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Association of Head and Neck Cancers in Chronic Osteomyelitis

A National Retrospective Cohort Study

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Abstract: The aim of study is to determine whether chronic osteomyelitis (COM) is linked to an increased risk of head and neck cancer (HNC).

We identify 17,033 patients with osteomyelitis and 68,125 subjects without osteomyelitis during 1996 to 2010 periods. Multivariable Cox proportional hazards regression analysis was used to measure the hazard ratio (HR) of head and neck cancer for the osteomyelitis cohort compared with the comparison cohort.

A total of 99 patients in the COM and 228 patients in the comparison cohort developed HNC during an average 5.12 years of follow-up period. The incidence rate of HNC in the COM cohort was 1.51-fold (95% confidence interval [CI]: 1.17–1.95) higher than that in the comparison cohort after adjusting gender, age, urbanization level, monthly income, and comorbidities. In subgroup analysis, younger (less than 45 years-old) and patients without comorbidities have greater risks (adjusted HR: 2.29 [95% CI:1.43–3.66] and 1.74 [95% CI:1.28–2.38] respectively).

This study results suggested the association between COM and HNC, particularly in younger population and patients without comorbidities.

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Abbreviations: CI = confidence interval, HR = hazard ratio, NHIRD = National Health Insurance Research Database.

INTRODUCTION

Head and neck cancers (HNC) are composed of a variety of cancers, which arise from oral cavity, pharynx, larynx, and salivary glands. Squamous cell carcinoma was the most common type of malignancy, and most patients were older than 50 years-old and male. More than 550,000 new cases of head and neck cancer squamous cell carcinoma (HNSCC) were diagnosed worldwide annually.[1] According to the epidemiology data from Ministry of Health and Welfare in Taiwan (http://www. mohw.gov.tw/cht/Ministry/), oral cancer was the 5th highest cause of cancer death in 2013. The well-known risk factors of HNC are smoking, alcohol consumption, betel nut chewing, chronic virus infection like human papillomavirus virus (HPV), and genetic differences.[2–4]

Chronic inflammation has been reported to be an important pathogenesis to develop malignancy.[3,5–7] For example, chronic ulcerative colitis is associated with colon cancer, and reflux esophagitis is connected to esophageal carcinoma. Many microorganisms have also been proved to play roles in cancer development. For example, *Helicobacter pylori* infection is associated with gastric cancer and chronic viral hepatitis associated with hepatocellular carcinoma. Moreover, recent studies disclosed increased incidence of HNC in patient with chronic periodontitis through activated inflammation.[8]

Osteomyelitis is an infection of bone that results from contiguous spread, penetrating injury, or hematogenous seeding.[9] The disease could become a chronic infection after acute stage if inadequate treatment or relapse. The clinical pattern may persist over months or even years and cause sustained low-grade inflammation.[10] Elevated systemic inflammatory markers such C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly observed in patient with osteomyelitis.[11,12] There are many causative pathogens of osteomyelitis and *Staphylococcus aureus* is the most common isolated microorganism.[11] Recently, chronic osteomyelitis (COM) is reported to have increased risk of coronary heart disease due to chronic systemic inflammatory status.[13]

However, there is no study to identify an association between this chronic inflammatory disease and the risk of HNC. Thus, we used the database from Taiwanese National Health Insurance, which covers most of the population of

Taiwan to explore the connection between osteomyelitis and HNC.

METHODS

Data Source

The National Health Insurance program of Taiwan is a universal insurance program established in 1995. It covers the comprehensive medical care of all Taiwanese residents, with a coverage rate of 99%. The National Health Insurance Research Database (NHIRD) is authorized to provide insured registration files and original reimbursement claims data in the 1996 to 2011 periods. For security and privacy purposes, patient identity data are scrambled cryptographically by the NHIRD. We used the registry of inpatient claims of all enrollees in Taiwan for this study. The diagnoses diseases coded was according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) in NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115). The IRB also specifically waived the consent requirement.

