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DISTINCTIVE FEATURES OF ORAL CANCER IN CHANGHUA: HIGHEST INCIDENCE, BUCCAL PREPONDERANCE, AND AN UNUSUAL RELATION WITH PREVALENCE OF BETEL QUID CONSUMPTION

彰化地區口腔癌特徵：高發生率，偏向頰黏膜，與嚼食檳榔盛行率之異常關係

Running title: Distinct feature of oral cancer in Changhua

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// Abstract

Purpose: Oral cancer is one of the fastest increasing malignancies in Taiwan. Among the counties on the island, Changhua has been ranked in the top three in the list of oral cancer incidence. We start the study to better characterize the epidemiology of oral cancer in the Changhua County.

Methods: We use the complete registered records of oral cancer from the data bank of Department of Health (DOH). We study the trend of incidence rate, age of distribution, and anatomic sites of oral cancer in Changhua. In addition, we correlate the incidence rate with known risk factors (betel quid chewing, smoking, and alcohol drinking) by regression method.

Results: Incidence rate of oral cancer in Changhua is among the highest in the world, and was the highest among the 23 counties in Taiwan in 2001 (45.07 per 10^5 per year). In the past 2 decades from 1982 to 2001, Changhua saw an alarming 5.3-fold increase in the incidence of male oral cancer. The most common site was buccal, while it was tongue in the rest counties. Finally, Changhua is the only outlier in our regression model, indicating an unusual relation between cancer incidence and prevalence of betel quid chewing in Changhua.

Conclusions: The high and fast increasing incidence of oral cancer in Changhua signifies the importance of this cancer locally, no less than that of liver cancer and lung cancer. An unusual relation with known risk factors (betel quid chewing, smoking, and alcohol drinking)

indicates other unknown factor/factors may be involved in the etiology of oral cancer in Changhua. Further study is needed, and is ongoing.

Key words: Betel quid; Incidence rate; Oral cancer

Introduction

Cancer has been the leading cause of death in Taiwan since 1982 [1]. A steady increase in the incidence of cancer has caused a great impact on both the patient and the society. In 1982, total cancer incidence stood at 117.77 per 10^5 men per year and 105.92 per 10^5 women per year [2]. The rates had increased to 278.02 and 243.40 in 2001, a warning 2.36-fold increase for men and a 2.30-fold increase for women in 2 decades. As a result, medical care for cancer patients has occupied a large portion of the spending of the National Health Insurance (NHI); at the same time, prevention of cancers is among the most urgent tasks to deal with.

Among neoplasms, oral cancer is one of the fastest increasing malignancies in Taiwan. In 1982, oral cancer incidence stood at 5.12 per 10^5 men per year and 1.54 per 10^5 women per year [2]. The rates had increased to 27.04 and 3.17 in 2001, an alarming 5.3-fold increase for men and a 2-fold increase for women in 2 decades. From studies in western countries, it has long been known that tobacco smoking and alcohol drinking play roles in the etiology of oral cancer and these two agents may act in synergy [3]. A 35-fold increase in the incidence of oral cancer was reported for tobacco and alcohol consumers than for non-users. In Taiwan, another etiological factor may play a more important role. Betel quid chewing (BQC) is practiced in Taiwan for centuries. A case control study in Taiwan[4] found that a 123-fold increase in the incidence of oral cancer for those who consume tobacco, alcohol, and betel quid than those who took none.

Prevention is always the best treatment. However, knowing the etiological factors is prerequisite of any effective preventive measures. The government in Taiwan has spent lots of effort to educate people on the risk of BQC, reminding chewers of the close relationship between the habit and oral cancer. However, it is an up-hill battle. People are reluctant to abandon a habit bringing them euphoria and excitement. The propaganda will result in a substantial decrease in the incidence of oral cancer, only when the major risk factors in the etiology are adequately addressed.

Changhua has ranked the top county in oral cancer incidence in Taiwan in recent years[2]. The incidence of male oral cancer in Changhua is also among the highest in the world (Table 1A). In the report, we analyze the data from DOH to study the epidemiology of oral cancer in Taiwan, with more emphasis on Changhua.

Methods:

We analyzed the registered records of 26761 patients in total, who were diagnosed with malignant oral cancer (I.C.D.-O-FT T-140, 141, 143, 146, 148, 149, please see appendix for details) in Taiwan from 1986 to 2001. The data was kindly provided by DOH. There were 3000 cases from the Changhua County in the records.

The age-standardized incidence rate (ASIR) is referred to as the incidence rate standardized according to age distribution based on year 2000 world standard population by WHO. The adjusted relative risk of getting oral cancer for people in Changhua to that for people in the rest areas in Taiwan is calculated by age strata with methods by Rothman and Boice [5]. The test of difference between Changhua and other regions in Taiwan in 2001 is based on the statistics proposed by Oleinick and Mantel [6].

