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Title: Risk of malignancy in patients with psoriasis: A 15-year nationwide population-based prospective cohort study in Korea

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Key words: Psoriasis, Comorbidity, Malignancy, Prospective cohort study, Korea

Abstract

***Background*:** The association between psoriasis and risk of malignancy has not been thoroughly evaluated in a large longitudinal cohort of Asian population.

***Objective*:** To determine the long-term risk of malignancy in Korean adult patients with psoriasis.

***Methods*:** We conducted a nationwide population-based prospective cohort study with a 15-year observational period. During the baseline period (1997-2000), total 1,773,786 Korean subjects who received health insurance from the National Health Insurance System were enrolled and 5,788 subjects were defined as a psoriasis group. The number of new-onset malignancy was collected during the observational period (2001-2015).

***Results*:** Patients with psoriasis had a higher adjusted hazard ratio (aHR) for development of overall malignancy (aHR 1.08, 95% confidence interval [CI] 1.00-1.18) and gastric cancer (aHR 1.31, 95% CI 1.08-1.58) compared to controls. The risks of non-Hodgkin lymphoma and non-melanoma skin cancer were significantly increased only in patients with psoriasis who received systemic treatments (aHR 2.86, 95% CI 1.07-7.61 and aHR 3.93, 95% CI 1.47-10.47, respectively).

***Conclusion*:** Psoriasis is associated with long-term risk for overall malignancy in Koreans, which was primarily driven by the increased risk of gastric cancer.

INTRODUCTION

A rapidly growing body of research including both scientific and epidemiological data indicates that psoriasis is not an isolated cutaneous disease, but rather a chronic systemic inflammatory disease.[1] An increased level of systemic inflammatory biomarkers including C-reactive protein and erythrocyte sedimentation rate was detected in the blood of patients with

psoriasis.[2-4] Also, a vast range of inflammatory cytokines involved in the pathogenesis of psoriatic skin lesions appears to be released into the systemic circulation of patients with psoriasis.[5-7] In addition, a wealth of epidemiological data supports that systemic inflammation in psoriasis is associated with various comorbidities including cardiometabolic diseases, gastrointestinal diseases, mood disorders, and infections.[8]

Recently, malignancies have been emerged as one of major concerns in patients with psoriasis since not only the chronic systemic inflammation in psoriasis itself but also the immunosuppressive treatments which are inevitable to majority of patients with moderate-to-severe psoriasis may have pro-tumorigenic effects.[9-12] Indeed, meta-analyses and subsequent large cohort studies have reported increased risks of overall malignancy and specific types of malignancies in patients with psoriasis compared to the general population.[13-18] However, most of existing studies were conducted in restricted periods of time without a prospective study design, resulting in limited evidence of direct causal relationship between psoriasis and subsequent development of malignancies. Moreover, these studies have generally included only Caucasian population, which further necessitate long-term large cohort study for Asians given that the ethnical, geographical and socioeconomic backgrounds affect the incidence of specific types of malignancies. A population-based cohort study by Chen *et al*. demonstrated an elevated risk of malignancies in psoriatic patients in Taiwanese population.[19] However, the data they used had a relatively short 7-year follow-up period and did not contain information on confounding factors for the development of cancers, which, in turn, limited the statistical power to support solid association.

By using Korean Cancer Prevention Study (KCPS) cohort of which the data were provided by National Health Insurance System (NHIS), the current study investigated the relative risk of malignancies in patients with psoriasis compared to subjects without psoriasis in Korea. This cohort study, consisting of more than 1.7 million Korean adults, prospectively assessed the risk of 17 types of malignancies for 15 years.

METHODS

Study population

The study design and baseline characteristics of KCPS have been described in our previous studies.[20,21] The NHIS provides health insurance to government employees, teachers, and their dependents. Approximately 96% of South Koreans are covered by the NHIS, through which all Korean citizens are eligible to participate in regular health examinations. The baseline was between 1997 and 2000, with 1,838,570 people aged 20 or older included in the initial cohort. All participants received a medical evaluation provided by the NHIS during the baseline period between 1997 and 2000. We excluded 1,811 individuals whose records of health examinations including body mass index (BMI), alcohol intake, blood pressure, fasting blood glucose level, and total cholesterol level were missing. 60,085 participants who self-reported to have cancer, or cardiovascular diseases (hypertension, heart disease, or stroke) at or prior to the baseline survey and 2,888 participants with an extremely low BMI (<15.0 kg/m^2) or an extremely short stature (<1.3 m) were also excluded. Thus, we initially recruited 1,775,068 subjects from the national sample cohort (Fig. 1). The Institutional Review Boards of Yonsei University approved the study.

