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Malignancy risk in Korean male patients with ankylosing spondylitis

Bora Nam[1] · Hyoungyoung Kim[1] · Eun Jin Jang[2] · Soo-Kyung Cho[1] · Yoon-Kyoung Sung[1] · Tae-Hwan Kim[1]

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Abstract

The objective of this study is to determine the overall and specific cancer risks in male patients with ankylosing spondylitis (AS). From the claims database of the Health Insurance and Review Assessment, male patients with AS without prior cancer history were selected ($n=21,780$). Stratified random samples of claims data were used as a reference general male population group ($n=342,361$). Incidence rates of overall and types of cancer were presented as number of events per 10,000 person-years with 95% confidence interval (CI). A standardized incidence ratio (SIR) was used to represent the association between AS and cancer, accounting for person-years at risk. Compared to a general male population group, the overall incidence of cancer was increased in male patients with AS (SIR 1.25, 95% CI 1.15–1.36). For specific malignancy types, the risks of male reproductive system malignancy (SIR 1.97, 95% CI 1.59–2.35) and pancreatic cancer (SIR 1.75, 95% CI 1.12–2.37) were increased. Male patients with AS had increased cancer risk, especially for male reproductive system and pancreatic cancer.

Keywords Ankylosing spondylitis · Cancer · Risk · Standardized incidence ratio

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that primarily affects the spine and sacroiliac joints. The prevalence of AS is three times higher in males than females. And there are some differences between sexes in clinical presentation; males are more prone to develop structural damage. The mainstream treatment for AS is non-steroidal anti-inflammatory drugs (NSAIDs), with anti-tumor necrosis factor (anti-TNF) therapy emerging as a treatment option [1]. With these therapies, symptoms of AS such as back pain and stiffness can be managed. However, to date, little attention has been paid to comorbidities that could be linked to AS, such as cancer.

The connection between inflammation and cancer has been recognized since the mid-nineteenth century. Rudolf Ludwig Carl Virchow first suggested that cancer gets initiated from chronic inflammation sites; this is known as the chronic irritation theory [2]. About 20% of cancers are estimated to be associated with chronic inflammation or persistent infections such as the association between inflammatory bowel disease and colorectal carcinoma, Barrett's esophagus and esophageal carcinoma, and hepatitis and hepatocellular carcinoma [3, 4]. Not only organ-localized inflammation but also systemic inflammation seems to be linked to malignancy risk. An association between inflammatory myopathy and cancer is well established; so initial cancer screening is recommended when first diagnosed [5]. Cancer is implicated in other rheumatic diseases such as rheumatoid arthritis [standardized

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✉ Tae-Hwan Kim
thkim@hanyang.ac.kr

Bora Nam
bora871011@gmail.com

Hyoungyoung Kim
khy1027@hotmail.com

Eun Jin Jang
jejstat@gmail.com

Soo-Kyung Cho
aushalten@naver.com

Yoon-Kyoung Sung
sungyk@hanyang.ac.kr

[1] Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Republic of Korea

[2] Department of Information Statistics, Andong National University, Andong, Republic of Korea

incidence ratio (SIR) 1.09, 95% confidence interval (CI) 1.06–1.13] [6], scleroderma (SIR 1.41, 95% CI 1.18–1.68) [7], and primary Sjogren's syndrome [pooled relative risk (RR) 1.53, 95% CI 1.17–1.88] [8].

However, few studies [9–12] have examined cancer risk with AS, and results of these studies were inconsistent. The objective of this study was to assess the risks of overall and site-specific cancer in male patients with AS.

Methods

Data sources

This study used claims data from the Health Insurance and Review Assessment (HIRA), the universal coverage system in South Korea. This system covers approximately 98% of the South Korean population. The claims data of HIRA include a broad range of information including patient demographic characteristics, diagnoses, surgical history, and drug prescriptions [13, 14].

Patients identification

To ensure accurate diagnoses, AS patients were defined as those with diagnosis codes for both AS [International Classification of Disease (ICD)-10 code M45] and rare intractable disease (RID) (code V140). The National Health Insurance (NHI) has registration programs for RIDs, including AS. Through this program, patients with RIDs are responsible for only 10% of their medical expenses. Therefore, before being admitted to the program, diagnoses are made by physicians and reviewed by the healthcare institution. And the criteria of AS in RID system are in accordance with the 1984 Modified New York Criteria. All individuals diagnosed with the two codes between 2012 and 2014 were included. Patients who were female, younger than 19 years, or had prior cancer history were excluded.

