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Original Article

Cancer risk in chronic rhinosinusitis: a propensity score matched case-control cohort study

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Abstract: Background: Chronic rhinosinusitis (CRS) have infection, innate immune disorder and chronic inflammation problems which are considered as potential mechanism of tumorigenesis. To estimate cancer risk in CRS using propensity scores matching (PSM) case-control cohort study. Methods: A nationwide retrospective case-control cohort study is conducted on claim data from National Health Insurance Research Database in Taiwan. From January 2000 to December 2005, case group included 32677 CRS patients (including 544 with surgery in case 1 group and 32133 without surgery in case 2 group), and control group included 98031 subjects without CRS which were matching by PSM method on all baseline characteristics. All subjects were followed up from January 2006 till December 2013, the risk of cancers were calculated during the period. Conditional logistic regression Analysis of Cancer Risk is used to calculate the odds ratio (OR) and 95% confidence interval (CI) for case, case 1 and case 2 compared with control group. The difference in cancer risk among case, case 1 and case 2 drew the conclusions of this paper. Results: The risk of cancers in head and neck (adjusted OR: 1.53, 95% CI: 1.33-1.75), colon (adjusted OR: 1.23, 95% CI: 1.09-1.39), liver (adjusted OR: 1.24, 95% CI: 1.09-1.41), lung (adjusted OR: 1.14, 95% CI: 1-1.3), skin (adjusted OR: 1.37, 95% CI: 1.05-1.79), breast (adjusted OR: 1.17, 95% CI: 1.01-1.36), prostate (adjusted OR: 1.85, 95% CI: 1.54-2.22) and bladder (adjusted OR: 1.48, 95% CI: 1.17-1.48) were statistical significantly higher in CRS patients than non-CRS group. Compared with CRS patients without surgery, risk of cancers in head and neck, colon, liver, lung, skin, breast, and prostate were higher in CRS patients receiving surgery. Conclusion: Cancer risk in CRS patients is significant high than non-CRS patients, especially in head and neck, breast, lung, bladder, colorectal, liver, prostate, and skin cancers. Surgical interventions in CRS patients could not decrease cancer risk in CRS patients.

Keywords: Chronic rhinosinusitis, cancer, risk, case-control

Introduction

Chronic rhinosinusitis (CRS) is defined as a complex inflammatory condition involving the paranasal sinuses and linings of the nasal passages that lasts 12 weeks or longer, despite attempts at medical management [1]. CRS is an endemic disease in Taiwan because Taiwan lies on the Tropic of Cancer, and its general climate is marine tropical with high temperature and humidity [2]. The northern and central regions are subtropical, whereas the south is tropical and the mountainous regions are temperate [2]. Such a hot and humid climate in Taiwan is suitable for the growth of allergens including dust mites, bacteria, and fungus having a strong association with CRS [3-7]. Almost half of Taiwanese have CRS diagnosis in his life [2].

CRS is a heterogeneous and multifactorial disease characterized by dysregulated inflammation [8]. Abnormalities in innate immune function, including sinonasal epithelial cell barrier

function, mucociliary clearance, response to pathogen-associated molecular patterns via pattern recognition receptors, and the contribution of innate immune cells [8]. The possible mechanism of increasing cancer risk might be contributed to CRS with innate immunity dysfunction and result in the promotion of tumor development and disease progression [9]. Moreover, CRS is also a pan-airway inflammation disease and some studies showed not only local inflammation but also positive association with other organ system inflammation induced increasing of cancer risk [10-13].

In most CRS cases, the disorder cannot be cured, and the goal of therapy is to reduce symptoms and improve quality of life [14, 15]. Multiple therapies are utilized in the management of CRS, including intranasal saline, intranasal and systemic glucocorticoids, antibiotics, and antileukotriene agents [16-22]. These are combined in various ways to manage specific subtypes of CRS. The aforementioned agents such as glucocorticoids [23, 24], and antibiotics [25, 26], agents were published with increasing cancer risk. Till now, there have been no solid evidences to support the current medical treatments [16-22]. Thus, finding out alternative treatment of CRS instead of steroid or antibiotics use could be valuable in prevalent CRS areas, like Taiwan.