To study the changes in onset age of oral cancer from 1986 to 2001, we divided the time period into four quadrenniums and plotted the ASIR with respect to onset age for each quadrennium in Changhua and in the rest areas in Taiwan.

DOH in Taiwan had conducted a survey in 2002[7] to study the prevalence rates of BQC, smoking and alcohol drinking in Taiwan. We fitted multiple linear regression models of the incidence rate of male oral cancer on prevalence rate of these risk factors, and used a diagnostic testing to detect if there is any outlying case, so called an outlier. An outlier is defined as a case that behaves differently from others in a model. The difference may be

caused by either an unusual relation between the explanatory variables and the response variable, or missing of other unknown, but important factors in the model. A case is diagnosed as an outlier if its external studentized residual[8] (ESR) is significantly large under a simultaneous comparison procedure, where the ESR is defined as the standardized, leave-one-out deviation of the observation from the fitted regression line.

Results

Incidence rate of oral cancer in Changhua is among the highest in Taiwan and in the world.

The incidence rate of oral cancer in the world in 2000 is shown in Table 1A[9]. The statistics is provided by WHO. It is clear that the incidence rate in Taiwan is in the middle. Among all 23 counties in Taiwan, Changhua had the highest male incidence rate, at 45.07 per 10^5 men per year in 2001 (Table 1B). The ASIR of oral cancer in 1982 in Taiwan was 5.12 per 10^5 men per year and 1.54 for women, and 27.04 per 10^5 men per year and 3.17 for women in 2001, a (5.28 and 2.06)-fold increase within the 20-year span. In 2001, the ASIR of oral cancer for men in the Changhua County is 45.07 per 10^5 men per year; whereas the rate in the other 22 counties as a whole was 25.74. To compare the incidence rate of oral cancer in Changhua and that in the rest areas in Taiwan, we divided the rest 22 counties into six regions (Table 1C). The adjusted relative risk of male oral cancer in Changhua to the rest areas in Taiwan is 1.77 in 2001 (Table 1C). The ASIR of male oral cancer in Changhua is at least 2-fold higher than that in the northern parts of Taiwan, and 1.3 to 1.5-fold higher than that in the eastern, central and southern part of Taiwan. These figures all reach the 1% level of significance.

We went on to plot the trends of the ASIR for Changhua and for the rest areas in Taiwan (Figure 1). The arithmetic distances between the two ASIR lines keep increasing; however, the relative risk had remained similar from 1995 to 2001 (data not shown here).

Oral cancer incidence in Changhua has an unusual relation with prevalence of betel quid chewing.

From studies in western countries and in Taiwan [3,4,10,11], it has long been known that tobacco smoking, alcohol drinking and BQC play roles in the etiology of oral cancer and these agents may act in synergy. According to a survey by Yang et al [12], the prevalence of BQC in Changhua ranked in the middle (12th in 23 counties); however, its incidence rate of male oral cancer was the highest, higher than that in the Taitung County (40.15 per 10^5 men in 2001), which had the highest prevalence rate in BQC.

DOH had also conducted a survey in 2002 [7] to study the prevalence rate of BQC, smoking and alcohol drinking for each of the 23 counties in Taiwan. We fitted multiple linear regression models of the county-wise crude incidence rates (CIR) of male oral cancer on the three prevalence rates of BQC, smoking and alcohol drinking. The model indicates that BQC is the most important factor after adjusting the other two factors. Based on the regression model of the rest 22 counties, the square of multiple correlation of coefficient (R^2) is 0.521, meaning that the three risk factors contribute 52.1% of the variation of male oral cancer incidence rate in these counties. However, the R^2 drops to 0.445 as Changhua being added. Among the 23 counties, Changhua is the one with the most deviation away from the regression line (Figure 2A). Using the external studentized residuals [8] as diagnostic statistics, male oral cancer in Changhua stands alone as the only significant "outlier" with a t-value of 2.2 (Figure 2B). The

unique status of Changhua may be caused by its excessively high incidence rate and mediocre prevalence rates of smoking, alcohol drinking and BQC. We varied the model by taking log transformation and replacing the actual rate with the rank number, and got similar result: male oral cancer incidence in Changhua has an unusual relation with the prevalence of BQC.

Onset age of male oral cancer is decreasing in Taiwan.

Here we define the onset age of cancer as the age at which the patient was first diagnosed with oral cancer. Cancer development is a continuous process, and it is hard to pinpoint the exact time when the transformation to cancer cells occurs.

We divided the 16-year time span, from 1986 to 2001, into four quadrenniums: Q1: 1986-1989, Q2: 1990-1993, Q3: 1994-1997 and Q4: 1998-2001. Numbers of male oral cancer cases in each quadrennium are 2674, 4641, 7543 and 11903, respectively.

