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ORIGINAL ARTICLE

Oral cancer in Taiwan: is diabetes a risk factor?

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Abstract
Objectives The association between diabetes and oral cancer is rarely studied. We investigated the trends of oral cancer in the Taiwanese general population and the possible link with diabetes.
Materials and methods The trend of age-standardized oral cancer incidence in 1979–2007 in Taiwan was calculated from the Taiwan Cancer Registry database. A total of 494,817 men and 503,723 women without oral cancer from a random sample of 1,000,000 individuals covered by the National Health Insurance were followed up from 2003 to 2005. Cox regression evaluated the adjusted relative risk considering potential detection bias and covariates.
Results The trends increased significantly in both sexes. Diabetic patients had a higher chance of oral cancer detection because they more frequently visited related medical professionals. Although diabetes status and duration were significantly associated with oral cancer in unadjusted models, none was significant after multivariable adjustment. For comorbidities, chronic obstructive pulmonary disease (a surrogate for smoking) and alcohol-related diagnoses were significant for men, and hypertension and alcohol-related diagnoses were significant for women. Additionally, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and insulin were significant with relative risk (95 % confidence interval) of 1.642 (1.174–2.295) and 2.136 (1.003–4.547), respectively, in men.
Conclusions Oral cancer is increasing in Taiwan. Diabetes is not a risk factor after multivariable adjustment.
Clinical relevance The increasing trend of oral cancer may not be ascribed to diabetes. The association between oral cancer and some comorbidities and medications requires confirmation and may provide strategies for the prevention of oral cancer.

Keywords Oral cancer · Diabetes · Cancer risk factor · Epidemiology

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Introduction

The etiology of oral cancer remains largely unknown. Classical risk factors include smoking, alcohol, poor oral hygiene, infection, inflammation, dietary factors, and betel nut chewing [1–4]. In Taiwan, oral cancer is currently the fourth most common cancer in men, but the 16th in women [5]. Although early studies conducted in Taiwan suggested that smoking and betel nut chewing are the two most important risk factors, they probably cannot fully explain the abrupt increase in oral cancer incidence in Taiwan [6–8].

Diabetes mellitus is a chronic disease characterized by increased blood glucose level, insulin resistance, hyperinsulinemia, chronic inflammation, and oxidative stress [9]. Recently, several cancers have been linked to diabetes, especially those involving liver, pancreas, endometrium, colorectum, bladder, and breast [10–13]. However, the association between diabetes and oral cancer is still unclear and studies on this issue are still sparse.

An early Hungarian retrospective study analyzing 610 inpatients with oral cancer compared to 574 controls found that diabetes was present in 24.3 % in the oral cancer group vs. 11.1 % in the control group ($P<0.01$) [14]. On the other hand, a recent cohort study conducted in the black and white US veterans with a large sample size of 4,501,578 individuals suggested a significantly lower risk of oral cancer in the diabetic patients (relative risk, 0.85; 95 % confidence interval, 0.82–0.89) [15]. However, this study recruited only male people and it also analyzed data of admission to veteran affairs hospitals.

To the best of our knowledge, population-based analyses on the link between diabetes and oral cancer are still lacking. Furthermore, diabetic patients may have more frequent visits to medical professionals and therefore are more likely to be diagnosed as having oral cancer. None of the previous studies evaluating the link between diabetes and oral cancer have taken into account this possibility of detection bias.

Therefore, the present study aimed at investigating (1) the secular trends of oral cancer in the general population of Taiwan by using the National Cancer Registry data and (2) the possible link between diabetes and oral cancer by using the population-based reimbursement database of the National Health Insurance (NHI), taking into account possible confounders and the potential detection bias including clinical visits to medical professionals such as the dentists or the doctors of the ears, nose, and throat (ENT) and/or a history of gingival and periodontal diseases.