CRS have infection, innate immune disorder and chronic inflammation problems which are considered as potential mechanism of tumorigenesis [27]. In this study, we want to estimate cancer risk in CRS patients using PSM in a national cohort study compared with non-CRS patients. Surgical interventions might be useful therapies to relief of symptoms and signs of CRS and removal of inflammatory pathogens related tissues might have potential to decrease cancer risk. Therefore, surgical interventions in CRS patients would be also evaluated the preventive effects of cancer risk in comparison of CRS patients without surgical interventions.

Patients and methods

Database

The nationwide retrospective case-control cohort study used administrative claims data from National Health Insurance Research Database (NHIRD) in Taiwan. NHIRD was maintained by National Health Insurance (NHI) program, which was launched in 1995. The NHIRD contains anonymous eligibility and enrollment information, as well as claims for outpatient and inpatient visits, pharmacological prescriptions and surgical procedures for nearly 99% of the entire population (23 million) in Taiwan. To date, numerous studies which used data from the Taiwanese NHI program have been published international peer-reviewed journals, so that the completeness and accuracy of this database has been generally recognized. The original data analyzed by this study consisted of 1 million subjects randomly selected from NHIRD. All the information that could be used to identify patients were encrypted to protect privacy and only for research purpose. This study was exempted from full review of Institutional Review Board of Taipei Medical University.

Selection of cases and controls

This retrospective cohort study was consisted of two study groups: a CRS cohort and a matched non-CRS comparison cohort.

The case cohort included patients aged more than 18 years old who had received a diagnosis of CRS (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 473.X) between January 2000 and December 2005 to prevent overestimating the risk of cancer, patients with a cancer diagnosis (ICD-9-CM codes 140-208) before CRS diagnosis, cancer diagnosis after CRS diagnosis within one year, and a history of cancer (ICD-9-CM codes 140-208) before December 2005 were excluded. The case cohort was divided into two subgroups according to whether received surgical interventions for CRS (Procedure codes 65001C, 65002C, 65003C, 65006C, 65009B, 65010B, 65011C, 65012B, 65013B and 65014B), one CRS subgroup with surgery and another one subgroup without surgery.

In order to reduce the bias due to confounding variables between case cohort and comparison cohort, we used propensity score matching (PSM) method in terms to all the baseline characteristics in **Table 1** to select subjects with out CRS on 1:3 ratios for each CRS patient. Subjects in comparison group also didn't have cancers before December 2005. Finally, 32677

Table 1. Characteristics of chronic rhinosinusitis patients and non-chronic rhinosinusitis patients with their propensity score-matched cohort

	Case, CRS, N (%)	Control, Non-CRS, N (%)	*P* value
Overall	32677	98031	
Age (years)			0.905
18-29	7721 (23.6)	23167 (23.6)	
30-39	7233 (22.1)	21419 (21.8)	
40-49	7126 (21.8)	21611 (22.0)	
50-59	5179 (15.8)	15559 (15.9)	
60-69	2898 (8.9)	8691 (8.9)	
≥70	2520 (7.7)	7584 (7.7)	
Sex			0.382
Male	15070 (46.1)	45485 (46.4)	
Female	17607 (53.88)	52546 (53.6)	
Monthly insured income			0.976
≤ NT$15,840	12041 (36.8)	36163 (36.9)	
NT$15,841-25,000	10840 (33.2)	32543 (33.2)	
≥ NT$25,001	9796 (30.0)	29325 (29.9)	
Geographical region			0.621
Northern	8839 (27.0)	26319 (26.8)	
Central	561 (1.7)	1625 (1.7)	
Southern	15567 (47.6)	46670 (47.6)	
Eastern	7710 (23.6)	23417 (23.9)	
Urbanization level			0.950
1 (most urbanized)	11823 (36.2)	35731 (36.4)	
2	9313 (28.5)	27726 (28.3)	
3	5256 (16.1)	15790 (16.1)	
4	4029 (12.3)	12122 (12.4)	
5	456 (1.4)	1312 (1.3)	
6	959 (2.9)	2851 (2.9)	
7	841 (2.6)	2499 (2.5)	
Comorbidity			
Hypertension	7721 (23.6)	23171 (23.6)	0.982
Hyperlipidemia	7136 (21.8)	21598 (22.0)	0.468
Diabetes	4379 (13.4)	13117 (13.4)	0.933