Control group

The HIRA provided stratified random samples of claims data with 32 strata (2 sex strata, 16 age strata). Using probabilistic sample extraction methods and validity tests, the sample represented the total population. We used this sample as a control group of a general male population over 19 years. The sample data included diagnoses, treatments, and drugs. Patients with malignancies of the male reproductive system of testicular and prostate cancer were grouped together to protect patient privacy [13, 14].

Observational period

The index date was defined as the date of first recorded claim for AS between 2012 and 2014. Because previous prevalent cancer may confound cancer incidence, we applied a 1-year washout period before the index date to exclude patients with cancer history. Follow-up ended at the time of diagnosis with cancer or the end of the study period (December 31, 2015). Thus, medical records were collected from 2011 to 2015.

Ascertainment of cancer

Overall and site-specific cancers were ascertained using ICD-10 codes (C00–C97). We divided cancer into two main types, hematologic malignancies and solid cancers. Hematologic malignancies were lymphoma (ICD-10: C81–C85), multiple myeloma (ICD-10: C90), leukemia (ICD-10: C91–C95), and unspecified malignant neoplasm of lymphoid, hematopoietic, and related tissue (ICD-10: C96). Others were in the category of solid cancers (ICD-10: C00–C80, C86, C89, C97).

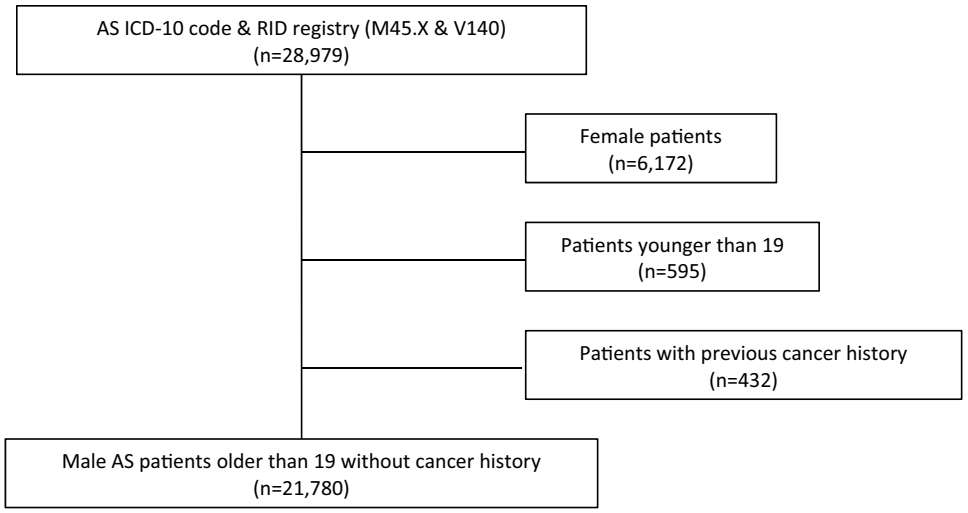
Statistical analysis

To compare distributions of demographic characteristics for the male general population group and male AS patients group, Chi-square test was used for categorical variables and *t* test for continuous variables. *P* values less than 0.05 were considered to be statistically significant. Incidence rate (IR) was presented as number of events per 10,000 person-years with 95% CI. For more accurate comparisons between the male AS patient group and the male general population group, we calculated age-adjusted incidence rates by dividing cancer events in the general population with corresponding age. SIR was defined as the ratio of observed to expected number of cancers in male AS patients, accounting for person-years at risk. SIR with 95% CI was used to represent the association between AS and malignancy.

Results

Demographic characteristics

Of 28,979 patients with AS, 7199 who did not satisfy the criteria were excluded. Therefore, 21,780 patients were included in this study (Fig. 1). The baseline characteristics of the patients are presented in Table 1. AS patients were younger than controls (mean age 39.4 ± 12.7 years vs. 43.7 ± 15.4 years, $P < 0.001$), because AS commonly occurs



AS, ankylosing spondylitis; ICD, international classification of disease; RID, rare intractable disease

Fig. 1 Flow chart of patient selection. AS, ankylosing spondylitis; ICD, International Classification of Disease; RID, rare intractable disease

Table 1 Baseline characteristics of male AS patients group and general male population group

