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Research Article

The Risk of Lymphoproliferative Disorders and Skin Cancers in Patients with Psoriasis and Inflammatory Bowel Disease Administered Biologics

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Few large population-based studies have investigated the effects of biologic agents on the risks of lymphoproliferative disorders (LPDs) and skin cancers in patients with psoriasis and inflammatory bowel disease (IBD). The objective of this study is to determine the effects of biologic agents on the risk of LPDs and skin cancers in South Korean patients with psoriasis and IBD. The Korean Health Insurance Review and Assessment Service database was reviewed, and patients newly diagnosed with psoriasis or IBD between 2008 and 2019 were included. The effects of exposure to biologics on the risk of cancer were assessed using multivariable Cox regression models. The study included 191,678 patients with psoriasis, 23,640 with Crohn's disease (CD), and 66,730 with ulcerative colitis (UC). The tumor necrosis factor (TNF)-α inhibitor was associated with increased risks of overall lymphoma (adjusted hazard ratio (aHR), 2.93; 95% confidence interval (CI), 1.01–8.50), non-Hodgkin lymphoma (NHL) (aHR, 2.98; 95% CI, 1.02–8.69), and cutaneous lymphoma (aHR, 3.46; 95% CI, 1.07–11.21) in patients with psoriasis. TNF-α inhibitor exposure was associated with increased risks of overall lymphoma (aHR, 3.70; 95% CI, 1.81–7.55) and NHL (aHR, 3.72; 95% CI, 1.81–7.62) in patients with CD, whereas it did not increase the risks of cancer in patients with UC. In conclusion, treatment with TNF-α inhibitors can increase the risks of LPDs in patients with psoriasis or CD.

1. Introduction

Psoriasis is a chronic systemic inflammatory disease that mostly affects the skin, with a prevalence of 1% to 3% in the general population [1–4]. Patients with psoriasis were reported to be at elevated risks for nonmelanoma skin cancer (NMSC) and melanoma [5–9]. The association between psoriasis and lymphoproliferative disorders (LPDs) has also been investigated [10–12]. Because of their effectiveness, biologic therapies targeting tumor necrosis factor (TNF)-α, interleukin (IL)-12/23, IL-17, and IL-23 have markedly altered treatment strategies for patients with severe psoriasis. However, the effects of biologic treatment on the risks of cancer in patients with psoriasis remain unclear.

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a condition characterized by chronic and recurrent inflammation of the intestines. In addition to being at a high risk of intestinal cancer, patients with IBD were reported to be at elevated risks for extraintestinal cancers, such as lymphoma and skin cancers, possibly due to the dysregulation of systemic immunity [13–15]. The risks of skin cancers and LPDs among IBD patients exposed to TNF-α inhibitors, which have been used extensively in biologic therapy for IBD since the 2000s, have been uncertain [16–19].

Biological agents for psoriasis and IBD may increase the risks of LPDs and skin malignancies, which have been associated with systemic immunomodulatory treatment

regimens [16, 20, 21]. The present nationwide population-based study was designed to determine the risks of LPDs and skin cancers in patients with psoriasis and IBD. Subsequently, the effects of biologic therapies on the development of these diseases were assessed in patients with psoriasis and IBD.

2. Methods

2.1. Database. The Korean National Health Insurance (NHI) is a mandatory nationwide system that covers almost the entire population in the Republic of Korea. All forms of NHI claiming data, including patient demographic characteristics, diagnosis using International Classification of Disease 10th revision (ICD-10) codes, ambulatory care, hospitalization, and pharmaceutical services, are maintained by the Health Insurance Review and Assessment Service (HIRA) [22]. The HIRA database includes a rare incurable disease (RID) registry, designed to provide more health insurance benefits to patients with more serious diseases including cancer.

2.2. Study Population. The study protocol was approved by the Institutional Review Board, and the study was performed according to the principles of the Declaration of Helsinki.

Patients with psoriasis were defined as those with at least one documented visit to a physician between 2008 and 2019, at which an ICD-10 code for psoriasis or psoriatic arthritis (L40, M071–073, and M090) was recorded and the patient prescribed topical vitamin D derivatives [23]. Patients with IBD were defined as those with at least one documented visit to a physician between 2008 and 2019, at which an ICD-10 code for CD (K500–509) or UC (K510–519) was recorded and the patient prescribed 5-aminosalicylic acid (5-ASA), an immunomodulator (azathioprine, 6-mercaptopurine, cyclosporine, or methotrexate) or a biologic agent (infliximab or adalimumab) [19].

Patients who had been diagnosed with psoriasis or IBD during a one-year washout period from January to December 2007 were excluded, as were patients diagnosed with any cancer prior to diagnosis with psoriasis or IBD and patients observed for less than 1 year. Ages at 5-year intervals and sex-specific cancer incidence of the general population were obtained from the National Cancer Registry, an official source of cancer data in Korea. Incident LPDs and skin cancers, including Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), cutaneous lymphoma, leukemia, NSMC, and melanoma, in patients with psoriasis and IBD were ascertained by simultaneous assessments of ICD-10 cancer codes and RID registration codes (V193) in the HIRA database to minimize misclassification. Because the ICD-10 codes do not include a definite category of cutaneous lymphoma, individual ICD-10 codes for lymphoma that can manifest as cutaneous lymphoma were included (Supplementary Table 1).