Data collection

All enrollees underwent standardized biennial medical examinations. The information on cigarette smoking (never, former, current), alcohol intake (grams of ethanol per day), and current participation in physical exercise (yes or no) were also collected by using self-reported questionnaires. Height and weight were measured, and BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). A standard mercury sphygmomanometer was used to measure blood pressure in a seated position. Total cholesterol and glucose levels were assayed from a fasting serum specimen. Each participating hospital in the examination had external quality control procedures which were supervised by the Korean Association of Laboratory Quality Control. [20]

Ascertainment of diseases associated with psoriasis

We collected outpatient and inpatient records from 1997 through 2015 deposited in the NHIS database. Outpatient treatment and hospitalization for psoriatic diseases were identified according to the 10^{th} revised codes of International Classification of Diseases (ICD-10) code L40. Since our study was specifically aimed to assess the long-term risk for malignancy among the patients with typical plaque type psoriasis, we excluded 1,282 individuals diagnosed with other clinical variants of psoriasis (L40.1; Generalized pustular psoriasis, L40.2; Acrodermatitis continua; L40.3; Pustulosis palmaris et plantaris, and L40.4; Guttate psoriasis). Then, psoriasis was defined using the ICD-10 codes L40.0 (psoriasis vulgaris) and L40.5 (arthropathic psoriasis [M07.0-M07.3]) registered by the responsible physicians. During the 15 years of observational period, 40,166 subjects in the control group had been newly diagnosed with any type of psoriatic diseases and were excluded in outcome analyses (Fig. 1). Patients with psoriasis were further categorized based on the use of systemic anti-psoriatic treatments (Tx). Psoriasis group with systemic Tx consisted of patients with

psoriasis who received treatment codes of phototherapy comprising narrowband ultraviolet B and psoralen plus ultraviolet A, cyclosporine, methotrexate, retinoids, azathioprine, and biologic agents as described and validated previously.[22,23] Control group who never received a diagnostic code consistent with psoriasis was also defined.

Follow-up and outcomes

Using computerized searches of data provided by the NHIS in Korea, outcomes were ascertained from diagnosis listed on hospital discharge summaries. Due to rare emigration from South Korea, follow-up was likely to be close to 100% complete.[24] The principal outcome variable was the development of malignancy based on national cancer registry data and hospitalization records. The observational period was from January 2000 to December 2015. Although Korea has a national cancer registry, reporting was not complete during the time of follow-up and, consequently, hospital admission files were used to identify the first admission event for malignancy. An incident malignancy case was defined based on either a positive report from the national cancer registry or an event of hospital admission for a cancer diagnosis.

Statistical analysis

Psoriasis was classified into 2 groups (psoriasis group without systemic Tx, psoriasis group with systemic Tx), and analyzed by overall psoriasis. Cox proportional hazard models were used to evaluate the association between psoriasis and 17 types of malignancies. Each type of malignancy was analyzed separately. Analyses were adjusted for the following covariates: age at entry (continuous); sex; smoking status (never, former, current smoker); alcohol consumption (yes, no); physical activity (yes, no); BMI (kg/m^2; continuous); hypertension (yes, no); diabetes (yes, no). Two-sided p-values were calculated, and the statistically

significant level was set at 0.05. All statistical analyses were conducted by SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics

Total 1,773,786 subjects were enrolled in a baseline period between 1997 and 2000. During the baseline period, we defined 1,767,998 subjects as a control group and 5,788 subjects as a psoriasis group (Fig. 1). Among subjects in a psoriasis group, 4,855 patients were classified as psoriasis without receiving any systemic Tx, and 933 patients have received at least 1 systemic Tx. Compared to controls, patients with psoriasis were older and had higher BMI, total cholesterol level, and systolic blood pressure. Psoriasis group had a greater portion of female, smokers, and subjects with dyslipidemia and diabetes compared to control group (Table 1).