	Male general population group ($n=342,361$)	Male AS patients group ($n=21,780$)	*P* value
Age[a] in years, mean ± SD	43.7 ± 15.4	39.4 ± 12.7	< 0.001
Duration of observation in years, mean ± SD	3.6 ± 0.6	3.3 ± 0.9	< 0.001
Number of comorbidities (%)			
Peptic ulcer disease	5577 (1.6)	1920 (8.8)	< 0.001
Mild liver disease	5223 (1.5)	882 (4.0)	< 0.001
Diabetes mellitus	8101 (2.4)	424 (2.0)	< 0.001
Peripheral vascular disease	2196 (0.6)	103 (0.5)	< 0.001
Cerebrovascular disease	2007 (0.6)	68 (0.3)	< 0.001
Chronic pulmonary disease	6716 (2.0)	234 (1.0)	< 0.001
Renal disease	726 (0.2)	25 (0.1)	0.0022

[a]Patient clinical information as described at index date

AS, ankylosing spondylitis; SD, standard deviation

in younger people [1]. Age differences between male AS patients and the general male population were associated with a high prevalence of other diseases in the control group, except for peptic ulcer disease and mild liver disease.

Cancer risk in patients with ankylosing spondylitis

The 28,979 patients with AS were observed for 71,046 person-years (mean duration of observation 3.26 ± 0.91 years). Among these patients, we observed 552 cases of cancer. The overall risk of cancer was significantly higher in male AS patients than in the general male population (SIR 1.25, 95% CI 1.15–1.36; Table 2). After dividing cancers into two main types, hematologic and solid malignancies, cancer risk was still higher for both types (SIR 1.70, 95% CI 1.06–2.34 for hematologic; SIR 1.24, 95% CI 1.13–1.34 for solid; Table 2).

The SIRs for different cancer types in males with AS are shown in Figs. 2 and 3. Male AS patients exhibited a greater risk of developing malignancies of the male reproductive system (SIR 1.97, 95% CI 1.59–2.35), which consisted of the types testicular and prostate cancer. Only one case of testicular cancer was observed for the entire follow-up period in the male AS patients. The others were prostate cancers (101 cases). Risk of pancreatic cancer was also higher in the AS patients than the general population (SIR 1.75, 95% CI 1.12–2.37).

Common cancer types in patients with ankylosing spondylitis

The most common types of cancer in male patients with AS are listed in Table 3. Prostate was the leading type of cancer

Table 2 Standardized incidence ratios for malignancies

Type of Malignancy	Male general population group	Male AS patients group		SIR (95% CI)
	IR (95% CI)	Age-adjusted expected IR	IR (95% CI)	
All malignancies	102.47 (100.68–104.26)	64.94 (63.68–66.19)	77.70 (71.21–84.18)	1.25 (1.15–1.36)
Hematologic malignancies	3.36 (3.04–3.69)	2.33 (2.08–2.58)	3.80 (2.37–5.23)	1.70 (1.06–2.34)
Solid malignancies	99.11 (97.35–100.87)	62.61 (61.38–63.84)	73.90 (67.57–80.22)	1.24 (1.13–1.34)

Incidence rate is the number of events per 10,000 person-years with 95% CI

AS, ankylosing spondylitis; IR, incidence rate; CI, confidence interval; SIR, standardized incidence ratio