2.3. Exposure to Biologics. Patients with psoriasis were defined as exposed to biologics if after being diagnosed with psoriasis, they had been prescribed at least one dose of a TNF-α inhibitor (etanercept, adalimumab, infliximab, or golimumab) or an IL-12/23 inhibitor (ustekinumab). An IL-17 inhibitor and an IL-23 inhibitor were not included because they have been covered by the Korean NHI since 2017. Patients with IBD were defined as exposed to biologics if after being diagnosed with IBD, they had been prescribed at least one dose of a TNF-α inhibitor (adalimumab or infliximab).

2.4. Outcomes and Statistical Analysis. Cancer incidence rates were calculated per 100,000 person-years. The standardized incidence ratios (SIRs), defined as ratios of observed to expected cancers, were calculated for specific cancers. The numbers of expected cancers were calculated by multiplying the age-, sex-, and year-specific cancer incidence rates of the general population and the person-years of patients with psoriasis or IBD. The 95% confidence intervals (CIs) for SIRs were estimated by applying the Poisson distribution. The effects of exposure to biologics on the risk of specific cancers in patients with psoriasis were assessed by multivariable Cox regression models, after adjusting for age, sex, type of insurance, exposure to immunomodulators or phototherapy during the first 90 days after diagnosis, Charlson comorbidity index (CCI) [24], and exposure to either TNF-α inhibitor or IL-12/23 inhibitor. The effects of exposure to biologics on the risk of specific cancers in patients with IBD were assessed by multivariable Cox regression models, after adjusting age, sex, type of insurance, exposure to immunomodulators during the first 90 days after diagnosis, and CCI. In these analyses, biologics exposure was treated as a variable associated with time, such that risk time would accumulate in nonexposed individuals until they were exposed to biologics. Results were presented as hazard ratios (HRs) with 95% CIs. All statistical tests were two tailed. All statistical analyses were performed using the SAS Enterprise Guide software version 7.1 (SAS Institute, Inc., Cary, NC), with P values less than 0.05 considered statistically significant.

2.5. Sensitivity Analyses. Sensitivity analysis was performed by increasing the minimal number of exposures to the TNF-α inhibitor to two or three times to be classified as the TNF-α inhibitor exposure group. Patients who were exposed to the TNF-α inhibitor but who did not fulfill the defined criteria were included in the nonexposed group.

Sensitivity analysis was also performed to assess the effect of the duration of TNF-α inhibitor exposure on the risks of LPDs and skin cancers. In this analysis, we conducted a nested case-control study in which patients with psoriasis or IBD who developed any cancer were matched with controls who never developed any cancer according to age, sex, index year, and observed duration at a case-to-control ratio of 1 : 2. The duration of TNF-α inhibitor exposure was determined by calculating the cumulative duration of TNF-α inhibitor prescriptions and considering the intervals between prescriptions. The effects of TNF-α inhibitor exposure <2 or ≥ 2 years on the risk of specific cancers in patients with psoriasis or IBD were assessed using

conditional logistic regression models. Results are presented as odds ratios (ORs) with 95% CIs.

3. Results

In total, 191,678 patients with psoriasis, 23,640 patients with CD, and 66,730 patients with UC were included in the study (Supplementary Figure 1). The baseline demographic characteristics of these patients are shown in Table 1. The median TNF-α inhibitor exposure durations were 2.41, 5.22, and 3.24 years for patients with psoriasis, Crohn's disease, and ulcerative colitis, respectively. The median exposure duration to IL-12/23 inhibitors in patients with psoriasis was 2.32 years.

3.1. Risks of Lymphoproliferative Disorders and Skin Cancers in Patients with Psoriasis. Compared with the general population, patients with psoriasis were at significantly higher risks for developing HL (SIR, 3.17; 95% CI, 1.98–4.79), NHL (SIR, 2.02; 95% CI, 1.77–2.30), leukemia (SIR, 1.42; 95% CI, 1.17–1.71), NMSC (SIR, 2.13; 95% CI, 1.88–2.40), and melanoma (SIR, 2.05; 95% CI, 1.37–2.94). Subgroup analyses according to sex showed that the risk of developing melanoma was not significantly higher in male patients with psoriasis (SIR, 1.61; 95% CI, 0.88–2.71), whereas the risk of leukemia in female patients with psoriasis was comparable to that of the general population (SIR, 1.30; 95% CI, 0.89–1.84). Subgroup analyses according to age showed that the risks of leukemia (SIR, 1.16; 95% CI, 0.72–1.78) and melanoma (SIR, 1.87; 95% CI, 0.38–5.46) were not significantly altered in patients with psoriasis under age 40 years (Supplementary Figure 2).