Study Population

This population-based retrospective cohort study identified a cohort of adult patients (age >=20 years) with chronic osteomyelitis (COM, ICD-9-CM 730.1) newly diagnosed during 2000 to 2010 from in-patient claims data. The date for diagnosis COM was defined as index date.

The comparison group was 4 times the size of the COM cohort and consisted of patients without COM and malignant history, selected randomly from the inpatient data files, frequency matched by age, gender, and the year of diagnosed COM. The patients with a history of any cancers at the baseline, less than 1 year of follow-up, or those with incomplete age or sex information, were excluded.

Demographic characteristics such as gender, age, urbanization level, and monthly income (record as NTD, new Taiwan dollar) were collected. According to Taiwan government stipulate the minimum wage for full-time employees in 2006, the lowest monthly income level was 15,840 NTD. The monthly income level was grouped into <=15,840, 15,840 to 25,000 and >25,000 NTD according to Lin's report.[14] The urbanization level of the townships in Taiwan were categorized according to the method developed by Liu et al,[15] which was derived from educational level of the population, population density, the ration of elder people, and occupation in general. Level 1 is the most urbanized, whereas level 5 was the lowest urbanized. Work salary determined the insurance premium amount of an individual.

Baseline comorbidities of these patients were also recorded. These included hypertension (ICD-9-CM 401–405), hyperlipidemia (ICD-9-CM 272), diabetes mellitus (DM, ICD-9-CM 250), chronic kidney disease (CKD, ICD-9-CM 585), smoking-related disease, alcohol-related disease and Epstein–Barr virus infection (EBV, ICD-9 075), human papillomavirus infection (HPV, ICD-9-CM 078.1 and 079.4), periodontal diseases (ICD-9-CM 523), transplant (ICD-9-CM V42.0, V42.1, V42.6-V42.8, and 996.81–996.85), and autoimmune diseases. Smoking-related disease included chronic obstructive pulmonary disease (COPD, ICD-9-CM 490–492, 494–496), asthma (ICD-9-CM 493), coronary artery disease (CAD, ICD-9-CM 410–414), and stroke (ICD-9-CM 430–438). Alcohol-related disease contained alcoholic psychoses (ICD-9-CM 291),

alcohol dependence syndrome (ICD-9-CM 303), alcoholic abuse (ICD-9-CM 305), alcoholic fatty liver damage (ICD-9-CM 571.0–571.3), excessive blood level of alcohol (ICD-9-CM 790.3), and personal history of alcoholism (V11.3). Autoimmunity disease included multiple sclerosis (ICD-9-CM 340), myasthenia gravis (358.0), systemic lupus erythematosus (ICD-9-CM 710.0), and rheumatoid arthritis (ICD-9-CM 714).

The primary outcome measure was development of head and neck cancer (HNC, ICD-9-CM 140–149) determined by catastrophic illness patient registry. The follow-up person-years were calculated for each participant since index date until the diagnosis of HNC, the end of 2011, or withdrawal from the insurance system.

Statistical Analysis

Data analysis compared distributions of demographic characteristics and comorbidities between the COM and comparison cohort. To examine categorical variables, the Chi-square test was used. To assess continuous variables between COM and comparison cohorts, Student's t-test was used. Incidence rates of HNC were calculated for both cohorts (per 1000 person-years) stratified by demographic characteristics and comorbidities. The incidence rate of HNC was calculated by using the number of incident HNC dividing by person-years at risk in both cohorts. The cumulative incidences of HNC were measured using the Kaplan–Meier method for both cohorts during the follow-up period, and the log-rank test was used to assess the differences between these curves.

We also used multivariable Cox proportional hazards regression analysis to measure the hazard ratio (HR) of HNC with 95% CI for the COM cohort compared with the comparison cohort, while adjusting for gender, age, urbanization level, monthly income, and comorbidities which with a significantly different in crude Cox proportional hazard regression. Risk of different type of HNC in COM cohort compared to comparison cohort was assessed. The type of HNC was stratified into oral cavity (ICD-9-CM 140, 142–145, and 149), lip (ICD-9-CM 142), oropharynx (ICD-9-CM 146), nasopharynx (ICD-9-CM 147), and hypopharynx (ICD-9-CM 148).