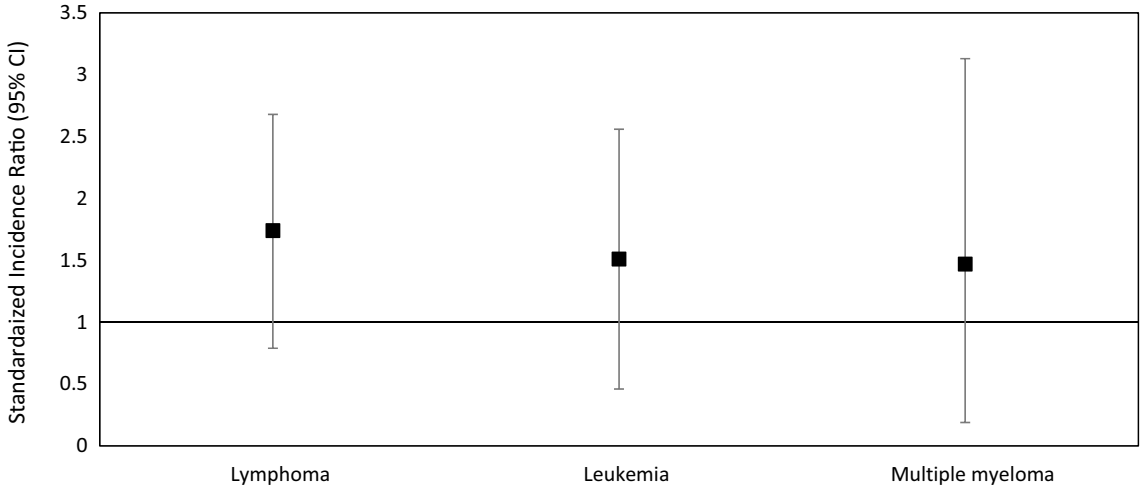
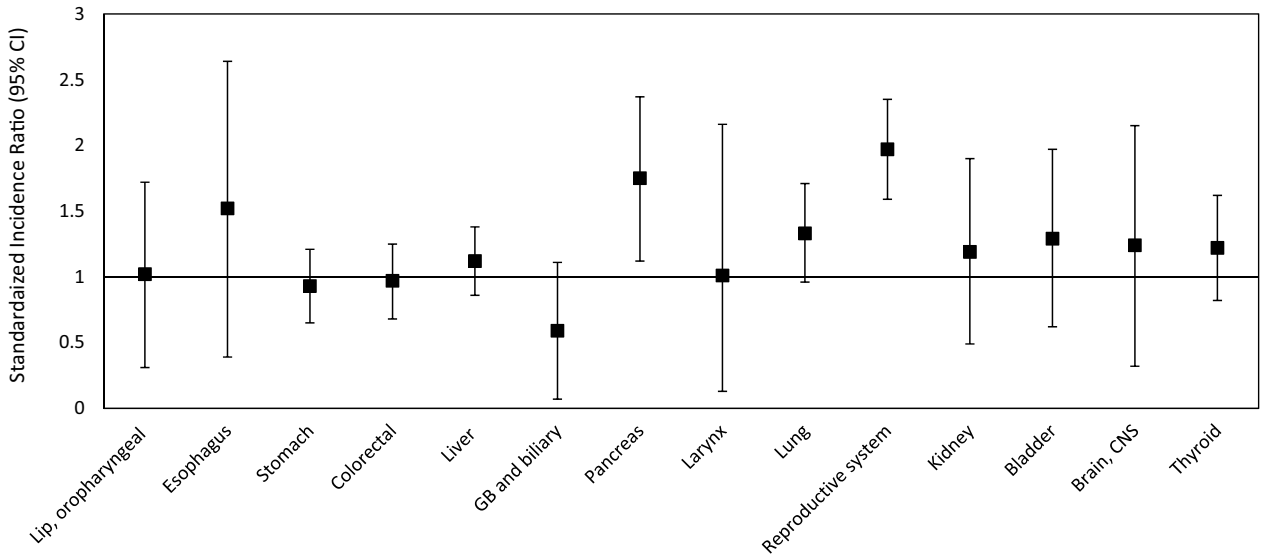


Fig. 2 Standardized incidence ratios of hematologic malignancies



GB, gallbladder; CNS, central nervous system

Fig. 3 Standardized incidence ratios of solid cancers. GB, gallbladder; CNS, central nervous system

Table 3 The most common types of malignancy observed in Korean male patients with AS

Ranking	Type of malignancy	Observed cases
1	Prostate	101 cases
2	Liver	70 cases
3	Lung	48 cases
4	Colorectal	45 cases
5	Stomach	43 cases

AS, ankylosing spondylitis

in this group (101 cases), followed by liver (70 cases), lung (48 cases), colorectal (45 cases), and stomach cancer (43 cases). The common cancer types were different in male AS patients than the general male population. The five most common cancers for the general male population, in descending order, were stomach, lung, colorectal, liver, and prostate [15].

Discussion

In this retrospective study, we determined the overall and site-specific cancer risks in male patients with AS. We demonstrated that the overall incidence of cancer was higher in male patients with AS than male general population. We observed that the risks of pancreatic cancer and malignancy of the male reproductive system, of which a majority was prostate cancer, were increased.