3.2. Risks of Lymphoproliferative Disorders and Skin Cancers in Patients with Psoriasis According to Biologics Exposure. Patients with psoriasis who were exposed to TNF-α inhibitors were at a significantly higher risk for developing NHL (SIR, 7.64; 95% CI, 2.06–19.57) than the general population (Supplementary Table 2). In contrast, the IL-12/23 inhibitor did not significantly alter the risk of any LPD or skin cancer (Supplementary Table 3). After adjusting for age, sex, type of insurance, exposure to immunomodulators or phototherapy, CCI, and exposure to the IL-12/23 inhibitor, treatment with TNF-α inhibitors was found to be associated with increased risks of overall lymphoma (adjusted HR (aHR), 2.93; 95% CI, 1.01–8.50), NHL (aHR, 2.98; 95% CI, 1.02–8.69), and cutaneous lymphoma (aHR, 3.46; 95% CI, 1.07–11.21) in patients with psoriasis. In contrast, treatment with IL-12/23 inhibitors was not associated with an increased risk of any assessable LPD or skin cancer in patients with psoriasis (Table 2).

The results of sensitivity analysis with different definitions for TNF-α inhibitor exposure are shown in Supplementary Table 4. The aHRs for overall lymphoma, NHL, and cutaneous lymphoma in the TNF-α inhibitor exposure ≥2 group were higher than in the TNF-α inhibitor exposure ≥1 group. Although the risk of overall lymphoma and NHL showed marginal statistical significance, the risk of cutaneous B-cell lymphoma (aHR, 4.24; 95% CI, 1.05–17.12) significantly increased with TNF-α inhibitor exposure ≥3. The effect of the duration of TNF-α inhibitor exposure could not be estimated in the adjusted models because of the very limited number of LPDs or skin cancers detected in the TNF-α inhibitor exposure group in this analysis.

3.3. Risks of Lymphoproliferative Disorders and Skin Cancers in Patients with Inflammatory Bowel Disease. Compared with the general population, patients with CD were at a significantly higher risk for developing NHL (SIR, 6.01; 95% CI, 4.40–8.01) and leukemia (SIR, 4.08; 95% CI, 2.64–6.02). Subgroup analyses according to age, however, showed that the risk of leukemia (SIR, 2.12; 95% CI, 0.85–4.36) in CD patients aged <40 years did not differ significantly from that in the general population (Supplementary Figure 3).

Patients with UC were at a significantly higher risk than the general population for developing HL (SIR, 3.21; 95% CI, 1.38–6.32), NHL (SIR, 1.72; 95% CI, 1.34–2.17), leukemia (SIR, 1.68; 95% CI, 1.23–2.24), and NMSC (SIR, 1.52; 95% CI, 1.18–1.93). Subgroup analyses by sex showed that the risk of developing NMSC was not significantly higher in male patients with UC (SIR, 1.35; 95% CI, 0.92–1.90). None of the assessable risks of cancers was increased in younger patients with UC (age <40 years) (Supplementary Figure 4).

3.4. Risks of Lymphoproliferative Disorders and Skin Cancers in Patients with Inflammatory Bowel Disease according to Biologics Exposure. Patients with CD who were exposed to TNF-α inhibitors were at a significantly higher risk for developing NHL (SIR, 9.51; 95% CI, 5.19–15.95) and leukemia (SIR, 5.75; 95% CI, 2.48–11.34) compared with the general population (Supplementary Tables 5–7). After adjusting for age, sex, type of insurance, exposure to immunomodulators, and CCI, exposure to TNF-α inhibitors was associated with increased risks of overall lymphoma (aHR, 3.70; 95% CI, 1.81–7.55) and NHL (aHR, 3.72; 95% CI, 1.81–7.62) in patients with CD, whereas exposure to TNF-α inhibitors did not increase any assessable risks of cancer in patients with UC (Tables 3 and 4).

Including patients whose minimal number of TNF-α inhibitor exposures had been increased to two or three in the TNF-α inhibitor exposure group resulted in even greater risks for overall lymphoma and NHL compared with the previous analysis of patients with CD. In addition, TNF-α inhibitor exposure ≥2 or 3 was associated with an increased risk of HL in patients with CD (Supplementary Tables 8 and 9).

To increase statistical power, the effects of the TNF-α inhibitor on cancer risks were evaluated in all patients with IBD. After adjusting for age, sex, type of insurance, exposure to immunomodulators, and CCI, exposure to TNF-α inhibitors was associated with increased risks of overall lymphoma (aHR, 2.47; 95% CI, 1.36–4.47), NHL (aHR, 2.53; 95% CI, 1.39–4.60), cutaneous lymphoma (aHR, 2.14; 95% CI, 1.02–4.48), cutaneous B-cell lymphoma (aHR, 2.42; 95% CI, 1.10–5.30), and leukemia (aHR, 3.11; 95% CI, 1.45–6.69)

Table 1: Demographic and clinical characteristics of patients with psoriasis, Crohn's disease, and ulcerative colitis.

