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Research Article

The association between inflammatory bowel disease and risk of prostate cancer: a population-based retrospective study based on Korean National Health Insurance Service database

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ABSTRACT

Background: The aim of this study was to determine whether inflammatory bowel disease (IBD) is associated with the risk of developing prostate cancer (PCa) through a population-based study.
Materials and methods: Male patients aged ≥40 years, diagnosed with IBD from 2010 to 2013 and without IBD were identified and followed-up till 2019. A matched cohort of male patients with and without IBD in a ratio of 1:4 was created based on age, income level, and Charlson comorbidity index. Multivariate Cox regression analysis was conducted to evaluate the association of IBD with the prescence of PCa and PCa requiring definitive treatment within 1 year of diagnosis. The hazard ratio (HR) and 95% confidence interval (CI) were stratified by Crohn's disease, ulcerative colitis (UC), and subtypes.
Results: After matching, 15,751 IBD patients and 62,346 controls were analyzed. Over a median follow-up period of 96 months, the HR for PCa was significantly increased in patients with IBD (HR: 2.44; 95% CI: 2.08–2.86, $P < 0.001$). IBD was also associated with PCa requiring definitive treatment within 1 year (HR: 2.67; 95% CI: 2.09–3.42, $P < 0.001$). In subgroup analysis, UC (HR: 2.83; 95% CI: 2.18–3.69, $P < 0.001$) showed higher risk of PCa requiring definitive treatment than for Crohn's disease (HR: 2.21; 95% CI: 1.43–3.43, $P = 0.0004$). All-cause death in patient-diagnosed PCa was the highest in UC of pancolitis (HR: 2.26; 95% CI: 0.99–5.16, $P = 0.054$), and the lowest in ulcerative proctitis (HR: 0.35; 95% CI: 0.21–0.60, $P = 0.0001$).
Conclusion: IBD was associated with an increased incidence of PCa in our matched analysis.

1. Introduction

Prostate cancer (PCa) has the second highest incidence and the 5th highest mortality worldwide.[1] There are several risk factors related to PCa including environmental factors such as dietary factors or inflammation.[2] The correlation between cancer and inflammation has been studied for decades.[3] Previous studies demonstrated that certain inflammations predispose individuals to cancers.[4] One hypothesis is that cellular and genetic damage causes cell proliferation.[5]

Inflammatory bowel disease (IBD) is chronic gastrointestinal inflammation, which is mainly represented by ulcerative colitis (UC) and Crohn's disease (CD), and is diagnosed by clinical, endoscopic, histological, and radiologic findings.[6–8] Commonly known hypothesis for the pathogenesis of IBD is that complex interactions between environments, genetics, and the host immune system lead to abnormal immunologic responses related to chronic intestinal inflammation.[9] Although IBD has the highest incidence in Western countries, it should be noted that the incidence has recently increased rapidly in Asia, Africa, and other parts of the world.[10]

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IBD patients have been reported to have an increased risk of several cancers, such as gastrointestinal cancer especially in colorectal region, or extraintestinal malignancies such as lymphoma, melanoma, or cholangiocarcinoma.[11] However, previous studies on the association between IBD and PCa are very limited[12] and are extremely rare in Asia.

Therefore, we planned a population-based cohort study and performed a relevance analysis for IBD and PCa using the National Health Insurance database. The aim of the present study was to examine the associations between IBD and the risk of PCa.

2. Materials and methods

2.1. Ethics statement

This study was approved by the local institutional review board. All data used for analysis were anonymized by the privacy guidelines of the Health Insurance Portability and Accountability Act and will be made available only in the data room provided by the National Health Insurance Corporation. Informed consent was waived by the committee for anonymized data analysis.