We also estimated the association between HNC and the severity of COM. The COM severity for each patient was presented by the duration days of hospital stay due to COM divided by the sum of follow-up days. Patients with COM severity were classed 3 levels by tertiles, such as mild level (T1), moderate level (T2), and severe level (T3).[13]

Finally, we assessed the risk of HNC in COM patients with different location compared to comparisons. The COM location was classed as shoulder (ICD-9-CM 730.11), upper arm (ICD-9-CM 730.12), forearm (ICD-9-CM 730.13), hand (ICD-9-CM 730.14), pelvic region and thigh (ICD-9-CM 730.15), lower leg (ICD-9-CM 730.16), ankle and foot (ICD-9-CM 730.17), and others.

All statistical analyses were performed using the SAS 9.4 statistical package (SAS Institute Inc., NC). A 2-tailed $P < 0.05$ was considered statistically significant.

RESULTS

The study population consisted of 17,033 patients with COM and 68,125 subjects without COM, with similar distributions in gender and age (Table 1). Patients with COM were more likely to reside in lower urbanized area (P-value < 0.0001) and to have lower monthly incomes (P-value < 0.0001) compared with patients without COM. The COM cohort had higher
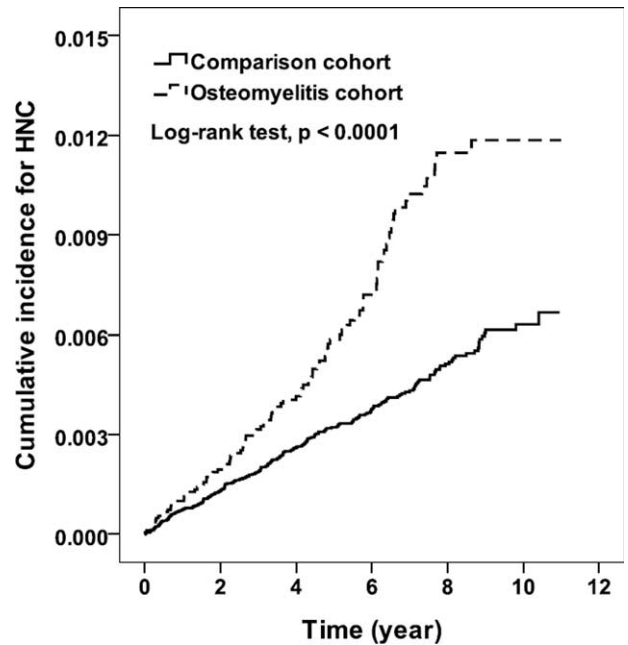
TABLE 1. Demographics in Study Subjects

Variable	Osteomyelitis N = 17,033		Comparison N = 68,125		P-Value
	N	%	n	%	
Men	11,075	65.0	44,293	65.0	0.96
Age, year					0.96
20−44	4796	28.2	19,184	28.2	
45−64	6152	36.1	24,608	36.1	
65+	6085	35.7	24,333	35.7	
Mean (SD)*	56.1	(17.4)	56.1	(17.4)	0.64
Urbanization level					<0.0001
1 (Highest)	3335	19.6	19,053	28.0	
2	4716	27.7	19,844	29.1	
3	2830	16.6	11,363	16.7	
4	3192	18.7	10,126	14.9	
5 (Lowest)	2959	17.4	7739	11.4	
Monthly income, NTD					<0.0001
<=15,840	5894	34.6	22,058	32.4	
15,841−25,000	8756	51.4	30,723	45.1	
>25,000	2383	14.0	15,344	22.5	
Comorbidity					
Diabetes	4337	25.5	4185	6.14	<0.0001
Hyperlipidemia	127	7.50	1977	2.90	<0.0001
Hypertension	4602	27.0	7806	11.5	<0.0001
CKD	655	3.85	439	0.64	<0.0001
Smoking-related diseases	3654	21.5	7098	10.4	<0.0001
Alcohol-related diseases	792	4.65	516	0.76	<0.0001
HPV	36	0.2	27	0.04	<0.0001
EBV	2	0.01	3	0.00	0.26
Periodontal	94	0.55	95	0.14	<0.0001
Transplant	21	0.12	15	0.02	<0.0001
Autoimmunity disease	251	1.47	190	0.28	<0.0001

CKD = chronic kidney disease, EBV = Epstein−Barr virus, HPV = human papillomavirus.

