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Head and neck cancer associated with increased rate of pulmonary tuberculosis in a population-based cohort study

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Abstract

The objective of this study was to examine the incidence and hazard ratio (HR) of pulmonary tuberculosis in patients with head and neck cancer in Taiwan.

This population-based retrospective cohort study was conducted to analyze the database of the Taiwan National Health Insurance Program. There were 2522 subjects aged 20 to 84 years with newly diagnosed head and neck cancer as the head and neck cancer group between 2000 and 2012, and 10,064 randomly selected sex- and age-matched subjects without any cancer as the noncancer group. The incidence of pulmonary tuberculosis at the end of 2013 was estimated in both groups. A multivariable Cox proportional hazards regression model was used to estimate the HR and 95% confidence interval (CI) for pulmonary tuberculosis being associated with head and neck cancer.

The overall incidence of pulmonary tuberculosis was 2.86-fold greater in the head and neck cancer group than that in the noncancer group (4.70 vs 1.64 per 1000 person-years, 95% CI, 2.53–3.24). After adjusting for confounding factors, the adjusted HR of pulmonary tuberculosis became 2.90 for the head and neck cancer group (95% CI, 2.11–3.99), compared with the noncancer group. In addition, male (adjusted HR 2.27, 95% CI, 1.29–4.00) and age (increase for 1 year, adjusted HR 1.06, 95% CI, 1.05–1.08) were associated with pulmonary tuberculosis.

Head and neck cancer is significantly associated with 2.90-fold increased hazard of pulmonary tuberculosis in Taiwan, compared with the general population.

Abbreviation: ICD-9 code = International Classification of Diseases, Ninth Revision, Clinical Modification.

Keywords: head and neck cancer, incidence, pulmonary tuberculosis, Taiwan National Health Insurance Program

1. Introduction

Tuberculosis remains to be a major public health problem worldwide due to its high infectivity and mortality. WHO reported that there were about 1.3 million deaths caused by tuberculosis in 2012.[1] To date, many risk factors for tuberculosis have been identified, including diabetes mellitus, splenectomy, appendectomy, cancer, and others.[2–6]

Two case-series studies have shown that about 3.1% to 6.6% of patients with head and neck cancer could have pulmonary tuberculosis.[7,8] In Cheng et al's meta-analysis of 6 studies conducted in the United Sates, head and neck cancer was the second common cancer, after hematologic malignancies, to be associated with developing active tuberculosis.[6] However, no such a study is available in Taiwan.

Tuberculosis remains to be highly prevalent in Taiwan. In Pan et al's cohort study in Taiwan, the standardized incidence ratio of tuberculosis among the healthcare workers was 1.93 (95% confidence interval [CI], 1.2–2.9) from 2006 to 2012, compared with the general population.[9] According to the report of Ministry of Health and Welfare in Taiwan, head and neck cancer remained to be the leading cause of cancer deaths in 2015, including oral cancer (the 5th) and nasopharyngeal cancer (the 15th).[10]

On the basis of the above review, we think that could be a link between pulmonary tuberculosis and head and neck cancer. If patients with head and neck cancer are at risk for developing pulmonary tuberculosis, periodic screening for pulmonary tuberculosis is an important strategy among these patients. Thus, early detection and early treatment of pulmonary tuberculosis can be performed. Therefore, we conducted a

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population-based retrospective cohort study to examine the incidence and hazard ratio (HR) of pulmonary tuberculosis in patients with head and neck cancer compared with the general population in Taiwan.

2. Methods

2.1. Study design and data source

This population-based retrospective cohort study was conducted to analyze the database of the Taiwan National Health Insurance Program. Taiwan is an independent country where >23 million residents live on.[11–31] The insurance program was set up in March 1, 1995. The enrollment rate was >99.6% of 23 million residents living in Taiwan at the end of 2015.[32] The details of the program have been written in previous studies.[33–37] This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

2.2. Identification of participants

Subjects aged 20 to 84 years who had been newly diagnosed with head and neck cancer between 2000 and 2012 were assigned as our head and neck cancer group, including oral cavity, lip, oropharynx, nasopharynx, and hypopharynx (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9 codes 140–149). To increase the statistical power, for each subject with head and neck cancer, approximately 4 randomly selected subjects without any cancer were assigned to the noncancer group. The index date was defined as the date of diagnosing head and neck cancer. The head and neck cancer group and the noncancer group were matched in terms of sex, age (every 5-year interval), comorbidities, and the year of the index date. Subjects with history of pulmonary tuberculosis before the index date were excluded from the study (Fig. 1).