2.2. Data sources

This population-based cohort study used data from Korean National Health Insurance Service (NHIS) database. The NHIS provides data of approximately 98% of the Korean citizens with health insurance, more than 50 milion, covering almost all medical data including demographics, various questionnaires conducted at the health check-up, diagnosis as codes, procedures covered by insurance, and prescription records. The health screening examinations are available to citizens who are aged 40 years or older.[13]

2.3. Study population and definitions

Male patients who were newly diagnosed with IBD at their age ≥40 between 2010 and 2013 were enrolled for the IBD group. IBD was subdivided into UC and CD, whereas IBD unspecified was excluded. Each category was defined by International Classification of Diseases, Tenth Revision (ICD-10) codes (Supplementary file 1). The control group was random-sampled from patients without IBD from 2010 to 2013, and propensity score was matched to IBD group on a 1:4 ratio by age, income level, and Charlson comorbidity index. Follow-up duration was ranging from 6 to 10 years in the IBD group and was 8 years in the control group, as determined by median date or enrollment.

The primary outcome of this study was the incidence of PCa, which was identified by ICD-10 code of C61. To exclude the patients who already had PCa before the onset of IBD, those who were identified as PCa within 1 year from the onset of IBD were excluded. As the Korean NHIS database does not provide serum prostate-specific antigen (PSA) level, pathologic reports of prostate biopsies, or reports of radiologic findings, it was impossible to identify clinically significant PCa (csPCa). Therefore, we suggested the incidence of PCa requiring the primary definitive treatments, including radical prostatectomy or radiation therapy within 1 year of diagnosis, instead of csPCa.

The secondary outcome was the effect of IBD on survival outcome of PCa patients. Since the cause of death is not specified in the korean NHIS database, we compared the overall survival of PCa patients according to the prescence of IBD.

2.4. Statistical analysis

We calculated the incidence rate and described as per 1,000 person-years. For categorical variables, the chi-squared test was used. For continuous variables, one-way analysis of variance test and T-test were used. Hazard ratios (HRs) were analyzed by multivariate Cox proportional hazard regression. Statistical significance was determined as two-sided P values <0.05. The Kaplan–Meier curves with long-rank tests were used for cumulative incidence and survival analysis. All statistical analyses were performed using SAS Enterprise guide version 7.1 (SAS Institute, Carrie, NC, USA).

3. Results

The total number of patients before matching was 984,819 (IBD: 15,776, control: 969,043). After propensity score matching (PSM), a total of 78,097 (IBD: 15,751, control: 62,346) patients were inclued for final analysis. The mean age of all matched patients was 56.84 ± 11.41 years. After matching, there were no significant differences in age, income level, and Charlson comorbidity index between the two groups. The subgroups of IBD were CD (n = 4,101, 26.0%) and UC (n = 11,650, 74.0%). Table 1 summarizes the general characteristics of the study population after PSM, whereas data before PSM are described in Supplementary Table 1.

The incidence rate of PCa (Table 2a) was significantly higher in the IBD group than in the control group (2.32 vs 0.89, P < 0.001). The patients with IBD showed a higher risk of PCa (HR: 2.44, 95% confidence interval [CI]: 2.08–2.86, P < 0.001). Given the subtypes of IBD, UC had the highest risk of PCa (HR: 2.46; 95% CI: 2.07–2.92, P < 0.001) compared to CD (HR: 2.40; 95% CI: 1.85–3.11, P < 0.001). Among the subtypes of UC and CD, ileocolic CD had the highest risk of PCa (HR: 2.93; 95% CI: 1.44–5.97, P < 0.001). The incidence rate of PCa requiring definitive treatments (Table 2b) was significantly higher in the IBD group than in the control group (0.95 vs 0.48, P < 0.001), showing a significant association with the presence of PCa requiring definitive treatment (HR: 2.67; 95% CI: 2.09–3.42, P < 0.001). When comparing the subtypes of IBD, UC presented a higher risk of PCa requiring definitive treatments (HR: 2.83; 95% CI: 2.18–3.69, P < 0.001) than CD (HR: 2.21; 95% CI: 1.43–3.43, P < 0.001). In subtypes of UC and CD, proctitis UC (HR: 3.03; 95% CI: 2.31–3.97, P < 0.001), and ileocolic CD (HR: 3.26; 95% CI:

Table 1
Baseline characteristics after 1:4 ratio propensity score matching in male

Variables	IBD (n = 15,751)	Control (n = 62,346)	P
Age	56.92 ± 11.47	56.82 ± 11.40	0.3341
Income level lowest 25%, n (%)	3457 (21.95)	13461 (21.59)	0.3311
DM	3676 (23.34)	14138 (22.68)	0.0771
HTN	5656 (35.91)	22250 (35.69)	0.6052
CCI			0.7988
≤1	13890 (88.18)	55033 (88.27)	
2	802 (5.09)	3208 (5.15)	
≥3	1059 (6.72)	4105 (6.58)	
Type of IBD			
UC	11650 (73.96)	NA	
Proctitis	10012 (63.56)	NA	
Lt sided colitis	506 (3.21)	NA	
Pancolitis	1156 (7.34)	NA	
CD	4101 (26.04)	NA	
Small intestine	1844 (11.71)	NA	
Colonic	1898 (12.05)	NA	
Ileocolonic	381 (2.42)	NA	
Duration of follow-up (yr, median [IQR])	7.85 (5.75–9.95)	8 (7.5–8.5)	NA
Total person-year follow-up, yr	120863.64	474421.17	NA

Values are presented as mean ± standard deviation or number (%).
CCI, Charlson comorbidity index; CD, Crohn's disease; DM, diabetes mellitus; HTN, hypertension; IBD, inflammatory bowel disease; IQR, interquartile range; NA, not applicable; UC, ulcerative colitis.

Table 2
Incidence and risk of prostate cancer and all-cause death

a. Incidence and risk of prostate cancer according to IBD

IBD	Subject, *n*	PCa, *n*	IR (1,000 person-years)	HR (95% CI)	*P*
No	62346	421	0.889619	1.000 (ref.)	
Yes	15751	278	2.316937	2.443 (2.084–2.864)	<0.0001
UC	11650	209	2.964006	2.458 (2.067–2.922)	<0.0001
UC-proctitis	9992	184	2.165827	2.517 (2.098–3.019)	<0.0001
UC-left sided colitis	502	9	2.784733	2.318 (1.194–4.501)	0.013
UC-pancolitis	1156	16	1.775378	1.817 (1.099–3.007)	0.02
CD	4101	69	2.252833	2.4 (1.853–3.108)	<0.0001
CD-small intestine	1823	32	2.318265	2.526 (1.748–3.649)	<0.0001
CD-colonic	1897	29	2.074648	2.267 (1.542–3.332)	<0.0001
CD-ileocolonic	381	8	2.810575	2.932 (1.439–5.974)	0.0031

b. Incidence and risk of prostate cancer requiring definitive treatment according to IBD

IBD	Subject, *n*	PCa, *n*	IR (1,000 person-years)	HR (95% CI)	*P*
No	62346	228	0.481681	1.000 (ref.)	
Yes	15751	114	0.947385	2.674 (2.093–3.415)	<0.0001
UC	11650	23	1.015542	2.833 (2.176–3.689)	<0.0001
UC-proctitis	9992	9	1.09628	3.027 (2.307–3.972)	<0.0001
UC-left sided colitis	502	11	0.759274	2.31 (0.737–7.239)	0.151
UC-pancolitis	1156	3	0.4428	1.34 (0.497–3.615)	0.5634
CD	4101	91	0.748603	2.213 (1.429–3.428)	0.0004
CD-small intestine	1823	84	0.650035	1.913 (0.978–3.744)	0.0582
CD-colonic	1897	3	0.784907	2.316 (1.257–4.267)	0.007
CD-ileocolonic	381	4	1.047452	3.263 (1.042–10.223)	0.0423

