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Original Article

Increased risk of lung cancer in Taiwanese female patients with chronic periodontitis: A nationwide population-based cohort study

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Abstract *Background/purpose:* Lung cancer is the most common cause of cancer death globally. However, the association between chronic periodontitis (CP) and lung cancer risk is still not very clear. The aim of study was to investigate whether the Taiwanese female patients with CP might have increased risk of lung cancer using a nationwide registry dataset in Taiwan.
Materials and methods: A retrospective cohort study was conducted by using Taiwanese Longitudinal Health Insurance Database. A total of 86,886 patients who were newly diagnosed with CP from 2001 to 2012 were selected. A 1:1 propensity-matched healthy patients without any type of periodontal diseases were captured randomly from the general population. The risk of lung cancer was analyzed by Cox proportional hazards regression models between CP and non-CP cohorts.
Results: 639 and 614 patients with newly diagnosed lung cancer were found in CP and non-CP cohorts, respectively. CP cohort exhibited a borderline significantly increased risk of lung cancer (relative risk:1.01 95 % CI: 0.90–1.12) as compared with non-CP cohort. The subgroup analysis of hazard ratio for sex difference, *P* for interaction was 0.042. The female patients with CP had a 1.23-fold higher risk of lung cancer than non-CP counterparts (95 % CI: 1.01–1.48, $P = 0.036$).
Conclusion: Taken together, the results of this nationwide population-based cohort study indicate that the Taiwanese female patients with CP exhibited a significantly higher risk of lung cancer than those female patients without CP.

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Introduction

Global lung cancer trends are rising approximately about 11.6 % of all new cancer cases in 2018.[1] It also remains the leading cause of cancer death in male and female combined.[2,3] Moreover, lung cancer ranks as the third most common cancer type and the second most common cause of cancer death in female.[2,3] The risk factors of lung cancer might be divided into tobacco smoking and non-tobacco factors including radon exposure, environmental pollution, occupational exposure, chronic lung disease, and lifestyle factors.[4]

Periodontal diseases including gingivitis and periodontitis are the most prevalent oral diseases worldwide. In Taiwan, the prevalence of periodontitis significantly increased from 1997 to 2013.[6] Chronic periodontitis (CP) is an incendiary reaction to oral microbiomes that evoke the inflammation and immune-related mediators resulted in alveolar bone loss and even tooth loss.[5] Smoking, inadequate oral hygiene, stress, and lifestyle factors are the well-known risk factors for periodontal diseases.[7] Accumulated evidences indicated the strong association between CP and many systemic conditions such as coronary heart disease, diabetes mellitus, and chronic obstructive pulmonary disease (COPD).[8]

Persistent periodontal inflammation and further induced-immune response may increase the risk of carcinogenesis.[9] CP and lung cancer share the same pathogenesis and common risk factors. However, the studies of association between periodontal diseases and lung cancer were disparity. Several observational studies, systematic review, and meta-analysis have reported the positive association,[10–15] but an evidence-based review had the negative findings in this regard.[16] Nevertheless, these studies have yielded the inconsistent results and the evidence still remains inconclusive.

Therefore, the cohort design with relatively large sample size is required to adequately assess causal claims as well as promote evidence-based interventions. In this study, the National Health Insurance Research Database (NHIRD) with almost 100 % Taiwanese population enrolled was used to evaluate the role of CP in increasing the subsequent risk of lung cancer.

Materials and methods

Data source

This study was approved by the Institutional Review Board, Chung Shan Medical University Hospital (CSMUH No.CS2-15017). The Longitudinal Health Insurance Research Database 2010 (LHIRD 2010), a sub databank of NHIRD, was conducted to assess the association of lung cancer and CP by a cohort study design. LHID2010 contains one million beneficiaries randomly sampled from the 2010 registry of beneficiaries in NHIRD. This database has encrypted patients' identification number, date of birth, sex, diagnosis, prescription, laboratory data, medical visits, and dental visits.[17–19]