Materials and methods

Study population

According to the Ministry of Interior, Taiwan, in 2005, >98.0 % of the Taiwanese population (22,770,383; 11,562,440 men and 11,207,943 women) was covered by the NHI. A random sample of 1,000,000 people insured by the NHI in 2005 was created by the National Health Research Institute for academic research. The National Health Research Institute is the only institute approved, as per local regulations, for conducting sampling of a representative sample of the whole population for the year 2005 with a predetermined sample size of 1,000,000 individuals. The reimbursement databases of these sampled individuals were retrieved and could be provided for academic research after approval. The identification information was scrambled for the protection of the privacy of the sampled individuals. The reimbursement databases from 1996 onwards were available. Sex, birth date, medications, and diagnostic codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) were retrieved for analyses in this study. Diabetes was coded 250.1–250.9 and oral cancer as 140, 141, 143, 144, 145, 146, 148, and 149.

Figure 1 shows a flow chart used for selecting cases in this study. Type 1 diabetes is always present from childhood and these patients may have a different oral cancer etiology and incidence. Furthermore, the incidence of type 1 diabetes is low in our population and the case number of type 1 diabetes in the selected study population was small (n= 270), and among them, none developed oral cancer during the follow-up period. Therefore, patients with type 1 diabetes were not considered in the analyses. After excluding subjects with type 1 diabetes (in Taiwan, patients with type 1 diabetes were issued a "severe morbidity card" after certified diagnosis), subjects for whom the living region was not known, subjects diagnosed with oral cancer before 2003, 494,817 men and 503,723 women, and without oral cancer were followed up from January 1, 2003 to December 31, 2005.

Statistical analyses

The trends of crude and age-standardized (to the 2000 World Health Organization population) incidence of oral cancer in the general population were first calculated for men and women, respectively, from the Taiwan Cancer Registry database for 1979–2007 [16]. Poisson regression evaluated whether the trends changed significantly, where the incidence was the dependent and the calendar year the independent variable.

Because oral cancer is much more common in men than in women in Taiwan [5], the analyses were conducted in separate sexes to identify possible difference in risk factors for different sexes. Furthermore, because age was not linearly associated with oral cancer incidence [5], it was treated as a categorical variable by classifying into the following subgroups: <25, 25–49, 50–59, and ≥60 years.

Age, diabetes status, diabetes duration, and other covariates found in the NHI reimbursement databases were determined as a status or a diagnosis on or before January 1, 2003. Oral cancer was only counted in cases in which incidence occurred within the 3-year period from January 1, 2003 to December 31, 2005. At first, we compared the following potential detection bias between diabetic patients and nondiabetic individuals by Chi square test: (1) visits to dentists, (2) visits to ENT doctors, (3) a previous diagnosis of gingival and periodontal diseases (ICD-9-CM 523), and (4) any of the above.

The association between oral cancer and diabetes status (diabetes status model: yes vs. no) and diabetes duration (diabetes duration model: no diabetes as referent vs. diabetes duration for <1 year, for 1–3 years, and for ≥3 years) were evaluated separately. Unadjusted and multivariable-adjusted relative risks and their 95 % confidence intervals were estimated from Cox regression for men and women, separately.

The covariates in the multivariable-adjusted models included: age, obesity (ICD-9-CM code: 278), hypertension (401–405), chronic obstructive pulmonary disease (COPD, 490–496, a surrogate for smoking), alcohol-related diagnoses (including alcoholism, alcoholic gastritis, alcoholic cirrhosis, and toxic effect of alcohol: 291, 303, 535.3, 571.0, 571.1, 571.2, 571.3, and 980.0), stroke (430–438), nephropathy (580–589), ischemic heart disease (410–414), peripheral arterial disease (250.7, 785.4, 443.81, and 440–448),