c. Incidence and risk of all-cause death in patients diagnosed prostate cancer

IBD	Subject, *n*	death, *n*	IR (1,000 person-years)	HR (95% CI)	*P*
No	421	90	75.96608	1.000 (ref.)	
Yes	278	30	34.18184	0.471 (0.311–0.712)	0.0004
UC	209	23	33.6586	0.468 (0.296–0.74)	0.0012
UC-proctitis	184	16	25.38342	0.354 (0.208–0.603)	0.0001
UC-left sided colitis	9	1	56.25289	0.722 (0.101–5.182)	0.7457
UC-pancolitis	16	6	170.3459	2.257 (0.987–5.1590)	0.0536
CD	69	7	36.02173	0.481 (0.223–1.038)	0.0622
CD-small intestine	32	2	23.65073	0.312 (0.077–1.265)	0.1029
CD-colonic	29	4	53.67574	0.711 (0.261–1.937)	0.5051
CD-ileocolonic	8	1	28.37554	0.398 (0.055–2.856)	0.3593

d. Incidence and risk of all-cause death in patients diagnosed prostate cancer requiring definitive treatment

IBD	Subject, *n*	death, *n*	IR (1,000 person-years)	HR (95% CI)	*P*
No	228	69	63.93622	1.000 (ref.)	
Yes	114	15	28.17331	0.447 (0.255–0.782)	0.0048
UC	91	12	27.65614	0.437 (0.237–0.807)	0.0082
UC-proctitis	84	9	21.92099	0.347 (0.173–0.695)	0.0028
UC-left sided colitis	3	1	106.7982	1.683 (0.233–12.16)	0.6058
UC-pancolitis	4	2	143.1511	2.255 (0.549–9.254)	0.259
CD	23	3	30.45103	0.491 (0.154–1.565)	0.2294
CD-small intestine	9	0	0	0	0.9843
CD-colonic	11	3	78.13391	1.285 (0.402–4.112)	0.6727
CD-ileocolonic	3	0	0	0	0.9899

CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; IR, incidence rate; PCa, prostate cancer; UC, ulcerative colitis.

1.04–10.22, $P = 0.0423$) had the highest risk of PCa requiring definitive treatments in UC and CD, respectively (Table 2b).

The incidence rate of all-cause mortality in PCa patients (Table 2c) was significantly lower in the IBD group than in the control group (HR: 0.47; 95% CI: 0.31–0.71, $P < 0.001$). The patients with PCa with UC had a slightly lower risk of all-cause death (HR: 0.47; 95% CI: 0.30–0.74, $P < 0.001$) than those with PCa with CD (HR: 0.48; 95% CI: 0.22–1.04, $P = 0.05$). Among subtypes of UC and CD, there was no significant difference in the risk of all-cause death. The incidence rate of all-cause death in patients with PCa requiring definitive treatments (Table 2d) was significantly lower in the IBD group than in the control group (HR: 0.45; 95% CI: 0.26–0.78, $P = 0.005$), especially in UC (HR: 0.44; 95% CI: 0.24–0.81, $P = 0.008$).

The IBD group was diagnosed with PCa at younger age than the control group (65.2 ± 9.0 years vs 68.4 ± 8.3 years, $P < 0.001$) (Table 3a). The duration between the onset of IBD and that of PCa was longer in UC (4.8 ± 2.5 years) than in CD (5.3 ± 2.3 years) but was not significantly ($P = 0.172$). The age at diagnosed PCa requiring definitive treatments (Table 3b) was younger in the IBD group than in the control group (66.9 ± 7.8 years vs 67.9 ± 7.9 years) without statistical significance ($P = 0.25$).

The cumulative incidence probability analysis (Fig. 1) and survival analysis (Fig. 2) are shown in Kaplan–Meier curves. There were significant differences among patients with and without IBD, and it also showed significant differences among patients with subtypes of IBD and without IBD.