Figure 3 shows the trends of ASIR of male oral cancer with respect to onset age for each quadrennium. Changhua has a bimodal pattern in Q4 (Figure 3A), with the first peak at age 45-49 and the other at 55-59. In contrast, the rest counties as a whole has only one peak at age 55-59 in Q4 (Figure 3B).

Table 2 lists the male cancer incidence rate in different age-strata with respect to each quadrennium. In Q4 (1998-2001), onset age 45-49 accounted for most oral cancer cases in both Changhua (18.5%) and the rest areas (17.6%). In contrast, the peak onset age in Q1 and

Q2 was either 50-54 or 55-59. Onset of male oral cancer is shifting to a younger age in recent years.

The most common site of oral cancer is buccal in Changhua, while it is tongue in the rest counties.

When studying the anatomical site of oral cancer for each county in Taiwan, we found that Changhua stood out; the most common site of oral cancer was *buccal mucosa* in Changhua. In contrast, it was the *tongue* in the rest counties (Table 3). From 1993 to 2001, the most frequent anatomical site for male oral cancer in Changhua was *buccal*, followed by *tongue*, *hypopharynx*, *gum oropharynx*, *palate*, *lip* and *floor of mouth* in descending order (Figure 4A). In contrast, it was the *tongue*, followed by *buccal*, *hypopharynx*, *oropharynx* and *gum* in the rest counties (Figure 4B).

Discussion

As an old saying put it; we are what we eat. We (Lian and Su) set out the study with a clear goal in our mind: to study the relationship between the earth, which feeds us, and health of people, who must feed on the earth. Because of geographic location, it is quite natural for us to focus on the Changhua County. We started by finding which type of cancer is peculiar in Changhua, for the diagnosis of cancer would cause the least argument, and environmental factors are likely involved in the etiology of cancer. Based on the cancer map by Liaw et al.[13], we found that oral cancer seemed a good starting point.

Many researchers [4,10,11,14] have indicated that BQC is the most potent risk factor for oral cancer in Taiwan. Ko et al.[4] estimated the adjusted odds ratio of BQC (user to non-user) to be 6.9, smoking 4.6, and alcohol drinking 2.2. The synergistic effect of these three substances would escalate the odds ratio to 123. In Chen's study [14] in 1987, 86.2% of the 167 oral cancer cases in southern Taiwan were habitual betel quid chewers (HBQCs). In Ko et al.'s study [4] in 1995, 71% of the 107 cases were HBQCs, but only 23.5% of the 200 controls were HBQCs. In another study by Lu et al.[10] in 1996, 82.5% of the 40 cases were HBQCs, while only 23.75% of the 160 controls were HBQCs. We fitted multiple linear regression models of the male oral cancer incident rate on the correspondent prevalence rate of smoking, alcohol drinking and BQC. Our results indicate that BQC is the most important factor after the other two factors adjusted, with a p-value less than 0.01. The square of multiple correlation of

coefficient (R^2) is 0.445, meaning the three factors contribute 44.5% of the variation of oral cancer incidence rate in Taiwan.

In our regression analysis, Changhua stands out as the only outlier, identified by testing procedure with external studentized t-value [8] of 2.2. The status of being an outlier may be caused by an unusual relation between the explanatory variables (smoking, alcohol drinking and BQC) and the response variable (the cancer incidence rate), or missing of other unknown factors in the model. We found that smoking, alcohol drinking and BQC are unable to explain the excessively high incidence rate of oral cancer in Changhua, hinting that other unknown factor or factors are present locally.

Among the male cancers in Taiwan in 2001, oral cancer ranked 4th with incidence rate of 27.04 per 10^5 men per year, about half of that of the top ranked liver cancer (52.6 per 10^5 men per year). As for Changhua, oral cancer ranked 3rd (45.07), next to liver cancer (58.9) and lung cancer (46.4). Judging from the trend of annual cancer incidence rate in Changhua (data not shown here), it is very likely that oral cancer in Changhua will overtake the other two in the near future.

Based on the data from the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) Program[15], sites of oral cancer from 1985-1996 in the United States were, from top to bottom, tongue, lip, mouth floor, and other sits. The order in Taiwan in 2001 was tongue, buccal, hypopharynx, oropharynx, gum, palate, lip and mouth floor. Except for the top

ranked tongue, which is the most common site in both countries, the orders are clearly different. To make the difference more remarkable, the order in Changhua in 2001 was buccal, tongue, hypopharynx, gum, and the other sites. Buccal preponderance is peculiar for oral cancer in Changhua. Case number of oral cancer in buccal area overtook the tongue since 1993 (Figure 4). Cases of buccal cancer keep increasing in recent years. Contrary to that, case number of tongue cancer peaked in 2000 but dipped in 2001.

