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Associations Between Chronic Rhinosinusitis and Cancers: A Nationwide Population-Based Cohort Study

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Objective: Chronic rhinosinusitis (CRS) is one of the most common chronic inflammatory diseases. The effect of chronic inflammation caused by CRS on the occurrence of various cancers has not been thoroughly evaluated. This study aimed to investigate the increased incidences of 10 types of cancers among CRS patients with/without nasal polyps (NP) using a national population-based database from the Korean Health Insurance Review and Assessment Service.

Study Design: A case–control cohort study.

Methods: We compared the prevalence of various comorbidities between CRS and control participants from a national cohort dataset of the Korean Health Insurance Review and Assessment Service.

Methods: CRS participants (n = 6,919) and non-CRS (n = 27,676) participants were selected from among the 514,866 participants from 2002 to 2015. A stratified Cox proportional hazards model was utilized to assess the hazard ratio (HR) of CRS for 10 types of cancers.

Results: A stratified Cox proportional hazard model demonstrated that the adjusted HR for hematologic malignancy was significantly higher in the CRS patients than in the controls regardless of the presence of NP (2.90 for total CRS; 2.15 for CRS with NP; 4.48 for CRS without NP). The HR for thyroid cancer was significantly higher in the CRS patients without NP but not in those with NP (1.50 for total CRS; 1.78 for CRS without NP).

Conclusion: This study showed that CRS participants had a significantly higher prevalence of hematologic malignancy and thyroid cancer.

Key Words: cancer, chronic rhinosinusitis, chronic inflammation, nasal polyp.

Level of Evidence: 4

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INTRODUCTION

Chronic rhinosinusitis (CRS) is a symptomatic condition characterized by inflammation of the paranasal sinuses and nasal cavities that persists for longer than 12 weeks despite medical treatments.[1] The prevalence of CRS was reported to be approximately 12% in the US population and 11% in the European population.[1–3] Current data indicate a symptom-based CRS prevalence of 10.9% in South Korea.[4] CRS is caused by several heterogeneous mechanisms involving persistent inflammation that is difficult to control. The dysregulated immune response plays a decisive role in the pathogenesis of CRS.[5]

Cancer is an important public health issue worldwide, and the burden with regard to incidence and mortality rose to 19.3 million new cases of cancer and 10.0 million deaths from cancer worldwide in 2020 according to the International Agency for Research on Cancer.[6,7] In South Korea, cancer is the leading cause of death, and 78,863 deaths and 232,255 new cancer cases occurred in 2017.[8,9]

The relationship between chronic inflammatory conditions and carcinogenesis had already been reported by 1863, when the accumulation of leukocytes in malignant lesions was demonstrated. Many studies have demonstrated that chronic inflammation promotes the development of cancer throughout malignant initiation and conversion, progression, local invasion, and distant metastasis.[10,11] Indeed, up to 25% of cancers worldwide are associated with chronic inflammation and infections with viral and bacterial organisms.[10–13] The elimination of pathogens, restoration of damaged tissue, and reduction in inflammatory signals can block chronic inflammation and consequently prevent carcinogenesis.[10]

Significant associations between CRS and the risks of various cancers have been described in population-based cohorts.[14,15] However, previous studies limited the subjects to those who were 65 years or older or had a follow-up period of only 8 years. The objective of the current study was to reveal whether CRS participants have increased incidences of 10 types of cancers, namely,

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gastric cancer, thyroid cancer, colorectal cancer, lung cancer, hepatic cancer, bladder cancer, pancreatic cancer, gallbladder and biliary duct cancer, kidney cancer, and hematologic malignancy, using a database with a national sample cohort of Korean adults with a relatively longer follow-up period of 14 years. We also analyzed how the incidence rates of these cancers varied depending on whether the CRS participants had nasal polyps.

METHODS

Ethics

The Hallym University Ethics Committee approved this study (2019-10-023). The Institutional Review Board waived the need to obtain written informed consent.

Study Population and Participant Selection

A detailed description of the Korean National Health Insurance Service-Health Screening Cohort data has been provided elsewhere.[16] CRS participants were selected from among 514,866 participants with 615,488,428 medical claim codes from 2002 through 2015 (n = 8,560). Individuals were included in the control group if they did not meet the criteria for CRS from 2002 through 2015 (n = 506,306). To select CRS participants who were diagnosed for the first time, CRS participants diagnosed in 2002 were excluded (n = 1,366, washout period). We excluded controls if they had been diagnosed with CRS without examinations of either paranasal sinuses (PNS) X-ray or computed tomography (CT) or diagnosed with CRS once (n = 123,209).