		Psoriasis *n* (%)	Crohn's disease *n* (%)	Ulcerative colitis *n* (%)
Total		191,678	23,640	66,730
Sex	Male	111,855 (58.4)	16,665 (70.5)	39,999 (59.9)
	Female	79,823 (41.6)	6,975 (29.5)	26,731 (40.1)
Age, years	Mean (SD)	42.72 (17.12)	31.4 (16.1)	42.4 (16.9)
Insurance type	Health insurance	183,821 (95.9)	22,930 (97.0)	64,791 (97.1)
	Medical aids	7,857 (4.1)	710 (3.0)	1,939 (2.9)
Charlson comorbidity index	Mean (SD)	0.76 (1.23)	0.84 (1.13)	0.90 (1.27)
	0	110,781 (57.8)	11,251 (47.6)	32,820 (49.2)
	1	48,679 (25.4)	8,124 (34.4)	19,911 (29.8)
	≥2	32,218 (16.8)	4,265 (18.0)	13,999 (21.0)
Comorbidities	Hypertension	36,129 (18.8)	2,066 (8.7)	11,545 (17.3)
	Type1 DM	1,092 (0.6)	62 (0.3)	282 (0.4)
	Type2 DM	21,782 (11.4)	1,972 (8.3)	7,187 (10.8)
	Dyslipidemia	41,133 (21.5)	5,494 (23.2)	17,310 (25.9)
	Alcoholic liver disease	3,349 (1.7)	289 (1.2)	1,038 (1.6)
	Rheumatoid arthritis	4,475 (2.3)	712 (3.0)	2,218 (3.3)
	Ankylosing spondylitis	813 (0.4)	206 (0.9)	418 (0.6)
	Ulcerative colitis	299 (0.2)		
	COPD	2,620 (1.4)	185 (0.8)	952 (1.4)
	Liver cirrhosis	976 (0.5)	101 (0.4)	289 (0.4)
	Chronic kidney disease	1,230 (0.6)	130 (0.5)	368 (0.6)
	Heart failure	2,384 (1.2)	248 (1.0)	827 (1.2)
Early use[a] of immunomodulators[b]		5,134 (2.7)	11,288 (47.7)	4,378 (6.6)
Early use[a] of phototherapy		25,584 (13.3)		
TNF-α inhibitor use		1,331 (0.7)	7,716 (32.6)	5,119 (7.7)
IL-12/23 inhibitor use		1,991 (1.0)		

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; IL, interleukin; SD, standard deviation; TNF, tumor necrosis factor. [a]Immunomodulators or phototherapy exposure during the first 90 days after diagnosis. [b]Immunomodulators for psoriasis include cyclosporine and methotrexate and those for Crohn's disease and ulcerative colitis include 6-mercaptopurine, azathioprine, cyclosporine, and methotrexate.

(Supplementary Table 10). A duration of TNF-α inhibitor exposure of less than 2 years was not associated with an increased risk of any specific type of cancer, whereas TNF-α inhibitor exposure ≥2 years was associated with marginally increased risks of overall lymphoma (adjusted OR (aOR), 9.33; 95% CI, 0.97–89.72) and NHL (aOR, 9.85; 95% CI, 1.01–96.51) in patients with IBD (Table 5).

4. Discussion

Several previous studies have reported associations between LPDs and psoriasis. The risk of HL was higher in patients hospitalized with psoriasis than in the general population (SIR, 3.3) [12]. In contrast, this association was not observed in a retrospective cohort study [11]. The present study found that this risk was higher in patients with psoriasis. Although several previous studies reported that the risk of NHL was not increased in patients with psoriasis [10–12, 25, 26], the present study showed that patients with psoriasis were at a significantly increased risk of NHL. Consistent with a few previous studies [9, 27, 28], the present study found an increased risk of leukemia in patients with psoriasis.

A meta-analysis showed that the risks of NMSC, including squamous cell carcinoma (SIR, 5.31) and basal cell carcinoma (SIR, 2.00), were significantly higher in patients with psoriasis than in the general population [5]. The association between psoriasis and melanoma, however, is unclear, as several studies have reported that patients with psoriasis are at an increased risk of melanoma [6–9], whereas a meta-analysis of 14 studies failed to show statistically significant results [5]. The present study, which included only a Korean population, found that the risks of both NMSC and melanoma were higher in patients with psoriasis.

Immunomodulating effects mediated by systemic treatments for psoriasis, including biologic agents, may contribute to the development of malignancies. Several prospective cohort studies showed that, compared with the general population, the risk of NMSC (SIR, 1.51–4.28) was higher in patients with psoriasis receiving TNF-α inhibitors [29–32]. However, it was unclear whether these increased risks were attributable to the TNF-α inhibitors or psoriasis itself. A systematic review assessing the effects of TNF-α inhibitors on the risk of cancer in patients with psoriasis did not find any significant association between TNF-α inhibitor and any cancer except for NMSC [33]. The present study found no association between TNF-α inhibitor treatment of patients with psoriasis and the development of skin cancers, although this may have been due to differences in study design and the small number of patients in the present study who developed skin cancer. To our knowledge, however, the present study is the first to show that TNF-α inhibitor treatment is associated with increased risks of NHL,

Table 2: Risks of lymphoproliferative disorders and skin cancers in patients with psoriasis according to exposure to biologics.

