

Squamous cell carcinoma of the tongue in patients older than 45 years

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Abstract: This study aims to evaluate the clinicopathological features, TNM status, AJCC staging and behavior of squamous cell carcinoma of the tongue (SCCT) in patients older than 45 years. The files of the Department of Pathology of the Hospital General de México were reviewed and all cases of SCCT in patients older than 45 years were selected. Clinicopathological features, treatment, follow-up, microscopic diagnosis, and IJCC and TNM staging were retrieved. Complete data from 60 cases were evaluated. They were more common in males (mean age = 63.9 years). Unexpectedly a high rate of tumors (38.3%) were in the base of the tongue (BT). Moderately and poorly differentiated SCCT were the most common. 16.7% presented lymph node invasion, 15% were recurrent tumors and BT carcinomas recurred more frequently. A high rate (81.7%) were stage II and 48.3% were low-risk patients. SCCTs in the studied population displayed different clinico-pathological and behavioral features compared with worldwide data. Our results suggest that BT tumors should be treated more aggressively than those in the mobile tongue. BT located tumors were more frequent than previously published. Additional frequency studies will define outcomes in age cohorts with a consensus cut-off for young and elderly populations. More population-based studies should be performed in Latin American regions to acquire accurate data on SCC incidence in elder subpopulations and to identify precisely the etiological factors in these patients.

Keywords: Carcinoma, Squamous Cell; Tongue.

Introduction

Squamous cell carcinoma (SCC) is the most common oral malignant neoplasm accounting for more than 90% of oral cancers.¹ For clinical purposes, the tongue is divided in two parts, the oral portion or mobile tongue (MT) and the base of the tongue (BT), that is anatomically considered part of the oropharynx. The most frequent BTSCC is the HPV-positive type and it is clinically, epidemiologically and microscopically a distinct form of the common head and neck SCC. It is frequently associated to HPV-16, is more common in males and the more commonly associated risk factors are the oral sex and the concomitant HPV infection.² HPV-negative SCC usually affects older patients and the more frequently associated risk factors are alcohol and tobacco.³ Both types of SCC have different



prognosis and it is well known that the HPV-positive type of SCC behaves better than the HPV-negative type.² In contrast MTSCCs are more frequently of the conventional type and the main risk factors are alcohol, tobacco and betel use and abuse.¹

Some reports showed better outcome in young patients, but others reported it was associated to a significant decrease in the survival rate.^{4,5,6}

Frequency of SCCT in Mexico has received little attention and data is scarce ranging its frequency from 22.9% to 59%^{7,8,9,10,11,12} and HPV association with oral SCC in Mexican population was not extensively studied.^{9,10,11} In these studies, it was concluded that HPV infection is present in more than 40% of oral SCC and that HPV-16 infects more than 55% of these cases.^{9,11} Interestingly, it was reported that using PCR amplification, HPV infection was 43.5%.¹⁰ To date, no detailed study on frequency, clinicopathological features and behavior of SCCT in 45 and older patients has been published.

The aims of the present study were to evaluate the clinicopathological features, TNM status, AJCC staging and behavior of tongue SCC in patients older than 45 years.

Methodology

A retrospective review of the archives from the Department of Pathology of the Hospital General de Mexico, in Mexico City, from 2001 to 2017 was performed after obtaining Institutional Research and Ethics Board approval. Demographic and clinical data, such as age, gender, location, treatment, microscopic features and degree of differentiation of the selected cases were retrieved. The SCC degree of differentiation was classified in well differentiated (WDSCC), moderately differentiated (MDSCC), poorly differentiated (PDSCC) or carcinoma in situ (CIS). TNM status were according to the WHO guidelines,¹³ and staging of the tumors was done according to the American Joint Committee on Cancer Classification.¹⁴ Also, data on BT and MT location of the SCCs were analyzed. Student T test was used and $p < 0.05$ was considered statistically significant. The SPSS 13.0 software (IBM, Chicago, Ill) was used for analysis. Data on drinking alcohol,

tobacco smoking, treatment and recurrence were also recorded.