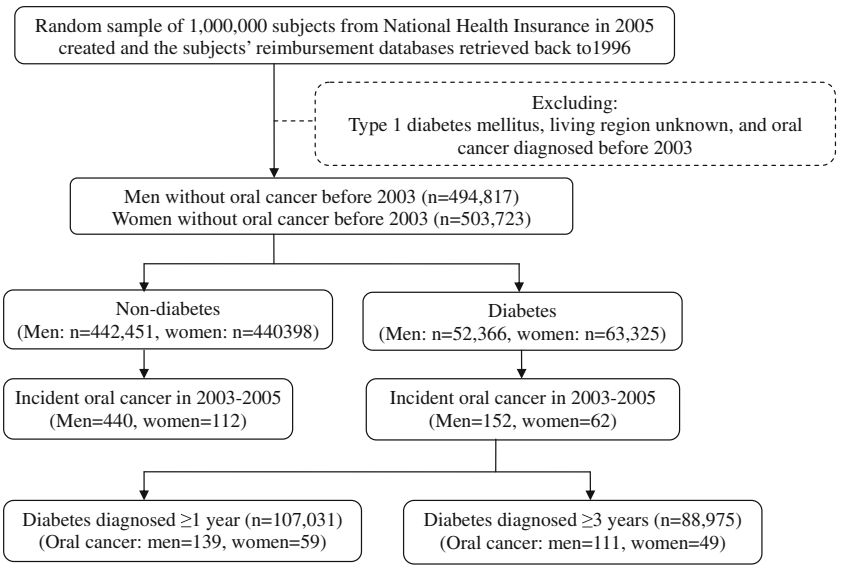

Fig. 1 Flow chart showing the procedures in the selection of study subjects

eye disease (250.5, 362.0, 369, 366.41, and 365.44), dyslipidemia (272.0–272.4), statins, fibrates, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), calcium channel blockers, sulfonylurea, metformin, insulin, acarbose, pioglitazone, rosiglitazone, living region, occupation, and potential oral cancer detection. The insured individuals were classified according to their occupation (a surrogate for socioeconomic status). The living region served as a surrogate for geographical distribution of some environmental exposure. Occupation was categorized into class I: civil servants, teachers, employees of governmental or private businesses, professionals, and technicians; class II: people without a specific employer, self-employed people, or seamen; class III: farmers or fishermen; and class IV: low-income families supported by social welfare or veterans. Living regions were classified as Taipei, northern, central, southern, and Kao-Ping/eastern.

Analyses were conducted using the SAS statistical software, version 9.1 (SAS Institute, Cary, NC). $P<0.05$ was considered statistically significant.

Results

Figure 2 shows the crude and age-standardized incidence trends in the general population in men and women. All trends were increasing significantly ($P<0.05$).

Table 1 compares the potential detection bias between the diabetic patients and the nondiabetic individuals in men and women. All of the variables differed significantly, showing a higher chance of oral cancer detection in the diabetic patients because they had a higher proportion of a previous diagnosis of gingival and periodontal diseases and more frequent visits to related medical professionals.

The unadjusted and multivariable-adjusted relative risks for men and women are shown in Table 2 and Table 3, respectively. In the unadjusted models, diabetes status and diabetes duration for 1–3 years and for ≥3 years were all significantly predictive for oral cancer in either men (Table 2) or women (Table 3). However, in the multivariable-adjusted models, none of them was significant (Tables 2 and 3). Age was an important risk factor for both sexes, and the highest relative risk associated with age was observed in the age of 50–59 years in men (Table 2) and in the age of ≥60 years in women (Table 3). In the multivariable-adjusted model, potential detection bias was not significantly predictive for oral cancer in men (Table 2), but was significant in women (Table 3). For the comorbidities evaluated, COPD and alcohol-related diagnoses were significant predictors in men (Table 2), but hypertension and alcohol-related diagnoses were significant for women (Table 3). For the medications, ACEI/ARB and insulin were significant and fibrate was borderline significant in men (Table 2), but none of the medications were significant in women (Table 3). Because none of the obese individuals and the users of acarbose or pioglitazone in women developed oral cancer, the relative risks for these variables could not be estimated (Table 3). Living region and occupation might also show a significant association in either men or women (Tables 2 and 3). People living in the two most urbanized regions (i.e., northern region and Taipei) had the lowest risk in either sex (Tables 2 and 3). In men, people living in central, southern, or Kao-Ping/eastern region had significantly higher risk than those living in Taipei (Table 2), but in women, only those living in southern and Kao-Ping/eastern regions had significantly higher risk (Table 3). With