Cancer	Biologics	HR	95% CI	*P* value	Adjusted HR[a]	95% CI	*P* value	Adjusted HR[b]	95% CI	*P* value
Overall lymphoma	TNF-α inhibitors	4.05	1.44–11.36	0.008	4.40	1.55–12.56	0.006	2.93	1.01–8.50	0.048
	IL-12/23 inhibitors	0.54	0.07–4.25	0.561	0.57	0.07–4.48	0.591	0.49	0.06–3.79	0.498
Hodgkin lymphoma	TNF-α inhibitors	NE	NE	NE	NE	NE	NE	NE	NE	NE
	IL-12/23 inhibitors	NE	NE	NE	NE	NE	NE	NE	NE	NE
Non-Hodgkin lymphoma	TNF-α inhibitors	4.20	1.49–11.82	0.007	4.57	1.60–13.06	0.005	2.98	1.02–8.69	0.045
	IL-12/23 inhibitors	0.56	0.07–4.40	0.582	0.58	0.07–4.63	0.610	0.50	0.07–3.87	0.511
Cutaneous lymphoma	TNF-α inhibitors	4.83	1.54–15.16	0.007	5.23	1.65–16.55	0.005	3.46	1.07–11.21	0.038
	IL-12/23 inhibitors	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cutaneous T-cell lymphoma	TNF-α inhibitors	4.31	0.60–30.93	0.146	4.27	0.58–31.35	0.153	3.17	0.36–28.29	0.301
	IL-12/23 inhibitors	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cutaneous B-cell lymphoma	TNF-α inhibitors	4.95	1.21–20.19	0.026	5.85	1.43–24.02	0.014	3.25	0.80–13.10	0.098
	IL-12/23 inhibitors	NE	NE	NE	NE	NE	NE	NE	NE	NE
Leukemia	TNF-α inhibitors	2.40	0.33–17.18	0.385	2.40	0.33–17.27	0.385	1.64	0.23–11.64	0.619
	IL-12/23 inhibitors	NE	NE	NE	NE	NE	NE	NE	NE	NE
Nonmelanoma skin cancer	TNF-α inhibitors	1.76	0.42–7.34	0.439	2.45	0.57–10.54	0.229	2.31	0.51–10.46	0.277
	IL-12/23 inhibitors	0.56	0.08–4.20	0.576	0.67	0.09–5.18	0.698	0.66	0.09–5.08	0.690
Melanoma	TNF-α inhibitors	NE	NE	NE	NE	NE	NE	NE	NE	NE
	IL-12/23 inhibitors	NE	NE	NE	NE	NE	NE	NE	NE	NE

CI, confidence interval; HR, hazard ratio; IL, interleukin; NE, not estimated; TNF, tumor necrosis factor. [a]Adjusted for age, sex, insurance type, and exposure to either TNF-α inhibitor or IL-12/23 inhibitor. [b]Adjusted for age, sex, insurance type, exposure to immunomodulators (cyclosporine or methotrexate) or phototherapy, Charlson comorbidity index, and exposure to either TNF-α inhibitor or IL-12/23 inhibitor.

Table 3: Risk of lymphoproliferative disorders and skin cancers in patients with Crohn's disease exposed to tumor necrosis factor-α inhibitors.

Cancer	HR	95% CI	P value	Adjusted HR[a]	95% CI	P value	Adjusted HR[b]	95% CI	P value
Overall lymphoma	1.83	0.95–3.51	0.071	3.69	1.87–7.30	<0.001	3.70	1.81–7.55	<0.001
Hodgkin lymphoma	1.86	0.96–3.58	0.064	NE	NE	NE	NE	NE	NE
Non-Hodgkin lymphoma	4.93	0.25–96.10	0.292	3.75	1.89–7.45	<0.001	3.72	1.81–7.62	<0.001
Cutaneous lymphoma	1.23	0.51–2.96	0.650	2.87	1.15–7.16	0.02	NE	NE	NE
Cutaneous T-cell lymphoma	0.94	0.10–8.90	0.957	NE	NE	NE	NE	NE	NE
Cutaneous B-cell lymphoma	1.29	0.50–3.38	0.600	3.52	1.30–9.55	0.01	NE	NE	NE
Leukemia	1.35	0.57–3.21	0.491	3.47	1.38–8.69	0.01	NE	NE	NE
Nonmelanoma skin cancer	1.36	0.34–5.52	0.667	NE	NE	NE	NE	NE	NE
Melanoma	NE	NE	NE	NE	NE	NE	NE	NE	NE

CI, confidence interval; HR, hazard ratio; NE, not estimated. [a]Adjusted for age, sex, and insurance type. [b]Adjusted for age, sex, insurance type, exposure to immunomodulators (6-mercaptopurine, azathioprine, cyclosporine, or methotrexate), and Charlson comorbidity index.