Incidence of malignancies among study participants

During the 15 years of observational period, the number of new-onset cases of malignancy was 144,814 in the control group and 551 in the psoriasis group, of which 465 cases were in the psoriasis group without systemic Tx and 86 cases in the psoriasis group with systemic Tx. The number of cancer events and incidence rates of each type of malignancy are summarized in Table 2.

Risk of malignancy in patients with psoriasis

Unadjusted hazard ratio with 95% CI demonstrated that patients with psoriasis had a significantly higher risk of overall malignancy, gastric cancer, and non-Hodgkin lymphoma compared to subjects without psoriasis. The risks for the development of each malignancy

were adjusted for several confounding factors and are demonstrated by adjusted hazard ratio (aHR) in Table 3. The aHR with 95% confidence interval (CI) showed significantly increased risks for overall malignancy (aHR 1.08, 95% CI 1.00-1.18) and gastric cancer (aHR 1.31, 95% CI 1.08-1.58) in patients with psoriasis compared to controls, of which the statistical significance was lost when the psoriatic patients without systemic Tx were excluded. The risks of non-Hodgkin lymphoma and non-melanoma skin cancer (NMSC) were significantly increased only in patients with psoriasis who received systemic Tx (aHR 2.86, 95% CI 1.07-7.61 and aHR 3.93, 95% CI 1.47-10.47, respectively).

To further analyze the risk of gastric cancer concretely, we excluded the subjects who were classified as smokers, drinkers, and patients with diabetes, respectively, since the smoking, alcohol consumption, and hyperglycemia are well-known risk factors for the development of gastric cancer.[25-27] In these sensitivity analyses, the positive association between psoriasis and gastric cancer was maintained (Table 4).

DISCUSSION

The findings of this population-based prospective cohort study suggest that patients with psoriasis in Korea are at an increased risk for the development of malignancy. Specifically, Korean psoriatic patients showed 31% increased risk for the development of gastric cancer compared to the general population. The risks of non-Hodgkin lymphoma and NMSC were also observed to be increased although the statistical significance was found in limited subgroups of patients. By this time, the long-term risk of malignancy in patients with psoriasis in Asian population has been scarcely investigated. Since not only the psoriasis-related gene signatures but also the cancer incidence and cancer molecular pathways differ widely based on the ethnicity, cancer risks in Asian psoriasis could not be directly reflected

by results from Caucasian population.[28-31] Considering relatively lower prevalence of psoriasis in Asian countries (0.3-0.4% prevalence rate) compared to western countries,[32] the results from our large-scale cohort consisting of more than 1.7 million participants enabled us to assess the significant risk of malignancy in Korean patients with psoriasis.

One previous population-based cohort study from Asian population was reported by Chen *et al*. demonstrating increased risks of cancers of oropharynx/larynx, liver, colon/rectum, bladder, and skin in Taiwanese patients with psoriasis.[19] However, the data they used did not contain some personal information such as smoking status, alcohol consumption, BMI, and past medical histories which might serve as a risk factors for certain cancers. Our current prospective cohort study collected lifestyle information including smoking status, alcohol consumption, and exercise status as well as history of hypertension and diabetes at biennial intervals, which enabled us to adjust for those confounding factors resulting in more accurate evaluation of risks of malignancy in Korean patients with psoriasis as reported in previous Western studies.[15,18]

Gastric cancer has been rarely investigated as an individual cancer type, otherwise has just been included in the category of digestive tract cancers in previous studies. A population-based cohort study from Taiwanese population demonstrated the absence of association between gastric cancer and psoriasis.[19] Gastric cancer is a cancer type of great interest in Korea as the Korean people have the highest incidence of gastric cancer in the world.[33] In Korea, gastric cancer is the most common cancer in men and has second highest prevalence rate among all cancers in men and women.[34] An increased risk of gastric cancer in psoriatic patients was observed in our study and the positive association was maintained when subjects with risk factors for gastric cancer including smoking, alcohol consumption, and diabetes

