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Cancer Risk in Patients with Intestinal Behçet's Disease: A Nationwide Population-Based Study

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Background/Aims: The relationship between intestinal Behçet's disease (BD) and cancer remains unclear. We conducted a nationwide, population-based study to determine the risk of cancer in patients with intestinal BD. **Methods:** Using the National Health Insurance claims records, we collected data on 365 patients who had been diagnosed with intestinal BD between 2011 and 2014. Standardized incidence ratios (SIRs) of overall and site-specific cancers in patients with intestinal BD in comparison with the general population were calculated. **Results:** Among 167 men with intestinal BD, four cases of cancer were observed; among 191 women with BD, eight cases of cancer were observed. The risk of all cancers was significantly higher in women with intestinal BD than in women of the general population (SIR, 4.27; 95% confidence interval [CI], 1.84 to 8.41). However, in men with intestinal BD, the risk of all cancers was not significantly higher than that in men of the general population (SIR, 2.08; 95% CI, 0.57 to 5.33). The risk of hematologic cancer was significantly higher in both men and women with intestinal BD than in their counterparts in the general population (SIR, 23.90; 95% CI, 2.89 to 86.32 in men; SIR, 34.47; 95% CI, 4.17 to 124.51 in women). In particular, patients with intestinal BD showed a higher risk of leukemia and myelodysplastic syndrome than the general population. **Conclusions:** Patients with intestinal BD demonstrated a higher risk of hematologic cancer, especially leukemia, than the general population. Furthermore, women with intestinal BD showed a higher risk of all cancers. **(Gut Liver 2018;12:433-439)**

Key Words: Intestinal Behçet's disease; Neoplasms; Population-based

INTRODUCTION

Behçet's disease (BD) is a chronic, multisystemic, immune-mediated disorder that is characterized by recurrent oral and/or genital ulcers, arthritis, and skin manifestations, as well as ocular, vascular, neurological, or intestinal involvement.[1,2] Immune-mediated diseases, which result from a dysregulated and hyperactive immune response, often cause chronic inflammation,[3,4] which can in turn, through inflammatory mediators, cause malignant cell transformation and carcinogenesis in surrounding tissues.[3,4] In addition, the immunomodulators used to treat immune-mediated diseases may affect cancer risk.[5] Indeed, several studies have demonstrated that a variety of systemic, inflammatory, and rheumatic autoimmune diseases (particularly rheumatoid arthritis [RA], systemic lupus erythematosus [SLE], Sjogren's syndrome, systemic sclerosis, and dermatomyositis), are associated with an increased risk of malignancy, especially lymphoma.[6,7] In a few case series and case reports, BD has been sporadically associated with malignancy; however, the results of these investigations remain controversial.[8-10] In particular, a number of studies have reported that BD is associated with hematologic diseases such as myelodysplastic syndrome (MDS) and aplastic anemia (AA), as well as with hematologic cancers.[8,9,11,12]

Intestinal BD is diagnosed when there are typical ulcerative lesions in the gastrointestinal (GI) tract and clinical findings that meet the diagnostic criteria for BD.[13,14] Given that Crohn's disease (CD) and ulcerative colitis (UC) increase the risk of intes-

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tinal cancer, probably because they involve chronic inflammation of intestine,[15-17] intestinal BD may also confer a high risk of colorectal cancer (CRC). However, until now, no data have been available regarding the risk of CRC in patients with intestinal BD. Thus, it is not known whether patients with intestinal BD require CRC surveillance in the same way as those with CD or UC do.

Additionally, because intestinal BD, similarly to CD and UC, involves extraintestinal organs, it may increase the risk of extraintestinal cancers. However, the association between intestinal BD and extraintestinal cancer also remains unclear. Several studies have evaluated the relationship between BD and cancer.[8-10] However, most of them were hospital-based chart reviews or case reports with inconsistent results, and none of them focused on intestinal BD. A number of Western population-based studies have provided useful information regarding cancer risk in CD and UC. It follows that a population-based study into this matter in East Asia, where the prevalence of intestinal BD is higher than in the West, is also necessary. Such a population-based study will allow us to understand the association between intestinal BD and cancer risk in a better way.

As the South Korean government operates a mandatory nationwide insurance system (National Health Insurance [NHI]), all information regarding healthcare use is entered into a comprehensive database that is operated by the Health Insurance and Review Agency (HIRA). Thus, the HIRA database provides reliable information that allows us to study the national epidemiology of intestinal BD. In the present study, we conducted a nationwide, population-based study using the HIRA database to determine the risk of all cancers, as well as that of site-specific cancers, in patients with intestinal BD.