Table 4: Risk of lymphoproliferative disorders and skin cancers in patients with ulcerative colitis exposed to tumor necrosis factor-α inhibitors.

Cancer	HR	95% CI	P value	Adjusted HR[a]	95% CI	P value	Adjusted HR[b]	95% CI	P value
Overall lymphoma	1.35	0.54–3.36	0.521	1.93	0.77–4.86	0.161	1.52	0.58–3.94	0.392
Hodgkin lymphoma	1.42	0.57–3.55	0.452	NE	NE	NE	NE	NE	NE
Non-Hodgkin lymphoma	2.47	0.30–20.67	0.403	2.03	0.81–5.12	0.132	1.57	0.60–4.08	0.358
Cutaneous lymphoma	1.54	0.55–4.29	0.412	2.12	0.75–5.97	0.155	1.48	0.50–4.38	0.479
Cutaneous T-cell lymphoma	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cutaneous B-cell lymphoma	1.62	0.58–4.54	0.355	2.28	0.81–6.44	0.121	1.67	0.56–4.97	0.355
Leukemia	1.38	0.42–4.49	0.593	2.30	0.70–7.59	0.170	NE	NE	NE
Nonmelanoma skin cancer	0.23	0.03–1.69	0.149	0.45	0.06–3.30	0.435	0.47	0.06–3.47	0.460
Melanoma	NE	NE	NE	NE	NE	NE	NE	NE	NE

CI, confidence interval; HR, hazard ratio; NE, not estimated. [a]Adjusted for age, sex, and insurance type. [b]Adjusted for age, sex, insurance type, exposure to immunomodulators (6-mercaptopurine, azathioprine, cyclosporine, or methotrexate), and Charlson comorbidity index.

cutaneous lymphoma, and overall lymphoma in patients with psoriasis. TNF-α inhibitor has also been associated with an increased risk of lymphoma in patients with rheumatoid arthritis, although these results could not be confirmed [34]. Although long-term extensions of clinical trials have found no association between TNF-α inhibitors and an increased risk of LPDs in patients with psoriasis [31, 35, 36], those studies may have been unable to detect the increased risk of this rare event. Population-based long-term observational studies, such as the present study, may be more suitable to assess these associations. In contrast to TNF-α inhibitors, the IL-12/23 inhibitor was not associated with any increased risk of LPDs or skin cancers in the present study, which is consistent with what was reported previously [37].

A population-based study found that patients with CD were at increased risks for hematologic cancers, overall skin cancers, and overall cancers [38]. Treatment of IBD patients with thiopurines have been associated with increased risks of NMSC and NHL [13, 15, 39, 40]. Patients with IBD have been reported to be at an increased risk of melanoma, an immunogenic tumor, with this risk being especially higher among patients treated with immunosuppressive agents, including thiopurines [41–43]. Another study based on Korean administrative data found that the skin cancer risk was not significantly altered in patients with IBD. In that study, female patients with CD were at an increased risk of NHL and leukemia, whereas female patients with UC were at an increased risk of NHL [19]. The present study, with a longer-term observation period, found that patients with CD and UC were each at increased risks of NHL and leukemia, regardless of sex. Furthermore, the risks of HL and NMSC were higher in overall UC patients and in female patients with UC.

Studies assessing the effect of the TNF-α inhibitor on cancer development in patients with IBD have yielded conflicting results. Patients with IBD who had been treated with thiopurines, TNF-α inhibitors, and methotrexate were found to be at higher risks for hematologic cancers, NHL, overall skin cancers, and overall cancers [38]. Thiopurine or TNF-α inhibitor treatment of patients with IBD was found to be associated with an increased risk of lymphoma [44], and recent treatment of CD patients with biologics, including TNF-α inhibitors, was found to be associated with an increased risk of NMSC (adjusted odds ratio, 2.07). [45] In addition, TNF-α inhibitor treatment for IBD was associated with an increased risk of melanoma [15]. A meta-analysis found that the risk of NHL was higher in CD patients exposed to a TNF-α inhibitor than in the general population (SIR, 3.23) [46]. In contrast to these findings, a meta-analysis of 21 placebo-controlled trials found that TNF-α inhibitor treatment was not associated with an increased overall cancer risk in patients with CD [47]. In addition, TNF-α inhibitor treatment of Japanese patients with IBD was not associated with increased risks of lymphoma and NMSC [18]. Other population-based studies also failed to find any association between TNF-α inhibitor treatment and the risks of lymphoma and skin cancer, including melanoma, in patients with

Table 5: Risk of lymphoproliferative disorders and skin cancers in patients with inflammatory bowel disease according to exposure duration to tumor necrosis factor-α inhibitors.