Further research is needed to explore the underlying cause/causes behind the excessively high incidence rate of male oral cancer here in Changhua and an unusual relation with the prevalence of BQC. A joint study group has been set up between Changhua Christian Hospital and National Changhua University of Education. We hope that this cooperation can make our work more efficacious, resulting in a better understanding of this rapid increasing malignancy with an unusual location preference and an unusual relation with known risk factors.

Appendix

I.C.D.-O-ET: International Classification of Diseases for Oncology, Field Trial Edition. These codes denote, T-140, lip; T-141, tongue; T-143, gum; T-144, floor of mouth; T-145.2, T-145.3, T-145.5, palate; T-145.0, buccal; T-145.1, T-145.4, T-145.8, T-145.9, other and unspecified parts of mouth; T-146, oropharynx; T-148, hypopharynx; T-149, other and ill-defined sites in lip, oral cavity and pharynx.

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Table 1. A) Worldwide oral cancer standardized incidence rate* in 2000.

Country	Men	Women	Country	Men	Women
Papua new Guinea	47.28	29.46	Swaziland	23.37	5.50
Sri Lanka	42.15	14.50	Croatia	22.79	3.60
Solomon Islands	37.75	24.15	India	22.40	9.31
Namibia	34.17	11.71	Pakistan	21.39	17.31
France	34.11	3.88	Brazil	18.38	4.00
Hungary	30.02	6.84	Australia	16.74	6.11
Taiwan	**26.98**	**2.85**	U.S.A	9.32	4.35
(Changhua)	**(45.07)**	**(2.4)**	Thailand	8.58	4.64
Slovakia	26.29	2.88	Hong Kong	7.40	3.09
Bangladesh	25.84	21.62	Singapore	6.24	2.23
			World	**10.25**	**4.02**

*age-standardized incidence rate (ASIR), per 10^5 men per year.

The table is abridged from Ferlay et al. [9].

Table 1. B). The ASIR* of male oral cancer in counties of Taiwan in 2001.

County	ASIR	County	ASIR	County	ASIR
Changhua	45.07	TaichungCity	28.93	Miaoli	18.00
Yunlin	41.18	Taichung	28.23	KeelungCity	17.62
Taitung	40.15	Nantou	27.28	Yilan	17.20
Chiayi	38.80	Taipei	26.40	Hsinchu	16.47
Pingtung	37.55	Hualien	26.17	TaipeiCity	14.09
Kaohsiung	36.04	TainanCity	24.10	HsinchuCity	14.02
KaohsiungCity	33.94	Tainan	21.81	Penghu	12.53
ChiayiCity	30.05	Taoyuan	19.43		
				Taiwan	**27.04**

*ASIR: age-standardized incidence rate, per 10^5 people per year.

Table 1. C) Comparison of male oral cancer incidence rate and relative risk of Changhua to other areas in Taiwan in 2001.

Region	CIR (2001)	ASIR (2001)	[7] adj. r.r. & 95%CI(2001)
Changhua	47.17	45.07	1
All other counties	27.11	25.74	1.77* (1.58-1.98)
[1]Northern Taiwan	21.95	20.90	2.08* (1.85-2.35)
[2]Mid-north of Taiwan	17.69	17.96	2.63* (2.24-3.08)
[3] Central Taiwan	31.54	31.24	1.42* (1.26-1.60)
[4] Southern Taiwan	34.30	31.58	1.52* (1.32-1.76)
[5] North-east of Taiwan	18.84	17.51	2.63* (2.08-3.32)
[6] Eastern Taiwan	35.91	31.91	1.39* (1.13-1.69)
Whole Taiwan	28.31	27.04	--

[1]Northern Taiwan: Taipei City and Taipei County, [2] mid-north of Taiwan: Taoyuan, Hsinchu and Miaoli Counties, [3] central Taiwan except Changhua: Taichung, Nantou and Yunlin Counties, [4] Southern Taiwan: Chiayi, Tainan, Kaohsiung, Pingtung and Penghu Counties, [5] North-east of Taiwan: Yilan and Keelung, [6] Eastern Taiwan: Hualien and Taitung Counties.

[7] adj. r.r.: adjusted relative risk of Changhua to rest areas in 2001, and the correspondent 95% confidence interval.

*: significant at the 1% level.

Table 2. Proportions of male cases in separate age-strata for each quadrennium.

	Quadre.	Age strata				
		40-44	45-49	50-54	55-59	60-64
Changhua	Q1	7.3%	14.6%	***19.3%***	15.6%	10.6%
	Q2	13.7%	13.7%	13.7%	**14.5%**	13.9%
	Q3	14.7%	**14.9%**	13.7%	14.1%	12.4%
	Q4	13.7%	***18.5%***	13.5%	13.3%	10.7%
Rest areas	Q1	9.5%	13.2%	14.7%	***15.6%***	12.6%
	Q2	12.3%	13.1%	**14.2%**	13.8%	12.0%
	Q3	14.1%	**14.7%**	13.1%	13.0%	11.0%
	Q4	14.3%	***17.6%***	14.6%	12.0%	9.9%

Table 3. Proportion (in %) of cancer cases from different anatomic sites.