Results

There were 470 cases of intraoral SCC. Of them, 284 were in tongue (60.4%) and 60 cases (21.1%) of SCC arising in tongue were found (Table 1). They were more common in males than in females (53.3% and 46.7% respectively; M:F rate 1.14:1) and this difference was statistically significant ($p < 0.03$). Ages of the patients were between 46 and 82 years with a mean age of 63.9 years (SD \pm 9.8 years). The degree of differentiation of the analyzed cases varied from poorly to moderately to well-differentiated SCC, and cases of carcinoma in situ (CIS) were also considered. It was a surprise to find that the most common was the MDSCC type (56.7%), followed by PDSCC (23.3%) and the less common were both WDSCC and CIS (10% respectively).

From the 60 analyzed cases, 61.7% were in the MT and unexpectedly, a high rate of SCCs (38.3%) were located in BT. This difference was statistically significant ($p < 0.01$). From these patients, 23 were drinkers (35%), 27 smoked cigarettes (45%), 19 patients did both (31.7%) and 29 of them were non-drinkers and non-smokers (48.3%). Our study included 10 cases with lymph node metastasis (16.7%) and nine cases (15%) presented recurrence from 24 to 120 months after surgical resection (mean= 89 months). Follow-up varied from 8 to 192 months (mean= 51 months). According to data in Table 2 on TNM and AJCC staging most cases were T2 (78.3%), followed by T4 (16.7%). Of them, the most common AJCC stage was stage II (81.7%) and 17% were in stage IVa. Treatment of the tumors varied from wide excision to hemiglossectomy. From 33 patients treated by wide excision only two of them recurred 36 and 46 months post-treatment. Hemiglossectomy was performed in 17 tumors graded T2 and two of them recurred (24, and 192 months after first excision). All 10 tumors with nodal involvement (16.7%) were treated with hemiglossectomy and radical neck dissection and of them, five cases (50%) were recurrent tumors. All of them were T4 tumors. Interestingly, 66.7% of the T3, 30% of the T4, and 2.4% of the T2 analyzed cases were

Table 1. Data from patients 45 years and older with SCC of the tongue.

Age (n)	Mean age (years)	Males (%)	Females (%)	Location			Degree of differentiation			Recurrences (%)
				BT (%)	MT (%)	WD (%)	MD (%)	PD (%)	CIS (%)	
46–50 (7)	48.1	7 (11.7)	0	3 (5)	4 (6.7)	1 (1.7)	3 (5)	1 (1.7)	2 (3.3)	1 (1.7)
51–55 (4)	54.2	0	4 (6.7)	1 (1.7)	3 (5)	0	2 (3.3)	2 (3.3)	0	0
56–60 (15)	57.9	11 (18.3)	4 (6.7)	4 (6.7)	11 (18.3)	1 (1.7)	11 (18.3)	1 (1.7)	2 (3.3)	0
61–65 (10)	62.9	3 (5)	7 (11.7)	5 (8.3)	5 (8.3)	0	6 (10)	3 (5)	1 (1.7)	3 (5)
66–70 (7)	68.6	7 (11.7)	0	2 (3.3)	5 (8.3)	1 (1.7)	4 (6.7)	2 (3.3)	0	1 (1.7)
70–75(8)	73.6	0	8 (13.3)	5 (6.7)	3 (6.7)	3 (5)	5 (8.3)	0	0	2 (3.3)
76–80 (7)	79	2 (3.3)	5 (11.7)	3 (5)	4 (6.7)	0	3 (5)	4 (6.7)	0	1 (1.7)
80 > (2)	82	2 (3.3)	0	0	2 (3.3)	0	0	1 (1.7)	1 (1.7)	1 (1.7)
Total (60)	63.9	32 (53.3)	28 (46.7)	23 (38.3)	37 (61.7)	6 (10)	34 (56.7)	14 (23.3)	6 (10)	9 (15)

SCC: Squamous cell carcinoma; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; CIS: Carcinoma in situ; BT: Base of the tongue; MT: Mobile tongue.

recurrent tumors and four of the nine recurrences (44.4%) occurred in low-risk patients (non-drinkers non-smokers). BTSCCs recurred more frequently than MTSCCs (21.7% and 8.1% respectively).