MATERIALS AND METHODS

1. Data source

This study used data that were provided by the NHI, which provides mandatory universal health insurance that covers all health services in South Korea, including admission, ambulatory care, and pharmaceutical services. Medical institutions submit information regarding healthcare use via an electronic form for reimbursement purposes; this information is integrated into the HIRA claims database, which covers the entire population of South Korea (51 million). The database contains information on all patients, including demographic characteristics; history of ambulatory care; principal diagnosis and comorbidities, as defined by the International Classification of Disease, 10th revision (ICD-10), prescriptions; and procedures.

2. Patient identification

In the present study, BD was diagnosed using the International Study Group diagnostic criteria for BD (recurrent oral ulceration plus two of the following criteria: recurrent genital ulceration, eye lesions, skin lesions, positive pathergy test).[1] To ensure accurate diagnosis, intestinal BD was only determined in cases that met the following three criteria: appropriate diagnostic code (ICD-10: M35.2), performance of colonoscopy, prescription of 5-aminosalicylic acid (5-ASA) from a gastroenterology clinic for >1 month.[18] Because 5-ASA is not used in the treatment of other organ involvement but only for intestinal involvement in BD, a prescription of 5-ASA can be regarded as confirmation of an intestinal BD diagnosis. It was for this reason that prescription of 5-ASA was included in the definition of intestinal BD, and the start date of the 5-ASA prescription was regarded as the date of intestinal BD diagnosis.

Beginning in 2006, the NHI initiated a registration program for 138 rare intractable diseases (RIDs), including BD, in order to subsidize the medical expenses of patients with RIDs. The diagnosis of BD must be made based on very strict diagnostic criteria (the International Study Group diagnostic criteria for BD) provided by the RID system and must be reviewed by the corresponding healthcare institution before being submitted to the NHI. Thus, data regarding RIDs are verified and reliable. However, intestinal BD cannot be identified separately in the RID program. In other words, only BD, but not intestinal BD, can be identified by the RID code (V139). Moreover, in South Korea, some patients may refuse to be registered in the RID program because job opportunities may be limited if they are registered in the RID program. Therefore, some patients with BD may have been missed through the RID program. For these reasons, we defined intestinal BD as cases that met the above three criteria rather than defining it with RID code. Instead, we investigated the proportion of patients with the RID code (V139) among patients who met the above three criteria.

The source population for this study consisted of all patients with NHI claims data between 2010 and 2014. Because previous prevalent cases may have confounded incidence, we established a washout period of 1 year. Ultimately, we analyzed patients who had been diagnosed with intestinal BD between January 1, 2011 and December 31, 2014.

3. Ascertainment of cancer incidence rates

To calculate the standardized incidence ratio (SIR) of cancer, we needed to determine the cancer incidence rate of the general population. For achieving this, data were taken from the National Cancer Registry (NCR). The NCR is widely used as an official source of cancer data in South Korea. Indeed, one South Korean study reported that when patients admitted to hospitals because of cancer were regarded as incident cases, cancer incidence rates were comparable between the NCR and insurance claims data.[19] Based on this previous study, we defined incident cancer cases as those who had been admitted to hospital because of cancer (ICD-10: C00-C96).

Furthermore, we investigated the number of incident cases of MDS (ICD-10: D46) and AA (ICD-10: D61) because many

previous studies have reported that BD is associated with these diseases.[8,9,11] We defined incident cases of MDS and AA as those who had been admitted to the hospital because of these diseases.

4. Statistical analysis

To determine whether patients with intestinal BD had a higher risk of cancer incidence than the general population, we calculated the SIR (a ratio of observed to expected cancers) of all cancers and of site-specific cancers in these patients. The number of newly diagnosed cancer cases constituted the number of observed cancer cases. The expected number of cancer cases was calculated by multiplying the 2013 cancer incidence rate of the general population (as reported by the NCR and standardized for sex and age) with the person-years of patients with intestinal BD. The 95% confidence intervals (CIs) of the SIRs were calculated using the Poisson distribution.

5. Ethical considerations

All identifiable personal information in medical records was de-identified to comply with the privacy rule of the Health Insurance Portability and Accountability Act. In addition, as the information in the HIRA database is encrypted, the database does not contain personal identifiers. This study protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University (IRB number: 4-2014-0796).

