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Original Article

Dental visits and colon-rectum cancer: A nationwide population-based nested case-control study in Taiwan

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Abstract *Background/purpose:* Although oral health and systemic diseases are closely associated, little is known about the utilization of ambulatory dental visits in patients prior to diagnosis of colon-rectum cancer (CRC). In this study, a nested case-control study based on the population-based health claim database was conducted to clarify the relationship between dental visits and CRC in Taiwan.
Materials and methods: From the Longitudinal Health Insurance Research Database 2010 (LHIRD 2010), we identified 4787 patients who were newly diagnosed with CRC from 2005 to 2013. We also recruited 19,148 control subjects matched in a 1:4 ratio based on sex and age at the index date from LHIRD 2010. Both groups were retrospectively traced back to 1997 to obtain any records of ambulatory dental visits that occurred within 8 years prior to the index date. ICD-9 codes 520–529 for diseases of oral cavity, salivary glands, and jaw were defined as dental visits.
Results: The mean frequency of dental visits within 8 years prior to index date among patients with CRC were significantly higher than the control group ($P = 0.005$). Patients with CRC had significantly higher proportions of certain co-morbidities than control group. However, periodontal treatment, caries filling, and tooth extraction were borderline and not significantly related to CRC after adjustment.
Conclusion: Our results indicate that the utilization of ambulatory dental visits is significantly increased in patients with CRC prior to its diagnosis. Certain co-morbidities may also affect the frequency of dental visits and the occurrence of CRC.

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Introduction

Colon-rectum cancer (CRC) is one of the most common cancers in the world. Although CRC was previously considered a "Western" disease, its worldwide incidence has increased in recent years.[1] There are more than 100 trillion species of microbes in the intestinal tract, which have a very important impact on human health.[2] CRC is a complex disease affected by many factors such as genetics, dietary habits, lifestyle, personal conditions, and even related to the ecology of intestinal microbiota.[3,4] A growing number of evidences showed that gut microbiota is associated with the occurrence of CRC.[3,5]

Fusobacterium nucleatum (*F. nucleatum*) is one of the common Gram-negative anaerobic bacteria in oral cavity which is highly associated with periodontitis.[6] Previous studies have indicated that the agg*regation of F. nucleatum* was observed in CRC.[5,7–9] In addition, *F. nucleatum* was found to originate from oral cavity by whole genome sequencing from the same patients.[10] Oral bacteria are not only limited in oral cavity, but may also be related to infection or inflammation in extra-oral sites.[11] Therefore, oral bacteria were proposed to transfer into colon-rectum to eliminate beneficial bacteria and then disrupt the balance of gut microbiota.[12]

Epidemiologic and clinical studies have proved that oral health could have the potential impact on the risk of CRC.[10,13] However, a prospective cohort study revealed that there was no association between periodontal disease, tooth loss, and CRC.[14] Thus, further studies on the association between oral health and CRC is warranted.

The advantages of nested case-control study design can identify the cases of disease within a defined cohort and select matched controls from the same cohort.[15] This design can provide the valid and precise estimation of the association. It is a cost-effective alternative for full-cohort analysis.[16] The equivalent time windows of exposure associated with dental disease in non-CRC controls as CRC cases is necessary to define. Therefore, the nested case-control design is used to explore the association of the occurrence of CRC with the utilization of ambulatory dental services prior to the diagnosis of CRC.

Materials and methods

Dataset and study sample

The LHIRD 2010, a part of the Taiwan National Health Insurance Research Database (NHIRD), was used for this study. LHIRD 2010 contains healthcare information, including both dental and medical data, derived from a random sample of 1 million beneficiaries selected from NHIRD in the year 2010.[17] It includes data on medical claims for both inpatient and outpatient visits, diagnosis codes, and the date of visits.[17] Many publications represented the epidemiological profiles of Taiwanese population were obtained from NHIRD.[18–22]

This study was approved by the Chung Shan Medical University Hospital Ethics Review Board (CSMUH No.CS2-15017). This study also complies with the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology for the observational studies.