were excluded. Exclusion of patients who received systemic treatments for psoriasis did not alter the results, whereas exclusion of patients without systemic treatments resulted in loss of positive association. Some previous researches indicate that gastric cancer and psoriasis have a shared inflammatory pathway in the pathogenesis. Su *et al*. demonstrated that interleukin (IL)-17-producing T helper (Th)17 cells were infiltrated in the gastric cancer tissue, and IL-1β, IL-21, and TGF- β were involved in the gastric cancer development by promoting Th17 cell generation.[35] Another study by Pinchuk *et al*. suggested that Th17 cells are induced during *Helicobacter pylori* infection and gastric cancer in the inflammatory milieu of gastric stroma.[36] In addition, IL-23/IL-17 axis have been reported to be associated with *Helicobacter pylori*-induced inflammation which is a major risk factor for gastric cancer.[37] Taken together, the IL-23/Th17 axis which comprise the major immunopathogenesis of psoriasis may also act as an inflammatory pathway in gastric carcinogenesis via *Helicobacter pylori* infection.[35-38] Although *Helicobacter pylori* infection has been falling due to better living conditions and sanitation, the prevalence is still higher in Korean population compared to the western countries.[39,40] Along with the shared immunopathogenesis of psoriasis and *Helicobacter pylori*-induced gastric cancer, this epidemiological difference might contribute to an increased risk of gastric cancer in psoriatic patients in our cohort, but not in previous Western studies. Still, more tailored researches are needed to elucidate the pathogenic link between gastric cancer and psoriasis.

A positive association between lymphoma and psoriasis has been supported by relatively abundant studies. A retrospective cohort study by Gelfand *et al*. revealed an increased risk of Hodgkin's lymphoma and cutaneous T cell lymphoma (CTCL) in British psoriatic patients.[41] More recent population-based prospective cohort study in UK presented the increased risks of CTCL and all lymphoma excluding CTCL.[15] In these 2 population-based cohort studies,

psoriasis group with systemic Tx showed the highest risks.[15,41] In a meta-analysis with 4 observational studies included, the risk of non-Hodgkin lymphoma was elevated.[13] Our result also showed an increased risk of non-Hodgkin lymphoma across all psoriasis groups though the statistical significance was only found in a psoriasis group with systemic Tx. The proportion of CTCL among non-Hodgkin lymphoma was different between psoriasis group (53.8%) and controls (15.5%). Given that the patients with CTCL are frequently misdiagnosed as having psoriasis in real-world practice, the possibility of misclassification of diseases, which might cause false positive results, should also be considered in the interpretation.

Although there have been conflicting results regarding the association between NMSC and psoriasis, a meta-analysis and a recent population-based cohort study demonstrated higher risks of NMSC in patients with psoriasis compared to general population.[13,15,42] In our study, the positive association was observed only in psoriasis group with systemic Tx.

It is challenging to evaluate the exact effect of chronic inflammatory nature of psoriasis to the development of malignancy in patients with psoriasis as both pro- and anti-inflammatory conditions may have pro-tumorigenic effects.[9-12] Patients with moderate-to-severe psoriasis might be subjected to more severe systemic inflammation compared to those with mild psoriasis.[43,44] Meanwhile, long-term systemic immunosuppressive treatments for those severe patients might obscure the effects of systemic inflammation to the tumorigenesis. On the other hand, a prolonged use of immunosuppressive drugs is another independent risk factor for carcinogenesis.[45] In our results, gastric cancer showed an increased risk in overall psoriasis group and psoriasis group without systemic Tx although the association was lost in the psoriasis group with systemic Tx. This result indicates that as for the association between

psoriasis and gastric cancer, the effect of systemic Tx could be excluded. On the other hand, as for non-Hodgkin lymphoma and NMSC of which the risks are increased only in psoriasis group with systemic Tx, the immunosuppression by the systemic Tx might play a major role in the tumorigenesis. Our results are consistent with previous studies suggesting that lymphoproliferative malignancies and NMSC are the two most common malignancies in solid organ transplant recipients who are exposed to prolonged immunosuppression.[12,45-47]

One of limitations of our study is the possibility of misclassification of diseases in ICD-10 code-based data sets in NHIS. However, we excluded psoriatic patients who got diagnostic code of variants of psoriasis to narrow the psoriasis group down to typical patients since clinical diagnosis of classic plaque type psoriasis is mostly unambiguous. Another limitation is a low absolute number of cancer cases in psoriasis group. Despite the large number of total subjects, the number of patients with psoriasis (n=5,788) as well as the mean age (44.25) was relatively low to analyze the large number of cancer outcomes. This might result in limited statistical power in certain types of cancers, e.g. the possibility of false negative outcomes of thyroid cancer, pancreatic cancer, kidney cancer and non-Hodgkin lymphoma. Lastly, our data set did not include information on disease severity such as Psoriasis Area Severity Index score, which limited the differentiation of the effect of disease severity from that of treatment exposure.