CRS, Chronic rhinosinusitis; NT$, New Taiwan Dollars; N, numbers.

cases (including 544 in case 1 group and 32133 in case 2 group) and 98031 controls were included in our analysis and followed up.

Outcomes

The study outcome was a diagnosis of cancer during January 2006 to December 2013. We excluded cancer diagnosis before CRS diagnosis, or cancer diagnosis after CRS diagnosis within one year. We divided cancers into the following 17 groups: head and neck (ICD-9-CM codes 140-149 and 161), esophagus (ICD-9-CM 150), stomach (ICD-9-CM 151), small intestine (ICD-9-CM 152), colon (ICD-9-CM 153-154), liver (ICD-9-CM 155), pancreas (ICD-9-CM 157), lung (ICD-9-CM 162), skin (ICD-9-CM 172-173), breast (ICD-9-CM 174), uterine (ICD-9-CM 180-184), prostate (ICD-9-CM 185), bladder (ICD-9-CM 188), kidney (ICD-9-CM 189), brain (ICD-9-CM 191), thyroid (ICD-9-CM 193) and hematological cancer (ICD-9-CM 200-208).

Statistical analysis

All the statistical analyses were conducted with the SAS software on Windows System (version 9.2, SAS Institute, Cary, NC). For all the statistical tests, significance was set at p value less than 0.05. Descriptive analyses were performed on all baseline characteristics, including age group (18-29, 30-39, 40-49, 50-59, 60-69, ≥70), gender (male, female), monthly income (New Taiwan Dollars [NT$] 0-15840, NT$15841-25000, ≥NT$25001), geographical location (northern, central, eastern, and southern Taiwan), urbanization level of the patients' residence (5 levels, with 1 being the most urbanized and 5 being the least), as well as comorbidities including hypertension (ICD-9-CM codes 401-405), hyperlipidemia (ICD-9-CM code 272), diabetes (ICD-9-CM codes 250). Chi-squared tests were conducted to compare the difference of distribution on baseline characteristics between case cohort and comparison cohort.

The risk of cancers was calculated during the 8-year follow-up period. For each cancer, Conditional logistic regression Analysis were used to calculate the odd ratio (OR) and 95% confidence interval (95% CI) for case, case 1, case 2 cohorts compared with control cohort, and subsequently examine their statistical significance with multivariate analysis under adjustment of age, Sex, Monthly insured income, Geographical regions, Urbanization levels, and Comorbidity. We investigated the difference on risk of cancers among these three case groups to identify

Table 2. Characteristics of chronic rhinosinusitis patients receiving surgical interventions or no surgical interventions

	Case 1, CRS with surgical interventions, N (%)	Case 2, CRS without surgical interventions, N (%)	*P* value
Overall	544	32133	
Age (years)			<0.001
18-29	106 (19.5)	7615 (23.7)	
30-39	103 (18.9)	7130 (22.2)	
40-49	117 (21.5)	7009 (21.8)	
50-59	108 (19.9)	5071 (15.8)	
60-69	61 (11.2)	2837 (8.8)	
≥70	49 (9.0)	2471 (7.7)	
Sex			<0.001
Male	333 (61.2)	14737 (45.9)	
Female	211 (38.79)	17396 (54.14)	
Monthly insured income			<0.001
≤NT$15,840	186 (34.2)	11855 (36.9)	
NT$15,841-25,000	188 (34.6)	10652 (33.1)	
≥NT$25,001	170 (31.2)	9626 (30.0)	
Geographical region			<0.001
Northern	124 (22.8)	8715 (27.1)	
Central	5 (0.9)	556 (1.7)	
Southern	282 (51.8)	15285 (47.6)	
Eastern	133 (24.4)	7577 (23.6)	
Urbanization level			<0.001
1 (most urbanized)	190 (34.9)	11633 (36.2)	
2	147 (27.0)	9166 (28.5)	
3	87 (16.0)	5169 (16.1)	
4	73 (13.4)	3956 (12.3)	
5	11 (2.0)	445 (1.4)	
6	15 (2.8)	944 (2.9)	
7	21 (3.9)	820 (2.6)	
Comorbidity			<0.001
Hypertension	155 (28.5)	7566 (23.5)	
Hyperlipidemia	132 (24.3)	7004 (21.8)	
Diabetes	83 (15.3)	4296 (13.4)	