Cancer	TNF-α inhibitor exposure	Matched OR	95% CI	*P* value	Adjusted OR[a]	95% CI	*P* value	Adjusted OR[b]	95% CI	*P* value
Overall lymphoma	No	1.00	Ref	0.008	1.00	Ref	0.019	1.00	Ref	0.136
	<2 years	2.97	1.01–8.76	0.049	2.55	0.84–7.70	0.098	1.60	0.48–5.40	0.448
	≥2 years	16.17	1.97–132.77	0.010	14.48	1.69–124.25	0.015	9.33	0.97–89.72	0.053
Hodgkin lymphoma	No	1.00	Ref	—	1.00	Ref	—	1.00	Ref	—
	<2 years	NE	NE	NE	NE	NE	NE	NE	NE	NE
	≥2 years	NE	NE	NE	NE	NE	NE	NE	NE	NE
Non-Hodgkin lymphoma	No	1.00	Ref	0.008	1.00	Ref	0.018	1.00	Ref	0.128
	<2 years	2.97	1.01–8.76	0.049	2.57	0.85–7.80	0.095	1.613	0.48–5.46	0.442
	≥2 years	16.17	1.97–132.77	0.010	14.99	1.73–129.92	0.014	9.85	1.01–96.51	0.049
Cutaneous lymphoma	No	1.00	Ref	—	1.00	Ref	—	1.00	Ref	—
	<2 years	2.50	0.67–9.31	0.172	2.48	0.66–9.33	0.180	1.64	0.38–7.14	0.512
	≥2 years	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cutaneous T-cell lymphoma	No	1.00	Ref	—	1.00	Ref	—	1.00	Ref	—
	<2 years	NE	NE	NE	NE	NE	NE	NE	NE	NE
	≥2 years	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cutaneous B-cell lymphoma	No	1.00	Ref	—	1.00	Ref	—	1.00	Ref	—
	<2 years	2.00	0.50–8.00	0.327	1.95	0.49–7.91	0.353	1.65	0.38–7.13	0.500
	≥2 years	NE	NE	NE	NE	NE	NE	NE	NE	NE
Leukemia	No	1.00	Ref	0.073	1.00	Ref	0.086	1.00	Ref	0.243
	<2 years	1.757	0.41–7.55	0.449	1.75	0.40–7.65	0.456	1.42	0.27–7.43	0.678
	≥2 years	7.090	1.32–38.07	0.022	6.61	1.24–35.26	0.027	4.68	0.77–28.27	0.093
Nonmelanoma skin cancer	No	1.00	Ref	0.895	1.00	Ref	0.632	1.00	Ref	0.490
	<2 years	1.33	0.22–7.98	0.753	1.66	0.26–10.70	0.595	0.93	0.10–8.55	0.946
	≥2 years	0.67	0.07–6.41	0.726	0.38	0.04–4.08	0.422	0.15	0.01–3.37	0.233
Melanoma	No	1.00	Ref	—	1.00	Ref	—	1.00	Ref	—
	<2 years	NE	NE	NE	NE	NE	NE	NE	NE	NE
	≥2 years	NE	NE	NE	NE	NE	NE	NE	NE	NE

CI, confidence interval; NE, not estimated; OR, odds ratio; Ref, reference; TNF, tumor necrosis factor. [a]Adjusted for insurance type and Charlson comorbidity index. [b]Adjusted for insurance type, exposure to medications (5-aminosalicylic acid, 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate), and Charlson comorbidity index.

IBD [17, 43, 48, 49]. The present study found that TNF-α inhibitor treatment was significantly associated with increased risks of overall lymphoma and NHL in patients with CD, whereas TNF-α inhibitor treatment was not significantly associated with the development of any LPD in patients with UC. Furthermore, prescription number-dependent increases in the risks of LPDs were observed only in patients with CD. In all patients with IBD, the risks of various LPDs but not skin cancers were associated with TNF-α inhibitor exposure. Among these patients, NHL was most likely to be associated with TNF-α inhibitor exposure because the risk of NHL was dependent on the duration of TNF-α inhibitor exposure in the sensitivity analysis.

In the present study, the effect of the TNF-α inhibitor exposure on the risk of LPDs was more prominent in patients with CD than in patients with UC or psoriasis. This might reflect the longer exposure duration and the higher exposure rate of the TNF-α inhibitor in CD patients. Also, the different baseline risks of LPDs in each disease might also have affected this result.

This study had several limitations. First, results could not be adjusted for several potential confounding factors, such as disease severity, smoking status, drinking habits, obesity, exposure to environmental ultraviolet radiation, and family history of malignancy, because the information was not available in the database. Results, however, were adjusted not only for age, sex, and type of insurance, but for type of treatments and CCI, to determine the baseline risks of LPDs and skin cancers in these patients. Given that IL-12/23 inhibitors, which were also prescribed for severe psoriasis, were not linked to an elevated risk of malignancies, the increased risks of LPDs in psoriasis patients on TNF-inhibitors were less likely to be due to the severity of the disease. In addition, exposure to immunomodulators or phototherapy, which was adjusted in the analyses, can act as indirect markers of disease severity. Second, we could not exclude the possibility that the association between psoriasis and cutaneous lymphoma was due to misdiagnosis. Third, as this study is an observation study based on administrative data, it is susceptible to possible surveillance bias. Fourth, the cutaneous lymphoma codes used in this study were incomplete because analysis was based on the ICD-10 classification system. Lastly, administration of a TNF-α inhibitor may have been selectively avoided in patients with a history of cancer before the wash-out period and in those at a high risk of cancer. This channeling may underestimate the risk of cancer among TNF-α inhibitor users.