61.7% of the whole sample were MTs. As it is in Table 3, they were more common in males (67.6%) than in female patients (32.4%). This difference was statistically significant ($p < 0.02$). Age of the patients was between 46 and 82 years with a mean age of 63.6 years. Most of the analyzed MT cases were MDSCCs (59.4%), followed by PDSCCs (21.6%) CIS (10.8%) and WDSCCs (8.1%) were the less common type. Most tumors were T2N0M0 (89.2%). Four were recurrent cases (10.8%) at 12, 24 and 36 months post resection. Two hemiglossectomies in T4 tumors and two wide

resections in one T2 and one T3 neoplasia were performed. 34 cases were stage II and three were stage IV. 31 tumors were treated by wide resection with two recurrences at 12 months, three were treated by hemiglossectomy without recurrence and three recurrent cases with nodal involvement were treated with hemiglossectomy and radical neck dissection. Four of the nine recurrences (44.4%) occurred in low-risk patients (non-drinkers non-smokers).

38.3% of the whole sample were BTSCCs. Table 4 shows they were more common in females (65.2%) than in male patients (34.8%). This difference was statistically significant ($p < 0.02$). Patients were between 48 and 80 years with a mean age of 64.6 years (SD \pm 10.1 years). Most of the analyzed MT cases

Table 2. Status of the analyzed tumors at diagnosis.

System	Whole sample	Well differentiated	Moderately differentiated	Poorly differentiated	Carcinoma in situ
TNM					
T2N0M0	47	5	26	13	3
T3N0M0	2	0	0	0	2
T3N2bM0	1	0	1	0	0
T4aN0M0	3	0	2	0	1
T4dN2bM0	7	1	5	1	0
AJCC*					
II	48	5	27	13	3
III	3	0	1	0	2
IVa	9	1	6	1	1

*American Joint Committee on Cancer Classification.

Table 3. Data on MTSCC in patients older than 45 years.

Age (n)	Male (%)	Female (%)	Degree of differentiation				Recurrences (%)
			WD (%)	MD (%)	PD (%)	CIS (%)	
46–50 (4)	4 (10.8)	0	0	2 (5.4)	0	2 (5.4)	1 (2.7)
51–60 (14)	9 (24.3)	5 (13.5)	1 (2.7)	9 (24.3)	3 (8.1)	1 (2.7)	0
61–70 (10)	9 (24.3)	1 (2.7)	0	7 (18.9)	3 (8.1)	0	0
71–80 (7)	1 (2.7)	6 (16.2)	2 (5.4)	4 (10.8)	1 (2.7)	0	2 (5.4)
81+ (2)	2 (5.4)	0	0	0	1 (2.7)	1 (2.7)	1 (2.7)
Total (37)	25 (67.6%)	12 (32.4%)	3 (8.1)	22 (59.4)	8 (21.6)	4 (10.8)	4 (10.8)

MTSCC: Mobile tongue squamous cell carcinoma; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; CIS: Carcinoma in situ.

were MDSCC (52.2%), followed by PDSCCs (26.1%) and 13% were of the WDSCC type. Most tumors were T2N0M0 (65.2%), followed by T4dN2bM0 (17.4%). Five were recurrent cases (17.4%) from 24 to 192 months post initial resection and 30.4% of the patients presented cervical node invasion. 21 hemiglossectomies (seven of them with radical node resection) were made. Most of the cases (65.2%) were stage II and 26.1% were stage IVa. Of the high-risk patients, 14 were smokers, 8 were drinkers and smokers and additionally, 39% were in the low risk group (non-smokers non-drinkers). All recurrences were in smokers.

The WDSCC group was 10% of the whole sample, there were 3 males and 3 females (50% respectively), with ages were between 49 and 72 years and a mean of 65.7 years (SD±9.7 years). Three cases were in BT and three were MTSCCs (50% respectively). One case presented node involvement. Three tumors were treated with hemiglossectomy (one with neck dissection) and wide excision was done in three cases (50% respectively). One recurrence was observed. Five (83.3%) were T2N0M0-stage II tumors and one was a T4dN2bM0-stage IVa neoplasms. Three patients

were drinkers and smokers and other three were non-drinkers non-smokers (50% respectively).