CRS, Chronic rhinosinusitis; NT$, New Taiwan Dollars; N, numbers.

the influence of CRS on risk of cancers and the influence of surgery on risk of cancers among CRS patients.

Results

Table 1 presents the distributions of demographic characteristics and comorbidities among case and comparison cohort. After propensity score matching method on all baseline characteristics, no statistical significance was observed on age group (P= 0.905), sex (P=0.382), monthly insured income (P=0.976), geographical region (P=0.621), urbanization level (P=0.950). Three comorbidities were also not statistically significant, hypertension (P=0.982), hyperlipidemia (P=0.468) and diabetes (P=0.652). We found that cases and controls were similar other than history of CRS. **Table 2** reveals that characteristics of CRS patients receiving surgical interventions or no surgical interventions. The PSM was not done between surgical interventions or not in case 1 and 2. Old age, male, non-urban, southern, and eastern resident areas were more in CRS patients receiving surgical interventions cohort (Case 1) (**Table 2**).

Table 3 shows conditional logistic regression Analysis of Cancer Risk among CRS patients compared with non-CRS patients within 8-year follow-up period. We found that 2148 (6.6%) CRS patients received cancers while 5400 (5.5%) non-CRS patients received cancers. Conditional logistic regression analysis indicated that compared with control cohort, adjusted OR for CRS patients were 1.24 (95% CI: 1.17-1.3) compared with non-CRS patients. Moreover, 50 (9.2%) in case 1 cohort with surgery and 2098 (6.5%) in case 2 cohort without surgery; adjusted ORs for Case 1 and case 2 were 1.56 (95% CI: 1.16-2.11) and 1.23 (95% CI: 1.17-1.3) compared with non-CRS patients (**Table 4**).

The risk of cancers in head and neck (adjusted OR: 1.53, 95% CI: 1.33-1.75), colon (adjusted OR: 1.23, 95% CI: 1.09-1.39), liver (adjusted OR: 1.24, 95% CI: 1.09-1.41), lung (adjusted OR: 1.14, 95% CI: 1-1.3), skin (adjusted OR: 1.37, 95% CI: 1.05-1.79), breast (adjusted OR: 1.17, 95% CI: 1.01-1.36), prostate (adjusted OR: 1.85, 95% CI: 1.54-2.22) and bladder (adjusted OR: 1.48, 95% CI: 1.17-1.48) were statistical significantly higher in CRS patients than control group (**Table 3**). Compared with

Table 3. Conditional logistic regression Analysis of Cancer Risk among chronic rhinosinusitis patients compared with non-chronic rhinosinusitis patients