Participant selection

This cohort study enrolled patients with newly diagnosed CP and a matched non-CP as a healthy control. The diagnosis of CP was based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code 523.4. The definition of CP cohort was patients with newly diagnosed CP from 2001 to 2012. In addition, the first time of CP diagnosis was recognized as the index date. To ensure the accuracy of CP diagnosis, only patients with at least three outpatient service claims were recruited. Non-CP cohort was randomly selected from 2000 to 2013 from participants who were never diagnosed with any type of gingivitis and periodontitis (ICD-9-CM code: 523) in order to ensure the accuracy of health periodontal condition. Non-CP control and CP exposure subjects were 1:1 matched using a propensity score by age, sex, monthly income, urbanization, and co-morbidities at the baseline. Flow chart of inclusion and exclusion criteria is illustrated in Fig. 1.

Assessment of lung cancer

All individuals with newly diagnosed lung cancer (ICD-9-CM code: 162) between January 2001 and December 2012 were screened from outpatient visits or hospitalization, respectively. All patients were traced until the occurrence of lung cancer, withdrawal from the health insurance system, or the end of 2013, whichever came first.

Covariates and factors associated with lung cancer

The baseline variables included age, gender, monthly income, urbanization, and comorbidities (Fig. 1). Comorbidities were defined before the index date within one year and who had at least one hospitalization record or two outpatient visits. These potential confounding factors included hypertension (ICD-9-CM: 401–405), hyperlipidemia (ICD-9-CM: 272.0–272.4), diabetes mellitus (ICD-9-CM: 250), obesity (ICD-9-CM = 278.0), COPD (ICD-9-CM: 490–496), chronic kidney disease (ICD-9-CM: 585), thyroid disease (ICD-9-CM = 240–246), asthma (ICD-9-CM = 493), heart failure (ICD-9-CM = 428), myocardial infarction (ICD-9-CM = 410–414), stroke (ICD-9-CM: 430–438), alcohol related diseases (ICD-9-CM = 291,303, 305.0, 571.0, 571.1, 571.3, 790.3, V11.3), anxiety (ICD-9-CM = 300.00),

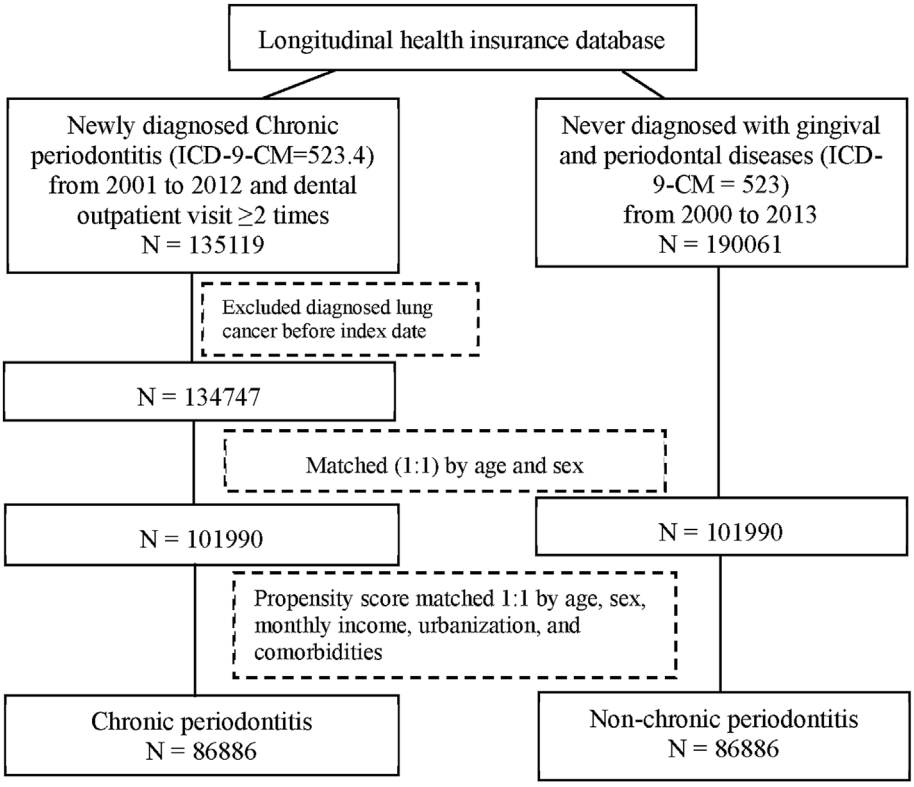

Figure 1 Flow diagram of patients' enrollment in the exposure and control cohorts.

depression (ICD-9-CM = 296.2, 296.3, 300.4, 311), and insomnia (ICD-9-CM = 780.52).