	Buccal	Tongue	Hypop-harynx	Oropha-rynx	Lip	Gum	Palate	Floor mouth
Changhua	29.68 [a]	25.85	13.30	7.07	4.57	7.32	5.15	2.33
Rest areas	24.84	26.91	12.69	8.65	4.25	6.52	5.41	2.52

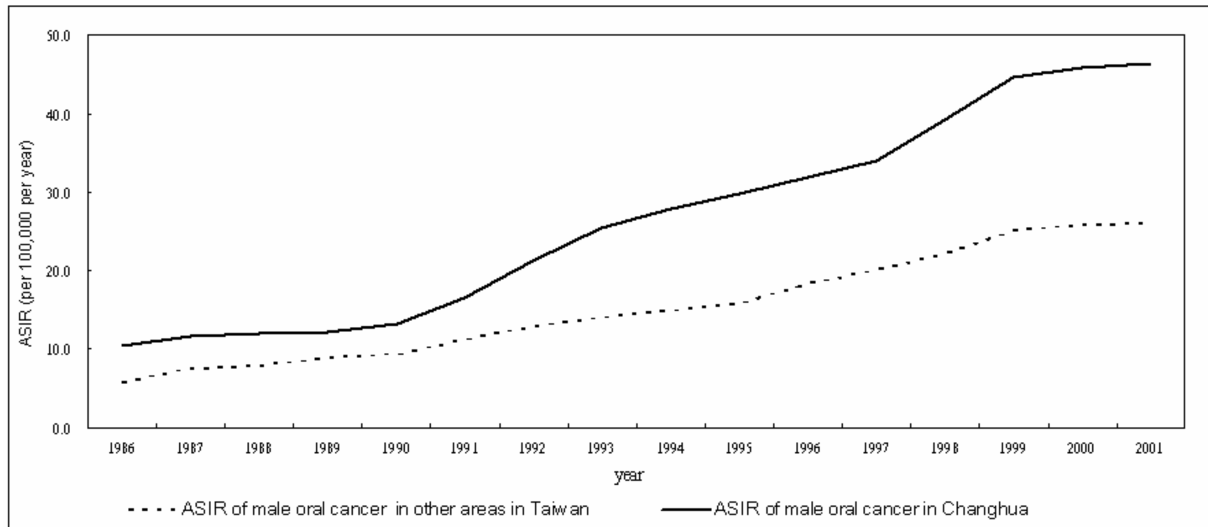


Fig.1. ASIR (age-standardized incident rate, 10^5 per men per year) of male oral cancer in Changhua vs. that in the rest areas in Taiwan from year 1986 to 2001.

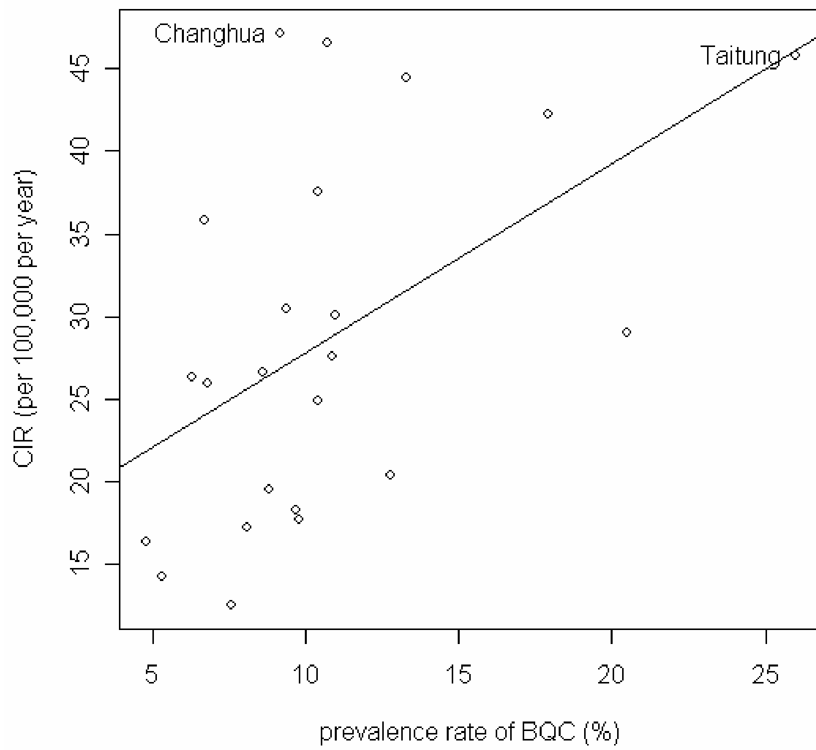


Fig.2. A) Scatter plot and regression line of crude incident rate (CIR, 10^5 per men per year) of male oral cancer vs. the prevalence rate (in %) of BQC in each county. Changhua is the county with the most deviation away from the regression line.