CRS participants were matched with control participants at a 1:4 ratio for age, sex, income, and region of residence. The controls were assorted and selected in order from top to bottom using a sequence of random numbers to avoid selection bias when deciding the matched participants. The matched controls were expected to be evaluated concurrently with each matched CRS participant (index date). The index date was defined as the earliest date of the visit where the participant was diagnosed with CRS from 2003 to 2015. The duration of longitudinal follow-up was calculated from the index date to the date of occurrence of cancers. The participants were excluded if they died prior to the index date. Participants who had a history of any cancer before the index date were excluded from both the CRS and control groups. The underlying comorbid diseases were evaluated before the index date. When the controls were matched with the CRS participants according to the index date, the control subjects who had a previous history of cancers before the index date were excluded to exclude the effect of premorbid cancer or its treatment, such as radiation therapy or chemotherapy.

Consequently, 275 participants were excluded from the CRS group. During the matching procedure, 355,421 control participants were excluded. Finally, 6,919 CRS participants were matched with 27,676 controls at a 1:4 ratio (Fig. 1). Among the CRS participants, 3,460 had CRS with nasal polyps (CRSwNP), and 3,459 had CRS without nasal polyps (CRSsNP).

Definition of Chronic Rhinosinusitis

CRS was identified by the International Classification of Diseases, tenth revision (ICD-10) code (J32) ≥ 2 times, and histories of head and neck CT. CRSwNP was defined as J33, and CRSsNP was defined as described in previous studies.[17,18]

Definition of Cancers

In this study, the incidences of the following 10 types of cancers were investigated: gastric cancer (ICD-10 code: C16), thyroid cancer (ICD-10 code: C73), colorectal cancer (ICD-10 codes: C18 to C21 and D010 to D013), lung cancer (ICD-10 codes: C34 and D022), hepatic cancer (ICD-10 codes: C22 and D015), bladder cancer (ICD-10 codes: C67 and D090), pancreatic cancer (ICD-10 codes: C25 and D017), gallbladder and biliary duct cancer (ICD-10 codes: C23 and C24), kidney cancer (ICD-10 codes: C64), and hematologic malignancy (ICD-10 codes: C81 to C96). To ensure diagnostic sensitivity, we chose only the participants who were diagnosed with the same ICD-10 codes ≥2 times.

Covariates

Age groups were divided based on 5-year intervals: 40–44…, and 85+ years old. A total of 10 age groups were specified. Income was categorized into five classes (class 1 [lowest income]-5 [highest income]). The region of residence was grouped into urban and rural areas.[16] Tobacco smoking, alcohol consumption, and obesity, as defined by body mass index (BMI, kg/m^2), were recorded. The Charlson comorbidity index (CCI) was calculated, with the exclusion of cancer and metastatic cancer.[16,19,20]

Statistical Analyses

Statistical analyses were conducted using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA). The standardized difference (SD) was used to compare general characteristics between the CRS and control groups. Stratified Cox proportional hazard models were constructed to evaluate the hazard ratios (HRs) with 95% confidence intervals (CIs) for various cancers in patients with CRS. In this analysis, simple and adjusted (for obesity, smoking, alcohol consumption, and CCI scores) models were constructed. The analysis was stratified by the variables used for matching, such as age, sex, income, and region of residence. Then, we constructed Kaplan–Meier curves and performed log-rank tests. To analyze the subgroups using stratified Cox proportional hazards models, we divided the participants by age (<55 and ≥55 years old) and sex. Two-tailed analyses were performed, and significance after Bonferroni correction was defined as a p value less than 0.005.

RESULTS

This study included 6,919 CRS participants and 27,676 non-CRS participants, with a mean follow-up duration of 7.74 (SD = 3.61) years. Table I presents the SDs in the baseline characteristics and comorbidities between the CRS and non-CRS cohorts. The average age of all participants was 55.56 (SD = 8.76) years. The SDs between the CRS and control participants were minimal for all characteristics (SD < 0.07) except for CCI scores (SD = 0.15).