Statistical analysis

The Student's t test and chi-square test were used to compare the demographic and clinical characteristics of patients with CP and those without any type of gingivitis and periodontitis. Cox proportional hazard models were applied to estimate the hazard ratios and 95 % confidence intervals (CI) of CP. The log-rank test was used to compare differences between CP and non-CP cohorts. All statistical analyses were performed with SPSS version 18 (SPSS, Chicago, IL, USA). The level of statistical significance was set at $P < 0.05$.

Results

Prior to propensity score matching, both the newly diagnosed CP group (n = 101,990) and the never-diagnosed periodontal diseases group (n = 101,990) were matched at a 1:1 ratio based on age and sex (Fig. 1). In order to mitigate bias in examining the connections between CP and the outcomes of lung cancer, propensity score matching was used to adjust the potential confounding factors. Finally, CP and non-CP cohorts included 86,886 and 86,886 individuals for further analysis. The demographic characteristics of CP and control group are shown in Table 1.

Cox proportional hazard model analysis for risk of lung cancers is shown in Table 2. In the adjusted model, there was no significant difference of developing lung cancer in the CP cohort compared with non-CP cohort ($P = 0.586$). The age groups ≥65 years old had 318.34-fold lung cancer risk than those who <18 years old group ($P < 0.001$). The male group had a higher risk of lung cancer than the female group (aHR: 1.60; 95 % CI: 1.42–1.80). In addition, patients with diabetes mellitus, obesity, COPD, asthma, myocardial infarction, and stroke demonstrated significant risk for lung cancer ($P < 0.05$).

As shown in Table 3, a total of 639 and 614 patients with newly diagnosed lung cancer were found in CP and non-CP cohorts, respectively. The incidence density (ID) rates of lung cancer in non-CP and CP cohorts was 0.90 and 0.91 per 1000 person-years, respectively. After Poisson regression analysis, CP cohort exhibited a borderline significant risk of lung cancer (relative risk:1.01 95 % CI: 0.90–1.12) as compared to non-CP cohort.

In Table 4, the subgroup analysis of HR by age revealed that there was no significant difference between CP and non-CP cohorts (P for interaction = 0.822). In addition, there was no significant difference for male patients with lung cancer between CP and non-CP cohorts (HR: 0.89, 95 % CI: 0.78–1.02). Female patients with CP had a 1.23-fold risk of lung cancer than non-CP participants (95 % CI: 1.01–1.48, $P = 0.036$). For gender difference, P for interaction was 0.042.

The cumulative incidence curve of lung cancer is illustrated in Fig. 2. After 13 years follow-up, the cumulative incidence of lung cancer in female patients with CP was higher than those in non-CP subjects (log rank test, $P = 0.036$).

Table 1 Demographic characteristics of chronic periodontitis and non-chronic periodontitis.