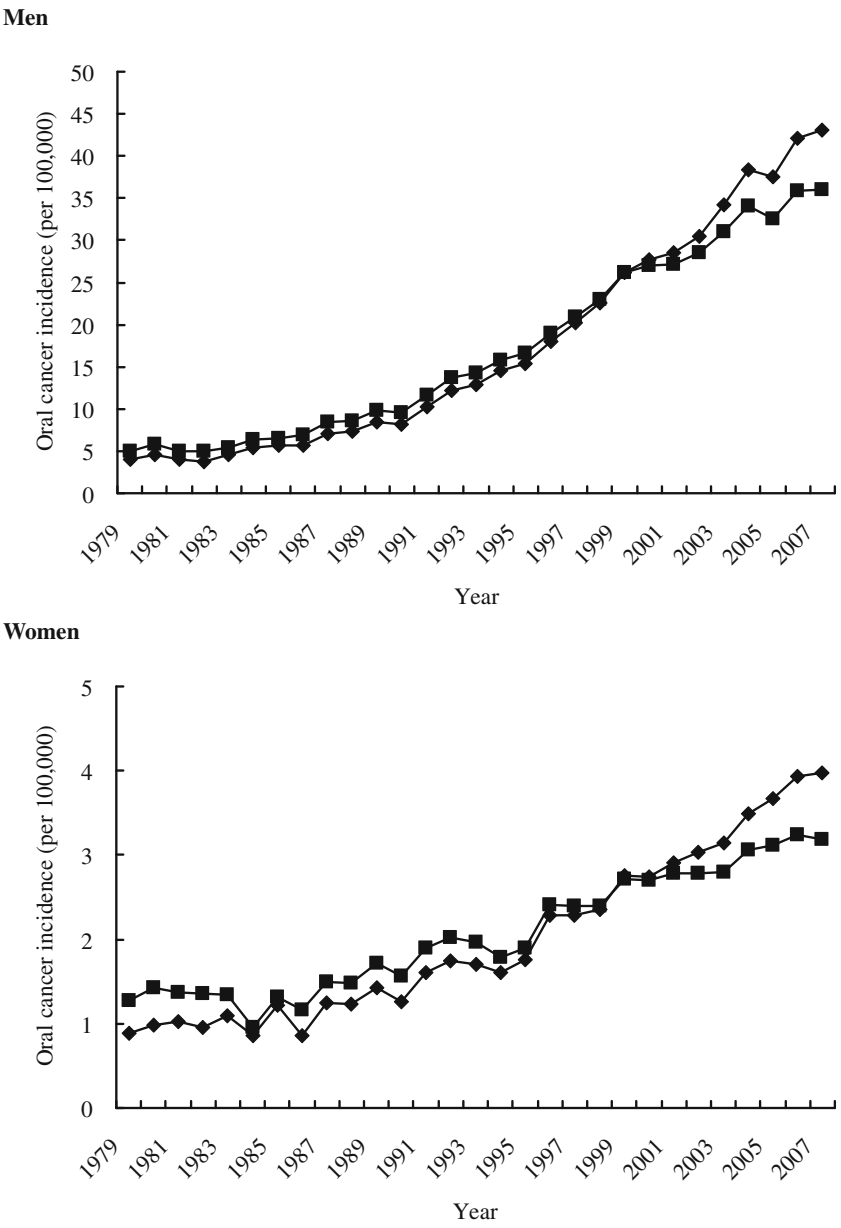

Fig. 2 Trends of oral cancer incidence in the general population of Taiwan from 1979 to 2007 in separate sex (*diamonds*: crude rate, *squares*: age-standardized rate using the 2000 World Health Organization population as referent). All trends are increasing significantly ($P<0.05$)

regards to occupation, men with occupations II, III, and IV had significantly higher risk of oral cancer than those with occupation I (Table 2). However, only women with occupation IV had significantly higher risk (Table 3).

Discussion

This is the first population-based study evaluating the risk of oral cancer in the diabetic patients and also the first study that considered the potential detection bias and adjusted for various potential confounders simultaneously. This study suggested that the trends of oral cancer were increasing significantly from 1979 to 2007 in either sex (Fig. 2), and diabetes was not a significant risk factor after multivariable adjustment. Therefore, the increasing incidence of oral cancer could not be ascribed to the uprising incidence [17] and prevalence [18] of diabetes during the same period in Taiwan. Alcohol-related diagnosis and comorbidities such as COPD or hypertension, living region, occupation, and some medications such as ACEI/ARB, insulin, and possibly fibrate might play some role on the increasing trend.