Studies on malignancy risk of AS are scarce and provide conflicting results. In one study of 6621 AS patients, overall cancer risk was not increased than general population (SIR 1.05, 95% CI 0.94–1.17). The risk of rectal cancer was decreased (SIR 0.41, 95% CI 0.15–0.89), while the risk of unspecified kidney cancer was increased (SIR 5.90, 95% CI 1.61–15.1) [9]. However, in a systemic review and meta-analysis study, overall malignancy risk of AS was increased (pooled RR 1.14, 95% CI 1.03–1.25). Patients with AS had a specific increased risk for digestive system malignancies (pooled RR 1.20, 95% CI 1.01–1.42), multiple myelomas (pooled RR 1.92, 95% CI 1.37–3.69), and lymphomas (pooled RR 1.32, 95% CI 1.11–1.57). However, the results could be biased because of variations in study designs and adjustment for covariates. Most studies were from Europe (17 from Europe, 2 from Asia, 3 from the United States, and 1 from another country) [16].

In a retrospective cohort study of 5452 AS patients from Taiwan, the overall incidence of cancer was elevated in AS patients (SIR 1.15, 95% CI 1.03–1.27), and AS carried an increased risk of hematological malignancy in both sexes (females SIR 2.09, 95% CI 1.04–3.74; males SIR 2.10, 95% CI 1.32–3.19); colon cancer in females (SIR 1.73. 95% CI 1.19–2.45); and bone and prostate cancer in males (SIR 3.33, 95% CI 1.08–7.77; SIR 1.64, 95% CI 1.04–2.47) in comparison with age- and sex-matched controls [12]. Korea and Taiwan have similar ethnicities and lifestyles. We found similar results in increased risk of overall cancer, hematological malignancies, and prostate cancer in male AS patients. However, comparing results for bone and pancreatic cancer is difficult due to differences in cancer categorization.

The relationship between cancer and rheumatic diseases is complicated. The reasons for this increased risk of cancer in rheumatic diseases have not been elucidated, but are hypothesized to be that chronic inflammation stimulates cytokines and chemokines that may induce DNA damage, inactivate tumor suppressor genes, stimulate cellular growth, and trigger angiogenesis [2, 4, 17]. A previous study found that elevated erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) were associated with increased cancer risk and greater cancer mortality in people with rheumatoid arthritis [18]. Other studies demonstrated that disease activity and duration were predictive of non-Hodgkin lymphoma risk in people with primary Sjogren's disease [17, 19, 20]. In addition to inflammation as a disease activity, genetic characteristics may affect carcinogenesis. Several studies observed that HLA B27, a class I surface antigen strongly associated with AS, is associated with increased risk of malignancies such as lymphoma and colorectal cancer [21–23].

It is interesting but not surprising that patients with AS had a significantly increased risk of male reproductive system malignancy, represented by prostate cancer. It may be influenced by sex hormones, because AS is a male-predominant disease that commonly starts at a young age. Several studies have investigated the role of sex hormones in developing prostate cancer. In a pooled analysis of 3886 patients with prostate cancer, no association was seen between prostate cancer and serum levels of sex hormones such as testosterone, dihydrotestosterone and estrogen [24]. In spite of that, debate continues about hormonal effects on prostate carcinogenesis because high-grade prostatic intraepithelial neoplasia, which is thought to be precursor of prostatic carcinoma, is hormone dependent [25, 26]. In a multicenter, randomized, double-blind, placebo-controlled study, risk of prostate cancer was reduced, compared to placebo, in a group assigned to receive dutasteride, a 5-alpha reductase that converts testosterone into dihydrotestosterone, which is the most active androgen in the prostate (RR reduction of 22.8%, 95% CI 15.2–29.8) [27]. Regarding the relationship between sex hormones and AS, evidence suggests that serum levels of adrenal and gonadal androgens are normal in people with AS [28]. Although the level of sex hormones may not be related to AS, the impact of sex hormones on pathogenesis is not yet clear as in prostate cancer. Evidence [29] of a protective effect of NSAIDs on prostate cancer risk

has heightened the need for further studies on the common mechanism of prostate carcinogenesis and AS pathogenesis. Because NSAIDs are the first line therapy in AS, we expect a potent mechanism overwhelming the NSAID protective effect on prostate cancer in AS patients.

Pancreatic cancer is a relatively rare but highly lethal disease. Most pancreatic cancer patients remain asymptomatic until an advanced stage. There is no standard screening program covering for pancreatic cancer. Several risk factors for this cancer have been identified such as cigarette smoking and chronic pancreatitis [30]. However, reliable evidence on a common mechanism with AS is unavailable yet. The evidence of our study suggests a direction for further research, although differences in access to medical services may act as a confounding variable.