4. Discussion

The local inflammatory response may affect carcinogenesis, the mechanism of which is presumed to be a local immune response due to tissue damage and necrosis or external pathogenic

Table 3
Age at prostate cancer and years from IBD to prostate cancer

a	All PCa	Age at PCa	*P*	IBD to PCa	*P*
	Total	67.1 ± 8.7	NA	NA	NA
	Control	68.4 ± 8.3	<0.0001	NA	NA
	IBD all	65.2 ± 9.0		4.9 ± 2.5	
	CD all	65.3 ± 9.5	<0.0001	5.3 ± 2.3	0.172
	UC all	65.2 ± 8.8		4.8 ± 2.5	
	CD-small intestine	65.5 ± 8.7	<0.0001	4.7 ± 2.4	0.0952
	CD-colonic	65.4 ± 5.4		6.4 ± 3.0	
	CD-ileocolonic	62.3 ± 11.0		5.3 ± 3.1	
	UC-proctitis	62.8 ± 8.9	0.0042	5.4 ± 2.3	0.0755
	UC-left sided colitis	67.1 ± 9.0		5.6 ± 2.2	
	UC-pancolitis	68.3 ± 12.5		3.6 ± 2.1	
b	PCa requiring definitive treatments	Age at PCa	*P*	IBD to PCa	*P*
	Total	67.6 ± 7.9	NA	NA	NA
	Control	67.9 ± 7.9	0.2514	NA	NA
	IBD all	66.9 ± 7.8		3.3 ± 2.1	
	CD all	67.3 ± 9.0	0.4945	3.7 ± 1.6	0.288
	UC all	66.8 ± 7.5		3.2 ± 2.2	
	CD-small intestine	66.9 ± 7.3	0.3086	3.2 ± 2.2	0.9821
	CD-colonic	70.0 ± 1.0		3.0 ± 1.9	
	CD-ileocolonic	61.8 ± 12.7		3.1 ± 1.7	
	UC-proctitis	64.0 ± 7.9	0.4111	3.6 ± 1.8	0.5385
	UC-left sided colitis	69.0 ± 9.5		4.1 ± 1.5	
	UC-pancolitis	71.3 ± 10.4		2.9 ± 1.5	

CD, Crohn's disease; IBD, inflammatory bowel disease; PCa, prostate cancer; UC, ulcerative colitis.

influence.[14] IBD and colorectal cancer, chronic hepatitis and liver cancer, gastritis and gastric cancer caused by Helicobacter pylori, bladder inflammation, and cystitis caused by schistosomiasis are well-known inflammations associated with the cancer.[15]

Burns et al[12] demonstrated higher rates of PCa (HR: 4.84; 95% CI: 3.34–7.02) and csPCa (HR: 4.04; 95% CI: 2.52–6.48) in the IBD group than in the control group. Although this study was a single-institution study, the cohort size was relatively large with 1,033 IBD patients and 9,306 matched controls, and the median follow-up period was not short at 6.5 years for the IBD group and 4.7 years for the control group. It is very valuable to provide information on PSA and csPCa. However, in this study, only 0.8% (8 for IBD group, 72 for control) were Asian, so information on Asians was very limited. Because previous studies reported that the effects of IBD on urinary cancer differ between Eastern and Western patients,[16] considering that most studies related to IBD and urinary cancer have been focused on Westerners, as mentioned earlier; large-scale studies in Asian popultions can provide a more comprehensive view. Our study is meaningful because it was conducted on a large scale in Asia. The value of HR is slightly lower in our study. Whether this is a difference due to ethnicity is still unclear, and more research is needed. Meyers et al[17] also reported increased risk of PCa in the IBD group (adjusted HR [aHR]: 1.31; 95% CI: 1.03–1.67), and only in UC (aHR: 1.47; 95% CI: 1.11–1.95) and not in CD (aHR: 1.06; 95% CI: 0.63–1.80) thorough a prospective population-based study with 2,311 IBD patients and 215,773 controls. However, in their study as well as in the case of the IBD group, the proportion of White patients was 95.3%, so information on Asians was very limited, and the lack of information on the rate and accuracy of self-reported IBD limits the evaluation. It is more meaningful because we extracted all IBD patients using the ICD-10 code and only analyzed patients with subtypes.