Cancers (ICD-9-CM)	Multivariate analysis*			
	Case, CRS, N (%)	Control, Non-CRS, N (%)	Adjusted OR (95% CI)	*P* value
Overall	2148 (6.6)	5400 (5.5)	1.24 (1.17, 1.3)	<0.001
Head and neck (140-149, 161)	307 (0.9)	611 (0.6)	1.53 (1.33, 1.75)	<0.001
Esophagus (150)	32 (0.1)	120 (0.1)	1.18 (0.55, 1.2)	0.295
Stomach (151)	78 (0.2)	271 (0.3)	1.88 (0.69, 1.14)	0.341
Small intestine (152)	16 (0.0)	36 (0.0)	1.36 (0.75, 2.45)	0.306
Colorectum (153-154)	373 (1.1)	933 (1.0)	1.23 (1.09, 1.39)	0.001
Liver (155)	344 (1.1)	847 (0.9)	1.24 (1.09, 1.41)	0.001
Pancreas (157)	63 (0.2)	165 (0.2)	1.16 (0.87, 1.55)	0.310
Lung (162)	324 (1.0)	879 (0.9)	1.14 (1, 1.3)	0.042
Skin (172-173)	79 (0.2)	177 (0.2)	1.37 (1.05, 1.79)	0.019
Breast (174)	236 (0.7)	606 (0.6)	1.17 (1.01, 1.36)	0.040
Uterine (180-184)	139 (0.4)	396 (0.4)	1.05 (0.87, 1.28)	0.610
Prostate (185)	190 (0.6)	326 (0.3)	1.85 (1.54, 2.22)	<0.001
Bladder (188)	101 (0.3)	211 (0.2)	1.48 (1.17, 1.88)	0.001
Kidney (189)	72 (0.2)	228 (0.2)	0.96 (0.74, 1.26)	0.783
Brain (191)	35 (0.1)	124 (0.1)	0.86 (0.59, 1.25)	0.421
Thyroid (193)	58 (0.2)	130 (0.1)	1.34 (0.98, 1.83)	0.064
Hematologic (200-208)	122 (0.4)	308 (0.3)	1.2 (0.97, 1.48)	0.085

*All the aforementioned variables in **Table 1** were used in the multivariate analysis. CRS, Chronic rhinosinusitis; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; OR, odd ratio; CI, confidence interval; N, numbers.

Table 4. Conditional logistic regressions Analysis of Cancer Risk among chronic rhinosinusitis patients receiving surgical interventions or no surgical interventions compared with non- chronic rhinosinusitis patients

Cancers (ICD-9-CM)	Multivariate analysis*			Multivariate analysis*		
	Case1, CRS with surgical intervention, N (%)	Adjusted OR (95% CI)	*P* value	Case 2 CRS without surgical intervention, N (%)	Adjusted OR (95% CI)*	*P* value
Overall	50 (9.2)	1.56 (1.16, 2.11)	0.004	2098 (6.5)	1.23 (1.17, 1.3)	<0.001
Head and neck (140-149, 161)	14 (2.6)	3.54 (2.06, 6.08)	<0.001	293 (0.9)	1.49 (1.29, 1.71)	<0.001
Esophagus (150)	1 (0.2)	1.15 (0.16, 8.28)	0.889	31 (0.1)	0.8 (0.54, 1.19)	0.279
Stomach (151)	1 (0.2)	0.58 (0.08, 4.15)	0.586	77 (0.2)	0.89 (0.69, 1.15)	0.371
Small intestine (152)	-	-	--	16 (0.0)	1.39 (0.77, 2.5)	0.277
Colorectum (153-154)	10 (1.8)	1.73 (0.92, 3.26)	0.091	363 (1.1)	1.22 (1.08, 1.38)	0.002
Liver (155)	7 (1.3)	1.27 (0.6, 2.69)	0.540	337 (1.0)	1.24 (1.09, 1.41)	0.001
Pancreas (157)	1 (0.2)	0.96 (0.13, 6.88)	0.967	62 (0.2)	1.17 (0.87, 1.56)	0.304
Lung (162)	7 (1.3)	1.2 (0.56, 2.57)	0.631	317 (1.0)	1.14 (1, 1.3)	0.046
Skin (172-173)	2 (0.4)	1.76 (0.43, 7.14)	0.430	77 (0.2)	1.37 (1.04, 1.79)	0.023
Breast (174)	4 (0.7)	1.52 (0.56, 4.12)	0.408	232 (0.7)	1.17 (1, 1.36)	0.047
Uterine (180-184)	1 (0.2)	0.58 (0.08, 4.14)	0.586	138 (0.4)	1.06 (0.87, 1.29)	0.570
Prostate (185)	7 (1.3)	3.17 (1.46, 6.93)	0.004	183 (0.6)	1.82 (1.51, 2.19)	<0.001
Bladder (188)	1 (0.2)	0.74 (0.1, 5.31)	0.765	100 (0.3)	1.5 (1.18, 1.9)	0.001
Kidney (189)	1 (0.2)	0.71 (0.1, 5.07)	0.731	71 (0.2)	0.97 (0.74, 1.26)	0.812
Brain (191)	2 (0.4)	2.85 (0.7, 11.6)	0.143	33 (0.1)	0.82 (0.56, 1.21)	0.318
Thyroid (193)	1 (0.2)	1.49 (0.21, 10.73)	0.690	57 (0.2)	1.34 (0.98, 1.83)	0.068
Hematologic (200-208)	4 (0.7)	2.15 (0.8, 5.8)	0.131	118 (0.4)	1.19 (0.96, 1.47)	0.117