The MDSCC group was the most numerous set of tumors, comprised 56.7% of the sample and was composed by 17 males and 17 females (50% respectively). Their ages were between 46 and 79 years (mean = 63.1 years; SD ± 8.9 years). Unexpectedly 35.3% of these SCCs were in BT and MTSCCs were 64.7%. Of the studied neoplasia, 79.4% were T2N0M0 and 11.8% were T4dN2bM0. 11.8% were recurrent tumors (three BTSCCs and one MTSCC), recurring from 12 to 36 months after first resection (mean = 21 months). 20.6% of the patients behaved nodal involvement (five BTSCCs and two MTSCCs). This difference was statistically significant ($p < 0.01$). 76.5% of the cases were stage II and 20.6% were in stage IVa. Of them, 47.1% were treated by hemiglossectomy and half of them included neck dissection. 52.9% of the patients were treated by wide surgical excision (all were with MT tumors). Of the high-risk patients ($n = 16$; 47.1%); 13 were drinkers and 14 were smokers. Of them, 11 were both, drinkers and smokers. Low risk affected patients (non-drinkers non-smokers) were 52.9%.

Table 4. Data on BTSCC in patients older than 45 years.

Age (n)	Male (%)	Female (%)	Degree of differentiation				Recurrences (%)
			WD (%)	MD (%)	PD (%)	CIS (%)	
46–50 (3)	3(13)	0	1(4.3)	1(4.3)	1(4.3)	0	0
51–60 (5)	2(8.7)	3(13)	0	4(17.4)	0	1(4.3)	0
61–70 (7)	2(8.7)	5(21.7)	1(4.3)	3(13)	2(8.7)	1(4.3)	4(17.4)
71–80 (8)	1(4.3)	7(30.4)	1(4.3)	4(17.4)	3(13)	0	1(4.3)
Total (23)	8(34.8)	15	3(13)	12(52.2)	6(26.1)	2(8.7)	5(21.7)

BTSCC: Base of the tongue squamous cell carcinoma; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; CIS: Carcinoma in situ.

14 patients composed the PDSCC group (41.2%), there were 8 males (57.1%) and 6 females (42.9%). This difference was statistically significant ($p < 0.05$). Their ages were between 49 and 82 years and the mean age was 67.3 years (SD \pm 11.2 years). As it was in the MDSCCs group, an unexpectedly high rate of patients harbored BTSCCs (42.8%), 57.2% of the patients showed tumors in the MT and also this difference was statistically significant ($p < 0.05$). Eight tumors were initially treated by wide local excision (57.1%) and six hemiglossectomies (42.8%) were performed (one included submandibular gland excision and radical neck dissection). 13 cases were T2N0M0-stage II and one was T4dN2bM0-stage IVa. Three were recurrent tumors (21.4%) recurring all 12 months after initial surgical excision. One tumor presented submandibular gland invasion and nodal involvement 96 months after initial surgical intervention. Five patients were drinkers (55.6%) seven were smokers, five patients were non-drinkers and non-smokers and three were both, drinkers and smokers. Two recurrent tumors occurred in smokers and one in a non-drinker and non-smoker patient.

There were six examples in the CIS group (17.6%); 4 males (66.7%) and 2 females (33.3%), with ages between 48 and 82 years (mean age= 59 years; SD \pm 12.6 years). Location of the tumors was three cases in each MT and BT (50% respectively). Three tumors were T2N0M0 (stage II), two corresponded to T3N0M0 (stage III) and one was T4aN0M0 (stage IVa). 66.7% of the tumors were initially treated by wide local excision and two hemiglossectomies were performed (one included radical neck dissection). One tumor recurred 12 months after initial surgical excision. Two patients were drinkers (55.6%), three smokers, two of them were both drinkers and smokers and three patients were non-drinkers and non-smokers. The recurrent tumor occurred in the non-drinker and non-smoker patient.

Discussion

Tongue cancers are SCCs mainly and they are more frequent in males.¹⁵ SCCT is a frequent malignant neoplasm presenting variable incidence with geographic and ethnic differences.¹ Other variables

are alcohol and tobacco use and VPH infection.¹⁶ Interestingly, the age-standardized rates (ASRs) are variable depending on the continent, geographical region, country and local area.¹⁷

Age

In several studies, preference for males varied among 48% and 86.4%¹⁸⁻²³ and the male frequency we found (53.3%) is within the above-mentioned range. In the literature, mean age is widely variable, it was from 64.3 to 47.5 years,^{18,21-24} and in our study, it was slightly lower (63.9 years).