Recently, results of meta-analysis reported scarce results in relationship between IBD and risk of PCa, but they demonstrated that UC patients in Asia were associated with an increased risk of PCa.[18,19] As mentioned earlier, large-scale studies conducted in the West are difficult to evaluate in Asians because the proportion of them is small. Jung et al[20] previously reported significantly increased standardized incidence ratio (SIR) of PCa in men with UC (SIR: 3.5; 2.1–5.5), not in CD (SIR: 1.0; 0.0–5.5). However, their study did not compare with the control group but with statistics of the general population, and the median follow-up time was as short as 2.14 years for CD and 2.2 years for UC. We performed comparative analysis with the control group, and since the follow-up period was much longer than 6 years, it can be said that it has an advantage in analyzing the long-term cancer occurrence of IBD.

One possible hypothesis to explain the correlation between IBD and PCa might be the microbiome environment. The prostate and gut microbiome has emerged as an issue in the relationship between PCa and inflammation.[21] Although the mechanisms are not yet clear, numerous data suggest that metabolites of the microbiome influence the pathogenesis of IBD.[22] Furthermore, recent studies have demonstrated differences in the gut microbiome with and without PCa.[23] Based on these, we can hypothesize that the

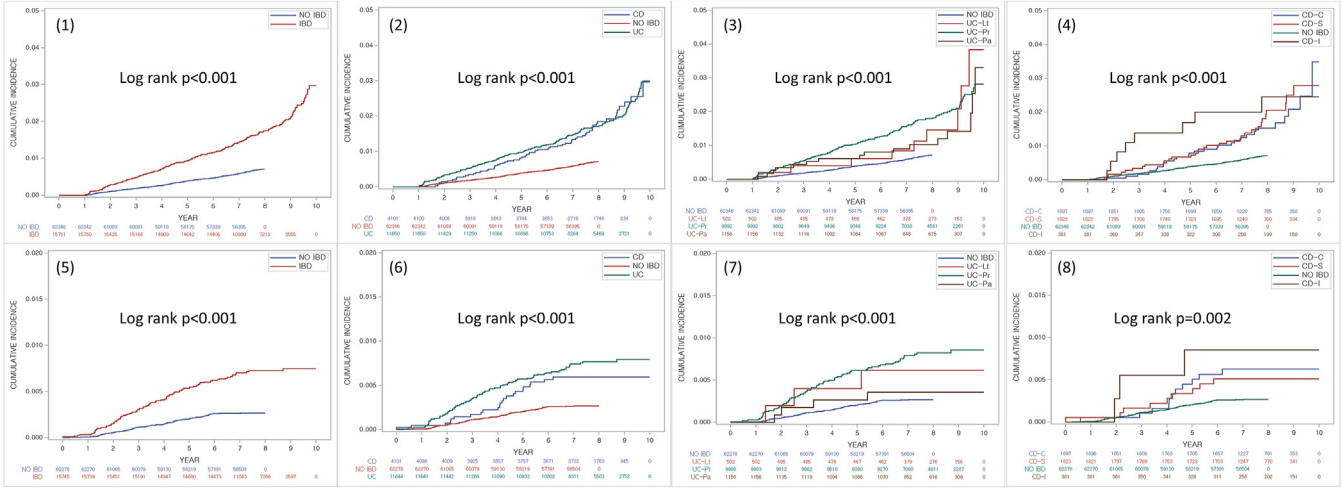

Figure 1. Kaplan–Meier curves of cumulative incidence probability analysis: (1) all prostate cancer, no IBD vs IBD; (2) all prostate cancer, no IBD vs UC vs CD; (3) all prostate cancer, no IBD vs UC subtypes (4); all prostate cancer, no IBD vs CD subtypes. (5) Prostate cancer requiring definitive treatments, no IBD vs IBD. (6) Prostate cancer requiring definitive treatments, no IBD vs UC vs CD. (7) Prostate cancer requiring definitive treatments, no IBD vs UC subtypes. (8) Prostate cancer requiring definitive treatments, no IBD vs CD subtypes. Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