2.3. Potential comorbidities

The potential comorbidities were included as follows: alcohol-related disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, gastrectomy, pneumoconiosis, as well as chronic liver disease including cirrhosis, hepatitis B infection, hepatitis C infection, and other chronic hepatitis. All comorbidities were diagnosed with ICD-9 codes. The accuracy of ICD-9 codes has been tested in previous studies.[38–48]

2.4. Major outcome

The major outcome was a new diagnosis of pulmonary tuberculosis that usually needed treatment (ICD-9 codes 010, 011, 012, and 018) during the follow-up period. Therefore, all subjects with pulmonary tuberculosis were discovered after cancer diagnosis. All study subjects were followed up with until they were diagnosed with pulmonary tuberculosis, death, or until the end of 2013.

2.5. Statistical analysis

The distributions of sex, age, and comorbidities were compared between the head and neck cancer group and the noncancer group via a χ^2 test for categorized variables and a t test for continuous variables. The incidence of pulmonary tuberculosis was estimated as the number of pulmonary tuberculosis events identified during the follow-up period, divided by the total follow-up person-years for each group. All variables were included in a univariable model. Next, variables that were found to be statistically significant in a univariable model were further included in a multivariable model. A multivariable Cox proportional hazards regression model was used to estimate the HR and 95% CI for the risk of pulmonary tuberculosis associated with head and neck cancer along with other comorbidities. All analyses were performed by SAS software

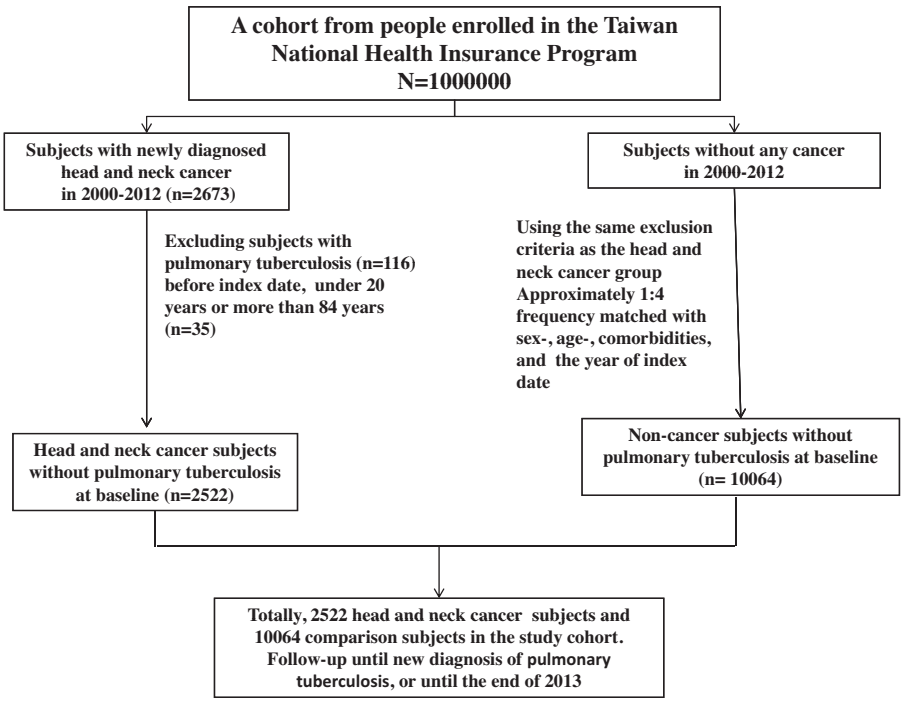

Figure 1. Flow chart revealing the selection process of study's subjects.

Table 1

Baseline characteristics between head and neck cancer group and noncancer group.

Variable	Head and neck cancer, N = 2522		Noncancer, N = 10,064		P*
	n	(%)	n	(%)	
Sex					.99
Female	328	(13.0)	1309	(13.0)	
Male	2194	(87.0)	8755	(87.0)	
Age group (y)					.81
20–39	358	(14.2)	1480	(14.7)	
40–64	1726	(68.4)	6838	(68.0)	
65–84	438	(17.4)	1746	(17.3)	
Age (y), mean (standard deviation)†	52.9	(12.3)	52.4	(12.6)	.10
Baseline comorbidities					
Alcohol-related disease	326	(12.9)	1286	(12.8)	.84
Chronic kidney disease	41	(1.63)	164	(1.63)	.99
Chronic liver disease	456	(18.1)	1802	(17.9)	.84
Chronic obstructive pulmonary disease	264	(10.5)	1056	(10.5)	.97
Diabetes mellitus	236	(9.36)	936	(9.30)	.93
Gastrectomy	4	(0.16)	12	(0.12)	.62
Pneumoconiosis	21	(0.83)	71	(0.71)	.50

Data are presented as the number of subjects in each group with percentages given in parentheses, or the mean with standard deviation given in parentheses.
* χ^2 test.
† *t*-Test comparing subjects with head and neck cancer and without any cancer.

version 9.2 (SAS Institute Inc., Cary, NC). The results were considered statistically significant when 2-tailed *P* values were <.05.

