



Lip, oral cavity and pharyngeal cancers in the population of the city of Belgrade in the period 1999–2010

Karcinomi usana, usne duplje i ždrela kod stanovništva grada Beograda u periodu 1999–2010

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Abstract

Background/Aim. Cancers of the lip, oral cavity and pharynx (LOCP) are frequently grouped together mainly because they have similar risk factors. The incidence rate of these cancers varies worldwide depending on the geographic location. The aim of this study was to determine trends in age-standardized incidence rates of LOCP cancers in the Belgrade population during a 12-year period, from 1999 to 2010. **Methods.** From The Serbian Cancer Registry (The Registry), we extracted all cases of LOCP cancers registered in Belgrade from January 1, 1999 to December 31, 2010. Joinpoint regression analysis was used to define trends and annual percentage change (APC). **Results.** A total number of 2,025 (1,509 in men and 516 in women) LOCP cancers were reported to the Registry during the study period. The age standardized rate (ASR) for the entire period and for all LOCP cancers, was 6.24 per 100,000 persons (10.35 for men and 2.86 for women). ASR for lip cancers decreased ($p < 0.001$) during the study period with APC of -8.4%. The ASR for oral cavity and pharyngeal cancers increased ($p < 0.05$). **Conclusion.** Our results show a significantly decreasing trend of the incidence rate for lip cancers in the population of the city of Belgrade between 1999 and 2010. On the contrary, the incidence of oral cavity and pharyngeal cancers increased for both men and women.

Key words:

lip neoplasms; mouth neoplasms; pharyngeal neoplasms; incidence; risk factors; sex; age group.

Apstrakt

Uvod/Cilj. Karcinomi usana, usne duplje i ždrela često se grupišu zajedno zbog sličnih faktora rizika. Incidencija ovih karcinoma u svetu je različita i zavisi od geografske lokacije. Cilj rada bio je da se utvrdi promena incidencije karcinoma usana, usne duplje i ždrela kod stanovništva Beograda u periodu od 1999. do 2010. godine. **Metode.** Iz Registra za maligne bolesti Republike Srbije izdvojeni su svi registrovani slučajevi karcinomi usana, usne duplje i ždrela u Beogradu, od 1. januara 1999. godine do 31. decembra 2010. godine. Trend kretanja i godišnji procenat promene incidencije izračunat je regresionom analizom uz pomoć tačaka spajanja (*joinpoint regression analysis*). **Rezultati.** U periodu istraživanja ukupno je registrovano 2 025 slučajeva (1 509 kod muškaraca i 516 kod žena) karcinoma usana, usne duplje i ždrela. Standardizovana stopa incidencije za sve karcinome iznosila je 6,24 na 100 000 stanovnika godišnje (10,35 za muškarce i 2,86 za žene). Standardizovana stopa incidencije za karcinome usana se smanjenjivala tokom perioda ispitivanja sa godišnjim procentom promene od -8.4% ($p < 0.001$). Standardizovana stopa incidencije za karcinome usne duplje i ždrela povećavala se ($p < 0.05$). **Zaključak.** Naši rezultati pokazuju konstantno opadanje trenda incidencije karcinoma usana kod stanovništva grada Beograda između 1999. i 2010. godine. Sa druge strane, incidencija karcinoma usne duplje i ždrela povećavala se kod oba pola.

Ključne reči:

usna, neoplazme; usta, neoplazme; farinks, neoplazme; incidencija; faktori rizika; pol; životno doba, grupe.

Introduction

Cancers of the lip, oral cavity (OC) and pharynx (LOCP) are frequently grouped together¹ mainly because they have similar risk factors. The incidence rate of these cancers varies worldwide depending on the geographic location. The highest incidence rates of OC and pharyngeal cancers are found in south Asia, Pacific regions, Latin America and in parts of central and east Europe². Oral and pharyngeal cancers are the sixth most common cancers in the world and the seventh in European Union^{2,3}. Globally, cancers of the OC and pharynx, when viewed as a group, are the seventh most common type of carcinoma in Serbia in 2009⁴. The major risk factors for LOCP cancers are use of tobacco, excessive alcohol consumption⁵⁻⁸ and persistent infections with human papillomavirus (HPV)⁹⁻¹². Other factors such as genetics, social inequality, nutritional factors and poor oral hygiene have also been reported¹³⁻¹⁷. The literature on the incidence rate of LOCP cancers in Serbia is scarce. In fact, to our knowledge, there is no published data that described the incidence rate of these cancers in Serbia. Registry-based studies are important because they provide valuable information for health policies planning and prevention in this growing health burden.