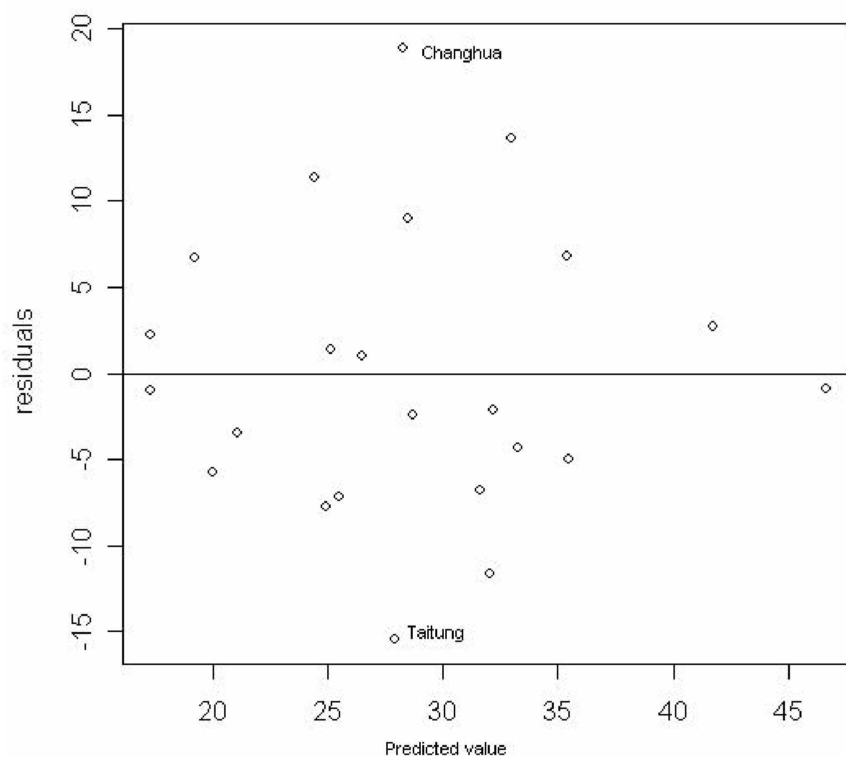


Fig.2. B) Residual plot of external studentized residual versus the fitted value from regressing incident rate on the prevalence rates of BQC, smoking and alcohol drinking. The most deviated point (Changhua) away from the zero line is the most potent outlier.