Stratified Cox proportional hazard models of incident cancer in the CRS group and the control group during the 14-year follow-up period are shown in Table II. We found that 656 (9.48%) CRS participants developed cancer, whereas 2,361 (8.53%) control participants developed cancers. Significant differences were found in the incidences of thyroid cancer (adjusted HR, 1.50 [95% CI = 1.16–1.94], p = 0.002) and hematologic malignancy (adjusted HR, 2.90 [95% CI = 2.03–4.16], p < 0.0001). Kaplan–Meier curves also showed higher cumulative

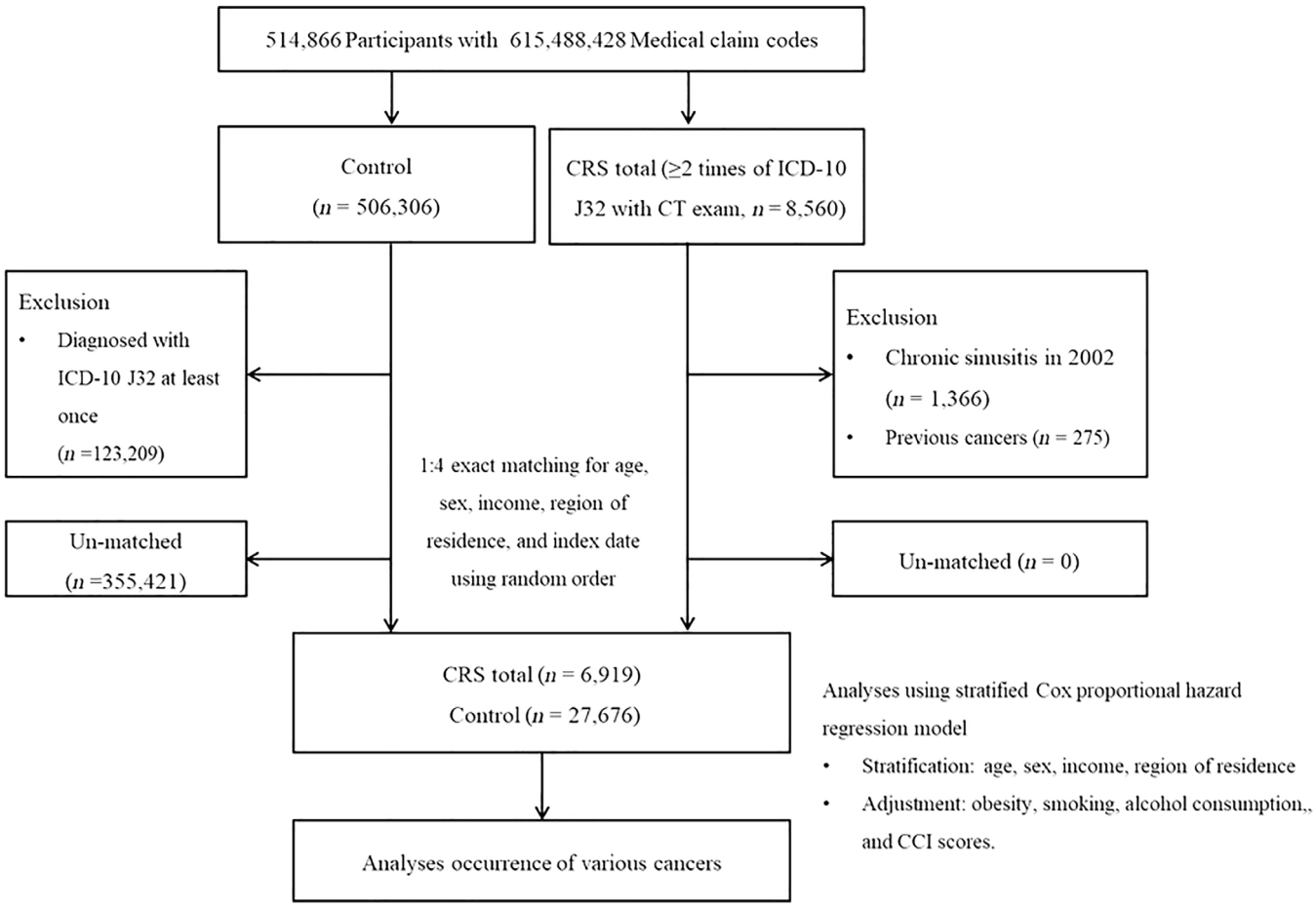

FIGURE 1. A schematic illustration of the participant selection process used in the present study. CCI = Charlson comorbidity index; CT = Computed tomography; ICD-10 = International classification of disease-10.

incidences of thyroid cancer and hematologic malignancy (Figure S1). CRS patients had a significantly higher likelihood of hematologic malignancy than the control participants, regardless of sex or age (<55 and ≥55 years old) (Table S1).