Microscopic differentiation

The degree of differentiation of the analyzed cases varied from poorly to moderately to well-differentiated SCC. It is important to point out that in previous studies, no cases of CIS were included and these data will impact in the final frequency of the studied SCCT and for this reason, our results on the degree of differentiation of the studied malignancies, were different to the previously reported. In other studies, the WDSCC was the most frequent, followed by the MD and the PD types. Differing with previously published data, the most common in our study was the MDSCC type, comprising more than half of the sample (56.7%), followed by the PDSCC (23.3%). Our results are only similar to those from the Ramdass et al. study,²¹ but completely different to those found in other studies showing that the WD type was the most common followed by the moderately differentiated type.^{18,22,23,24} It is interesting to note, that in this study, a high proportion of low risk patients developed SCCT. This data does not agree with previous studies showing that high risk patients comprise the high proportion of the analyzed samples.^{21,22,23,24,25,26} Probably these differences may arise from difficulties in the evaluation of tobacco or alcohol consumption levels. This can occur when clinical histories are reviewed retrospectively.

As it was previously reported,^{27,28,29,30,31} MTSCCs were more frequently found than BTSCC. Compared with previous reports,^{27,28,29} this study revealed a lower proportion of BTSCCs, but other studies showed a similar BTSCC rate.^{30,31} The mean age of 65.7 years

detected in this study, was similar to previously reported data.^{8,9,10,11,12,20,28,32}

TNM Classification

Compared with previous reports,^{32,33} a high rate of T2 tumors was found (78.3%) and interestingly, no T1 tumors were detected. 81.7% of the tumors were AJCC stage II and it is also a high rate compared with previously published studies.^{28,32,33} Our data on nodal involvement (15%) was the same as that for Chinese population²⁴ and low compared with previously reported data.^{32,33} 15% of the analyzed SCCTs recurred, this rate was higher to that reported in Chinese patients²⁴ and similar to the proportion found in the Mäkitie et al study.³³ 88.9% of the recurrences were in 61 years and older patients and surprisingly, 44.4% occurred in low-risk patients (non-drinkers non-smokers). These features were not previously reported. BTSCCs recurred more frequently (21.7%) than MTSCCs (8.1%).

In this study, WDSCCs were the less common type of carcinoma and together with the male:female ratio of 1:1 we found, both features were never reported for SCCT. Lymph node involvement and recurrence were low and it can be associated to the fact that 83.3% were T2-stage II tumors. An unreported feature for this kind of tumors was to find that 50% of the affected patients were in the low-risk group (non-drinkers non-smokers). This finding suggests that the role of risk factors should be reevaluated in this population.

An unexpected result was that in our study, the MDSCC was the most common of the analyzed tumors (56.7%), contrasting with previous data From Finland and India reporting that WDSCC was the most frequent SCCT.^{20,23} 50% of the analyzed patients were males with a mean age of 63.1 years and interestingly, 35.3% of the SCCs were in BT. BT located tumors were more frequent than previously published and as it was stated by Westra et al.,² this finding could be related with the increase of HPV infection. 79.4% were T2-stage II neoplasia, 11.8% were recurrent tumors and 20.6% behaved nodal involvement. As it was with WDSCCs, the proportion of low risk affected patients (non-drinkers non-smokers) was high (52.9%). Opposed to data from previously reported studies,^{18,22,23,24} 41.2% of the

sample were PDSCCs and 57.1% of them were males with a mean age of 67.3 years. As it was detected in the MDSCCs group, an unexpectedly high rate of patients harbored BTSCCs (42.8%). To our surprise, a high rate of cases was T2-stage II (92.8%) and 21.4% were recurrent tumors. As in WDSCCs and MDSCCs, a high proportion of affected patients (55.6%) were in the low-risk group (non-drinkers and non-smokers). We included in this study clinico-pathological data on six cases of CIS. This kind of tumors never were included in previous SCCT series.

As it was with the whole sample and opposed to data from the literature,^{27,28,29,30,31} most of the analyzed MT cases were MDSCC, followed by PDSCCs and the newly included CIS type. In this study, they were more common in females and mean age was 64.6 years. Additional to published data, we found that 89.2% of the MT located carcinomas were T2, 92% were stage II with 10.8% of recurrent cases and all recurrences appeared in smokers.