RESULTS

1. Study population

In total, 365 patients with intestinal BD were newly diagnosed between 2011 and 2014. Of 365 patients, 308 (84.4%) met the RID code (V139). We excluded seven patients with an existing cancer, and 358 patients with intestinal BD were included in the present study; they were followed up until December 31, 2014 (Fig. 1).

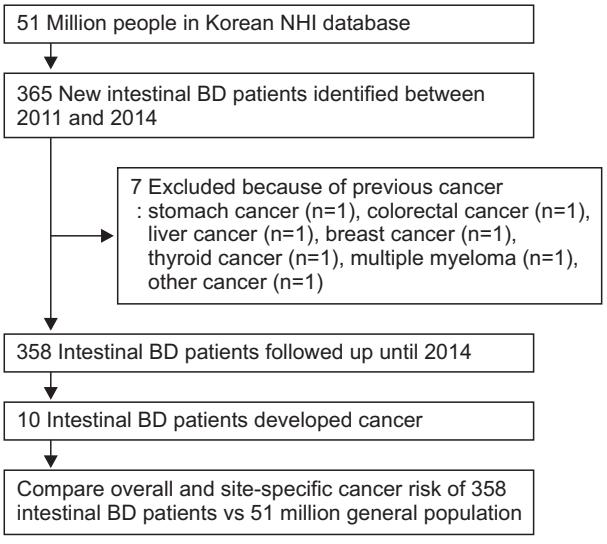

Fig. 1. Flow chart of the study process.
NHI, National Health Insurance; BD, Behçet's disease.

The 358 patients with intestinal BD were followed for 715 person-years (median follow-up time, 1.93 years; range, 0.003 to 3.96 years). The demographic and clinical characteristics of the study population are presented in Table 1. The mean age at BD diagnosis was 43.9±14.4 years, and 46.7% of the patients were men.

2. Cancer risk in patients with intestinal BD

The SIRs of site-specific cancers in patients with intestinal BD are presented in Table 2. Among the 167 men with intestinal BD, four cases of cancer were observed (vs 1.92 expected); this did not constitute a significant difference in the risk of all cancers between men with intestinal BD and those in the general population (SIR, 2.08; 95% CI, 0.57 to 5.33). Regarding solid cancers in men, one developed stomach cancer (vs 0.36 expected: SIR, 2.82; 95% CI, 0.07 to 15.68) and one developed CRC (vs 0.29 expected: SIR, 3.48; 95% CI, 0.09 to 19.38). The risk of solid cancer was not significantly higher in men with intestinal BD than in the general population (SIR, 1.15; 95% CI, 0.14 to 4.17). In contrast, men with intestinal BD did have a significantly higher incidence of hematologic cancer (SIR, 23.90; 95% CI, 2.89 to 86.32); two developed leukemia (vs 0.03 expected: SIR, 79.18; 95% CI, 9.59 to 286.02).

Among the 191 women with intestinal BD, eight cases of cancer were observed (vs 1.87 expected); thus, such women were at a higher risk of all cancers than those in the general population (SIR, 4.27; 95% CI, 1.84 to 8.41). Women with intestinal BD also had a higher risk of hematologic cancer (SIR, 34.47; 95% CI, 4.17

Table 1. Baseline Characteristics of the Study Population

Characteristic	No. (%)	Person-year
Total	358	715
Sex		
Men	167 (46.7)	348
Women	191 (53.4)	367
Age at diagnosis, yr		
<40	129 (36.0)	268
≥40	229 (64.0)	447
Thiopurines ever use		
No	231 (64.5)	433
Yes	127 (35.5)	282
Biologics ever use		
No	341 (95.3)	686
Infliximab	9 (2.5)	15
Adalimumab	8 (2.2)	14
Thiopurines and biologics ever use		
No	344 (96.1)	690
Yes	14 (3.9)	25

Table 2. Risk of Site-Specific Cancer in Patients with Intestinal Behçet's Disease

Cancer (ICD-10)	Men			Women		
	Observed, n	Expected, n	SIR (95% CI)	Observed, n	Expected, n	SIR (95% CI)
All cancer (C00–C96)	4	1.92	2.08 (0.57–5.33)	8	1.87	4.27 (1.84–8.41)
Solid cancer	2	1.73	1.15 (0.14–4.17)	4	1.74	2.29 (0.63–5.87)
Stomach (C16)	1	0.36	2.82 (0.07–15.68)	-		
Colon and rectum (C18–C20)	1	0.29	3.48 (0.09–19.38)	-		
Corpus uteri (C54)	-			1	0.05	21.67 (0.55–120.74)
Ovary (C56)	-			1	0.04	24.70 (0.62–137.60)
Kidney (C64)	-			1	0.02	48.34 (1.22–269.32)
Thyroid (C73)	-			1	0.71	1.41 (0.04–7.87)
Hematological cancer	2	0.08	23.90 (2.89–86.32)	2	0.06	34.47 (4.17–124.51)
Non-Hodgkin lymphoma (C82–C85, C96)	-			1	0.03	31.73 (0.80–176.79)
Leukemia (C91–C95)	2	0.03	79.18 (9.59–286.02)	1	0.02	56.24 (1.42–313.32)
Other (remaining cancer codes)	-			2*	0.07	27.44 (3.32–99.11)