Although the results were not significant, we note the gastrointestinal cancers. The SIRs for gastric cancer (SIR 0.93, 95% CI 0.65–1.21), colorectal cancer (SIR 0.97, 95% CI 0.68–1.25), and biliary cancer (SIR 0.59, 95% CI 0.07–1.11) tended to decrease, while the SIR for esophageal cancer (SIR 1.52, 95% CI 0.39–2.64) tended to increase. A high prevalence of inflammatory bowel disease (IBD) in AS is well established, and IBD is considered to have genetic and pathophysiologic similarities to AS. We did not identify the prevalence of IBD in this study, but one study found that between 5 and 10% of AS cases are associated with IBD [31]. The increased risk of colorectal cancer with IBD is well known. A meta-analysis reported a pooled SIR of 1.7 for colorectal cancer in patients with IBD (95% CI 1.2–2.2) [32]. However, our study observed a trend toward slightly decreased rather than increased risk of colorectal cancer. This result could be an effect of NSAIDs, the first line therapy for AS. Several studies have concluded that NSAIDs are associated with lowered colorectal cancer risk [33–35]. Although data regarding NSAIDs for prevention of cancers other than colorectal are less consistent, NSAIDs may reduce the risk of gastric cancer and malignancies of the biliary system [36, 37]. Cancer is a multifactorial disease, so we cannot explain these trends as only the effect of NSAIDs. Further study is needed concerning the effects of NSAIDs.

To our knowledge, this is the first large cohort study on the malignancy risk of AS patients in Korea. This study is meaningful because the incidence of cancer varies depending on geographic location and race/ethnicity. We analyzed patients with both AS (ICD-10 code M45) and RID codes (code V140). High reliability was possible with this selection strategy because patients must meet strict diagnostic criteria to register in the RID system.

Despite these strengths, a few weaknesses should be noted. First, although we used stratified random samples that represent the general male population and calculated age-adjusted incidence rates to allow for reasonable comparisons, confounding factors could still exist; for example, inaccuracy of diagnosis information, possibility of insufficient sampling for rare cancers and differences in accessibility to healthcare systems. Due to the nature of claims data, inaccuracy of diagnosis has been an issue and could be fatal bias. However, the diagnosis in the claims data of HIRA tends to be more accurate in cases of severe disease such as cancers rather than mild diseases [13]. Differences in medical access could influence the detection rate of cancer, especially for early and rare cancers. Second, when HIRA provided general population samples, prostate and testicular cancer was grouped to protect patient privacy. Furthermore, the control group may not have sufficient cases for rare cancers; so, malignancy risk in patients with ankylosing spondylitis could be over-estimated. Therefore, we had to compare incidence rates for these cancers in an AS and a control group as malignancies of the male reproductive system. However, using data on male AS patients, we showed that the majority of cancers was of the prostate (101 observed cases) rather than testicular (1 observed case). Third, due to data characteristics and study design, it was difficult to handle confounding variables such as disease duration, disease activity, smoking habits and medications. We cannot rule out possible effects of these variables on carcinogenesis. Last, we focused on only male patients because AS is considered as a male-predominant disease in its incidence and disease severity [1]. A sex difference also exists in the incidence of several cancer types. Further study concerning cancer risk in female patients with AS is needed.

In conclusion, male patients with AS had increased overall cancer risk, especially for pancreatic cancer and malignancies of the male reproductive system, mainly represented by prostate cancer. A large, prospective cohort study is required to confirm the results of this study.

Author contributions Conceptualization: HK, SKC, YKS, THK. Formal analysis: HK, EJJ. Investigation: BN, HK. Methodology: YKS, EJJ. Writing—original draft: BN. Writing—review and editing: YKS, THK.

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Compliance with ethical standards

To protect patient privacy, the National Health Insurance (NHI) stores beneficiary identifications in an encrypted format and provides data to the public without individual identifiers. Using these data allowed our study to be included in exemption categories (Institutional Review Board file no. HYUH 2018-12-027).

Conflict of interest The authors have declared no conflicts of interest.