By the utilization of LHIRD 2010, we were able to retrospectively capture 8 years of ambulatory dental visits before the index date. The index date was defined as the first date of CRC diagnosis between the years 2005 and 2013 in CRC cases and matched dates in non-CRC controls. In this study, 4787 patients newly diagnosed with CRC using the International Classification of Diseases-ninth revision (ICD-9) codes 153.x and 154.x were identified between 2005 and 2013. The date of their first CRC diagnosis was defined as the index date. Additionally, we captured 19,148 non-CRC individuals who were individually matched based on sex and age as of the index date as illustrated in Fig. 1.

Dental diseases and interventions

Both groups were then retrospectively traced back 8 years before the index date to retrieve any records of disease diagnosis and interventions during dental visits. The ICD-9 codes ranged from 520 to 529 for the diseases of oral cavity, salivary glands, and jaw were defined as dental visits.

Dental interventions based on National Health Insurance (NHI) eatment codes for periodontal treatment, caries filling, and teeth extraction were further stratified the association with CRC. Periodontal treatment included scaling (91003, 91004), subgingival curettage/root planing (91006, 91007, 91008), and periodontal flap surgery (91009, 91010). Caries filling was defined with amalgam fillings (89001, 89002, 89003, 89101, 8910 2, 89103) and composite resin fillings (89004, 89005, 89008, 89009, 89010, 89012, 89104, 89105, 89108, 89109, 89110, 89112). Treatment codes 92013, 92014, 92015, 92016 were represented as tooth extraction.

Statistical analysis

All analyses were performed by SAS software (Version 9.4; SAS Institute, Inc., Cary, NC, USA). The demographic characteristics of the study population were statistically analyzed using the Student's t-test for continuous variables and the chi-square test for categorical variables. Comparisons of median of dental visits between case and control groups were estimated by the Mann—Whitney *U* test. Conditional logistic regression was used to estimate crude odds ratios (ORs) and adjusted odds ratios (aORs) with a 95 % confidence intervals (CI) for the case group compared with the control group.

Results

The demographic characteristics of CRC and control group are shown in Table 1. Total 4787 subjects with CRC and 19,148 subjects without CRC were recruited in this study. The percentage of male and female were about 54.79 % and 45.21 %, respectively. The most subjects were aged between 60 and 79 years old. Patients with CRC also have significantly higher proportions of diseases such as diabetes mellitus ($P < 0.001$), hypertension ($P < 0.001$), hyperlipidemia ($P < 0.001$), chronic kidney disease ($P < 0.001$), stroke ($P = 0.0161$), esophageal ulcers ($P < 0.001$),

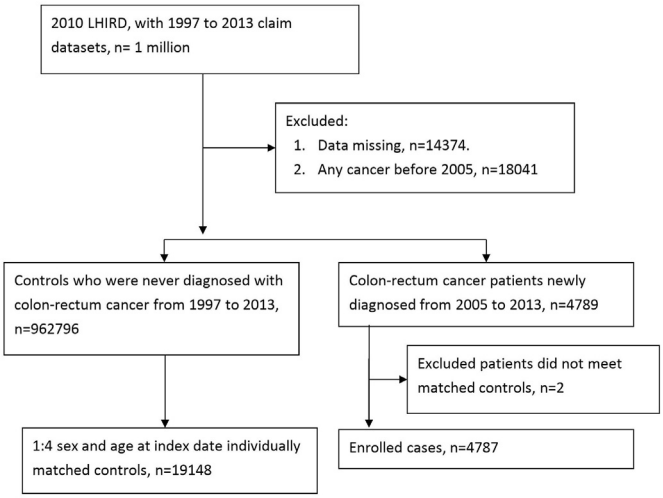

Fig. 1 The flowchart of this nationwide population-based nested case-control study.

allergies ($P = 0.0398$), chronic obstructive pulmonary disease ($P = 0.0006$), hepatitis ($P < 0.001$), and thyroid disorder ($P = 0.0022$).