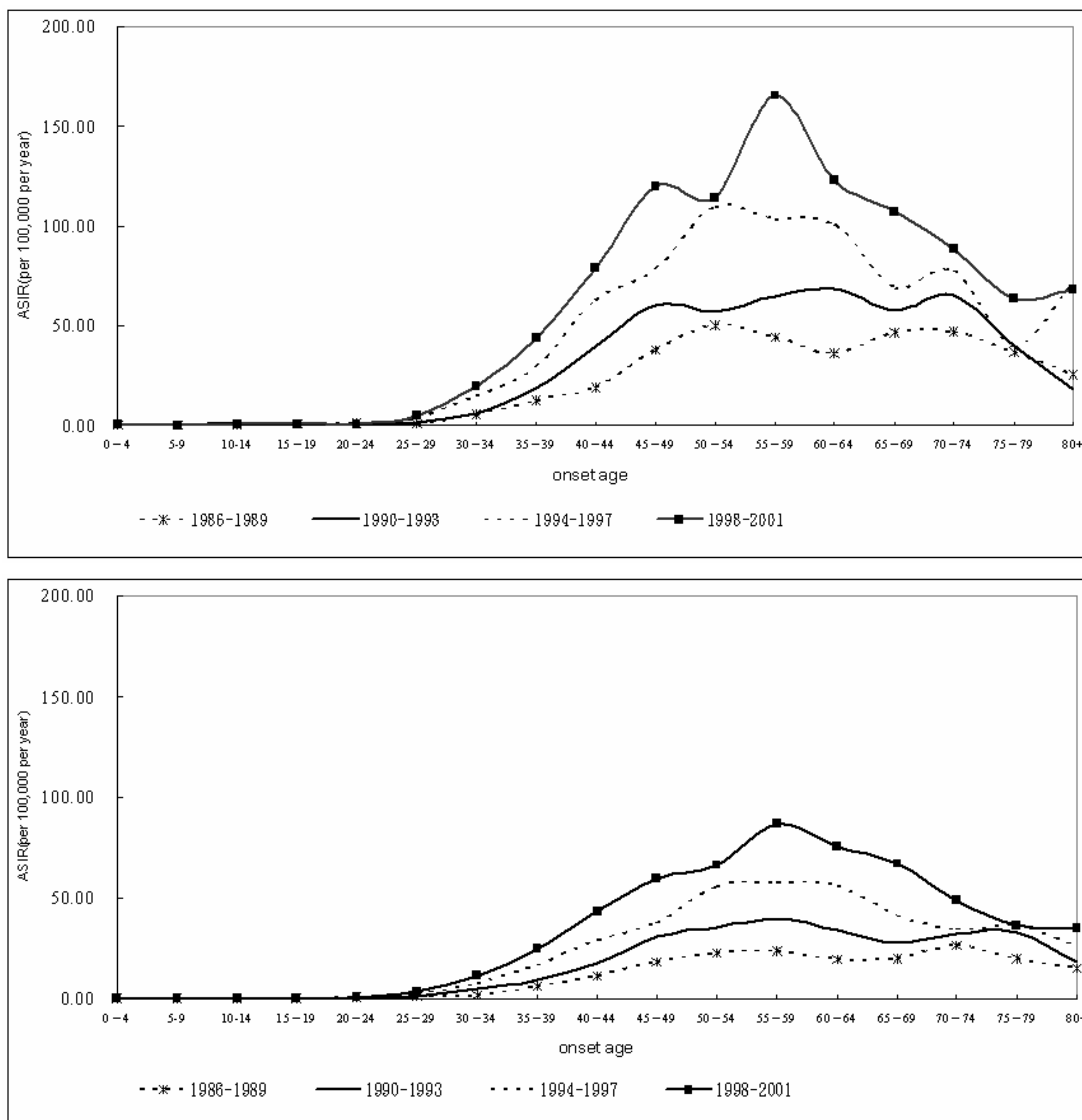
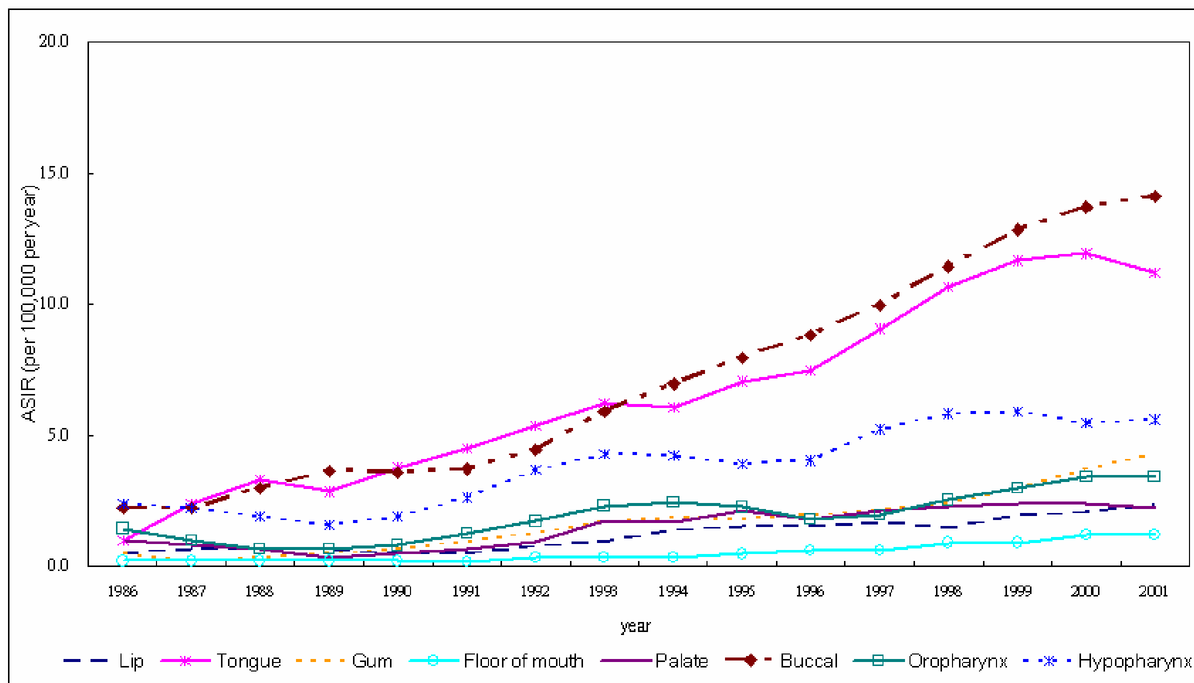


Fig.3. A,B) Trends of ASIR (10^5 per men per year) of male oral cancer with respect to onset age for each quadrennium in Changhua (A), and in the rest areas (B)