The Hungarian case–control study suggested a higher risk [14] but the US cohort study showed a significantly lower risk [15] in people with diabetes. Both studies used hospitalized data and the US study recruited a highly specific group of male veterans. The differences in ethnicities, use of hospitalization samples, and case–control design in the Hungarian study vs. the cohort design with a specific

Table 1 Comparisons of visits to dentists and/or doctors of the ears, nose, and throat (ENT) and a history of gingival and periodontal diseases that might potentially lead to the diagnosis of oral cancer between diabetic patients and nondiabetic individuals for separate sexes

Examination	Diabetes mellitus				*P* value
	No		Yes		
	n	%	*n*	%	
Visits to dentists					
Men					
No	145,124	92.38	11,973	7.62	<0.0001
Yes	297,337	88.04	40,395	11.96	
Women					
No	122,521	90.48	12,885	9.52	<0.0001
Yes	317,887	86.30	50,443	13.70	
Visits to ENT doctors					
Men					
No	175,669	90.36	18,733	9.64	<0.0001
Yes	266,792	88.80	33,635	11.20	
Women					
No	145,711	89.12	17,792	10.88	<0.0001
Yes	294,697	86.62	45,536	13.38	
Gingival and periodontal diseases					
Men					
No	231,481	93.16	16,992	6.84	<0.0001
Yes	210,980	85.64	35,376	14.36	
Women					
No	204,883	91.39	19,314	8.61	<0.0001
Yes	235,525	84.25	44,014	15.75	
Any of the above					
Men					
No	86,837	93.24	6293	6.76	<0.0001
Yes	355,624	88.53	46,075	11.47	
Women					
No	72,438	92.83	5593	7.17	<0.0001
Yes	367,970	86.44	57,735	13.56	

professional in the US study might have explained the different results observed. It should be pointed out that the Hungarian study did not detail on the selection of the control and there were discrepancies in the distribution of age and sex between the cases and the controls [14]. The mean age of the case group was older than the control group (56 vs. 51 years) and there were more men than women in the case group (men vs. women, 425 vs. 175 in the case group and 351 vs. 223 in the control group). Furthermore, there was no regression model creation and no consideration of the effects of potential confounders such as smoking and alcohol drinking in the Hungarian study. In the US veterans cohort study, obesity, COPD, and alcohol-related diagnosis were considered for adjustment, but other comorbidities, diabetes duration, types of diabetes, medications, and possible detection bias were not considered for analyses [15]. Furthermore, biased estimates could not be excluded in the US study because the results showed that diabetic men had a 7 % significantly lower risk of overall cancer than nondiabetic individuals, which was in contrary to most studies showing a significantly higher risk of cancer in the diabetic patients [10].

We admitted that we could not adjust for the potential confounding effect of betel nut chewing in the present study because of the lack of such information. However, it has been well-demonstrated that betel nut chewing is mainly a hobby in the male population [19–21], and we had tried to segregate this sexual effect by analyzing the data in separate sexes. It is worthy to note that betel nut chewing may not explain the dramatic increase in the trends of oral cancer incidence during the past two–three decades in Taiwan, especially in the female general population (Fig. 2), because betel nut chewing is very uncommon among the female population in Taiwan [19–21].

It should also be mentioned that because betel nut chewing is highly associated with smoking [21] and can be a risk factor for obesity [22], diabetes [23], hypertension [21], nephropathy [24], and ischemic heart disease [25], the consideration of obesity, hypertension, nephropathy, and the smoking-related comorbidities such as COPD and cardiovascular diseases in the multivariable-adjusted models (Tables 2 and 3) might have partially adjusted for the effect of betel nut chewing.

Some medications, namely ACEI/ARB, insulin, and possibly fibrate, seemed to be associated with the risk of oral cancer in men (Table 2). There was no explanation for such links at this moment. However, because such a link could not be demonstrated in women, the findings should be confirmed by future studies. Geographical distribution and socioeconomic status, as indicated by living region and occupation, respectively, did significantly impact the risk (Tables 2 and 3). People living in Metropolitan Taipei region and the northern region (both are more urbanized areas) and those with a higher socioeconomic status as indicated by occupation I had the lowest risk (Tables 2 and 3).