The mean and median number of dental visits during 8-year period before the index date among CRC and control group are shown in Table 2. The frequency of dental visits of the CRC group was higher than the control group in each year. The closer to the index date, the number of dental visits of the case group and the control group was gradually increased, especial within 4 years. The overall mean ($P = 0.005$) and median number ($P < 0.0001$) of dental visits within 8 years among patients with CRC were significantly higher than the control group, respectively.

Further stratification by frequency of dental visit within 8-year prior to index date was shown in Table 3. The mean dental visits of CRC group were significantly higher that the control group in 0–8 year ($P < 0.001$), 0–4 year ($P < 0.001$), 4–8 year ($P = 0.0098$), respectively. In addition, logistic regression analysis was used to further analyze each group by inter-quartile range. Before the adjustment, patients with relative higher number of dental visits had higher risks of CRC. However, after the adjustment of urbanization and co-morbidities, the number of dental visits was not significant related to the risk of CRC.

The association between dental treatments and CRC before the index date is shown in Table 4. Logistic regression analysis showed that periodontal treatments, caries restoration and tooth extraction were positively associated with the development of CRC in 0–8 year, 0–4 year, 4–8 year subgroup group, respectively. However, after adjustment of urbanization and co-morbidities, these dental treatments had no significant correlation with CRC in each subgroup, respectively.

Discussion

To the best of our knowledge, this is the first study to investigate the relationship of dental visits and CRC by using registry health databank. In this study, patients with CRC were found to suffer from many co-morbidities. Similar results were demonstrated that the most common co-morbidities in patients with CRC were hypertension, cardiovascular diseases, diabetes, and chronic obstruction pulmonary disease.[23,24] Further investigation is required to delve deeper into the potential mechanisms by which these co-morbidities may affect the connection between dental health and CRC.

In this nested case-control study, our results demonstrated that the frequency of dental visits in CRC group was higher than that in the control group during 8-year period. Oral health status is well-known to affect systemic health.[25,26] Previous studies have shown that the risk of dental diseases such as periodontal disease, dental caries, and tooth loss are increasing with age.[27,28] This might partial explain that CRC and dental problems may interact with each other. Oral flora imbalance may also promote colorectal specific flora imbalance leading the occurrence of CRC.[11]

The stratification by frequency of dental visit prior to index date demonstrated that there were not significantly associated with CRC after adjustment. The results were borderline significantly increased in each subgroup. This indicated that urbanization and some co-morbidities would affect the occurrence of dental disease and CRC at the same time. In Taiwan, the Health Promotion Administration, Ministry of Health and Welfare provides fecal immunochemical testing for people aged between 50 and 74 every two years to mitigate the risk of CRC in the general population. This might cause the confounding variable effect in this study. It is worthwhile to conduct further evaluation.

Previously, one report has shown that fewer teeth, periodontal disease might be at a modest increased risk of developing CRC.[29] However, our results revealed that periodontal treatment, caries filling, and tooth extraction were not significantly associated with CRC after adjustment for comorbidities. Similar findings were reported by Michaud et al.[14] In Taiwan, NHI offers free dental prophylaxis twice every 180 days. This unique policy might influence the association between the risk of CRC and the utilization of ambulatory dental services. Therefore, these discrepancies still need to further evaluation.

Table 1 The demographic characteristics of study population.