* Chi-square test and *t*-test.

FIGURE 1. Cumulative incidence for head and neck cancer between osteomyelitis and comparison cohort.

percentage of the comorbidities with DM, hyperlipidemia, hypertension, CKD, smoking-related disease, alcohol-related disease, HPV infection, periodontal disease, transplant, and autoimmune disease compared to the comparison cohort (*P*-value < 0.0001 for all).

The Kaplan−Meier estimates of the cumulative incidence of HNC among the patients with and without COM are shown in Figure 1. Risk of developing HNC is significantly higher in the COM cohort than in the comparison cohort (log-rank test, *P*-value < 0.0001). During an average 5.12 years of follow-up period, 99 patients in the COM cohort and 228 patients in the comparison cohort developed HNC (Table 2). The incidence rate of HNC in the COM cohort was 1.93-fold higher than that in the comparison cohort (1.24 vs 0.64 per 1000 person-years). Patients with COM had a significantly increased risk of developing HNC (adjusted HR = 1.51, 95% CI = 1.17−1.95) compared with those without COM. Gender-specific analysis showed that the incidence rates of HNC in women and men with COM were 0.22 and 1.76 per 1000 person-years, respectively, which are higher than those in the comparison cohort (0.20 and 0.87 per 1000 person-years, respectively). In addition, men with COM had a higher risk of HNC than without COM (adjusted HR = 1.56, 95% CI = 1.20−2.05). Age-specific

analysis showed that patients with COM had a higher risk of developing HNC than that of the comparison cohort, only in those with age younger than 45 years-old. Comorbidity-specific analysis showed that patients with COM had a significant risk of HNC compared to those without COM for those without any comorbidity (adjusted HR = 1.74, 95% confidence interval [CI] = 1.28−2.38).

Furthermore, we observed that patients with COM had a significantly increased cancer risks of oral cavity (adjusted HR = 1.58, 95% CI = 1.12−2.21) and hypopharynx (adjusted HR = 2.10, 1.15−3.84) compared to patients without COM (Table 3). Table 4 presented the association between HNC and the severity of COM. The incidence of HNC increased gradually while the severity of COM increased from mild to severe. Compared to comparisons, the adjusted risks were 1.07, 1.15, and 3.17-fold in mild, moderate, and severe COM groups, respectively. Last, we assessed the risk of HNC in COM patients compared to comparisons among COM locations. Patients in pelvic region and thigh had a significant higher risk of HNC than comparisons (adjusted HR = 1.72, 95% CI = 1.09−2.71) (Table 5).

DISCUSSION

Research has indicated lifestyle like smoking, alcohol habits; chronic virus infection and genetic differences are risks to develop subsequently HNC.[3,4,16] To our knowledge, this is the first study to examine the association between COM and HNC. In current study, we found that patients diagnosed with COM exhibited a higher incidence rate of HNC (1.24 vs 0.64 per 1000 person-years) and an HR of 1.51 (95% CI = 1.17−1.95) by adjusted hypertension, hyperlipidemia, diabetes mellitus, smoking-related diseases, alcohol-related diseases, transplant recipients,[17−20] auto-immune diseases, and virus infection (EBV and HPV).