Nevertheless, our study has certain strengths. Using large, population-based database consisting of more than 1.7 million subjects, we defined the explanatory values in the baseline period and prospectively followed the outcomes for 15 years during observational period, which enabled us to assess the temporal relationship between psoriasis and malignancy in Asians. In addition, our study included 17 categories of individual

malignancies in the analysis, providing comprehensive information on risks in patients with psoriasis.

In summary, our study which is the first population-based cohort study on malignancy risk among patients with psoriasis in Korea provides the further evidence that there is an increased risk of overall malignancy in patients with psoriasis. The association between psoriasis and malignancy was primarily driven by the increased risk of gastric cancer. Non-Hodgkin lymphoma and NMSC should be a concern in patients with psoriasis who receive systemic Tx. Future works should more concisely analyze the effect of disease severity and the types of treatment exposure and should adjust for more individual risk factors for each type of cancer.

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Figure legends

Figure 1. Flowchart of study cohort selection.

Table 1. Baseline characteristic of study participants between non-psoriasis and psoriasis

	Control (n=1,767,998)	**Psoriasis (n=5,788)**	**p-value**
	Mean (SD)		
Age, year	43.50 (12.89)	44.25 (12.82)	<.0001
Body mass index, kg/m^2	23.20 (2.92)	23.29 (2.87)	0.013
Total cholesterol, mg/dL	190.11 (36.68)	192.70 (36.92)	<.0001
Systolic Blood Pressure	121.45 (16.36)	122.08 (16.22)	0.003
Fasting Glucose, mg/dL	91.72 (24.07)	92.34 (25.56)	0.062
	% (n)		
Sex (Female)	39.24 (680,320)	34.62 (2,004)	<.0001
Smoking status			<.0001
Ex smokers	8.85	10.79	
Current smokers	36.05	39.53	
Drinking (Yes)	53.46	53.47	0.983
Exercise (Yes)	49.93	50.26	0.615
Dyslipidemia[#]	9.35	10.45	0.004
Hypertension[†]	24.54	24.62	0.892
Diabetes[‡]	4.53	5.32	0.004

SD, standard deviation

[#] Dyslipidemia was defined as total cholesterol ≥240.

[†] Hypertension was defined as systolic blood pressure ≥140mmHg or a history of treatment for hypertension.

[‡] Diabetes was defined as fasting serum glucose ≥126 mg/dL or a history of treatment for diabetes.

Table 2. Incidence rates and adjusted hazard ratios of malignancies in patients with psoriasis compared to the general population

Type of malignancy	Control	Psoriasis		
		Overall psoriasis	No systemic Tx	With systemic Tx
Overall malignancy				
Number of events	144,814	551	465	86
Incidence rate* per 100,000 PY	538.9	598.1	618.8	480.5
Laryngeal cancer				
Number of events	1,273	4	4	0
Incidence rate* per 100,000 PY	4.6	8.3	9.6	0
Esophageal cancer				
Number of events	2,393	10	7	3
Incidence rate* per 100,000 PY	8.8	7.7	6.7	12.4
Thyroid cancer				
Number of events	20,675	71	59	12
Incidence rate* per 100,000 PY	64.9	69.0	69.9	62.6
Lung cancer				
Number of events	12,737	47	41	6
Incidence rate* per 100,000 PY	54.8	64.2	67.3	50.9
Gastric cancer				
Number of events	21,524	105	93	12
Incidence rate* per 100,000 PY	80.3	121.3	132.5	57.0
Colon cancer				
Number of events	14,758	58	50	8
Incidence rate* per 100,000 PY	53.6	59.6	63.5	36.6
Rectal cancer				
Number of events	10,499	38	33	5
Incidence rate* per 100,000 PY	37.6	38.4	41.0	25.0
Liver cancer				
Number of events	17,351	67	56	11
Incidence rate* per 100,000 PY	60.6	60.7	62.2	54.3