In conclusion, compared with the general Korean population, Korean patients with psoriasis were at significantly higher risks for developing HL, NHL, leukemia, NMSC, and melanoma. Treatment with TNF-α inhibitors was associated with increased risks of overall lymphoma, NHL, and cutaneous lymphoma in patients with psoriasis. Patients with CD were at significantly higher risks for developing NHL and leukemia, whereas patients with UC were at significantly higher risks for developing HL, NHL, leukemia, and NMSC. Although the impact of TNF-α inhibitors on LPDs was not noticeable in patients with UC, TNF-α inhibitor exposure was dose-dependently associated with increased risks of overall lymphoma and NHL in patients with CD. Patients with psoriasis and IBD should be carefully monitored for incident LPDs and skin cancers. The potential ability of TNF-α inhibitors to increase LPDs should be considered when choosing these agents for systemic treatment of patients with psoriasis or CD.

Data Availability

The data used to support the findings of this study are available on reasonable request.

Disclosure

The funding sources had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, and approval of the manuscript; and the decision to submit the manuscript for publication. Abstract presentation was done at "https://www.jidonline.org/action/showPdf?pii=S0022-202X%2823%2900627-9."

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

JM Jung, CH Won, and WJ Lee had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design, data acquisition, data analysis/interpretation, drafting manuscript, critical revision of the manuscript, and final approval were done by JM Jung, YJ Kim, SE Chang, MW Lee, CH Won, and WJ Lee. *Statistical analysis* was performed by JM Jung and YJ Kim. *Technical support* was given by YJ Kim and WJ Lee. *Supervision* was done by CH Won and WJ Lee.

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Supplementary Materials

Supplementary Figure 1. Flow Chart of the Study. CD, Crohn's disease; IBD, inflammatory bowel disease; NHI, National Health Insurance; UC, ulcerative colitis.

Supplementary Figure 2. Standardized Incidence Ratios of Lymphoproliferative Disorders and Skin Cancers in Patients with Psoriasis. CI, confidence interval; SIR, standardized incidence ratio. Supplementary Figure 3. Standardized Incidence Ratios of Lymphoproliferative Disorders and Skin Cancers in Patients with Crohn's Disease. CI, confidence interval; SIR, standardized incidence ratio. Supplementary Figure 4. Standardized Incidence Ratios of Lymphoproliferative Disorders and Skin Cancers in Patients with Ulcerative Colitis. CI, confidence interval; SIR, standardized incidence ratio. Supplementary Table 1. International Classification of Disease 10th Revision Codes for Specific Cancers. Supplementary Table 2**.** Standardized Incidence Ratios of Lymphoproliferative Disorders and Skin Cancers in Patients with Psoriasis Exposed and Not Exposed to Tumor Necrosis Factor-α Inhibitor. Supplementary Table 3. Standardized Incidence Ratios of Lymphoproliferative Disorders and Skin Cancers in Patients with Psoriasis Exposed and Not Exposed to Interleukin-12/23 Inhibitor. Supplementary Table 4. The effect of biologics on the risks of lymphoproliferative disorders and skin cancers in patients with psoriasis according to the minimal number of tumor necrosis factor-α inhibitor exposures. Supplementary Table 5. Standardized Incidence Ratios of Lymphoproliferative Disorders and Skin Cancers in Patients with Crohn's Disease Exposed and Not Exposed to Tumor Necrosis Factor-α Inhibitor. Supplementary Table 6. Standardized Incidence Ratios of Lymphoproliferative Disorders and Skin Cancers in Patients with Ulcerative Colitis Exposed and Not Exposed to Tumor Necrosis Factor-α Inhibitor. Supplementary Table 7. Standardized Incidence Ratios of Lymphoproliferative Disorders and Skin Cancers in Patients with Inflammatory Bowel Disease Exposed and Not Exposed to Tumor Necrosis Factor-α Inhibitor. Supplementary Table 8. The effect of biologics on the risks of lymphoproliferative disorders and skin cancers in patients with Crohn's Disease according to the minimal number of tumor necrosis factor-α inhibitor exposures. Supplementary Table 9. The effect of biologics on the risks of lymphoproliferative disorders and skin cancers in patients with ulcerative colitis according to the minimal number of tumor necrosis factor-α inhibitor exposures. Supplementary Table 10. Risk of lymphoproliferative disorders and skin cancers in patients with inflammatory bowel disease exposed to tumor necrosis factor-α inhibitors. (*Supplementary Materials*)

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