The aim of this study was to present and analyze trends in age-standardized incidence rates (ASR) of LOCP cancers in the Belgrade population during a 12-year period (1999–2010).

Methods

Type of study, data sources and study population

This retrospective descriptive epidemiological study gives the incidence rate of LOCP cancer during a 12-year study period.

Data were obtained from the Serbian Cancer Registry (The Registry), which covers the complete population of Serbia, excluding Kosovo. The Registry was established in 1970, but in the period from 1986 to 1998, the quality of data collection was rather scarce. After 1998, a new methodology was applied which substantially improved data quality and the Registry became a member of International Agency for Research on Cancer (IACR) and European Network of Cancer Registries (ENCR). Sources of data collection for the Registry are hospitals and out-patient's health institutions, oncology clinics, as well as dispensaries and institutes, pathology laboratories, death reports and health insurance funds. Cancer reporting is obligatory by law in Serbia and information on all potential new cases must be reported to the Registry. Our study was conducted in the city of Belgrade, which had a population of 1,568,754 persons in 1999 and 1,639,505 in 2010. Information on the Belgrade population size and migration in the past was obtained from the Statistical Office of the Republic of Serbia.

Coding and analysis

From The Registry, we extracted all cases of LOCP cancers registered in Belgrade from January 1, 1999 to December 31, 2010 according to the International Classification of Dis-

eases Tenth revision (ICD-10)¹. These cancers included: lip (ICD-10: C00), tongue (ICD-10: C01-C02), gum (ICD-10: C03), floor of the mouth (ICD-10: C04), palate (ICD-10: C05), cheek mucosa and other part of mouth (ICD-10: C06), tonsil (ICD-10: C09), oropharynx (ICD-10: C10), pyriform sinus (ICD-10: C12), hypopharynx (ICD-10: C13) and other ill-defined part of the lip, mouth and pharynx (ICD-10: C14). Cancers of nasopharynx (ICD-10: C11), nasal cavity (ICD-10: C30.0), skin of lip (ICD-10: C44.0) were excluded from this study. Tumors are grouped as lip cancers (ICD-10: C00), OC cancers (ICD-10: C01-C06) and pharyngeal cancers (ICD-10: C09-C10, C12-C14). We used the term "lip, oral cavity and pharyngeal cancers" to encompass all tumors. Tumors were classified according to the International Classifications of Diseases of Oncology, 3rd Edition (ICDO-3)¹⁸. Morphology codes for the selected cases included: 8000, 8010, 8020-1, 8032-3, 8050-2, 8070-6 and 8084. Only invasive cancers were included in the study (*ie* containing "3" as the last digit in the morphology code).

For the purpose to avoid the effect of differences in population age structures and to allow comparison between our data and data from other areas we used the direct standardization method to the world standard population¹⁹. Firstly, we aggregated all new cases from the Registry per age group and divided these with the age-stratified population estimate for every year. After estimating age-specific rates, we applied these rates to the reference population – the world standard population. ASR were reported as the incidence *per* 100,000 persons yearly.

All patients were classified in five age groups: below 39, 40–49, 50–59, 60–69 and over 70 years of age. Trends and annual percentage change (APC) of the incidence rate with corresponding 95% confidence intervals (CI) were calculated by performing joinpoint regression analyses to identify the years in which a significant change in incidence rates occurred. For regression analyses, we used Joinpoint Regression Program version 4.1.0 (available at <http://surveillance.cancer.gov/joinpoint>). The trend was considered to be significant increasing (positive change) or decreasing (negative change) when the *p*-value was below 0.05 ($p < 0.05$).

Results

A total number of 2,025 cases (1,509 in men and 516 in women) of LOCP cancers that fulfilled the criteria were reported to the Registry during the study period. In the same period, the Registry recorded 99,668 cases of all types of carcinoma (ICD-10: C00-C96), 50,575 in men and 49,093 in women. LOCP cancers comprised about 2.03% of all carcinomas recorded in population the Belgrade (2.98% in men and 1.05% in women). Table 1 presents distribution of all LOCP cancers in Belgrade, according to the site of the tumor, age and gender of the patients. The men represented 74.5% of all the persons and the women 25.5%. The men to women ratio was 2.9 : 1. The most common site in men and women was the OC cancers. Most cases were aged 40–69 (58.3%) and less than 4% below the age of 39.