TABLE 2. The Association Between Head and Neck Cancer and Osteomyelitis by Demographic Characteristics and Comorbidity

	Osteomyelitis			Comparison			HR (95% CI)	
	Event No.	Person-years	Rate[†]	Event no.	Person-years	Rate[†]	Crude	Adjusted
Overall	99	80,111	1.24	228	355,686	0.64	1.93 (1.52–2.44)[***]	1.51 (1.17–1.95)[**]
Gender								
Women	6	27,366	0.22	24	120,841	0.20	1.10 (0.45–2.70)	0.94 (0.37–2.43)
Men	93	52,745	1.76	204	234,844	0.87	2.03 (1.59–2.60)[***]	1.56 (1.20–2.05)[**]
Age, year								
20–44	35	27,430	1.28	49	114,352	0.43	2.99 (1.94–4.61)[***]	2.29 (1.43–3.66)[***]
45–64	47	29,632	1.59	107	132,436	0.81	1.96 (1.39–2.77)[***]	1.37 (0.94–2.01)
65+	17	23,048	0.74	72	108,897	0.66	1.10 (0.65–1.87)	1.00 (0.58–1.74)
Comorbidity								
None	53	49,885	1.06	180	306,062	0.59	1.81 (1.33–2.45)[***]	1.74 (1.28–2.38)[***]
Diabetes	24	15,664	1.53	18	15,431	1.17	1.31 (0.71–2.42)	1.06 (0.56–2.03)
Hyperlipidemia	6	4354	1.38	7	7439	0.94	1.48 (0.50–4.41)	0.60 (0.18–1.97)
Hypertension	13	15,786	0.82	29	29,243	0.99	0.82 (0.43–1.58)	0.54 (0.27–1.09)
CKD	2	1715	1.17	3	1367	2.19	0.56 (0.09–3.38)	0.16 (0.02–1.65)
Smoking-related diseases	14	12,701	1.10	23	27,602	0.83	1.32 (0.68–2.56)	0.90 (0.45–1.83)
Alcohol-related diseases	22	3005	7.32	11	2197	5.01	1.48 (0.72–3.05)	1.63 (0.77–3.44)
HPV	0	115	0.00	1	108	9.26	–	–
EBV	0	4	0.00	0	19	0.00	–	–
Periodontal	1	333	3.00	0	345	0.00	–	–
Transplant	2	71	28.06	0	65	0.00	–	–
Autoimmunity disease	0	841	0.00	0	1000	0.00	–	–

Adjusted for age, gender, urbanization level, monthly income, and comorbidity (except EBV). [**]$P < 0.01$, [***]$P < 0.001$. CI = confidence interval, CKD = chronic kidney disease, EBV = Epstein–Barr virus, HPV = human papillomavirus, HR = hazard ratio.
[†] Per 1000 person-years.

The linkage between cancer and inflammation were explored since 19th century. Transcription factors (STAT3, NF-κB, and HIF1α), chemokines, cytokines (interleukin-1, interleukin-6), prostaglandins, COX2, and tumor necrosis factor have been identified to play roles between inflammation and cancer.[5,7] HNC was suggested to have association with levels of COX-2, prostaglandin E2 (PGE2), and upregulation or over-expression of NF-kB in previous researches.[3] Two case–control studies demonstrated nonsteroidal anti-inflammatory drugs (NSAID) potentially decreased risk of squamous cell carcinoma of the head and neck,[21,22] and inhibition of cyclooxygenase-2 and prostaglandin was considered a major mechanism. These results supported the linkage between HNC and chronic systemic inflammation.

COM is a chronic low-grade inflammatory disease due to difficult in eradiation of bacteria. Elevated CRP was frequently observed in patient with COM.[11,12] CRP was reported to be linked with cardiovascular diseases first and has recently been connected to prognosis of several cancers such as breast cancer, kidney cancer, and multiple myeloma.[6] Erlinger et al reported higher CRP concentrations were observed among persons who subsequently develop colon malignancy due to inflammation.[23,24] In 2014, Choudhury et al[25] disclosed significant elevation in serum CRP levels in patients with HNSCC and they concluded CRP could help to predict risk for development of HNSCC. In animal study, significantly elevated TNF-mRNA level was noted in experimental *Staphylococcus aureus* acute osteomyelitis in rats.[26] Kalinka et al[27] found that *Staphylococcus*

TABLE 3. The Association Between Different Type of Head and Neck Cancer and Osteomyelitis