This study has several strengths. It is population-based with a large nationally representative sample. The database included outpatients and inpatients and we caught the diagnoses from both sources. Cancer is considered as a severe morbidity by the NHI and most medical co-payments can be waived. Therefore, the detection rate would not tend to differ among different social classes. The use of medical record also reduced the potential bias related to self-reporting.

Limitations included a lack of actual measurement of confounders such as obesity, smoking, alcohol drinking,

Table 2 Relative risks for oral cancer derived from Cox proportional hazards regression for men

Model/variables	Interpretation	Diabetes status model			Diabetes duration model		
		RR	95 % CI	*P*	RR	95 % CI	*P*
Unadjusted							
Diabetes	Yes vs. no	2.682	(2.182, 3.297)	<0.0001	–		
Diabetes duration	<1 year vs. no diabetes	–			1.243	(0.556, 2.781)	0.5963
	1–3 years vs. no diabetes	–			3.027	(2.081, 4.403)	<0.0001
	≥3 years vs. no diabetes	–			2.817	(2.212, 3.588)	<0.0001
Multivariable-adjusted							
Age, years	25–49 vs. <25	22.734	(12.752, 40.529)	<0.0001	22.753	(12.763, 40.562)	<0.0001
	50–59 vs. <25	37.733	(20.797, 68.462)	<0.0001	37.754	(20.809, 68.500)	<0.0001
	≥60 vs. <25	25.904	(14.092, 47.618)	<0.0001	25.856	(14.065, 47.534)	<0.0001
Diabetes	Yes vs. no	1.195	(0.892, 1.601)	0.2334	–		
Diabetes duration	<1 year vs. no diabetes	–			0.598	(0.263, 1.359)	0.2192
	1–3 years vs. no diabetes	–			1.432	(0.946, 2.167)	0.0896
	≥3 years vs. no diabetes	–			1.232	(0.882, 1.720)	0.2212
Obesity	Yes vs. no	0.442	(0.062, 3.150)	0.4148	0.447	(0.063, 3.188)	0.4217
Hypertension	Yes vs. no	0.914	(0.698, 1.197)	0.5139	0.915	(0.699, 1.198)	0.5169
COPD	Yes vs. no	1.249	(1.022, 1.526)	0.0301	1.247	(1.020, 1.525)	0.0311
Alcohol-related diagnoses	Yes vs. no	3.345	(2.405, 4.653)	<0.0001	3.355	(2.412, 4.667)	<0.0001
Stroke	Yes vs. no	1.040	(0.760, 1.423)	0.8071	1.038	(0.759, 1.421)	0.8138
Nephropathy	Yes vs. no	0.843	(0.593, 1.196)	0.3381	0.840	(0.592, 1.193)	0.3307
IHD	Yes vs. no	0.937	(0.710, 1.237)	0.6456	0.936	(0.709, 1.235)	0.6401
PAD	Yes vs. no	0.889	(0.580, 1.362)	0.5878	0.887	(0.578, 1.359)	0.5804
Eye disease	Yes vs. no	1.140	(0.608, 2.140)	0.6826	1.126	(0.599, 2.116)	0.7133
Dyslipidemia	Yes vs. no	0.943	(0.710, 1.253)	0.6871	0.943	(0.709, 1.253)	0.6862
Statin	Yes vs. no	1.291	(0.861, 1.935)	0.2163	1.289	(0.860, 1.933)	0.2193
Fibrate	Yes vs. no	1.360	(0.962, 1.923)	0.0816	1.353	(0.956, 1.914)	0.0878
ACEI/ARB	Yes vs. no	1.642	(1.174, 2.295)	0.0037	1.643	(1.175, 2.298)	0.0037
CCB	Yes vs. no	1.013	(0.714, 1.437)	0.9423	1.014	(0.715, 1.438)	0.9394
Sulfonylurea	Yes vs. no	0.745	(0.441, 1.259)	0.2716	0.737	(0.434, 1.250)	0.2572
Metformin	Yes vs. no	1.367	(0.797, 2.345)	0.2561	1.364	(0.791, 2.352)	0.2638
Insulin	Yes vs. no	2.136	(1.003, 4.547)	0.0491	2.164	(1.014, 4.619)	0.0459
Acarbose	Yes vs. no	0.194	(0.026, 1.434)	0.1082	0.195	(0.026, 1.438)	0.1088
Pioglitazone	Yes vs. no	1.701	(0.219, 13.198)	0.6115	1.703	(0.219, 13.235)	0.6107
Roasiglitazone	Yes vs. no	1.151	(0.437, 3.035)	0.7760	1.138	(0.431, 3.004)	0.7948
Living region	Northern vs. Taipei	1.087	(0.819, 1.442)	0.5635	1.087	(0.819, 1.442)	0.5635
	Central vs. Taipei	1.395	(1.097, 1.775)	0.0067	1.395	(1.096, 1.775)	0.0068
	Southern vs. Taipei	1.342	(1.035, 1.741)	0.0262	1.340	(1.034, 1.737)	0.0272
	Kao-Ping/eastern vs. Taipei	1.442	(1.138, 1.827)	0.0024	1.440	(1.136, 1.824)	0.0025
Occupation	II vs. I	1.900	(1.504, 2.400)	<0.0001	1.900	(1.505, 2.400)	<0.0001
	III vs. I	2.266	(1.786, 2.875)	<0.0001	2.267	(1.786, 2.877)	<0.0001
	IV vs. I	1.839	(1.460, 2.316)	<0.0001	1.839	(1.461, 2.317)	<0.0001
Potential detection	Yes vs. no	0.933	(0.759, 1.147)	0.5086	0.932	(0.758, 1.145)	0.5009