ICD-10, International Classification of Diseases 10th revision; SIR, standardized incidence ratio; CI, confidence interval.
*C88.9 (malignant immunoproliferative disease, unspecified) and C78.6 (secondary malignant neoplasm of retroperitoneum and peritoneum).

Table 3. Demographic and Clinical Characteristics of Intestinal Behçet's Disease Patients with Cancer

Patient no	Sex	Age, yr*	Cancer type	Intestinal BD duration until cancer diagnosis, yr	BD duration until cancer diagnosis, yr	Corticosteroids use	Thiopurines use	Biologics use
1	M	69	Stomach	0.94	1.31	No	No	No
2	M	47	Sigmoid colon	0.03	2.08	No	No	No
3	F	39	Corpus uteri	0.90	2.04	No	No	No
4	F	27	Kidney	0.15	2.37	No	No	No
5	F	51	Thyroid	0.03	0.27	Yes	No	No
6	M	62	Leukemia	0.93	1.49	Yes	Yes†	No
7	M	58	Leukemia	1.19	1.24	Yes	No	No
8	F	51	Leukemia	0.81	3.00	Yes	No	Yes
9	F	56	Other (C88.9‡)	1.54	2.08	No	No	No
10	F	55	Ovary, non-Hodgkin lymphoma, and other (C78.6‡)	2.26	3.72	Yes	Yes§	Yes

BD, Behçet's disease; M, male; F, female.
*Age at the time of cancer diagnosis; †Azathioprine 25 mg for 2 months; ‡C88.9 (malignant immunoproliferative disease, unspecified) and C78.6 (secondary malignant neoplasm of retroperitoneum and peritoneum); §Azathioprine 50 mg for 10 months.

to 124.51); one developed non-Hodgkin lymphoma (NHL) (vs 0.03 expected: SIR, 31.73; 95% CI, 0.80 to 176.79) and one developed leukemia (vs 0.02 expected: SIR, 56.24; 95% CI, 1.42 to 313.32). Regarding solid cancers, there was one case of corpus uteri cancer (SIR, 21.67; 95% CI, 0.55 to 120.74), one of ovarian cancer (SIR, 24.70; 95% CI, 0.62 to 137.60), one of renal cancer (SIR, 48.34; 95% CI, 1.22 to 269.32), and one of thyroid cancer (SIR, 1.41; 95% CI, 0.04 to 7.87) among the women with intestinal BD. The risk of renal cancer was significantly higher in women with intestinal BD than in the general population; however, the risk of all solid cancers was not significantly higher (SIR, 2.29; 95% CI, 0.63 to 5.87).

The demographic and clinical data of patients who developed cancer during the study period are shown in Table 3. The mean age at cancer diagnosis was 51.5±11.9 years, and the median disease duration until the time of cancer diagnosis was 0.91 years (range, 0.03 to 2.26 years). One patient (No. 10) developed both ovarian cancer and NHL; she was treated using thiopurines and biologics before her NHL diagnosis. Of the three patients who developed leukemia, two (Nos. 6 and 8) had been treated using thiopurines and biologics before their leukemia diagnosis.

Because many studies have reported that BD is associated with MDS and AA,[8,9,11] we further investigated the risk of these diseases in patients with BD in the present study. The result showed that one man and one woman developed MDS after their intestinal BD diagnosis; it followed that patients with

intestinal BD had a significantly higher risk of MDS than the general population (vs 0.008 expected: SIR, 118.62; 95% CI, 3.00 to 660.88 in men and vs 0.005 expected: SIR, 218.98; 95% CI, 5.54 to 1220.06 in women). Additionally, three of the women in the present study had developed MDS before their intestinal BD diagnosis. The SIR of AA in patients with intestinal BD were not calculated because the incidence rate of AA in the general population was not available; nonetheless, we identified four patients (two men and two women) who developed AA after their intestinal BD diagnosis.