	Control n = 19,148	Colon-rectum cancer n = 4787	*P* value
Age at index date			1.0000
<40	1068 (5.58 %)	267 (5.58 %)	
40—59	6312 (32.96 %)	1578 (32.96 %)	
60—79	8936 (46.67 %)	2234 (46.67 %)	
≥ 80	2832 (14.79 %)	708 (14.79 %)	
Sex			1.0000
Female	8656 (45.21 %)	2164 (45.21 %)	
Male	10,492 (54.79 %)	2623 (54.79 %)	
Urbanization			0.0156
Urban	11,179 (58.38 %)	2895 (60.48 %)	
Sub-urban	5404 (28.22 %)	1310 (27.37 %)	
Rural	2565 (13.4 %)	582 (12.16 %)	
Co-morbidities			
Diabetes mellitus	5662 (29.57 %)	1695 (35.41 %)	<0.0001
Hypertension	10,326 (53.93 %)	2753 (57.51 %)	<0.0001
Hyperlipidaemia	7969 (41.62 %)	2267 (47.36 %)	<0.0001
Chronic kidney disease	2604 (13.60 %)	785 (16.40 %)	<0.0001
Depression	587 (3.07 %)	165 (3.45 %)	0.1762
Stroke	3293 (17.2 %)	894 (18.68 %)	0.0161
Ulcer of esophagus	3052 (15.94 %)	1009 (21.08 %)	<0.0001
Allergies	11,203 (58.51 %)	2879 (60.14 %)	0.0398
COPD	7260 (37.92 %)	1945 (40.63 %)	0.0006
Hepatitis	6231 (32.54 %)	1821 (38.04 %)	<0.0001
Thyroid disorders	1490 (7.78 %)	437(9.13 %)	0.0022
Osteoporosis	5511 (28.78 %)	1417(29.60 %)	0.2632

COPD: chronic obstructive pulmonary disease.

Table 2 The frequency of dental visits between 2005 and 2013 prior to index date of colon-rectum cancer in the case and control group.

	Mean ± SD			Median (Q1-Q3)		
Time before index date	Control	Case	*P* value	Control	Case	*P* value
0—1 year	1.30 ± 2.59	1.39 ± 2.67	0.0508	0 (0—2)	0 (0—2)	0.0202
1—2 years	1.28 ± 2.53	1.42 ± 2.76	0.0013	0 (0—2)	0 (0—2)	0.0002
2—3 years	1.26 ± 2.53	1.35 ± 2.70	0.0413	0 (0—2)	0 (0—2)	0.1153
3—4 years	1.23 ± 2.50	1.40 ± 2.68	<0.0001	0 (0—1)	0 (0—2)	<0.0001
4—5 years	1.22 ± 2.49	1.27 ± 2.47	0.1981	0 (0—1)	0 (0—2)	0.0067
5—6 years	1.16 ± 2.37	1.23 ± 2.53	0.0898	0 (0—1)	0 (0—1)	0.0869
6—7 years	1.16 ± 2.36	1.22 ± 2.47	0.1029	0 (0—1)	0 (0—2)	0.1937
7—8 years	1.13 ± 2.33	1.15 ± 2.32	0.4779	0 (0—1)	0 (0—1)	0.2313
Total in 8 years	9.73 ± 12.02	10.43 ± 12.55	0.0005	6 (1-14)	7 (1-15)	<0.0001

SD: standard deviation.
Q: quartile.

This study has several limitations. First, the sample sizes recruited in the nested case-control study are usually smaller than epidemiological study designs. This might lead to uncertainty in the estimated relationship between exposure and outcome. Second, LHIRD 2010 is lack of some important data which can influence both oral health and CRC such as socioeconomic status and smoking habit. In addition, the diagnosis based on ICD-9 codes can not determine the severity of dental diseases and the stage of CRC. Third, the data solely relied on insurance treatment codes for determination might introduce sampling bias. People who did not use the NHI service were not included in this nationwide registration system. The sample size might be underestimated. Fourth, cohort study design may be necessary to assess the cause-relationship between dental visits and CRC.

In summary, this study demonstrated that the frequency of dental visits was significantly increased in patients with CRC preceding its diagnosis. Certain co-morbidities would influence the development of dental diseases and CRC at

Table 3 The relationship between the frequency of dental visits and prior to diagnosis of colon-rectum cancer within 8-year period from 2005 to 2013.