A complete ASR (to the world standard population) of all cases according to gender and years of observation were shown in Table 2. ASR for the entire study period and for all

LOCP cancers, were 6.24 *per* 100,000 persons (10.35 for the men and 2.86 for the women). In the men ASR for LOCP cancers increased from 10.26 in 1999 to 13.40 *per* 100,000 persons in 2010 (APC, 0.9%; 95% CI: -3.1, 5) and in the women ASR remained almost stable (APC, -0.4%; 95% CI: -3.6, 2.9). Joint-

point regression analysis showed the decrease trend of ASR for LOCP cancers, for both gender combined, in the time period 1999–2007 with APC of -3.6% (95% CI: -7.9, 0.9) and increase trend in the last three years of the study period (APC, 17.7%; 95% CI: -4.6, 45.3) (Figure 1).

Table 1

Distribution of lip, oral cavity and pharyngeal cancer in Belgrade by gender and age, 1999–2010

Parameter	Primary site of cancer, n (%)			Total
	Lip	Oral cavity	Pharynx	
Gender				
men	280 (75.9)	692 (71.8)	537 (77.6)	1509 (74.5)
women	89 (21.1)	272 (28.2)	155 (22.4)	516 (25.5)
Age group (years)				
≤ 39	1 (0.3)	57 (5.9)	18 (2.6)	76 (3.7)
40–49	26 (7.1)	123 (12.8)	90 (13.0)	239 (11.8)
50–59	68 (18.4)	294 (30.5)	207 (29.9)	569 (28.1)
60–69	122 (33.0)	266 (27.6)	223 (32.2)	611 (30.2)
≥ 70	152 (41.2)	224 (23.2)	154 (22.3)	530 (26.2)
Total	369 (100)	964 (100)	692 (100)	2025 (100)

Table 2

Age-standardized incidence rate (*per* 100,000 person) of lip, oral cavity and pharyngeal cancers by sex and year of diagnosis

Year of diagnosis	Men		Women		Overall	
	WASR	(95 % CI)	WASR	(95 % CI)	WASR	(95 % CI)
1999	10.26	8.44–12.07	3.00	2.11–3.88	6.33	5.37–7.29
2000	11.33	9.41–13.25	2.92	2.06–3.78	6.75	5.76–7.74
2001	11.46	9.54–13.38	3.75	2.73–4.76	7.27	6.23–8.30
2002	11.90	9.94–13.87	2.19	1.47–2.92	6.64	5.66–7.62
2003	7.17	5.66–8.67	3.19	2.28–4.11	4.97	4.13–5.81
2004	8.43	6.78–10.07	2.38	1.56–3.21	5.12	4.25–5.99
2005	8.54	6.88–10.20	3.33	2.36–4.30	5.68	4.76–6.60
2006	9.38	7.66–11.09	2.32	1.56–3.07	5.48	4.74–5.17
2007	8.60	7.00–10.19	2.46	1.65–3.26	5.17	4.34–6.01
2008	8.97	7.32–10.62	2.67	1.87–3.48	5.48	4.62–6.34
2009	14.17	12.04–16.29	3.30	2.38–4.23	8.21	7.12–9.29
2010	13.40	11.40–15.40	3.04	2.23–3.85	7.68	6.68–8.68
All years	10.35	9.83–10.87	2.86	2.61–3.10	6.24	5.97–6.51
APC*	0.9%, -3.1% to 5%		-0.4%, -3.6% to 2.9%		0.4%, -2.9 to 3.8%	

*Annual percentage change and 99% confidence interval; WASR – world age standardized rate; CI – confidence interval.