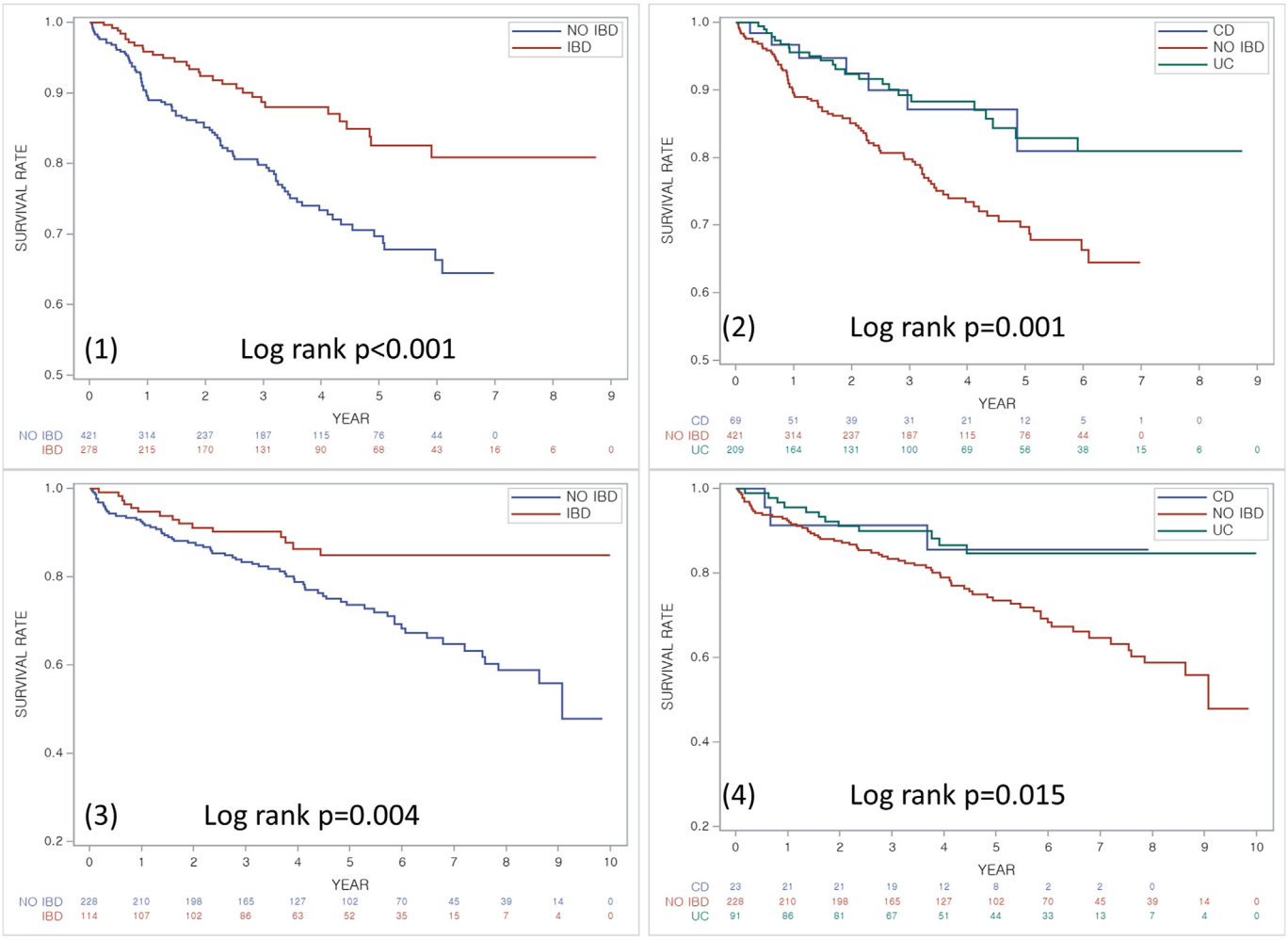

Figure 2. Kaplan–Meier curves of overall survival of patients diagnosed with prostate cancer: (1) all prostate cancer, no IBD vs IBD. (2) All prostate cancer, no IBD vs UC vs CD. (3) Prostate cancer requiring definitive treatments, no IBD vs IBD. (4) Prostate cancer requiring definitive treatments, no IBD vs UC vs CD. Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

possibility that the gut microbiome may be associated with IBD and PCa. Disturbance of the normal microbiome can be associated with cancer, such as the relationship between gastric cancer and *Helicobacter pylori*, and may affect the pathogenesis and treatment response.[24] More research seems to be needed on this. If further research on the microbiome progresses and research on clinical outcomes such as IBD and PCa is combined, it is expected to have a ripple effect from the pathogenesis of PCa to treatment and prevention.

Our result also revealed that among patients with PCa, IBD was significantly associated with favorable overal survival outcome, despite that patients with IBD were likely to be diagnosed with overall PCa and PCa, requiring definitive treatment. This might be explained by several reasons. IBD itself has been reported not to show significant difference in overall mortality.[25] Considering that it is detected early, localized PCa could show nearly 100% of 5-year overall survival, patients with IBD might be likely to undergo close routine medical monitoring, resulting in favorable survival outcome. Indeed, our results revealed that the IBD group was diagnosed with PCa at a younger age than the control group.

There are few limitations in the present study. First of all, the current study was conducted on a single ethnic group in only one country. In addition, the Korean NHIS database does not provide several information, such as digital rectal exam, serum PSA level, pathologic report of prostate biopsy, and radiologic findings. This caused difficulties in distinguishing significant or high-risk PCa. The information about chronic inflammatory condition, including complete blood count, C-reactive protein, or drug information (e.g., nonsteroidal anti-inflammatory drug or steroid) was also inavailable, which could affect the severity of IBD. The endoscopic