Pancreas cancer				
Number of events	5,067	23	23	0
Incidence rate* per 100,000 PY	19.3	20.7	24.9	-
Gall bladder cancer				
Number of events	2,371	6	4	2
Incidence rate* per 100,000 PY	9.8	7.7	7.2	8.8
Kidney cancer				
Number of events	3,765	19	15	4
Incidence rate* per 100,000 PY	12.1	15.7	15.1	20.1
Non-Hodgkin lymphoma				
Number of events	2,329	13	9	4
Incidence rate* per 100,000 PY	8.4	11.7	9.9	20.7
Leukemia				
Number of events	1,794	3	3	0
Incidence rate* per 100,000 PY	6.5	2.3	2.9	-
Prostate cancer				
Number of events	9,339	37	28	9
Incidence rate* per 100,000 PY	63.5	53.3	50.3	66.1
Breast cancer				
Number of events	6,958	20	15	5
Incidence rate* per 100,000 PY	21.3	18.6	17.5	23.3
Cervical cancer				
Number of events	1,794	3	3	0
Incidence rate* per 100,000 PY	14.9	5.3	9.0	-
Non-melanoma skin cancer				
Number of events	1,717	8	4	4
Incidence rate* per 100,000 PY	7.0	8.1	5.2	20.5

CI, confidence interval; HR, hazard ratio; PY, person year; Tx, Anti-psoriatic treatments

* Incidences were standardized to the age distribution in the 2005 Korean population

Table 3. Hazard ratios of malignancies in patients with psoriasis compared to the general population

Type of malignancy	Psoriasis		
	Overall psoriasis	No systemic Tx	With systemic Tx
Overall malignancy			
Unadjusted HR (95% CI)	**1.14 (1.05-1.24)**	**1.15 (1.05-1.27)**	1.09 (0.88-1.35)
Adjusted HR (95% CI) *	**1.08 (1.00-1.18)**	**1.10 (1.00-1.20)**	1.00 (0.81-1.20)
Laryngeal cancer			
Unadjusted HR (95% CI)	0.94 (0.35-2.52)	1.13 (0.42-3.01)	-
Adjusted HR (95% CI) *	0.78 (0.29-2.07)	0.94 (0.35-2.51)	-
Esophageal cancer			
Unadjusted HR (95% CI)	1.26 (0.68-2.35)	1.06 (0.50-2.22)	2.29 (0.74-7.08)
Adjusted HR (95% CI) *	1.06 (0.57-1.98)	0.90 (0.43-1.88)	1.90 (0.61-5.88)
Thyroid cancer			
Unadjusted HR (95% CI)	1.03 (0.82-1.30)	1.03 (0.80-1.33)	1.06 (0.60-1.86)
Adjusted HR (95% CI) *	1.10 (0.87-1.39)	1.08 (0.83-1.39)	1.22 (0.69-2.15)
Lung cancer			
Unadjusted HR (95% CI)	1.11 (0.83-1.48)	1.15 (0.85-1.57)	0.86 (0.39-1.91)
Adjusted HR (95% CI) *	0.95 (0.72-1.27)	1.00 (0.74-1.36)	0.72 (0.33-1.61)
Gastric cancer			
Unadjusted HR (95% CI)	**1.47 (1.21-1.77)**	**1.55 (1.26-1.90)**	1.02 (0.58-1.79)
Adjusted HR (95% CI) *	**1.31 (1.08-1.58)**	**1.40 (1.14-1.71)**	0.87 (0.50-1.53)
Colon cancer			
Unadjusted HR (95% CI)	1.18 (0.91-1.53)	1.22 (0.92-1.61)	0.99 (0.49-1.97)
Adjusted HR (95% CI) *	1.08 (0.84-1.40)	1.13 (0.86-1.49)	0.86 (0.43-1.73)
Rectal cancer			
Unadjusted HR (95% CI)	1.09 (0.79-1.50)	1.13 (0.80-1.59)	0.87 (0.36-2.08)
Adjusted HR (95% CI) *	0.99 (0.72-1.36)	1.04 (0.74-1.46)	0.75 (0.31-1.81)
Liver cancer			