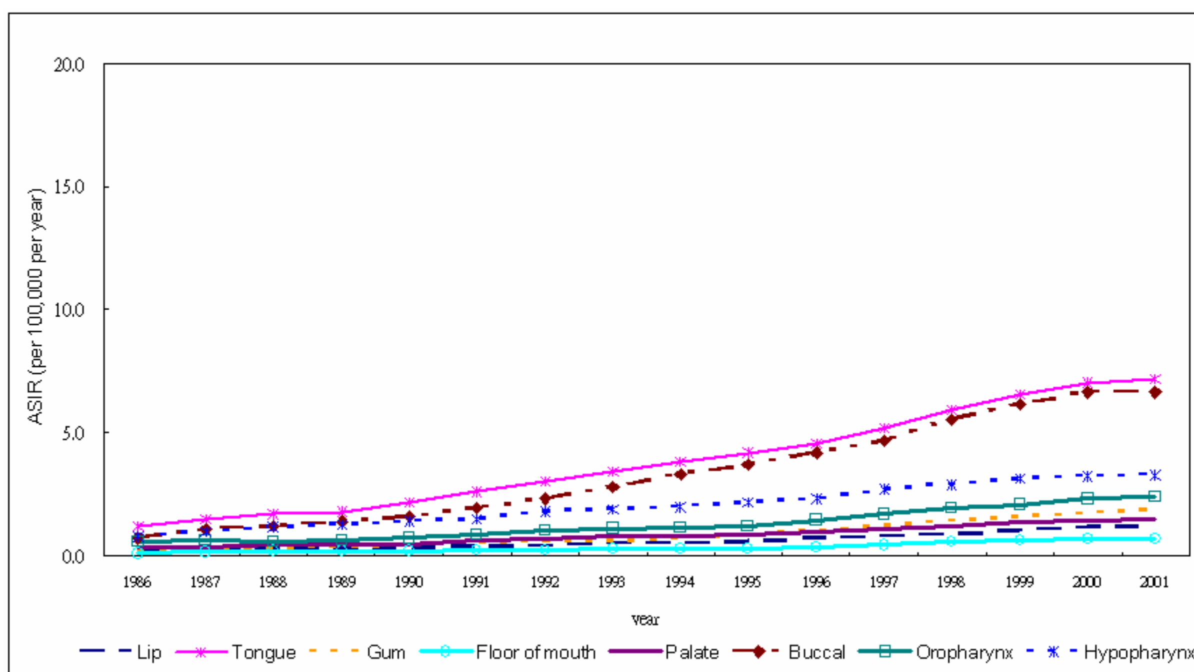


Fig.4. A,B) ASIR (10^5 per men per year) of male oral cancer in separate anatomic sites, including tongue, buccal, hypopharynx, oropharynx, gum, palate, lip and floor of mouth, in Changhua (A), and in the rest areas (B) from 1986 to 2001.

Table Headings

Table 1. A) Worldwide oral cancer standardized incidence rate* in 2000.

Table 1. B). The ASIR* of male oral cancer in counties of Taiwan in 2001.

Table 1. C) Comparison of male oral cancer incidence rate and relative risk of Changhua to other areas in Taiwan in 2001.

Table 2. Proportions of male cases in separate age-strata for each quadrennium.

Table 3. Proportion (in %) of cancer cases from different anatomic sites.

Figure Legends

Fig.1. ASIR (age-standardized incident rate, 10^5 per men per year) of male oral cancer in Changhua vs. that in the rest areas in Taiwan from year 1986 to 2001.

- - - - ASIR of male oral cancer in the rest areas in Taiwan , —— ASIR of male oral cancer in Changhua

Fig.2. A) Scatter plot and regression line of crude incident rate (CIR, 10^5 per men per year) of male oral cancer vs. the prevalence rate (in %) of BQC in each county. Changhua is the county with the most deviation away from the regression line.

B) Residual plot of external studentized residual versus the fitted value from regressing incident rate on the prevalence rates of BQC, smoking and alcohol drinking. The most deviated point (Changhua) away from the zero line is the most potent outlier.

Fig.3. A,B) Trends of ASIR (10^5 per men per year) of male oral cancer with respect to onset age for each quadrennium in Changhua (A), and in the rest areas (B)

- -✳- 1986-1989 , —— 1990-1993 , - - - - 1994-1997 , —■— 1998-2001 .

Fig.4. A,B) ASIR (10^5 per men per year) of male oral cancer in separate anatomic sites, including tongue, buccal, hypopharynx, oropharynx, gum, palate, lip and floor of mouth, in Changhua (A), and in the rest areas (B) from 1986 to 2001.

— — Lip , —✳— Tongue , - - - - Gum , —○— Floor of mouth , —— Palate , —◆- Buccal ,

—□— Oropharynx , -✳- Hypopharynx .