All CRS participants were divided into two groups based on the absence or presence of nasal polyps (CRSwNP or CRSsNP groups). In the CRSwNP group (Table III), the incidence of hematologic malignancy was significantly higher than that in the control group (crude HR, 2.16 [95% CI = 1.33–3.49] and adjusted HR, 2.15 [95% CI = 1.33–3.49]). For hepatic cancer in the CRSwNP group, the crude HR was not significant, but the adjusted HR (0.47 [95% CI = 0.29–0.77]) was significant after adjusting for age, sex, income, region of residence, obesity, smoking, alcohol consumption, and CCI score. The Kaplan–Meier curve also demonstrated a significant difference in the incidence of hematologic malignancy and hepatic cancer in the CRSwNP group (Figure S2).

In the CRSsNP group (Table IV), the incidences of thyroid cancer and hematologic malignancy were significantly higher than those in the control group (adjusted HR, 1.78 [95% CI = 1.27–2.51] and 4.48 [95% CI = 2.56–7.86], respectively). However, the incidence of colorectal cancer was significantly lower (adjusted HR, 0.53 [95% CI = 0.36–0.80]). The Kaplan–Meier curves also revealed significant differences in the cumulative incidences of thyroid cancer, hematologic malignancy, and colorectal cancer between the CRSsNP and control groups (Figure S3).

DISCUSSION

In this large longitudinal case–control cohort study, we evaluated the associations between CRS and 10 types of cancers. We found that CRS had strong associations with hematologic malignancy and thyroid cancer, with 3.00-fold and 1.50-fold higher incidences of these cancers in the CRS group than in the control group, respectively. These higher incidences were independent of other possible confounding factors, including age, sex, income, region, obesity, smoking, alcohol consumption, and CCI score. Interestingly, we also discovered that the CRSsNP cohort had a reduced incidence of colorectal cancer (adjusted HR = 0.53), and the CRSwNP cohort had a reduced risk of hepatic cancer (adjusted HR = 0.47). We searched the English-language literature in PubMed with search criteria that included all occurrences in the title or abstract of the terms such as chronic sinusitis, cancer, and risk. There were only eight population-based studies, and all but two studies focused on lung cancer or

TABLE I.
General Characteristics of Participants.

Characteristics	Total participants		
	Chronic rhinosinusitis (*n*, %)	Control (*n*, %)	Standardized difference*
Total number	6,919 (100.0)	27,676 (100.0)	
Age (years old)†			0.00
40–44	422 (6.1)	1,688 (6.1)	
45–49	1,214 (17.6)	4,856 (17.6)	
50–54	1,495 (21.6)	5,980 (21.6)	
55–59	1,412 (20.4)	5,648 (20.4)	
60–64	1,055 (15.3)	4,220 (15.3)	
65–69	710 (10.3)	2,840 (10.3)	
70–74	395 (5.7)	1,580 (5.7)	
75–79	161 (2.3)	644 (2.3)	
80–84	45 (0.7)	180 (0.7)	
85+	10 (0.1)	40 (0.1)	
Sex			0.00
Male	4,201 (60.7)	16,804 (60.7)	
Female	2,718 (39.3)	10,872 (39.3)	
Income			0.00
1 (lowest)	836 (12.1)	3,344 (12.1)	
2	818 (11.8)	3,272 (11.8)	
3	1,066 (15.4)	4,264 (15.4)	
4	1,492 (21.6)	5,968 (21.6)	
5 (highest)	2,707 (39.1)	10,828 (39.1)	
Region of residence			0.00
Urban	3,247 (46.9)	12,988 (46.9)	
Rural	3,672 (53.1)	14,688 (53.1)	
Obesity‡			0.06
Underweight	122 (1.8)	547 (2.0)	
Normal	2,225 (32.2)	9,541 (34.5)	
Overweight	2,065 (29.9)	7,674 (27.7)	
Obese I	2,313 (33.4)	9,110 (32.9)	
Obese II	194 (2.8)	804 (2.9)	
Smoking status			0.08
Nonsmoker	4,555 (65.8)	17,986 (65.0)	
Past smoker	981 (14.2)	3,404 (12.3)	
Current smoker	1,383 (20.0)	6,286 (22.7)	
Alcohol consumption			0.01
<1 time a week	4,588 (66.3)	18,214 (65.8)	
≥1 time a week	2,331 (33.7)	9,462 (34.2)	
CCI score‡			0.15
0	4,877 (70.5)	21,343 (77.1)	
1	1,328 (19.2)	4,114 (14.9)	
≥ 2	714 (10.3)	2,219 (8.0)	
All cancer	476 (6.9)	1,700 (6.1)	0.03
Gastric cancer	100 (1.5)	420 (1.5)	0.01
Thyroid cancer	82 (1.2)	215 (0.8)	0.04
Colorectal cancer	77 (1.1)	387 (1.4)	0.03
Lung cancer	85 (1.2)	284 (1.0)	0.02
Hepatic cancer	47 (0.7)	234 (0.9)	0.02
Bladder cancer	16 (0.2)	55 (0.2)	0.01
Pancreatic cancer	20 (0.3)	84 (0.3)	0.00
Gallbladder and biliary duct	20 (0.3)	66 (0.2)	0.01
Kidney cancer	11 (0.2)	36 (0.1)	0.01
Hematologic malignancy	53 (0.8)	71 (0.3)	0.07