	Osteomyelitis		Comparison		HR (95% CI)	
Cancer Type (ICD-9-CM)	Event No.	Rate[†]	Event No.	Rate[†]	Crude	Adjusted
Oral cavity (140, 142–145, 149)	56	0.70	126	0.35	1.97 (1.44–2.70)[***]	1.58 (1.12–2.21)[**]
Lip (141)	3	0.04	6	0.02	2.24 (0.56–8.96)	2.35 (0.55–10.1)
Oropharynx (146)	9	0.11	23	0.06	1.74 (0.81–3.77)	1.01 (0.43–2.40)
Nasopharynx (147)	9	0.11	42	0.12	0.95 (0.46–1.96)	0.89 (0.41–1.92)
Hypopharynx (148)	22	0.27	31	0.09	3.16 (1.83–5.45)[***]	2.10 (1.15–3.84)[*]

Adjusted for age, gender, urbanization level, monthly income, and comorbidity (except EBV). [*]$P < 0.05$, [**]$P < 0.01$, [***]$P < 0.001$. CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification.
[†] Per 1000 person-years.

TABLE 4. Incidence and HR for Head and Neck Cancer Stratified by the Severity of Chronic Osteomyelitis

Severity	N	Event No.	Rate[†]	HR (95% CI)	
				Crude	Adjusted
Comparison	68,125	228	0.64	1.00	1.00
Mild (T1)	5654	29	0.77	1.20 (0.82–1.77)	1.07 (0.72–1.59)
Moderate (T2)	5555	26	0.94	1.47 (0.98–2.21)	1.15 (0.75–1.74)
Severe (T3)	5824	44	2.95	4.69 (3.39–6.50)***	3.17 (2.22–4.53)***
p for trend				<0.0001	<0.0001

Adjusted for age, gender, urbanization level, monthly income and comorbidity (except EBV). ***$P < 0.001$. CI = confidence interval, HR = hazard ratio.
[†] Per 1000 person-years.

aureus isolated from COM could express high levels of agr and sarA and induce inflammation in the host cells. These findings possibly explained that inflammation related to COM may contribute to develop HNC.

In our study, the osteomyelitis group had 1.93 times crude HR to develop HNC than the comparison group and 1.51 times after adjusting age, gender, urbanization level, monthly income, and comorbidity (Table 2). Males with osteomyelitis were at 1.56-fold greater risks. In contrast to older patients (more than 65 years-old), younger patients with osteomyelitis were more likely to develop HNC than that of comparison cohorts. Previous epidemiologic analysis has shown disproportionally increased incidence of head and neck squamous cell carcinoma (HNSCC) in younger patients (younger than 45 years old) without exposure to alcohol and tobacco, compared to those above 45 years old.[28] Chronic HPV infection and genetic predisposition can explain part of incidence variation but there are still some undetermined questions. Our study highlighted that chronic inflammatory disease might be a factor involved in HNC in younger patients. In addition, higher incidence of HNC was found in patient without any comorbidity in our study. We believed that the relatively stronger association between COM and HNC in younger or patients without comorbidities may be attributable to less traditional risk factors compared with the elderly or those with comorbidities, which may result a greater association between COM and HNC.

Oral cavity and hypopharynx are prevalent sites of HNC in patients with osteomyelitis and had 1.58 and 2.10 times adjusted HR, respectively (Table 3). Opposed to oral and hypopharynx cancer, incidence of lip, oropharynx, and nasopharynx cancer (NPC) shows no significant difference compared with control cohorts. The possible reason in oropharynx and lip groups maybe is relatively smaller sample size, which may reduce our statistical significance. NPC is a rare malignancy in the world but more common in specific populations including southern China, Southeast Asia, and Taiwan. Epstein–Barr virus infection is thought to play a critical role.[29–33] Although we tried to adjust infection of EBV but many unrecorded subclinical infection might confound current study result and underestimate impact of COM to NPC.