DISCUSSION

In this first population-based analysis on cancer risk in intestinal BD, we found that patients with intestinal BD (both men and women) had a higher risk of hematologic cancer, especially leukemia. Although men with intestinal BD were not at increased risk of all cancers, women with intestinal BD were.

Given that BD is an immune-mediated disease, it is interesting, but not surprising, that patients with intestinal BD had a higher risk of hematological cancer in the present study. This result corroborates previous studies reporting higher risks of hematological cancers in patients with autoimmune diseases such as RA, SLE, and Sjogren's syndrome.[6,7] Additionally, several hospital-based studies have reported that BD is associated with hematological cancers, especially MDS.[8,9,11] On the same note, two recent Taiwanese population-based studies showed that patients with BD had a higher risk of hematological malignancy (SIR, 4.2), especially NHL (SIR, 6.2 to 8.3).[20,21] The present study also demonstrated that patients with intestinal BD had a higher risk of hematologic cancer and MDS than the general population. Similarly, a South Korean hospital-based study indicated that intestinal ulceration was a characteristic finding in BD associated with bone marrow failure such as MDS and AA.[12] Although the pathogenesis of hematologic cancers in patients with intestinal BD is unclear, several mechanisms linking intestinal BD and hematologic cancers have been posited. Firstly, BD may have affect bone marrow cells. Several inflammatory cytokines, including tumor necrosis factor-α (TNF-α) interferon-γ, interleukin (IL)-6, and IL-8, play a role in the pathophysiology of both BD and hematologic cancers.[22-25] High TNF-α expression has also been implicated in the increased reactive oxygen species (ROS) production that is observed in $CD34^+$ bone marrow cells.[24] Such frequent cytokine-mediated stimuli, as well as increased ROS production by neutrophils, may play a role in the development of hematologic cancers. Secondly, immune-mediated diseases and hematological cancers have similar genetic susceptibilities and environmental triggers (e.g., Epstein-Barr virus infection).[26] These shared factors may be involved in the development of hematologic cancers in patients with intestinal BD. Indeed, one previous study reported that the cancer risk in patients with BD was highest within the first-year of follow-up, with 75% of hematological malignancies found within the first year.[20] The authors also emphasized that hematological malignancies appear earlier than non-hematological malignancies.[20] Our results also indicated that the risk of hematological cancer was higher in the early stage of the disease, because we could only investigate cancer risk at early stage of the disease (the median follow-up duration after intestinal BD diagnosis was 2 years). The early occurrence of hematological cancers in patients with intestinal BD may be due to the pathophysiological mechanisms that are shared by the diseases. Based on our results, we would suggest that hematological malignancies be screened for early after intestinal BD diagnosis. Thirdly, intestinal BD and hematologic cancers are linked in that immune dysregulation in intestinal BD may compromise immune surveillance against neoplasia and thus allow dysplastic cells to escape detection by the immune system. Fourthly, immunosuppressive drugs administered for intestinal BD may increase hematological malignancy risk. In fact, in the present study, thiopurines and/or biologics had been given to three out of four patients who developed hematological cancer. Finally, the disruption of the GI tract barrier caused by intestinal BD may expose patients to challenge from various microorganism antigens, leading to immune dysregulation that contributes to the development of neoplasia. Some studies support this model.[8,9] For instance, in a Chinese study, GI involvement was identified as an independent risk factor for malignancies, in patients with BD.[8] Another South Korean study also demonstrated that intestinal involvement was more frequent in BD patients with malignancy than in those without.[9]

In particular, patients with intestinal BD had a higher risk of leukemia; the concomitant occurrence of BD and leukemia has been found in a few case reports.[27-29] Leukemia may be associated with BD because (1) tumor-associated antigens form immune complexes and cause vascular damage, (2) leukemic cells directly affect the vascular wall, or (3) antibodies directed against leukemic cells cross-react with endothelial cells and lead to direct vascular damage.[30]