	Before PSM		ASD	After PSM		ASD
	Chronic periodontitis (N = 101,990)	Non-chronic periodontitis (N = 101,990)		Chronic periodontitis (N = 86,886)	Non-chronic periodontitis (N = 86,886)	
Age			<0.001			0.003
<18	8979 (8.8)	8979 (8.8)		8034 (9.2)	8027 (9.2)	
18–64	82,286 (80.7)	82,286 (80.7)		70,633 (81.3)	70,551 (81.2)	
≥65	10,725 (10.5)	10,725 (10.5)		8219 (9.5)	8308 (9.6)	
Mean ± SD	40.6 ± 17.3	40.6 ± 17.3	<0.001	40.2 ± 17.1	39.6 ± 17.0	0.034
Sex			<0.001			0.002
Female	45,659 (44.8)	45,659 (44.8)		39,233 (45.2)	39,334 (45.3)	
Male	56,331 (55.2)	56,331 (55.2)		47,653 (54.8)	47,552 (54.7)	
Monthly income			0.387			0.347
<NT $25,000	66,373 (65.1)	82,583 (81.0)		56,911 (65.5)	69,189 (79.6)	
NT $25,000–NT $40,000	13,355 (13.1)	9837 (9.6)		11,283 (13.0)	8965 (10.3)	
>NT $40,000	22,262 (21.8)	9570 (9.4)		18,692 (21.5)	8732 (10.0)	
Urbanization			0.303			0.006
Urban	67,592 (66.3)	53,512 (52.5)		53,735 (61.8)	53,496 (61.6)	
Suburban	28,150 (27.6)	36,286 (35.6)		26,972 (31.0)	27,163 (31.3)	
Rural	6248 (6.1)	12,192 (12.0)		6179 (7.1)	6227 (7.2)	
Hypertension	11,749 (11.5)	9110 (8.9)	0.085	7961 (9.2)	8224 (9.5)	0.010
Hyperlipidemia	5545 (5.4)	2891 (2.8)	0.131	2788 (3.2)	2849 (3.3)	0.004
Diabetes mellitus	5138 (5.0)	3972 (3.9)	0.055	3525 (4.1)	3677 (4.2)	0.009
Obesity	134 (0.1)	81 (0.1)	0.016	83 (0.1)	79 (0.1)	0.002
Chronic obstruction pulmonary disease	1899 (1.9)	1258 (1.2)	0.051	1064 (1.2)	1188 (1.4)	0.013
Chronic kidney disease	426 (0.4)	392 (0.4)	0.005	311 (0.4)	339 (0.4)	0.005
Thyroid disease	1522 (1.5)	657 (0.6)	0.083	640 (0.7)	656 (0.8)	0.002
Asthma	1667 (1.6)	1098 (1.1)	0.048	987 (1.1)	1063 (1.2)	0.008
Heart failure	512 (0.5)	535 (0.5)	0.003	384 (0.4)	419 (0.5)	0.006
Myocardial infarction	3818 (3.7)	2230 (2.2)	0.092	2086 (2.4)	2129 (2.5)	0.003
Stroke	1804 (1.8)	1751 (1.7)	0.004	1412 (1.6)	1453 (1.7)	0.004
Alcohol related diseases	195 (0.2)	184 (0.2)	0.003	152 (0.2)	162 (0.2)	0.003
Anxiety	1949 (1.9)	989 (1.0)	0.079	953 (1.1)	959 (1.1)	0.001
Depression	1389 (1.4)	607 (0.6)	0.078	601 (0.7)	603 (0.7)	<0.001
Insomnia	2163 (2.1)	1246 (1.2)	0.070	1194 (1.4)	1224 (1.4)	0.003

PSM: propensity score matching.
ASD: absolute standardized difference.

Discussion

To the best of our knowledge, this is the most recent nationwide cohort study reported that CP patients exhibited a borderline significant increased risk of lung cancer in Taiwan. Multivariate Cox regression analysis indicated that the risk of lung cancer in female patients with CP exposure was higher than in non-CP group. In addition, the relationship between CP exposure and lung cancer risk demonstrated the sex difference in Taiwanese population.

Several systematic review and meta-analysis articles demonstrated a significant association between periodontal diseases and the incidence of lung cancer.[10,13,14] Two of them concluded that women with periodontal diseases have higher risk of lung cancer.[10,13] However, one review reported the prominence in men.[14] Therefore, the results of sex difference still need a large-scale and well-designed studies with adequately control for multiple confounding factors to explore the association between periodontal diseases and lung cancer.

Previously, a retrospective elderly community cohort study enrolled 82,548 study participants in Taipei, Taiwan found that male patient with periodontitis have higher risk of lung cancer.[12] On the contrary, a nationwide matched cohort study in Taiwan between 2000 and 2006 reported that periodontitis was associated with a 1.9-fold increased risk of lung cancer among women compared to those with gingivitis.[13] Recently, a nationwide cohort study using Korean National Health Insurance Service National Sample Cohort showed that the risk of incident lung cancer was higher in individuals with CP than in those without CP, especially high in female patients.[14]

Table 2 Cox proportional hazard model analysis for the risk of lung cancer.