Unadjusted HR (95% CI)	1.16 (0.91-1.47)	1.16 (0.89-1.51)	1.16 (0.64-2.09)
Adjusted HR (95% CI) *	1.01 (0.80-1.28)	1.02 (0.78-1.33)	0.97 (0.53-1.74)
Pancreas cancer			
Unadjusted HR (95% CI)	1.37 (0.91-2.06)	**1.63 (1.09-2.46)**	-
Adjusted HR (95% CI) *	1.24 (0.82-1.86)	1.49 (0.99-2.25)	-
Gall bladder cancer			
Unadjusted HR (95% CI)	0.76 (0.34-1.69)	0.61 (0.23-1.62)	1.55 (0.39-6.16)
Adjusted HR (95% CI) *	0.72 (0.32-1.61)	0.58 (0.22-1.54)	1.42 (0.36-5.69)
Kidney cancer			
Unadjusted HR (95% CI)	1.52 (0.97-2.39)	1.43 (0.86-2.38)	1.94 (0.73-5.16)
Adjusted HR (95% CI) *	1.38 (0.88-2.17)	1.33 (0.80-2.20)	1.66 (0.62-4.42)
Non-Hodgkin Lymphoma			
Unadjusted HR (95% CI)	**1.63 (1.04-2.56)**	1.38 (0.72-2.66)	**3.13 (1.18-8.35)**
Adjusted HR (95% CI) *	1.67 (0.97-2.88)	1.30 (0.68-2.51)	**2.86 (1.07-7.61)**
Leukemia			
Unadjusted HR (95% CI)	0.50 (0.16-1.56)	0.60 (0.19-1.86)	-
Adjusted HR (95% CI) *	0.47 (0.15-1.47)	0.57 (0.18-1.77)	-
Prostate cancer			
Unadjusted HR (95% CI)	1.11 (0.80-1.53)	1.01 (0.70-1.47)	1.53 (0.80-2.94)
Adjusted HR (95% CI) *	0.97 (0.70-1.34)	0.89 (0.61-1.28)	1.37 (0.71-2.63)
Breast cancer			
Unadjusted HR (95% CI)	0.98(0.63-1.52)	0.86 (0.52-1.42)	1.73 (0.72-4.16)
Adjusted HR (95% CI) *	0.98 (0.63-1.52)	0.86 (0.52-1.42)	1.72 (0.71-4.12)
Cervical cancer			
Unadjusted HR (95% CI)	0.33 (0.08-1.30)	0.19 (0.03-1.34)	1.13 (0.16-8.03)
Adjusted HR (95% CI) *	0.33 (0.08-1.33)	0.20 (0.03-1.39)	1.10 (0.15-7.78)
Non-melanoma skin cancer			
Unadjusted HR (95% CI)	1.41 (0.70-2.82)	0.84 (0.32-2.24)	**4.24 (1.59-11.32)**
Adjusted HR (95% CI) *	1.33 (0.66-2.67)	0.81 (0.30-2.14)	**3.93 (1.47-10.47)**

Tx, Anti-psoriatic treatments; HR, hazard ratio; CI, confidence interval

*Adjusted for age, sex, smoking status, alcohol consumption, exercise, body mass index, hypertension and diabetes

Table 4. Sensitivity analysis of risk for gastric cancer in patients with psoriasis

Subgroup	Adjusted hazard ratio (95% Confidence interval)
Primary analysis	1.31 (1.08-1.58)
Limit to never smokers *	1.51 (1.22-1.87)
Limit to alcohol non-users #	1.34 (1.05-1.71)
Limit to subjects without hypertension †	1.37 (1.09-1.73)
Limit to subjects without diabetes mellitus ‡	1.31 (1.08-1.61)

*Adjusted for age, sex, alcohol consumption, exercise, body mass index, hypertension and diabetes

#Adjusted for age, sex, smoking status, exercise, body mass index, hypertension and diabetes

†Adjusted for age, sex, smoking status, alcohol consumption, exercise, body mass index and diabetes

‡Adjusted for age, sex, smoking status, alcohol consumption, exercise, body mass index and hypertension