findings or pathologic reports of IBD were also not available, making it impossible to evaluate the severity of IBD. Furthermore, our study could not exclude bias related to early detection of PCa due to clinically occurred as early exposure to serum PSA check at outpatient clinic. There is a possibility of the IBD group being more likely to be exposed to PSA laboratory exam earlier than controls, which is difficult to eliminate in epidemiologic studies even with strict study design based on observational data received from the registry. Finally, further study that is based on Korean NHIS database should be performed to update the result of the present study, including more recent database.

For these reasons, the results of the present study should be interpreted carefully. It is meaningful to generate hypotheses through tendencies and to verify those hypotheses through large-scale studies. This suggests that strict follow-up is recommendable because patients with IBD may be more likely to be diagnosed PCa, which may serve as a basis for further investigation into the relationship between the two.

5. Conclusion

IBD was associated with an increased incidence of PCa, and it was more significant in UC than in CD. The incidence rate of all-cause death was significantly lower in the group that diagnosed PCa after the onset of IBD than in the group that diagnosed PCa without IBD. Clinicians should explain to patients with IBD that they are at higher risk of being diagnosed with PCa and recommend appropriate screening.

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Author contributions

GJ: Data collection, Data analysis, Manuscript writing. JKK: Project development, Manuscript editing. HK: Data management, Data analysis. JL: Data management, Data analysis. SKH: Project development, Manuscript editing. All the authors approved and contributed to the final manuscript.

Data availability statement

All data disclosure is not possible due to the policy of National Health Insurance Corporation.

Conflicts of interest

This study was conducted in the absence of commercial or financial relationships that could be interpreted as potential conflicts of interest. The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2024.05.001.

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