CCI = Charlson comorbidity index.
*χ^2 test. Significance at $p < 0.05$.
†Obesity (BMI, body mass index, kg/m^2) was categorized as <18.5 (underweight), ≥18.5 to <23 (normal), ≥23 to <25 (overweight), ≥25 to <30 (obese I), and ≥30 (obese II).
‡CCI scores were calculated without cancer and metastatic cancer.

nasopharyngeal cancer. Moreover, previous studies have generally overlooked the subtypes of CRS. None of the previous studies reported the cancer prevalence stratified by the subtypes of CRS. This study is the first to report an evaluation of the relationships between 10 types of cancers and CRS subtypes during long-term follow-up.

Previous studies have tried to evaluate whether there are positive associations between CRS and the risks of various cancers. As was found in the current study, Anderson et al. and Beachler et al. reported that CRS was associated with an increased risk of lymphoma in participants older than 65 years.[15,21] As in our study, Beachler et al. showed negative associations of CRS with colorectal cancer and hepatic cancer (adjusted HR, 0.86 and 0.90, respectively).[15] Contrary to our results, Xia et al. showed that CRS patients had higher risks of colorectal cancer, lung cancer, hepatic cancer, and bladder cancer (adjusted odds ratio, 1.23 [95% CI = 1.09–1.39]; 1.14 [95% CI = 1.00–1.30]; 1.24 [95% CI = 1.09–1.41]; 1.48 [95% CI = 1.17–1.88], respectively) but not thyroid cancer or hematologic malignancy through a retrospective case–control study in Taiwan.[14] Koh et al. reported that CRS patients had a 1.59-fold increased risk of lung cancer in a population-based cohort of 63,257 Singaporean Chinese patients.[22] Ng et al. also found that CRS patients had a 3.52-fold greater risk of developing the adenocarcinoma subtype of lung cancer in a Taiwanese population-based cohort of 65,360 individuals.[23] These results were not compatible with the outcomes of the current study, in which CRS patients did not have a significantly higher risk of lung cancer. The impact of CRS on various cancers can vary according to ethnicity and geographic factors that affect the prevalence of cancer. For example, lung cancer is the second-most common cancer in Taiwan and Singapore but not in South Korea, where the 5-year cancer prevalence rate was 9.1% in 2018, ranking fifth.[6,24,25] International variations in lung cancer incidence are

TABLE II.
Adjusted Hazard Ratios (95% Confidence Intervals) of CRS for Various Cancers.

