, another study showed that the association between chronic inflammatory disease and prostate cancer could be explained by detection bias owing to frequent hospital care.[29] To date, the association between IBD and increased risk of prostate cancer might have been supported among Western countries,[9,14,15,30] despite opposite findings,[20–22,31] but its relevant evidence is limited in Asia.

Globally, the age-standardized incidence rate for prostate cancer was lower in South Korea (27.0 per 100,000) than in Oceania (79.1/100,000 persons), North America (73.7 per 100,000 persons), and Europe (62.1 per 100,000 persons).[32]

However, prostate cancer was the fifth most common cancer, and its incidence increased from 1437 cases in 1999 to 10,212 cases in 2015.[33] Moreover, the incidence rate increased 1.5-fold in the 80–84 age group and 4-fold in the 50–69 age group from 1999 to 2012 in South Korea.[34] This was presumed to be associated with an increase in prostate-specific antigen (PSA) screening.[33] Considering prostate cancer shows more aggressive clinical features in Korean patients compared to Western patients,[35] it is necessary to identify risk factors for prostate cancer. As we do not yet have a screening program like that of Europe, there is a need for an adequate recommendation for cancer screening such as PSA.[25]

Our study has several limitations. First, this was an observational study and so it was not able to establish causation. Second, there were several unverified confounders, such as family history, dietary supplements, and disease activity during follow-up. Third, we could not assess some potential confounding factors; laboratory data such as PSA level; lifestyle or personal health behaviors, including smoking and alcohol intake; and physiological characteristics such as body mass index. However, our results minimize selection and referral bias by using large-scale administrative data obtained from the majority of the Korean population. Fourth, we did not have information on the proportion of IBD patients or non-IBD patients who were in the screening program, which might be related to detection bias.

In conclusion, we did not find an increased risk of prostate cancer in patients with IBD compared to non-IBD patients. Additional studies are warranted in other Asian countries to determine whether the causation between chronic inflammation and the risk of prostate cancer exists in IBD patients.

Declarations

Author contribution(s)
Ji Eun Na: Conceptualization; Data curation; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

Tae Jun Kim: Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Validation; Writing – review & editing.

Yeong Chan Lee: Data curation; Formal analysis; Methodology; Writing – review & editing.

Ji Eun Kim: Supervision; Writing – review & editing.

Eun Ran Kim: Supervision; Writing – review & editing.

Sung Noh Hong: Supervision; Writing – review & editing.

Dong Kyung Chang: Supervision.

Young-Ho Kim: Conceptualization; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

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Supplemental material
Supplemental material for this article is available online.

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