Main data obtained analyzing this Mexican population is compared with similar studies in Table 5.^{26,27,30,34} Data in this table shows that frequency, clinical features and behavior complemented with different treatment modalities of the tumors analyzed in this study is different in many aspects compared with SCCT cases from other countries. Data in this table strongly suggests that clinical features and behavior of these tumors in Mexican population should be reviewed to identify precise role of the etiological factors in these patients. Also, our results showed that a high rate of patients with SCCT were low-risk patients (non-drinkers and non-smokers). These results strongly suggest that in Mexican population risk factors should be re-evaluated as causative influences in development of these neoplasms.

Conclusions

It is important to point out that to date, age categorization of the studied populations used by many authors was very variable and new incidence studies will define outcomes in age cohorts using a consensus cut-off for young and elderly populations.

To date, there are few studies published on this matter and we suggest that more population-based

Table 5. Comparative data from previous studies in patients older than 45 years with SCCT.

Data	Authors					
	Mobile tongue			Base of the tongue		
	Goepfert	Goldstein	This study	Zhen	Krishnatreya	This study
% of sample	NDR	NDR	61.7	4.4%	76.1	38.3
Mean age	47.9 yrs	57.6 yrs	63.6 yrs	63.0 yrs	58.0 yrs	64.6 yrs
Male	69%	59.9%	67.6%	73.0%	79.3%	34.8%
Female	31%	40.1%	32.4%	27.0%	20.7%	65.2%
Tumor stage						
T1	53%	48.2%	0%	NDR	NDR	0%
T2	28%	36.0%	86.5%	NDR	NDR	78.3
T3	6%	10.7%	2.7%	NDR	NDR	5.0
T4	5%	5.1%	10.8%	NDR	NDR	16.7
Nodal stage						
N0	56%	56.6%	89.2%	NDR	NDR	78.3%
N1	17%	18.4%	0%	NDR	NDR	0%
N2	28%	25.2%	10.8%	NDR	NDR	21.7%
N3	0%	0%	0%	NDR	NDR	0%
Metastases				7.6%	3.8	
M1	0%	NDR	8.1%	NDR	NDR	30.4%
M2	0%	NDR	0%	NDR	NDR	0%
M3	0%	NDR	0%	NDR	NDR	0%
AJCC Stage						
I	39%	26.6%	0%	9.1%	1.0%	0%
II	14%	31.7%	91.9%	12.0%	8.2%	65.2%
III	11%	26.3%	0%	21.0%	43.4%	8.7
IV	36%	15.4%	8.1%	57.1%	47.4%	26.1%
Differentiation						
WD	31%	20.3%	5.0%	12.8%	NDR	13.0%
MD	50%	70.5%	36.7%	50.0%	NDR	52.2%
PD	19%	9.2%	13.3%	35.8%	NDR	26.1%
CIS	NDR	NDR	6.7%	NDR	NDR	8.7%
Recurrence	25%	54.5	10.8	NDR	NDR	21.7
Treatment						
Hemiglossectomy	22%		16.2		NDR	91.3
Glossectomy	8%	74.1%	NDR	43.8%	NDR	NDR
Neck dissection	100%	75%	8.1	NDR	NDR	30.4
Smokers	56%	65%	35.1	NDR	NDR	34.7
Drinkers	17%	59.8%	40.5	NDR	NDR	60.9
Drinker-smoker	NDR	25.7%	29.7	NDR	NDR	34.8
No drinker-smoker	NDR	74.3	54.0	NDR	NDR	39.1

SCCT : Squamous cell carcinoma of the tongue; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; CIS: Carcinoma in situ; NDR: No data recorded.

studies should be performed to get accurate data on SCCT incidence in elder subpopulations and to identify precisely the etiological factors in these patients.

Our results suggest that BT tumors should be treated more aggressively than those in the mobile tongue.

BT located tumors were more frequent than previously published and this could be related with increase of HPV infection.

More population-based studies should be performed in Latin American regions to get accurate

data on SCC incidence in elder subpopulations and to identify precisely the etiological factors in these patients.

Risk factors in Mexican population should be re-evaluated as causative influences in development of these neoplasms.

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