3. Results

3.1. Baseline characteristics of the study population

Table 1 reveals the baseline characteristics of the study population. There were 2522 subjects in the head and neck cancer group and 10,064 subjects in the noncancer group, with similar distributions of sex and age. The mean ages (standard deviation) of the study's subjects were 52.9 (12.3) years for the head and neck cancer group and 52.4 (12.6) years for the noncancer group, without statistical significance (*t* test, *P* = .1). There were no significant differences of comorbidities between the head and neck cancer group and noncancer group (χ^2 test, *P* > .05).

3.2. Incidence of pulmonary tuberculosis in the study population stratified by sex, age, and follow-up period

Table 2 reveals that the overall incidence of pulmonary tuberculosis was 2.86-fold greater in the head and neck cancer group than that in the noncancer group (4.70 vs 1.64 per 1000 person-years, 95% CI, 2.53–3.24). As stratified by sex and age, the incidences of pulmonary tuberculosis were all higher in the head and neck cancer group than those in the noncancer group.

During the first 6 months of follow-up, the head and neck cancer group had a higher incidence of pulmonary tuberculosis than the noncancer group (14.1 vs 1.4 per 1000 person-years, incidence rate ratio 10.1, 95% CI, 8.8–11.6). Even after 6 months of follow-up, the head and neck cancer group still had a higher incidence of pulmonary tuberculosis than the noncancer group (3.64 vs 1.66 per 1000 person-years, incidence rate ratio 2.20, 95% CI, 1.92–2.51).

Using the Kaplan–Meier model, we have revealed that the cumulative incidence of pulmonary tuberculosis was higher in the head and neck cancer group than that in the non-head and neck cancer group (3.74% vs 1.70% at the end of follow-up; *P* < .001; Fig. 2).

3.3. Association of pulmonary tuberculosis with head and neck cancer and comorbidities

Table 3 reveals the HR of pulmonary tuberculosis associated with head and neck cancer and comorbidities. After adjusting for confounding factors including sex, age, chronic obstructive pulmonary disease, and diabetes mellitus, the multivariable Cox

Table 2

Incidence of pulmonary tuberculosis estimated by sex and age between head and neck cancer group and noncancer group.

Variable	Head and neck cancer				Noncancer				IRR†	(95% CI)
	N	Event	Person-years	Incidence*	N	Event	Person-years	Incidence*		
All	2522	56	11,918	4.70	10,064	124	75,591	1.64	2.86	(2.53–3.24)
Sex										
Female	328	4	1966	2.03	1309	9	10,179	0.88	2.30	(1.61–3.29)
Male	2194	52	9952	5.23	8755	115	65,412	1.76	2.97	(2.61–3.39)
Age group (y)										
20–39	358	2	1933	1.03	1480	4	11,840	0.34	3.06	(2.14–4.37)
40–64	1726	36	8471	4.25	6838	67	52,487	1.28	3.33	(2.88–3.85)
65–84	438	18	1513	11.9	1746	53	11,264	4.71	2.53	(1.89–3.37)

* Incidence rate: per 1000 person-years.
† IRR (incidence rate ratio): head and neck cancer versus noncancer (95% CI)

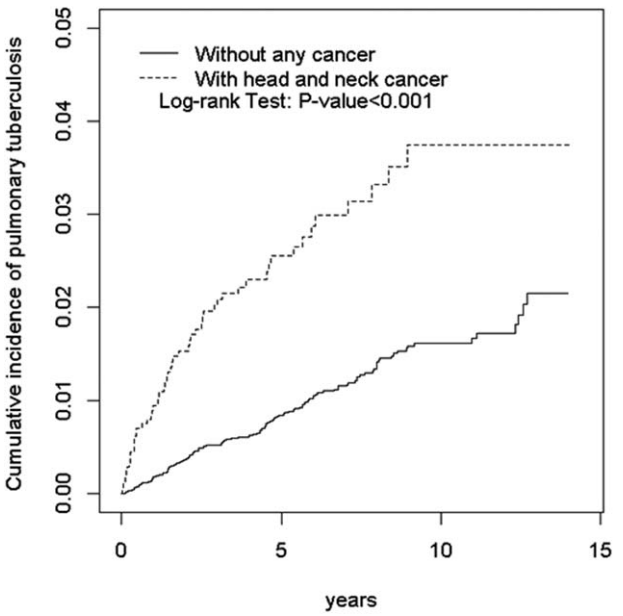

Figure 2. Kaplan–Meier model reveals that the head and neck cancer group had a higher cumulative incidence of pulmonary tuberculosis than the noncancer group (3.74% vs 1.70% at the end of follow-up; $P < .001$).