*All the aforementioned variables in **Table 1** were used in the multivariate analysis. CRS, Chronic rhinosinusitis; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; OR, odd ratio; CI, confidence interval; N, numbers.

CRS patients without surgery, risk of cancers in head and neck (case 1: adjusted OR: 3.54, 95% CI: 2.06-6.08; case 2: adjusted OR: 1.49, 95% CI: 1.29-1.71), colon (case 1: adjusted OR: 1.73, 95% CI: 0.92-3.62; case 2: adjusted OR: 1.22, 95% CI: 1.08-1.38), liver (case 1: adjusted OR: 1.27, 95% CI: 0.6-2.69; case 2: adjusted OR: 1.24, 95% CI: 1.09-1.41), lung (case 1: adjusted OR: 1.2, 95% CI: 0.56-2.57; case 2: adjusted OR: 1.14, 95% CI: 1-1.3), skin (case 1: adjusted OR: 1.76, 95% CI: 0.43-7.14; case 2: adjusted OR: 1.37, 95% CI: 1.04-1.79), breast (case 1: adjusted OR: 1.52, 95% CI: 0.56-4.12; case 2: adjusted OR: 1.17, 95% CI: 1-1.36), and prostate (case 1: adjusted OR: 3.17, 95% CI: 1.46-6.93; case 2: adjusted OR: 1.82, 95% CI: 1.51-2.19) were higher in CRS patients after surgery, while risk of bladder cancer (case 1: adjusted OR: 0.74, 95% CI: 0.1-5.31; case 2: adjusted OR: 1.5, 95% CI: 1.18-1.9) was lower in CRS patients after surgery (**Table 4**).

Discussion

CRS is very endemic and around 50% Taiwanese population diagnosed of CRS in his life [2]. The very common disease, CRS in Taiwan should be alert if CRS is association with risk of any fatal malignancy risk [10, 12, 13]. Physicians in Taiwan should be aware of CRS with potential threatening diseases and try to decrease the risk of associated serious diseases. Keep standard treatment guideline to eradicate CRS might be a choice. Unfortunately, most therapies for CRS have not been validated in randomized trials, although a consensus group has identified areas in which trials are needed [16]. In 2016, several systematic reviews evaluated the main therapies discussed in this review and concluded that the evidence supporting most of them was of low quality, further emphasizing the need for more rigorous research in these disorders [17-22]. Steroid and antibiotics use seems to increase cancer risk in patients [23-26]. Finding out alternative drugs like antileukotriene instead of steroid or antibiotics use might be valuable and in high prevalent CRS regions [28, 29], like Taiwan and some studies showed antileukotriene could decrease cancer risk [30, 31]. We also want to estimate the preventive effects of cancer risk using surgical interventions for removal of inflammatory tissues in CRS patients. If preventive effects of cancer risk using surgical intervention are worthy, we might have other therapeutic choice for CRS patients rather than steroid or antibiotics use. Since CRS cannot be “cured” in most patients, and therapy is intended to reduce symptoms and improve quality of life [14, 15]. Thus, the goals of CRS therapy should include control of mucosal inflammation and edema, maintenance of adequate sinus ventilation and drainage, prevention of contacting, colonizing or infecting micro-organismst, and reduction in the number of acute exacerbations [14, 15]. Steroids and antibiotics might be preserved to second lines of treatments.