COPD chronic obstructive pulmonary disease, *IHD* ischemic heart disease, *PAD* peripheral arterial disease, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker

betel nut chewing, family history, lifestyle, diet, hormones, and genetic parameters. In addition, we did not have biochemical data for evaluating their impact. For example, the levels of blood glucose and hemoglobin A_{1C} were not available from the reimbursement database, and it was not possible to evaluate whether patients with poorer glycemic

Table 3 Relative risks for oral cancer derived from Cox proportional hazards regression for women

Model/variables	Interpretation	Diabetes status model			Diabetes duration model		
		RR	95 % CI	*P*	RR	95 % CI	*P*
Unadjusted							
Diabetes	Yes vs. no	3.582	(2.574, 4.984)	<0.0001	–		
Diabetes duration	<1 year vs. no diabetes	–			2.237	(0.712, 7.030)	0.1682
	1–3 years vs. no diabetes	–			2.381	(1.112, 5.098)	0.0255
	≥3 years vs. no diabetes	–			4.145	(2.893, 5.938)	<0.0001
Multivariable-adjusted							
Age, years	25–49 vs. <25	7.542	(3.233, 17.591)	<0.0001	7.546	(3.235, 17.601)	<0.0001
	50–59 vs. <25	21.431	(8.913, 51.528)	<0.0001	21.483	(8.936, 51.650)	<0.0001
	≥60 vs. <25	30.185	(12.506, 72.852)	<0.0001	30.052	(12.448, 72.555)	<0.0001
Diabetes	Yes vs. no	1.223	(0.789, 1.895)	0.3684	–		
Diabetes duration	<1 year vs. no diabetes	–			0.894	(0.279, 2.862)	0.8501
	1–3 years vs. no diabetes	–			0.935	(0.422, 2.070)	0.8680
	≥3 years vs. no diabetes	–			1.386	(0.861, 2.232)	0.1791
Obesity	Yes vs. no	–			–		
Hypertension	Yes vs. no	1.654	(1.094, 2.501)	0.0170	1.652	(1.092, 2.499)	0.0174
COPD	Yes vs. no	1.077	(0.761, 1.524)	0.6747	1.075	(0.760, 1.521)	0.6830
Alcohol-related diagnoses	Yes vs. no	3.757	(1.385, 10.188)	0.0093	3.735	(1.377, 10.130)	0.0097
Stroke	Yes vs. no	0.979	(0.599, 1.601)	0.9335	0.976	(0.597, 1.596)	0.9225
Nephropathy	Yes vs. no	1.178	(0.710, 1.957)	0.5258	1.175	(0.708, 1.952)	0.5329
IHD	Yes vs. no	0.880	(0.573, 1.352)	0.5596	0.878	(0.571, 1.350)	0.5538
PAD	Yes vs. no	0.973	(0.537, 1.763)	0.9283	0.968	(0.534, 1.754)	0.9143
Eye disease	Yes vs. no	1.217	(0.475, 3.115)	0.6827	1.176	(0.459, 3.016)	0.7355
Dyslipidemia	Yes vs. no	0.974	(0.624, 1.520)	0.9086	0.986	(0.632, 1.539)	0.9503
Statin	Yes vs. no	0.646	(0.308, 1.352)	0.2462	0.641	(0.306, 1.343)	0.2391
Fibrate	Yes vs. no	0.573	(0.277, 1.183)	0.1323	0.564	(0.273, 1.166)	0.1222
ACEI/ARB	Yes vs. no	1.117	(0.636, 1.963)	0.6994	1.126	(0.640, 1.978)	0.6810
CCB	Yes vs. no	0.691	(0.380, 1.256)	0.2249	0.695	(0.382, 1.264)	0.2329