proportional hazards regression model revealed that the adjusted HR of pulmonary tuberculosis was 2.90 for the head and neck cancer group (95% CI, 2.11–3.99), compared with the noncancer group. In addition, male (adjusted HR 2.27, 95% CI, 1.29–4.00) and age (increase for 1 year, adjusted HR 1.06, 95% CI, 1.05–1.08) were associated with pulmonary tuberculosis.

3.4. Hazard ratio of pulmonary tuberculosis stratified by head and neck cancer and comorbidities

Table 4 reveals the HR of pulmonary tuberculosis stratified by head and neck cancer and comorbidities. To reduce the potential confounding effects caused by comorbidities, as a reference of subjects without any cancer and without any comorbidity, the adjusted HR of pulmonary tuberculosis was 3.60 (95% CI, 2.45–5.28) for subjects with head and neck cancer and without any comorbidity.

3.5. Hazard ratio of pulmonary tuberculosis stratified by head and neck cancer and anticancer chemotherapy and radiation therapy

Table 5 reveals the HR of pulmonary tuberculosis stratified by head and neck cancer and anticancer chemotherapy and radiation therapy. As a reference of subjects without any cancer and without receiving anticancer chemotherapy and radiation therapy, the adjusted HR of pulmonary tuberculosis was 1.26 (95% CI, 0.62–2.58) for subjects with head and neck cancer and without receiving anticancer chemotherapy and radiation therapy. The adjusted HR of pulmonary tuberculosis increased to 3.73 (95% CI, 2.66–5.23) for subjects with head and neck cancer and receiving anticancer chemotherapy or radiation therapy.

Table 3

Cox model measured hazard ratio and 95% CI of pulmonary tuberculosis associated with head and neck cancer and comorbidities.

	Crude	Adjusted*
Variable	**HR (95% CI)**	**HR (95% CI)**
Sex (male vs female)	2.04 (1.16–3.58)	2.27 (1.29–4.00)
Age (per 1 y)	1.06 (1.05–1.08)	1.06 (1.05–1.08)
Head and neck cancer (yes vs no)	2.72 (1.98–3.73)	2.90 (2.11–3.99)
Baseline comorbidities (yes vs no)		
Alcohol-related disease	1.02 (0.70–1.62)	
Chronic kidney disease	1.34 (0.43–4.20)	
Chronic liver disease	1.15 (0.79–1.67)	
Chronic obstructive pulmonary disease	2.80 (1.98–3.97)	1.40 (0.97– 2.03)
Diabetes mellitus	1.85 (1.22–2.81)	1.25 (0.82–1.89)
Gastrectomy†	—	
Pneumoconiosis	0.91 (0.13–6.47)	

* Variables which were found to be statistically significant in the univariable model were further examined in the multivariable model. Adjusted for sex, age, chronic obstructive pulmonary disease, and diabetes mellitus.

† There was no event of pulmonary tuberculosis among subjects with gastrectomy.

4. Discussion

In this population-based, retrospective cohort study, we found that the incidence of pulmonary tuberculosis was higher in patients with head and neck cancer, compared with those without any cancer (4.70 vs 1.64 per 1000 person-years; Table 2). The incidence of pulmonary tuberculosis in our study seemed to be much higher than that in Pan et al's study focusing on the healthcare workers in Taiwan, who are also at risk of pulmonary tuberculosis (470 vs 63.1 per 100,000 person-years).[9] This finding highlights that patients with head and neck cancer may have a higher risk of developing pulmonary tuberculosis than the general population and the healthcare workers.

After adjustment for confounding factors, we found that head and neck cancer was significantly associated with 2.90-fold increased hazard of pulmonary tuberculosis. To reduce the confounding effects of comorbidities, a subanalysis revealed that the adjusted HR of pulmonary tuberculosis was 3.60 for patients with head and neck cancer alone and without comorbidities. This

Table 4

Hazard ratio of pulmonary tuberculosis stratified by head and neck cancer and comorbidities.