In current study, the risk of HNC increased with the severity of COM (Table 4). The association between acute osteomyelitis and HNC showed no significant association (HR = 1.43, $P = 0.11$, data not shown in the result and table). The findings are compatible with the duration and severity of chronic inflammation could contribute to HNC. The association between HNC and the different location of COM was showed in Table 5. The direct association between COM of head and neck regions and HNC could not be analyzed due to without corresponding codes for osteomyelitis at head and neck region in ICD-9. Patients with pelvic region and thigh COM had a significantly higher risk of head and neck cancer than

TABLE 5. The Association Between Head and Neck Cancer and Location of Chronic Osteomyelitis

Osteomyelitis Location (ICD-9-CM)	N	Event No.	Rate[†]	HR (95% CI)	
				Crude	Adjusted
Comparison	68,125	228	0.64	1.00	1.00
shoulder (730.11)	224	1	0.79	1.23 (0.17–8.78)	0.98 (0.14–6.99)
Upper arm (730.12)	298	2	1.29	2.01 (0.50–8.10)	1.82 (0.45–7.35)
Forearm (730.13)	340	3	1.66	2.59 (0.83–8.10	1.93 (0.62–6.08)
Hand (730.14)	584	5	1.56	2.42 (0.99–5.87)	2.14 (0.89–5.21)
Pelvic region and thigh (730.15)	3264	22	1.55	2.42 (1.56–3.75)***	1.72 (1.09–2.71)*
Lower leg (730.16)	5897	30	0.98	1.52 (1.04–2.23)*	1.25 (0.85–1.85)
Ankle and foot (730.17)	3425	19	1.36	2.12 (1.33–3.39)**	1.54 (0.94–2.53)
Others	3001	17	1.28	1.99 (1.22–3.27)**	1.65 (0.99–2.73)

Adjusted for age, gender, urbanization level, monthly income and comorbidity (except EBV). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification.
[†] Per 1000 person-years.

comparisons (HR = 1.70, 95% CI = 1.08–2.68). Femur is one of long bones in our bony system. Hematogenous long bone osteomyelitis is not common among adults due to different anatomy from children (vascular change with age) and might cause delay diagnosis. Traumatic injury or infection of prosthesis is the other possible causes of long bone osteomyelitis. COM of long bone among adults, the diagnosis is often delay and hard to treat.[34,35] Similar to osteomyelitis of femur, the diagnosis and treatment of pelvic osteomyelitis is difficult.[36,37] The longer duration of chronic inflammation may contribute to develop of HNC.

STRENGTHS AND LIMITATIONS

Our study uses a large population database exceeding 22 million enrollees in a national insurance program which includes more than 98% of the population of Taiwan and more than 17,000 cases of osteomyelitis were included into our study. Large sample size could increase the statistical power of our study and decrease selective bias. In addition, the patients in both cohorts were carefully matched by sex, age, and confounding factors.

There are some limitations in our study. First, the principle concern is the precise between coding of COM and HNC. However, insurance payments were examined by National Health Insurance Administration (the former Bureau of National Health Insurance) and may greatly decrease improper coding. Second, lifestyle information such as consumption, smoking habit, betel nut chewing, dietary habits, and data of family history was lacking in the present study and might have some bias. However, based on Yeh[38] and Tseng's[39] studies, we added the adjustment of smoking-related disease and the alcohol-related diseases to reduce smoking and alcoholism related confounder. Third, based on ICD-9 code, we cannot distinguish histologic types of cancer. However, according to Taiwan Cancer Registry (http://tcr.cph.ntu.edu.tw/main.php?Page = N1), similar to global epidemiology, the majority of head and neck cancer patients (more than 90%) are diagnosed with the squamous cell carcinomas in Taiwan. Fourth, the evidence derived from a retrospective cohort study is generally lower methodological quality than that from the prospectively randomized trial because a retrospective cohort study is subject to have many biases due to lack of the necessary adjustments or possibly unmeasured or unknown confounding factors.

CONCLUSION

The present study suggested that the incidence of increasing HNC in patients with COM was 1.51 times than in a comparison cohort without osteomyelitis after matching age, sex, and comorbidities. For the patients aged between 20 and 44 years-old with osteomyelitis, the risk of subsequently developing HNC was significantly higher than the comparison cohorts. The findings of current study could be used to develop measures for HNC prevention especially for younger patients with COM. Further prospective molecular study to clarify the relationship between HNC and COM is warranted.

ACKNOWLEDGMENTS

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