Dependent variable	IR per 1000 person-year		IRD per 1000 person-years (95% CI)	Hazard ratios for cancers			
	CRS (n = 6,919)	Control (n = 27,676)		Crude†	p value	Adjusted†‡	p value
All cancer (n = 2,176)	9.48	8.53	0.96 (0.90 to 1.02)	1.10 (0.99–1.22)	0.065	1.06 (0.96–1.18)	0.262
Gastric cancer (n = 520)	1.94	2.07	−0.13 (−0.19 to −0.06)	0.92 (0.74–1.15)	0.454	0.89 (0.71–1.11)	0.284
Thyroid cancer (n = 297)	1.59	1.05	0.54 (0.21 to 0.87)	1.53 (1.19–1.97)	0.001*	1.50 (1.16–1.94)	0.002*
Colorectal cancer (n = 464)	1.49	1.90	−0.41 (−0.82 to 0.00)	0.78 (0.61–1.00)	0.048	0.75 (0.59–0.96)	0.024
Lung cancer (n = 369)	1.64	1.39	0.25 (−0.11 to 0.62)	1.16 (0.91–1.48)	0.223	1.17 (0.91–1.49)	0.214
Hepatic cancer (n = 281)	0.91	1.14	−0.24 (−0.56 to 0.08)	0.78 (0.57–1.07)	0.128	0.67 (0.49–0.92)	0.014
Bladder cancer (n = 71)	0.31	0.27	0.04 (−0.12 to 0.20)	1.13 (0.65–1.97)	0.666	1.10 (0.63–1.93)	0.730
Pancreatic cancer (n = 104)	0.39	0.41	−0.02 (−0.22 to 0.17)	0.92 (0.57–1.50)	0.744	0.90 (0.55–1.47)	0.671
Gallbladder and biliary duct (n = 86)	0.39	0.32	0.06 (−0.11 to 0.24)	1.16 (0.70–1.91)	0.567	1.15 (0.69–1.91)	0.594
Kidney cancer (n = 47)	0.21	0.18	0.04 (−0.09 to 0.17)	1.23 (0.62–2.42)	0.553	1.19 (0.60–2.35)	0.621
Hematologic malignancy (n = 124)	1.02	0.35	0.68 (0.47 to 0.89)	3.00 (2.10–4.29)	<0.001*	2.90 (2.03–4.16)	<0.001*

CRS = chronic rhinosinusitis; IR = incidence rate; IRD = incidence rate difference.
*Stratified Cox proportional hazard regression model, significance with Bonferroni correction at $p < 0.005$.
†Models were stratified by age, sex, income, and region of residence.
‡The model was adjusted for age, sex, income, region, obesity, smoking, alcohol consumption, and CCI scores.

affected by tobacco epidemics or inhalable ambient chemicals such as fine particulate matter air pollution and the burning of solid fuel in households.[26–28]

The detailed pathological mechanisms underlying the relationships between CRS and various cancers are unclear. Several studies have reported that the chronic inflammatory response is possibly related to certain pathways of carcinogenesis. The overexpression of some specific inflammatory cytokines is observed in all general hematologic malignancies.[29] Nievergall et al. demonstrated that newly diagnosed CML patients had higher plasma levels of IL-6 and TNFα than healthy controls.[30] Next, several studies have revealed that ROS, which are produced by inflammatory cells such as neutrophils and fibroblasts throughout the respiratory burst, especially in CRS, which is one of the most common chronic inflammatory diseases,[31,32] may participate in both the pathogenesis of CRS and carcinogenesis. ROS coordinates angiogenesis, which is critical for tumor growth, by elevating VEGF induction by cancer cells and affecting the invasion and migration of cancer cells by inducing epithelial to mesenchymal transition, reducing cell adhesion, and degrading the extracellular matrix.[33,34]

Shirkhoda et al. reported that allergic rhinitis patients had a reduced risk of papillary thyroid cancer (adjusted odds ratio, 0.07) in a case–control study.[35] In other population-based epidemiologic studies, Hwang et al. and Meinhold et al. showed a positive association between thyroid cancer and asthma (adjusted HR, 1.23 and 1.49, respectively).[36,37] In the current study, the adjusted HR for thyroid cancer was significantly higher in the absence of nasal polyps. The CRSsNP group had a slightly (1.24-fold) higher incidence of hepatic cancer, but the difference did not achieve statistical significance compared with the control group. Nasal polyposis is frequently associated with allergic sensitization to aeroallergens, and the prevalence is higher in subjects with asthma than in those without asthma.[1,38] Unfortunately, we did not have information on the presence of allergic rhinitis or asthma, including allergy tests for specific aeroallergens, plasma levels of immunoglobulin E, and eosinophils. If the subgroup analysis was to be performed again with consideration of the confounding factors related to allergies, a different outcome might be obtained.