In **Table 3**, Cancer risk increasing in head and neck, colorectal, liver, lung, skin, breast, prostate, and bladder cancers was noted in CRS cohort compared with non-CRS cohorts. These associations between CRS and cancer risk might be contributed to systemic inflammation and medical agents use in CRS patients. Cigarette smoking also play an important role in CRS patients and cancer risk, because smoking also be an etiology of CRS and cancer. However, in female specific cancer like breast cancer was also increasing in CRS patients, but the smoking habits in Taiwanese women is scarcely. Obviously, increasing of cancer risk in CRS patients could not be explained completely and all contributed to cigarette smoking. Studies have revealed that the chronic infection or inflammation of paranasal sinus, nose, throat, and lower respiratory tract may increase the risk of head and neck cancers, suggesting that persistent inflammation and infection of the upper airway mucosa may render the head and neck mucosa more susceptible to carcinogenesis [13, 32-35].

Our study is compatible with previous studies showed lung cancer risk increasing in CRS patients compared with non-CRS patients (**Table 3**) [10, 12]. Possible mechanisms underlying the shared pathophysiology between the upper and lower airway are the so-called nasal-bronchial reflex, inflammation caused by smoking, mouth breathing caused by nasal obstruction and pulmonary aspiration of nasal contents [10, 12]. Interestingly, the digestive system cancers like colorectal and liver cancer risk also increase in CRS patients compared with non-CRS patients. The potential mechanism might be contributed to CRS related disorder of innate immune system and swallowing of

inflammation pollutants, bacteria, or fungus contents within nasal mucopurulent drainage into CRS patients' digestive system [27, 36-39]. Some previous studies have shown high prevalence of CRS in inflammation bowel diseases patients and have noticed to the role of CRS treatment in improvement of ulcerative colitis [40, 41]. In previous studies, some pathogens like Staphylococcus enterotoxin B are known as causes of illness that swallowed with the post nasal drip, would increase the permeability of intestine mucosa, and finally could lead to the intestinal ulcer [42]. Chronic ulcerative colitis is proved to be association with colorectal risk factor [43, 44]. In addition, the irritant contents of inflammation pollutants, bacteria, or fungus related toxins stay longer time in colorectal organs and return into liver via enterohepatic circulation [45-47]. These pathophysiologic metabolism and circulation increase stay time of toxins in colorectum and liver and contributed to digestive organs inflammation resulted in following colorectal or liver cancers [36]. In the past, the similar theory of toxin in other bacteria (Helicobacter pylori infection) via the same enterohepatic circulation was found and also increase liver and colon cancer risk compared with non-Helicobacter pylori infection patients [46, 48-53].

CRS patients have higher risk of skin cancer and breast cancer compared with non-CRS patients. CRS induced innate immune system disorder would result in tumor proliferation and progression [8, 9]. Moreover, use of steroid and antibiotics for management of CRS also bring in risk of skin cancer increasing [23-26]. Our study is the first article to show CRS patients have higher risk of skin, breast, bladder, and prostate cancer. CRS induced innate immunity dysfunction and the outcome of an immune response toward an evolving breast neoplasm is largely determined by the type of immune response elicited [8, 9]. Immune responses involving chronic activation of humoral immunity, infiltration by Th2 cells, and protumor-polarized innate inflammatory cells result in the promotion of tumor development and disease progression [8, 9]. It has been established that cancer can be promoted or exacerbated by inflammation and infections. Indeed, chronic inflammation orchestrates a tumor-supporting microenvironment that is an indispensable participant in the neoplastic process [27]. The mechanisms that link infection, innate immunity, inflammation, and cancer are being unraveled at a fast pace [27]. The critical role of chronic inflammatory diseases is well established [54], and its tumor-promoting effects have been demonstrated [55]. Cytokines produced by inflammatory cells in the microenvironment can promote tumor cell survival [27]. Cytokines produced by inflammatory cells are also associated with increased risk of prostate cancer, bladder cancer, hepatocellular carcinoma, and breast cancer [27].