In contrast, the risk of solid cancers was not significantly higher in patients with intestinal BD than in the general population, except for renal cancer in women. Both CD and UC increase the risk of intestinal cancer, probably because they involve chronic intestinal inflammation.[15-17] Therefore, we speculate that intestinal BD is associated with a higher risk of CRC as well, especially colon cancer that is confined to the ileocecal region, which is the most commonly involved region in cases of intestinal BD. In support of this claim, one previous case report showed colon cancer arising in an ileocecal ulcer scar that had been caused by intestinal BD.[31] In addition, a Chinese study involving 41 BD patients who had developed malignancies reported that CRC was the most common solid tumor associated with BD.[8] However, contrary to our expectation, only one patient in the present study developed sigmoid colon cancer, and intestinal BD was not significantly associated with a higher risk

of colon cancer. Although CRC surveillance is recommended in patients with CD or UC,[32] it may not be necessary in patients with intestinal BD. The short duration of follow-up in the present study meant that we could only assess cancer risk in the early stages of BD; we could not analyze the long-term cancer risk. Therefore, it may be that we found an increased risk of hematologic cancer, but not solid cancer including colon cancer, because hematological cancer develops faster than solid cancer after it has been triggered. In future, extended, long-term studies are needed to clarify the causal relationship between intestinal BD and colon cancer.

Meanwhile, the risk of renal cancer was higher in women with intestinal BD than those of the general population (SIR, 48.3; 95% CI, 1.2 to 269.3). Even though only a single woman with BD developed renal cancer, the result reached statistical significance because the number of patients with intestinal BD was very small, and because renal cancer was very rare in the general population. Therefore, it may not be that women with intestinal BD really had a higher risk of renal cancer. In future, large-scale studies are required to identify solid cancers that are associated with intestinal BD.

In the present study, the risk of all cancers was significantly increased in women with intestinal BD (SIR, 4.3; 95% CI, 1.8 to 8.4), but not in men with intestinal BD (SIR, 2.1; 95% CI, 0.6 to 5.3). This corroborates a Taiwanese population-based study showing that women with BD (SIR, 1.80; 95% CI, 1.14 to 2.7), but not men with BD (SIR, 1.08; 95% CI, 0.53 to 1.98), have a higher risk of all cancers.[20] Moreover, a Chinese study also revealed that female gender was an independent risk factor for malignancy in patients with BD.[8] Female gender may also be a risk factor for malignancy in patients with intestinal BD.

The present investigation was the first national, population-based study regarding cancer risk in patients with intestinal BD. Nonetheless, it had several limitations. Firstly, even though we used the nationwide NHI database, our cohort of 358 patients with intestinal BD, which yielded 12 cases of cancer, was not large enough to analyze the risk of each site-specific cancer correctly. However, because intestinal BD is very rare, our study is meaningful. Secondly, we did not verify the diagnostic accuracy of intestinal BD. As we used insurance claims data, it is possible that some patients with intestinal BD had been missed, or that patients without intestinal BD had been misdiagnosed. To overcome this limitation, we only included cases of BD that had been diagnosed using the pertinent diagnostic code, wherein a colonoscopy had been performed, and wherein 5-ASA had been prescribed from a gastroenterology clinic for >1 month. Moreover, we confirmed that most patients (84.4%) met the RID code (V139). Therefore, we believe that the definition of intestinal BD diagnosis in the present study was reliable. Thirdly, the duration of follow-up was too short to assess the development of intestinal BD-associated cancers comprehensively. We were able to investigate cancer risk in the early stages of intestinal BD, but not long-term cancer risk. However, our study did not focus on cancer that occurred during treatment subsequent to a diagnosis of intestinal BD, but rather on the relationship between intestinal BD itself and cancer development. We speculate that patients with a predisposition toward developing intestinal BD have dysregulated immune responses even before the diagnosis of intestinal BD. This dysregulated immune response may affect cancer development even in the early stages of the disease. In addition, considering that dysregulated immune responses may occur after the onset of the first symptoms rather than after the objective diagnosis of intestinal BD or it may develop before the onset of the first symptoms as well, incident cancers diagnosed in the early stages of intestinal BD are likely to be related to intestinal BD itself. Fourthly, the risk of cancer was not stratified according to the use of thiopurines and/or biologics because the number of cases was too small. Therefore, there was a limitation in evaluating the effects of medication on cancer development. Fifthly, there might have been a detection bias through enhanced screening of cancer. Patients with intestinal BD are more likely to need health care and physician visits, as compared to the general population, and thus, they may have a higher rate of cancer detection than the general population. Finally, we did not investigate cancer risk in all patients with BD, focusing only on patients with intestinal BD. Future population-based studies must determine the type of cancers associated with BD, as well as whether the risk of various cancers differs between patients who have intestinal BD and those who have BD that does not involve the intestine.

In conclusion, both men and women with intestinal BD had a higher risk of hematologic cancer, especially leukemia. Women with intestinal BD also had a higher risk of all cancers. Further long-term studies are required to clarify the influence of intestinal BD itself, and its medication, on cancer development.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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