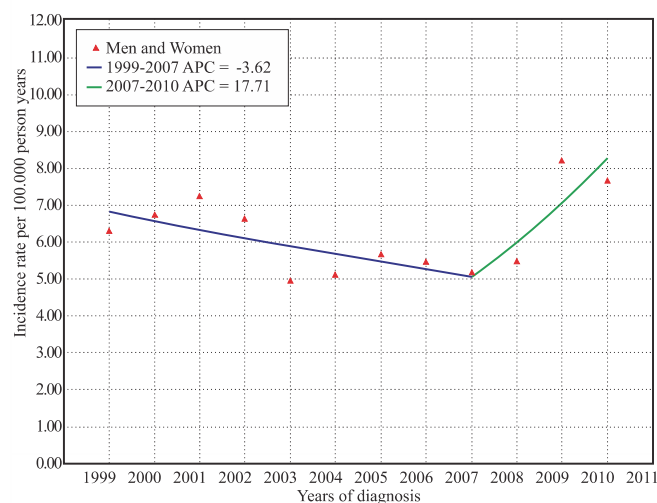


Fig. 1 – Joinpoint analyses of age standardized incidence rates (world standard population) of lip, oral cavity and pharyngeal cancer in Belgrade, 1999–2010, with annual percentage change (APC).

Considering lip cancers (ICD-10: C00) separately, there was a significantly decreasing trend ($p < 0.001$) of ASR, for both gender combined, throughout the whole study period (1999–2010) with APC of -8.4% (95% CI: -11.4, -5.3). In the males, ASR for lip cancer significantly decreased ($p < 0.001$) from 2.77 in 1999 to 1.27 *per* 100,000 persons in 2010 (APC, -7.7%; 95% CI: -10.2, 5.2) and in the females from 0.82 in 1999 to 0.30 in 2010 (APC -9.7%, 95% CI: -17.7, -1; $p < 0.05$) (Figure 2).

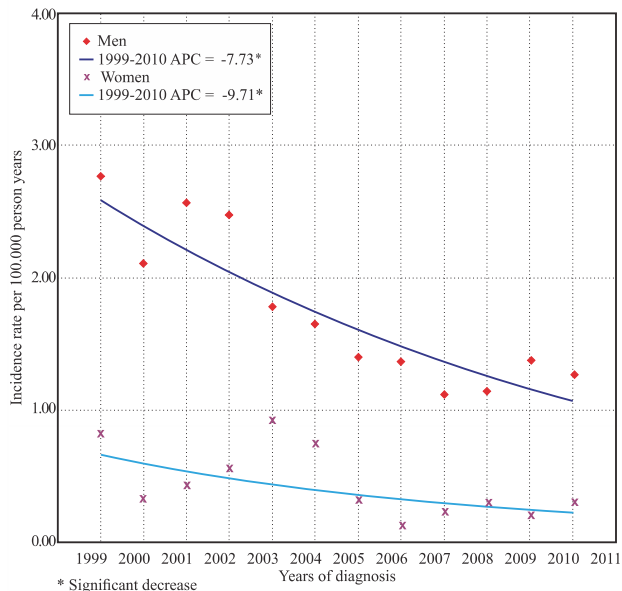


Fig. 2 – Jointpoint analyses of age standardized incidence rates (world standard population) of lip cancer in Belgrade, 1999–2010, with annual percentage change (APC).

When OC cancers (C01-C06) are considered separately there was almost a double increase of ASR in the men from 3.75 (95% CI: 2.64, 4.86) in 1999 to 7.23 (95% CI: 3.63, 6.06) *per* 100,000 persons in 2010 and in the women from 1.56 (95% CI: 2.64, 4.86) in 1999 to 1.62 (95% CI: 3.63, 6.06) in 2010. Jointpoint regression analysis showed that ASR for OC cancers increased significantly ($p < 0.05$) from 2004 to 2010 in the men (APC, 14.7%; 95% CI: -21.6, 29.9) and non-significant increase in the women from 2007 to 2010 (APC, 16.9%; 95% CI: -21.6, 29.9) (Figure 3).

When pharyngeal cancers (ICD-10: C09-C10, C12-C14) are considered separately from the other cancers there was a significantly increased trend ($p < 0.05$) of ASR in the period 2003–2010 with APC of 5.7% (95% CI: 0.5, 11.2). In the men, a low increase of ASR for pharyngeal cancers was observed from 1999–2010 (APC, 0.4%; 95% CI: -4.1, 5) while in the women the increase was significant ($p < 0.05$) with APC of 5.7% (95% CI: 0.2, 11.4) from 0.62 in 1999 to 1.12 in 2010 (Figure 4).