References

1. Braun J, Sieper J (2007) Ankylosing spondylitis. Lancet 369(9570):1379–1390. https://doi.org/10.1016/S0140-6736(07)60635-7
2. Balkwill F, Mantovani A (2001) Inflammation and cancer: back to virchow? Lancet 357(9255):539–545. https://doi.org/10.1016/S0140-6736(00)04046-0
3. Coussens LM, Werb Z (2002) Inflammation and cancer. Nature 420(6917):860–867. https://doi.org/10.1038/nature01322
4. Munn LL (2017) Cancer and inflammation. Wiley Interdiscip Rev Syst Biol Med. https://doi.org/10.1002/wsbm.1370
5. Yang Z, Lin F, Qin B, Liang Y, Zhong R (2015) Polymyositis/dermatomyositis and malignancy risk: a metaanalysis study. J Rheumatol 42(2):282–291. https://doi.org/10.3899/jrheum.140566
6. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S (2015) Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther 17:212. https://doi.org/10.1186/s13075-015-0728-9
7. Onishi A, Sugiyama D, Kumagai S, Morinobu A (2013) Cancer incidence in systemic sclerosis: meta-analysis of population-based cohort studies. Arthritis Rheum 65(7):1913–1921. https://doi.org/10.1002/art.37969
8. Liang Y, Yang Z, Qin B, Zhong R (2014) Primary Sjogren's syndrome and malignancy risk: a systematic review and meta-analysis. Ann Rheum Dis 73(6):1151–1156. https://doi.org/10.1136/annrheumdis-2013-203305
9. Feltelius N, Ekbom A, Blomqvist P (2003) Cancer incidence among patients with ankylosing spondylitis in Sweden 1965–95: a population based cohort study. Ann Rheum Dis 62(12):1185–1188
10. Askling J, Klareskog L, Blomqvist P, Fored M, Feltelius N (2006) Risk for malignant lymphoma in ankylosing spondylitis: a nationwide Swedish case-control study. Ann Rheum Dis 65(9):1184–1187. https://doi.org/10.1136/ard.2005.047514
11. Hellgren K, Smedby KE, Backlin C, Sundstrom C, Feltelius N, Eriksson JK, Baecklund E, Askling J (2014) Ankylosing spondylitis, psoriatic arthritis, and risk of malignant lymphoma: a cohort study based on nationwide prospectively recorded data from Sweden. Arthritis Rheumatol 66(5):1282–1290. https://doi.org/10.1002/art.38339
12. Chang CC, Chang CW, Nguyen PA, Chang TH, Shih YL, Chang WY, Horng JT, Lee OK, Ho JH (2017) Ankylosing spondylitis and the risk of cancer. Oncol Lett 14(2):1315–1322. https://doi.org/10.3892/ol.2017.6368
13. Kim JA, Yoon S, Kim LY, Kim DS (2017) Towards actualizing the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. J Korean Med Sci 32(5):718–728. https://doi.org/10.3346/jkms.2017.32.5.718
14. Kim L, Kim JA, Kim S (2014) A guide for the utilization of Health Insurance Review and Assessment Service National Patient Samples. Epidemiol Health 36:e2014008. https://doi.org/10.4178/epih/e2014008
15. Jung KW, Won YJ, Kong HJ, Lee ES, Community of Population-Based Regional Cancer R (2018) Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2015. Cancer Res Treat 50(2):303–316. https://doi.org/10.4143/crt.2018.143
16. Deng C, Li W, Fei Y, Li Y, Zhang F (2016) Risk of malignancy in ankylosing spondylitis: a systematic review and meta-analysis. Sci Rep 6:32063. https://doi.org/10.1038/srep32063
17. Egiziano G, Bernatsky S, Shah AA (2016) Cancer and autoimmunity: harnessing longitudinal cohorts to probe the link. Best Pract Res Clin Rheumatol 30(1):53–62. https://doi.org/10.1016/j.berh.2016.03.001
18. Llorca J, Lopez-Diaz MJ, Gonzalez-Juanatey C, Ollier WE, Martin J, Gonzalez-Gay MA (2007) Persistent chronic inflammation contributes to the development of cancer in patients with rheumatoid arthritis from a defined population of northwestern Spain. Semin Arthritis Rheum 37(1):31–38. https://doi.org/10.1016/j.semarthrit.2007.01.002
19. Baimpa E, Dahabreh IJ, Voulgarelis M, Moutsopoulos HM (2009) Hematologic manifestations and predictors of lymphoma development in primary Sjogren syndrome: clinical and pathophysiologic aspects. Medicine (Baltimore) 88(5):284–293. https://doi.org/10.1097/MD.0b013e3181b76ab5
20. Baldini C, Pepe P, Luciano N, Ferro F, Talarico R, Grossi S, Tavoni A, Bombardieri S (2012) A clinical prediction rule for lymphoma development in primary Sjogren's syndrome. J Rheumatol 39(4):804–808. https://doi.org/10.3899/jrheum.110754
21. Alcalay M, Bontoux D, Maire P, Matuchansky C, Alcalay D, Tanzer J (1982) HLA-B27 and colorectal cancer. N Engl J Med 307(7):443–444. https://doi.org/10.1056/NEJM198208123070718
22. Au WY, Hawkins BR, Cheng N, Lie AK, Liang R, Kwong YL (2001) Risk of haematological malignancies in HLA-B27 carriers. Br J Haematol 115(2):320–322
23. Hammer RE, Richardson JA, Simmons WA, White AL, Breban M, Taurog JD (1995) High prevalence of colorectal cancer in HLA-B27 transgenic F344 rats with chronic inflammatory bowel disease. J Investig Med 43(3):262–268
24. Endogenous H, Prostate Cancer Collaborative G, Roddam AW, Allen NE, Appleby P, Key TJ (2008) Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst 100(3):170–183. https://doi.org/10.1093/jnci/djm323
25. Bostwick DG, Cheng L (2012) Precursors of prostate cancer. Histopathology 60(1):4–27. https://doi.org/10.1111/j.1365-2559.2011.04007.x
26. Bostwick DG, Liu L, Brawer MK, Qian J (2004) High-grade prostatic intraepithelial neoplasia. Rev Urol 6(4):171–179
27. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, Pettaway CA, Tammela TL, Teloken C, Tindall DJ, Somerville MC, Wilson TH, Fowler IL, Rittmaster RS, Group RS (2010) Effect of dutasteride on the risk of prostate cancer. N Engl J Med 362(13):1192–1202. https://doi.org/10.1056/nejmoa0908127
28. Straub RH, Struharova S, Scholmerich J, Harle P (2002) No alterations of serum levels of adrenal and gonadal hormones in patients with ankylosing spondylitis. Clin Exp Rheumatol 20(6 Suppl 28):S52–S59
29. Shang Z, Wang X, Yan H, Cui B, Wang Q, Wu J, Cui X, Li J, Ou T, Yang K (2018) Intake of non-steroidal anti-inflammatory drugs and the risk of prostate cancer: a meta-analysis. Front Oncol 8:437. https://doi.org/10.3389/fonc.2018.00437
30. Kamisawa T, Wood LD, Itoi T, Takaori K (2016) Pancreatic cancer. Lancet 388(10039):73–85. https://doi.org/10.1016/S0140-6736(16)00141-0
31. Rudwaleit M, Baeten D (2006) Ankylosing spondylitis and bowel disease. Best Pract Res Clin Rheumatol 20(3):451–471. https://doi.org/10.1016/j.berh.2006.03.010
32. Lutgens MW, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B (2013) Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. Inflamm Bowel Dis 19(4):789–799. https://doi.org/10.1097/MIB.0b013e31828029c0
33. Rostom A, Dube C, Lewin G, Tsertsvadze A, Barrowman N, Code C, Sampson M, Moher D, Force USPST (2007) Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review