The adjusted HRs for colorectal cancer in the CRSsNP cohort and hepatic cancer in the CRSwNP cohort compared with the controls were significantly reduced. These cancers are well known to be typical models of carcinogenesis associated with chronic inflammation. For example, inflammatory bowel disease (IBD) relates to the progression of colorectal cancer,[39] and hepatitis B virus (HBV) or HCV infection is an important cause of chronic liver disease progressing to hepatocellular carcinoma.[40] Conversely, Qiu et al. and Song et al. demonstrated that the activation of HBV infection-associated immunity reduced the risk of liver metastasis from colorectal cancer.[41,42] Whether alterations in sinus-associated immunity due to infections with microorganisms contribute to the impairment of carcinogenesis in CRS patients remains unclear. On the other hand, some medications can reduce the risks of carcinogenesis and metastasis. Rothwell et al. identified that daily aspirin can prevent distant metastasis based on evidence from randomized controlled trials involving 987 patients newly diagnosed with a new solid cancer.[43] Lamb et al. reported that broad-spectrum antibiotics targeting mitochondrial functions, such as tetracycline and chloramphenicol, can eradicate cancer stem cells.[44] We considered 17 comorbidities by calculating the CCI score but did not

TABLE III.
Crude and Adjusted Hazard Ratios (95% Confidence Intervals) of CRSwNP for Various Cancers.

Dependent variable	IR per 1000 person-year		IRD per 1000 person-years (95% CI)	Hazard ratios for cancers			
	CRSwNP (n = 3,460)	Control (n = 13,840)		Crude†	p value	Adjusted†‡	p value
All cancer (n = 1,165)	8.96	8.60	0.36 (−0.88 to 1.61)	1.03 (0.89–1.19)	0.684	1.00 (0.87–1.16)	0.965
Gastric cancer (n = 282)	1.88	2.11	−0.23 (−0.83 to 0.37)	0.88 (0.65–1.19)	0.399	0.84 (0.62–1.14)	0.272
Thyroid cancer (n = 142)	1.22	0.98	0.24 (−0.18 to 0.66)	1.26 (0.86–1.86)	0.234	1.24 (0.85–1.83)	0.268
Colorectal cancer (n = 245)	1.80	1.78	0.02 (−0.54 to 0.58)	1.01 (0.74–1.37)	0.965	0.98 (0.71–1.33)	0.881
Lung cancer (n = 204)	1.72	1.42	0.30 (−0.20 to 0.81)	1.18 (0.85–1.63)	0.322	1.23 (0.89–1.70)	0.219
Hepatic cancer (n = 160)	0.72	1.27	−0.56 (−1.00 to −0.11)	0.56 (0.35–0.89)	0.014	0.47 (0.29–0.77)	0.003*
Bladder cancer (n = 40)	0.25	0.30	−0.05 (−0.27 to 0.17)	0.81 (0.36–1.84)	0.621	0.76 (0.33–1.73)	0.509
Pancreatic cancer (n = 59)	0.36	0.44	−0.09 (−0.36 to 0.18)	0.79 (0.40–1.57)	0.504	0.81 (0.41–1.61)	0.554
Gallbladder and biliary duct (n = 55)	0.36	0.41	−0.05 (−0.31 to 0.21)	0.85 (0.43–1.69)	0.647	0.83 (0.41–1.66)	0.592
Kidney cancer (n = 22)	0.18	0.15	0.02 (−0.14 to 0.19)	1.21 (0.44–3.31)	0.710	1.22 (0.44–3.37)	0.705
Hematologic malignancy (n = 74)	0.93	0.44	0.50 (0.19 to 0.80)	2.16 (1.33–3.48)	0.002*	2.15 (1.33–3.49)	0.002*

CRS = chronic rhinosinusitis; CRSwNP = CRS with nasal polyps; IR = incidence rate; IRD = incidence rate difference.
*Stratified Cox proportional hazard regression model, significance with Bonferroni correction at $p < 0.005$.
†Models were stratified by age, sex, income, and region of residence.
‡The model was adjusted for age, sex, income, region, obesity, smoking, alcohol consumption, and CCI scores.