Discussion

LOCP were not common in our study before the age of 40 years (4% of all the cases) and more than half of the patients were between 40 and 69 years. During a 12-year study

period, there was no sign of the increasing percentage of LOCP cancer cases in men or women under the age 40 years. This finding is mainly in accordance with the literature^{20–22} although recent reports suggest the increased number of young patients^{23,24}. The literature from the most countries around the world presents at least about twice higher level of oral cancer in men than in women as we found in our study^{11,12,25,26}. This observation points to the fact that age and sex should be considered as one of the risk factors of developing LOCP cancers.

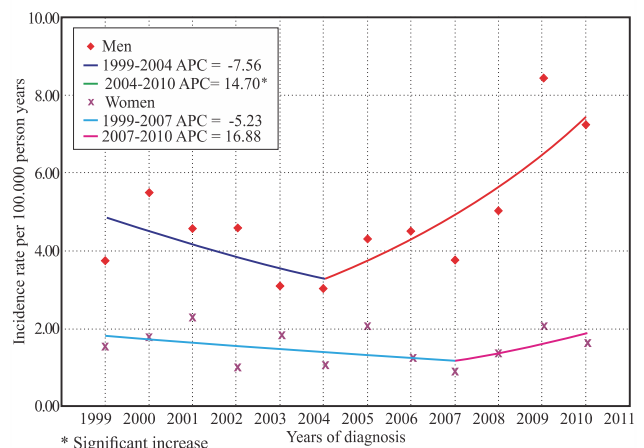


Fig. 3 – Jointpoint analyses of age standardized incidence rates (world standard population) of oral cancer in Belgrade, 1999–2010, with annual percentage change (APC).

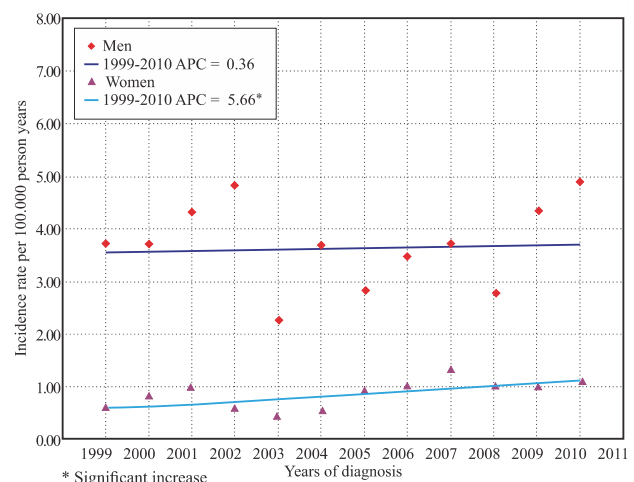


Fig. 4 – Jointpoint analyses of age standardized incidence rates (world standard population) of pharyngeal cancer in Belgrade, 1999–2010, with annual percentage change (APC).

We have shown a decline in the incidence rate for LOCP cancers, taken together, in most of the time of the study period. The main impact on this decrease had a significantly decreasing trend for lip cancers. The decreasing incidence rate of lip cancer has also been reported from Denmark¹², Portugal²⁷, Finland²⁸, Israel²⁵, and Australia²⁶. Blomberg et al.¹² (2010) reported a significant decrease trend in age-standardized incidence rate in Danish male population from 3.36 in 1978 to 0.83 in 2007 and with APC of -5%.

Declines in lip cancers incidence rate may be attributed to a decrease in the number of smokers in Belgrade population. In Serbia, after 1999, several preventive and promotional anti-smoking activities have been initiated. The committee for Smoking Prevention was set up, World Health Organization (WHO) Framework Convention on Tobacco Control was signed and ratified, Tobacco Control Office was established and Tobacco Control Strategy for the Republic of Serbia was adopted²⁹. The Ministry of the Health of Republic of Serbia in National Health Survey appraised reduction in smoking rate in Serbia by 6.9% after the year 2000³⁰. Tobacco smoking is a well-recognized risk factor of developing lip cancer⁵⁻⁷. Another cause of decreasing trend of lip cancer may be due to changes in the perception of patients for this, in contrast to oral and pharyngeal cancers, highly visible malignancy. This awareness could lead to increasing the removal lesion in the early stadium of the tumors (*eg carcinoma in situ*). In our study, only invasive cancers were included, which containing “/3” as the last digit of the morphology code.