Although there is no PSM done in CRS receiving surgical interventions or not, the CRS without surgery (Case 2) were very similar with CRS and non-CRS cohorts. But old, male, non-urban and southern or eastern resident areas were more in the CRS receiving surgery cohort. Therefore, we also do multivariate analysis to adjust the bias in Case 1 and Case 2 (**Table 4**). However, CRS with surgical interventions have higher risk of cancers after multivariate analysis. The reason might be indications for surgical interventions are for more severe CRS patients who have inflammatory tissue related obstruction, failure of intensive medical treatment, or bony erosion or extension of disease beyond the sinus cavities; so that even surgical removal of fungus, bacterial, and necrotic tissues, inflammatory processes or symptoms would not be stopped immediately [56]. Surgical interventions in CRS patients are intended to restore physiologic sinus ventilation and drainage, which can facilitate the gradual resolution of mucosal disease. However, because surgical interventions do not directly treat the underlying inflammatory disorder, sinus surgery must be followed by medical management to control inflammatory processes or symptoms will invariably return [56]. Therefore, surgical interventions cannot decrease cancer risk in CRS patients compared with CRS patients without surgery. However, if earlier surgical interventions before failure of medical treatment could be beneficial of decreasing risk of cancers, it is unresolved in the current study.

The strength in our study was the leading and large cohort study with PSM to estimate cancers risk in CRS patients compared with non-CRS patients. This is also the first study to evaluate the preventive effect of surgical interventions in CRS patients' cancer risk. Our find-

ings recommend cancer risk is significant high in CRS patients compared with non-CRS patients, especially head and neck cancer, breast cancer, lung cancer, prostate cancer, bladder cancer, skin cancer colorectal cancer and liver cancers; this may be because infection, innate immunity disorder, inflammation might be contributed to cancer risk. Surgical interventions for removal of inflammatory tissues could not decrease risk of cancer in CRS patients. All cancer risk factors in our study after PSM were more homogenous than other studies. The outcomes in our study could be a reference for clinical practice of medical treatments in CRS including steroid, antibiotics use or not, because no sufficient evidences to support these current medical therapies is correct [16-22]. The outcomes also remind clinical physicians of the eight specific cancers risk while treating CRS patients.

This study has some limitations. First, because all patients with colon adenocarcinoma were enrolled from an Asian population, the corresponding ethnic susceptibility remains unclear; hence, our results should be cautiously extrapolated to non-Asian populations. Second, there was relatively small sample size in CRS receiving surgical interventions. The conclusion of surgical intervention in CRS patients might be limited. However, in comparison of non-CRS patients, cancer risk is significant higher in CRS patients. Therefore, the conclusion of primary end-point in our study will not be overturned. Third, the diagnoses of all comorbid conditions were based on ICD-9-CM codes. Nevertheless, the Taiwan Cancer Registry Administration randomly reviews charts and interviews patients to verify the accuracy of the diagnoses, and hospitals with outlier chargers or practices may be audited and subsequently be heavily penalized if malpractice or discrepancies are identified. Therefore, to obtain crucial information on population specificity and disease occurrence, a large-scale randomized trial comparing carefully selected patients undergoing suitable treatments is essential. Finally, the NHIRD does not contain information regarding dietary habits, smoking history, socioeconomic status, or body mass index, all of which may be risk factors for cancer. However, considering the magnitude and statistical significance of the observed effects in this study, these limitations are unlikely to affect the conclusions.

Conclusions

Cancer risk in CRS patients is significant high than non-CRS patients, especially in head and neck, breast, lung, bladder, colorectal, liver, prostate, and skin cancers. Surgical interventions in CRS patients could not decrease cancer risk in CRS patients.

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Disclosure of conflict of interest

None.

Abbreviations

CRS, Chronic rhinosinusitis; NHIRD, National Health Insurance Research Database; NHI, National Health Insurance; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NT$, New Taiwan Dollars; OR, odd ratio; CI, confidence interval; PSM, propensity scores matching.

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