Variable		Event	Person-years	Incidence*	Adjusted HR† (95% CI)
Head and neck cancer	Comorbidities‡				
No	No	75	63,363	1.18	(Reference)
No	Yes	49	12,268	4.01	1.87 (1.28–2.72)
Yes	No	40	9910	4.14	3.60 (2.45–5.28)
Yes	Yes	16	2008	7.47	3.49 (1.99–6.14)

* Incidence rate: per 1000 person-years.

† Adjusted for sex and age.

‡ Comorbidities including chronic obstructive pulmonary disease and diabetes mellitus.

Table 5

Hazard ratio of pulmonary tuberculosis stratified by head and neck cancer and anticancer chemotherapy and radiation therapy.

Variable		Event	Person-years	Incidence*	Adjusted HR† (95% CI)
Head and neck cancer	Anticancer chemotherapy or radiation therapy				
No	No	122	75,329	1.62	(Reference)
Yes	No	8	3540	2.26	1.26 (0.62–2.58)
Yes	Yes	48	8379	5.73	3.73 (2.66–5.23)

* Incidence rate: per 1000 person-years,

† Adjusted for sex, age, chronic obstructive pulmonary disease, and diabetes mellitus.

finding indicates that even in the absence of comorbidities, head and neck cancer alone remains to be significantly associated with the risk of pulmonary tuberculosis.

We also found that the incidence was particularly high during the first 6 months of follow-up, but the risk of pulmonary tuberculosis remained to persist even after 6 months. According the above discussion, we suggest that periodic screening for pulmonary tuberculosis is an important strategy among patients with head and neck cancer in Taiwan, particularly during the first 6 months of follow-up and those comorbid with any comorbidity.

Although the underlying mechanisms of the association between pulmonary tuberculosis and head and neck cancer cannot be completely elucidated in an observational study, we summarize the recent literature as follows. First, Pressoir et al reported that 30.9% of cancer patients had malnutrition.[49] In the meanwhile, malnutrition may potentially contribute to tuberculosis.[50,51] Therefore, cancer-related malnutrition substantially causes cancer patients to be more susceptible to pulmonary tuberculosis. Second, immune defects caused by the underlying cancer itself or by treatment-related factors including anticancer chemotherapy and radiation therapy may also increase the host's susceptibility to pulmonary tuberculosis.[52,53] That can partially explain why the adjusted HR of pulmonary tuberculosis was high for patients with head and neck cancer and receiving anticancer chemotherapy or radiation therapy (adjusted HR 3.73; Table 5).

5. Limitation

The study has several limitations. First, due to the inherent limitation of the database, some risk factors for head and neck cancer, including alcohol consumption, cigarette smoking, and betel quid chewing,[54] were not recorded. However, we included alcohol-related disease and chronic obstructive pulmonary disease for adjustment, but the limitation related to betel quid chewing cannot be overcome. Second, due to the same limitation, there were not images or reports of chest x-ray. We were unable to determine whether patients had a reactivation of latent tuberculosis or a new infection of tuberculosis, but we think that a new diagnosis of pulmonary tuberculosis usually means that treatment is needed. This point has been mentioned in section of major outcome. Third, although the adjusted HR of pulmonary tuberculosis was 1.26 for subjects with head and neck cancer alone and without receiving anticancer chemotherapy and radiation therapy, it did not reach statistic significance (95% CI, 0.62–2.58). Somebody may think that anti-cancer chemotherapy and radiation therapy, not head and neck cancer itself, has the link with pulmonary tuberculosis. To the contrary, we think that it is due to the event number too small to reach statistic significance (only 8 events of pulmonary tuberculosis in the subgroup, Table 5). Fourth, head and neck cancer includes cancer from oral cavity, lip, oropharynx, nasopharynx, or hypopharynx. Subgroup analysis is required for these specific diseases, and then their specific contribution to pulmonary tuberculosis can be evaluated. Due to the outcome number being not large enough, we were unable to make such an analysis. However, it indicates a further direction for this issue.

6. Strength

The strength of the study is that it contained a large number of cancer patients and comparison subjects to increase its statistical power. Although cancer has been known as a risk factor for tuberculosis, yet little research focuses on the association between pulmonary tuberculosis and head and neck cancer alone. Even though not a novel topic, this study confirms that patients with head and neck cancer have a higher risk of pulmonary tuberculosis than patients without any cancer.

7. Conclusions

We conclude that the incidence of pulmonary tuberculosis is higher in patients with head and neck cancer in Taiwan, compared with the general population. The incidence is particularly high during the first 6 months of follow-up. Head and neck cancer is significantly associated with 2.90-fold increased hazard of pulmonary tuberculosis. Even in the absence of comorbidities, the risk of pulmonary tuberculosis still exists in patients with head and neck cancer alone.

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