prepared for the US Preventive Services Task Force. Ann Intern Med 146(5):376–389
34. Flossmann E, Rothwell PM, British Doctors Aspirin T, The UKTIAAT (2007) Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 369(9573):1603–1613. https://doi.org/10.1016/S0140-6736(07)60747-8
35. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, Tang J, Rosenstein RB, Wittes J, Corle D, Hess TM, Woloj GM, Boisserie F, Anderson WF, Viner JL, Bagheri D, Burn J, Chung DC, Dewar T, Foley TR, Hoffman N, Macrae F, Pruitt RE, Saltzman JR, Salzberg B, Sylwestrowicz T, Gordon GB, Hawk ET, Investigators APCS (2006) Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 355(9):873–884. https://doi.org/10.1056/NEJMoa061355
36. Wu CY, Wu MS, Kuo KN, Wang CB, Chen YJ, Lin JT (2010) Effective reduction of gastric cancer risk with regular use of nonsteroidal anti-inflammatory drugs in *Helicobacter pylori*-infected patients. J Clin Oncol 28(18):2952–2957. https://doi.org/10.1200/JCO.2009.26.0695
37. Burr NE, Talboys RJ, Savva S, Clark A, Phillips M, Metcalfe M, Dennison A, Robinson R, Lewis MP, Rhodes M, Rushbrook S, Hart AR (2014) Aspirin may prevent cholangiocarcinoma: a case-control study from the United kingdom. Dig Dis Sci 59(7):1567–1572. https://doi.org/10.1007/s10620-014-3056-z