Sulfonylurea	Yes vs. no	0.831	(0.366, 1.888)	0.6584	0.815	(0.354, 1.874)	0.6296
Metformin	Yes vs. no	1.028	(0.433, 2.443)	0.9493	0.998	(0.414, 2.408)	0.9967
Insulin	Yes vs. no	2.292	(0.746, 7.047)	0.1477	2.204	(0.717, 6.773)	0.1677
Acarbose	Yes vs. no	–			–		
Pioglitazone	Yes vs. no	–			–		
Rosiglitazone	Yes vs. no	0.897	(0.202, 3.982)	0.8867	0.881	(0.199, 3.907)	0.8673
Living region	Northern vs. Taipei	0.853	(0.477, 1.525)	0.5919	0.850	(0.476, 1.519)	0.5831
	Central vs. Taipei	1.143	(0.713, 1.831)	0.5793	1.142	(0.713, 1.830)	0.5811
	Southern vs. Taipei	2.048	(1.324, 3.168)	0.0013	2.038	(1.317, 3.153)	0.0014
	Kao-Ping/eastern vs. Taipei	1.602	(1.046, 2.452)	0.0302	1.599	(1.044, 2.448)	0.0308
Occupation	II vs. I	1.085	(0.692, 1.701)	0.7216	1.086	(0.693, 1.703)	0.7190
	III vs. I	0.957	(0.609, 1.504)	0.8487	0.956	(0.608, 1.502)	0.8444
	IV vs. I	1.760	(1.185, 2.613)	0.0051	1.762	(1.186, 2.616)	0.0050
Potential detection	Yes vs. No	1.858	(1.070, 3.226)	0.0279	1.852	(1.067, 3.217)	0.0286

None of the obese patients and users of acarbose or pioglitazone developed oral cancer in women

COPD chronic obstructive pulmonary disease, *IHD* ischemic heart disease, *PAD* peripheral arterial disease, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker

control might have a greater risk of developing oral cancer. It should also be stressed that the validity for the use of surrogate markers of COPD for smoking and alcohol-related diagnoses for alcohol use must be cautious and conservative

because people who used tobacco or alcohol might not have related diagnoses and the etiologies for the development of these related diseases may be multifactorial, relying on both genetic and environmental factors.

In summary, this study suggests that oral cancer is increasing in men and women in the general population of Taiwan during the past decades. Diabetes is not a risk factor, and therefore, the increasing trends of oral cancer may not be ascribed to the increasing prevalence and incidence of diabetes over the same period. The association between oral cancer and comorbidities (such as COPD, hypertension, and alcohol-related diagnoses) and medications (such as ACEI/ARB, insulin, and possibly fibrate) requires further exploration, which may provide strategies for the prevention of oral cancer.

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Conflict of interest The author declares that there is no duality of interest associated with this manuscript.

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