	Univariate	*P* value	Multivariate[a]	*P* value
	HR (95 % CI)		HR (95 % CI)	
Group				
Non-chronic periodontitis	Reference		Reference	
Chronic periodontitis	1.00 (0.89–1.11)	0.951	0.97 (0.87–1.08)	0.586
Age				
<18	Reference		Reference	
18–64	67.88 (9.55–482.54)	<0.001	58.04 (8.17–412.50)	<0.001
≥65	455.25 (64.01–3237.94)	<0.001	318.34 (44.73–2265.76)	<0.001
Sex				
Female	Reference		Reference	
Male	1.57 (1.40–1.76)	<0.001	1.60 (1.42–1.80)	<0.001
Monthly income				
<NT $25,000	Reference		Reference	
NT $25,000–NT $40,000	0.76 (0.63–0.92)	0.004	1.17 (0.96–1.43)	0.113
>NT $40,000	0.85 (0.73–0.99)	0.041	1.26 (1.06–1.50)	0.008
Urbanization				
Urban	Reference		Reference	
Suburban	1.04 (0.92–1.18)	0.550	0.94 (0.83–1.06)	0.323
Rural	1.66 (1.39–1.99)	<0.001	1.23 (1.03–1.49)	0.026
Hypertension	3.71 (3.27–4.22)	<0.001	1.21 (1.03–1.41)	0.022
Hyperlipidemia	2.60 (2.08–3.25)	<0.001	0.97 (0.77–1.23)	0.802
Diabetes mellitus	3.77 (3.19–4.45)	<0.001	1.62 (1.35–1.95)	<0.001
Obesity	3.86 (1.45–10.29)	0.007	2.77 (1.03–7.44)	0.043
Chronic obstruction pulmonary disease	5.69 (4.59–7.06)	<0.001	1.68 (1.33–2.13)	<0.001
Chronic kidney disease	3.39 (1.92–5.98)	<0.001	1.32 (0.74–2.34)	0.345
Thyroid disease	1.32 (0.75–2.32)	0.344	1.08 (0.61–1.92)	0.781
Asthma	3.66 (2.77–4.85)	<0.001	1.58 (1.17–2.12)	0.003
Heart failure	3.30 (2.01–5.40)	<0.001	0.77 (0.46–1.27)	0.305
Myocardial infarction	4.36 (3.61–5.28)	<0.001	1.31 (1.06–1.61)	0.013
Stroke	4.62 (3.68–5.80)	<0.001	1.38 (1.08–1.75)	0.009
Alcohol related diseases	2.08 (0.78–5.56)	0.143	1.46 (0.55–3.91)	0.449
Anxiety	1.64 (1.06–2.55)	0.028	0.79 (0.50–1.24)	0.306
Depression	1.15 (0.60–2.21)	0.679	0.58 (0.30–1.13)	0.111
Insomnia	2.74 (2.00–3.75)	<0.001	1.28 (0.92–1.76)	0.139

HR: hazard ratio.
CI: confidence intervals.
[a] Adjusted for age, sex, monthly income, urbanization, and comorbidities.

Table 3 Poisson regression of relative risk of chronic periodontitis group and non-chronic periodontitis group.

	Non-chronic periodontitis	Chronic periodontitis
N	86,886	86,886
Person-years	682,586	705,607
Lung cancer case	614	639
ID (95 % CI)	0.90 (0.83–0.97)	0.91 (0.84–0.98)
Relative risk (95 % CI)	Reference	1.01 (0.90–1.12)

N: number.
ID: incidence density (per 1000 person-years).
CI: confidence intervals.

The inconsistent and inconclusive results between the association of periodontal diseases and lung cancer may be explained as followings. The definition of periodontal diseases including gingivitis and periodontitis was without consistency. As the classification of periodontal diseases was periodically to align and update the classification scheme to the current evidences, a new classification scheme for periodontal diseases and conditions was launched in 2017.[20] However, the diagnosis of periodontal diseases from national health insurance system of Taiwan and South Korean are based on ICD codes. Due to the long-term lasting inflammatory reactions with putative

Table 4 Subgroup analysis for the risk of lung cancer.