TABLE IV.
Crude and Adjusted Hazard Ratios (95% Confidence Intervals) of CRSsNP for Various Cancers

Dependent variable	IR per 1000 person-year		IRD per 1000 person-years (95% CI)	Hazard ratios for cancers			
	CRSsNP (n = 3,459)	Control (n = 13,836)		Crude†	p value	Adjusted†‡	p value
All cancer (n = 1,011)	10.10	8.44	1.65 (0.30 to 3.00)	1.19 (1.03–1.38)	0.020	1.14 (0.98–1.32)	0.082
Gastric cancer (n = 238)	2.02	2.03	0.00 (−0.64 to 0.64)	0.98 (0.71–1.34)	0.878	0.96 (0.69–1.32)	0.777
Thyroid cancer (n = 155)	2.02	1.13	0.89 (0.37 to 1.41)	1.82 (1.29–2.56)	0.001*	1.78 (1.27–2.51)	0.001*
Colorectal cancer (n = 219)	1.13	2.04	−0.91 (−1.52 to −0.30)	0.56 (0.37–0.83)	0.004*	0.53 (0.36–0.80)	0.002*
Lung cancer (n = 165)	1.55	1.35	0.20 (−0.33 to 0.73)	1.15 (0.80–1.65)	0.464	1.16 (0.80–1.68)	0.438
Hepatic cancer (n = 121)	1.13	0.99	0.14 (−0.32 to 0.59)	1.14 (0.74–1.75)	0.554	0.93 (0.60–1.45)	0.761
Bladder cancer (n = 31)	0.38	0.23	0.14 (−0.09 to 0.37)	1.58 (0.73–3.44)	0.249	1.72 (0.78–3.76)	0.178
Pancreatic cancer (n = 45)	0.42	0.37	0.05 (−0.23 to 0.32)	1.15 (0.57–2.31)	0.706	1.09 (0.54–2.22)	0.804
Gallbladder and biliary duct (n = 31)	0.42	0.22	0.20 (−0.03 to 0.43)	1.80 (0.84–3.84)	0.129	2.04 (0.93–4.48)	0.077
Kidney cancer (n = 25)	0.25	0.20	0.05 (−0.16 to 0.26)	1.24 (0.50–3.11)	0.646	1.19 (0.47–3.00)	0.718
Hematologic malignancy (n = 50)	1.13	0.24	0.89 (0.60 to 1.18)	4.75 (2.72–8.28)	<0.001*	4.48 (2.56–7.86)	<0.001*

CRS = chronic rhinosinusitis; CRSsNP = CRS without nasal polyps; IR = incidence rate; IRD = incidence rate difference.
*Stratified Cox proportional hazard regression model, significance with Bonferroni correction at $p < 0.005$.
†Models were stratified by age, sex, income, and region of residence.
‡The model was adjusted for age, sex, income, region, obesity, smoking, alcohol consumption, and CCI scores.

consider the history of underlying colorectal and hepatic diseases such as IBD, HBV, or HCV infection, and oral medication histories and further analysis is needed.

The strengths of this study are its large sample size and population-based design. In addition, the longitudinal design of this study allowed us to assess the incidence of various cancers over time after the diagnosis of CRS and calculate the cumulative incidences of various cancers in this population. We also acknowledge several limitations. First, we lacked data on breast cancer, cervical cancer, and prostate cancer, which are classified as sensitive diseases, because the Korean National Health Insurance Service-Health Screening Cohort database does not provide information on sensitive diseases. Second, we were unable to directly investigate and analyze the pathological mechanisms to determine causal relationships between CRS and various cancers. Third, although this study considered the subgroups of CRS according to the presence of nasal polyps, CRS has been recognized as a heterogeneous disease and is characterized as a

constellation of inflammatory conditions.[45] Additionally, we used the database with a national cohort of Korean adults, so it cannot be generalized to all populations. The database is bulky and very granular but based heavily on ICD-10 codes, which is not always accurate. Additionally, patients with chronic underlying diseases, such as hypertension, hyperlipidemia, and diabetes, are likely to visit medical institutions more frequently than healthy volunteers, which increases the probability of being diagnosed with CRS. For this reason, detection or surveillance bias may have occurred in this study. Moreover, we tried to select the patients who were claimed by ICD-10 code (J32) more than once and underwent head and neck CT according to the definition of CRS to determine the true CRS. Despite these efforts, the database had inherent weaknesses, and the subjects who did not meet the definition of CRS may have been included if the clinician entered the ICD-10 code (J32) incorrectly more than twice. Thus, detection or surveillance bias may have occurred in this study.

CONCLUSION

The current study investigated whether CRS is significantly associated with the incidences of various cancers. CRS was associated with an increased incidence of hematologic malignancy and thyroid cancer.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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