Dental visits (times)	Control n = 19,148	Case n = 4787	Crude OR (95 % CI)	aOR (95 % CI)
0–8 year before index date				
Mean ± SD	9.73 ± 12.02	10.43 ± 12.55	$P^{\dagger} < 0.0001$	
0	4200 (21.93 %)	959 (20.03 %)	Reference	Reference
1–7	6594 (34.44 %)	1580 (33.01 %)	1.05 (0.96–1.15)	1.00 (0.91–1.09)
8–14	3654 (19.08 %)	1019 (21.29 %)	1.23 (1.11–1.36)	1.14 (1.03–1.26)
>14	4700 (24.55 %)	1229 (25.67 %)	1.15 (1.05–1.26)	1.04 (0.94–1.14)
0–4 year before index date				
Mean ± SD	5.07 ± 7.19	5.56 ± 7.65	$P^{\dagger} < 0.0001$	
0	6588 (34.41 %)	1535 (32.07 %)	Reference	Reference
1–2	3173 (16.57 %)	764 (15.96 %)	1.04 (0.94–1.14)	1.00 (0.90–1.10)
3–7	4663 (24.35 %)	1197 (25.01 %)	1.11 (1.02–1.21)	1.04 (0.96–1.14)
>7	4724(24.67 %)	1291 (26.97 %)	1.18 (1.08–1.28)	1.09 (1.00–1.18)
4–8 year before index date				
Mean ± SD	4.66 ± 6.62	4.87 ± 6.79	$P^{\dagger} = 0.0098$	
0	6760 (35.30 %)	1595 (33.32 %)	Reference	Reference
1–2	3239 (16.92 %)	832 (17.38 %)	1.09 (0.99–1.20)	1.04 (0.95–1.14)
3–7	4850 (25.33 %)	1202 (25.11 %)	1.05 (0.97–1.14)	0.99 (0.91–1.08)
>7	4299 (22.45 %)	1158 (24.19 %)	1.14 (1.05–1.24)	1.05 (0.96–1.15)

$P^{\dagger}$ was estimated by Student's t-test for comparison of mean of dental visits number between case and control group.
CI: confidence intervals.
Crude odds ratio was estimated by using conditional logistic regression.
aOR: odds ratio adjusted for urbanization and co-morbidities by using conditional logistic regression.

Table 4 The relationship between the different dental treatment and prior to diagnosis of colon-rectum cancer within 8-year period from 2005 to 2013.

	0–8 year before index date		0–4 year before index date		4–8 year before index date	
	Crude OR (95 % CI)	aOR (95 % CI)	Crude OR (95 % CI)	aOR (95 % CI)	Crude OR (95 % CI)	aOR (95 % CI)
Periodontal treatment						
Without use	Reference	Reference	Reference	Reference	Reference	Reference
With use	1.11 (1.04–1.19)	1.04 (0.97–1.11)	1.07 (1.01–1.14)	1.01 (0.95–1.08)	1.08 (1.01–1.15)	1.02 (0.95–1.09)
Caries restoration						
Without use	Reference	Reference	Reference	Reference	Reference	Reference
With use	1.09 (1.02–1.16)	1.03 (0.96–1.10)	1.10 (1.03–1.17)	1.05 (0.98–1.12)	1.04 (0.97–1.11)	0.99 (0.92–1.06)
Teeth extraction						
Without use	Reference	Reference	Reference	Reference	Reference	Reference
With use	1.08 (1.01–1.15)	1.04 (0.97–1.11)	1.08 (1.01–1.15)	1.05 (0.98–1.12)	1.06 (0.99–1.13)	1.02 (0.95–1.09)

CI: confidence intervals.
Crude odds ratio was estimated by using conditional logistic regression.
aOR: odds ratio adjusted for urbanization and co-morbidities by using conditional logistic regression.

the same time. Periodontal treatment, caries filling, and tooth extraction were borderline and not significantly related to CRC after adjustment. The awareness of dental health of patients with CRC by colorectal surgeon is necessary.

Declaration of competing interest

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

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