	Chronic periodontitis		Non-chronic periodontitis		HR (95 % CI)	*P* value
	Number	Lung cancer case	Number	Lung cancer case		
Age						
<18	8034	1	8027	0	N/A	N/A
18-64	70,633	371	70,551	356	1.00 (0.86—1.15)	0.976
≥65	8219	267	8308	258	0.98 (0.83—1.17)	0.851
					P for interaction = 0.822	
Sex						
Female	39,233	242	39,334	190	1.23 (1.01—1.48)	0.036
Male	47,653	397	47,552	424	0.89 (0.78—1.02)	0.106
					P for interaction = 0.009	

HR: hazard ratio.
CI: confidence intervals.
N/A: not applicable.

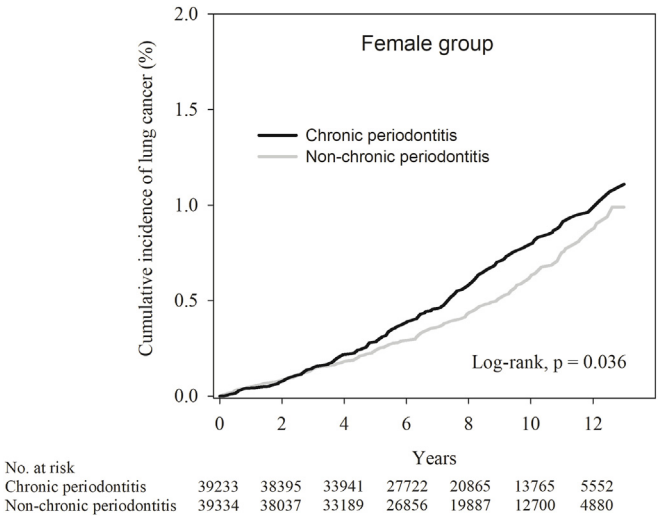

Figure 2 Kaplan—Meier plot for the cumulative incidence of lung cancer in female patients with chronic periodontitis and comparison group.

periodontal pathogens were found to be associated with carcinogenesis,[9] the so-called "chronic" type of periodontitis may be more suitable and clinical relevance for the evaluation of lung cancer concurrence. Taken together, CP may play an important role in the pathogenesis of lung cancer. Regular dental check-up and prophylaxis are required for lung cancer patients.

From our findings and most of previous reports, the risk of lung with CP exposure was frequent found in female patients. The reasons of sex different are not quite clear. Many studies have indicated the sex hormones estrogens as well as progesterone play an important role in lung carcinogenesis in female patients, especial without smoking.[21,22] Within periodontium, gingival tissues exist various receptors of female sex steroid hormones.[23] These sex hormones were found to play a key role in periodontal disease progression. More specifically, these effects seem to differentiate by sex as well as lifetime period.[24] Therefore, the actual roles among sex hormones, CP, and lung cancer in female patients are worth to further evaluation.

Some potential limitations should be addressed. First, the comprehensive data of lung cancer staging, driver mutation status, subtype of pathology, and treatment types were not available in NHIRD. Second, the habits of smoking, a major risk of CP and lung cancer, cancer cannot be obtained from this nationwide longitudinal database. Third, the severity of CP could not truly be interpreted by ICD-9 codes from NHIRD. Finally, the unrecognized CP who did not have any dental claims might be included in the healthy controls.

Despite these limitations, this study has several strengths. To our knowledge, this analysis is the nationwide population-based study to examine the risk of CP patients with lung cancer. Cohort study design can provide a higher level of evidence to suggest a causal relationship rather than the case—control design. Moreover, National Health Insurance Administration has established strict guidelines for cancer diagnosis. This can ensure the accuracy of original data used.

In conclusion, this nationwide cohort study indicated an increased risk of lung cancer in female patients with

CP. Regular dental examination and prophylaxis not also benefit for CP, but also good for lung cancer concurrence, especial in female population. Further prospective studies are needed to evaluate the causal relationship or other unrecognized etiologies between CP and lung cancer.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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