In contrast to lip cancer ASR for carcinoma of the OC has doubled between 1999 and 2010 in Belgrade population. We observed a significantly increasing trend for OC cancers among men from 2004 to 2010 (APC, 14.7%, $p < 0.05$) and rapid, but not significant among women after the year 2007. Increasing trends of pharyngeal cancers were also showed from 1999 to 2010 (APC, 5.7%, $p < 0.05$). Our results confirm the rising incidence trends for oral and pharyngeal cancers reported in some European countries, such as Denmark¹², Norway³¹, United Kingdom²⁰, Netherland²¹, Portugal²⁷ and Germany³². Hwang et al.³³ (Canada) recently reported the increasing incidence rate of pharyngeal and oral cancers during the time period 1992–2007 with the highest incidence rate in Nova Scotia. Increasing incidence trends of OC and pharyngeal cancers in our study along with decreasing incidence trends of lip cancers and reduction in tobacco smoking rate suggests that different or additional etiological factors are involved in the development of OC and pharyngeal cancers. The major risk factors for cancers of the OC are tobacco use, excessive consumption of alcohol and infections with HPV^{11, 12, 21, 34}. These factors could act separately or synergistically, together^{8, 35}. The APC values of the incidence rate of OC cancer in our study are higher than those observed in the abovementioned developed western countries^{12, 21, 27, 31}. These observed divergence in values of the incidence rates of OC cancer are most likely related to socioeconomic and demographic factors. Many studies show links between oral cancer incidence and socioeconomic status^{14-16, 36}. Auluck et al.¹³ (British Columbia, Canada) reported that socioeconomic status could be responsible for the increasing incidence trends of pharyngeal and oral cancers. In their study, the highest incidence rates in men, for both pharyngeal and oral cancers were observed in neighborhoods with the most deprived socioeconomic status. Most of the people in Serbia lack sufficient money to live at a standard consid-

ered comfortable or normal as in the above-mentioned developed countries. In such poor environments people are more prone to consume alcohol or smoke cigarettes to cope with difficulties or to avoid bad feeling. Although Serbia reduced the number of smokers after the year of 2000 still almost 40% of the male population and 30% of the female population are smokers³⁰. According to WHO reports, consumption of alcohol *per capita* in Serbia, in the age older than 15 years, changed from 9.2 liters in 2003–2005 to 12.6 in 2008–2010³⁷. The same report shows 6.8 times higher prevalence of heavy episodic drinking in male than in female population. The changing pattern of alcohol consumption in Serbia and higher prevalence of heavy male drinkers along with a large percentage of male smokers are likely to be reasons for sex differences in the observed incidence rate of OC cancers in the population of Belgrade. Another possible explanation for the increased incidence rate is HPV infection as a consequence of changing sexual habits over the past years. Numerous authors agree that the increasing number of lifetime sexual partners and increasing numbers of oral sex partners are important risk factors for HPV infection and oral and pharyngeal carcinoma^{9, 10, 21}. Hemminki et al.³⁸ showed a high incidence rate of tonsil and tongue cancers among husbands of cervical cancer patients.

To our knowledge, this study is the first registry-based study in Serbia that analyzed trends of LOCP cancers in more than one and a half million population, covered a long period (12 years). Our study has limitations similar to other registry-based studies. The Serbian Cancer Registry does not record risk behaviors such as smoking or alcohol consumption. Data on smoking and alcohol consumption presented in this paper are related to the whole country but not just to the population of Belgrade. The quality of the observed incidence rates may be influenced by the incompleteness of registration in the first years of the study period, but we believe such influences were small.

Conclusion

Our results show a significantly decreasing trend of the incidence rate for lip cancers in the population of the city of Belgrade between 1999 and 2010. On the contrary, the incidence rate of oral cavity and pharyngeal cancers considerably increased in both men and women. The increase in the incidence rate of oral cavity carcinoma in our study is greater than in some developed countries. By these findings, we would like to highlight the problem of a continuously increasing incidence rate of oral cavity and pharyngeal cancers to the health authority. Given the trend in recent years it will be an undoubted increase in the future since Serbia has no program for early detection of premalignant or malignant oral lesions. In face of these facts, serious national research, education and prevention program should be taken to ensure the reduction of this type of cancer in the future.

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