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# The pattern of lip cancer occurrence over the 1990–2011 period in public hospitals in Madrid, Spain

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**BACKGROUND: Some regions of Spain along with Canada and Australia have the highest rates of lip cancer in the world. The objective of this study was to examine the trends in the pattern of occurrence of lip cancer in Madrid, Spain.**

**METHODS: Data were extracted from the Central Tumour Registry of Madrid, between 1990 and 2011. Variables examined were age, sex, topographic and morphological location and tumour histology. Two consecutive periods, 1990–2001 and 2002–2011, were studied by descriptive and analytical methods, and the data from the two periods were statistically compared.**

**RESULTS: A total of 881 cases were registered during the period 1990–2011. Comparing data between the two periods (1990–2001 and 2002–2011), subtle variations in age, histology and location were noted. Gender ratios remained constant. The mean age increased from 66.3 to 69.7 years ($P < 0.05$). In the second period, the histological distribution showed an increase in frequency of basal cell carcinoma, from 2.1% to 4.7%, while the frequency of squamous cell carcinomas remained constant. Basal cell carcinoma no longer predominantly occurred in women, decreasing from 80% to 21.1% ($P < 0.001$). The distribution by gender of squamous cell carcinoma had become more equal due an increase in its frequency in women ($P < 0.001$). Frequency of tumours on lip mucosa and commissure had increased between the two periods ($P < 0.004$).**

**CONCLUSIONS: The pattern of lip cancer reported to Public Hospitals of Madrid is changing: declining rates are noted since 2001–02. However, it is necessary to monitor these data to confirm the observed trends in future years.**

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## Introduction

According to the European Cancer Observatory (ECO), the estimated number of new cases of lip, oral and pharyngeal cancer in Europe was 99 630 in 2012, and the estimated number of deaths from these cancers was 43 662 (1, 2). According to the same source, in Spain, lip, oral and pharyngeal cancers represent the tenth most common cancers overall (the fifth in men and sixteenth in women) (1, 2). Granada, traditionally considered as one of the areas with the highest incidence of lip cancer (LC) in Spain (3) (both genders; lip 3.2 per 100 000 person-years; oral cavity 2.6 per 100 000), has been overtaken by Cuenca, an area near Madrid, which has shown an age-standardised rate (European) ASR (E) of 4.8 per 100 000, with a marked difference between genders; ASR (E) 9.9 among men vs. 0.1 among 100 000 women (3).

Epidemiology of LC indicates that certain specific parts of Spain, along with Canada and Australia, have some of the highest rates in the world (4, 5). This is a disease that occurs predominantly in men around 65 years, with fair skin and light eyes (6). LC is commonly encountered in the lower lip vermillion with histology of squamous cell carcinoma (SCC) in 95% of cases. It exhibits a particular geographical pattern and has been linked to very specific risk factors: especially early and prolonged exposure to sunlight (6), working outdoors (7), immunosuppression among transplant recipients (e.g. kidney transplants) (8, 9), certain peculiar habits in smoking (e.g. resting a cigarette against the lip or pipes with a heated pipe stem), viral infections, endogenous factors (10–16). Some antihypertensive medications used by specific population groups (17, 18) have been cited. The disease is more common in low socioeconomic groups (19–21).

However, this classic pattern of LC, described in previous decades, may be experiencing changes, possibly related to life-style changes. For decades, there has been a steady decline in the number of cases (6) particularly after 2000 (22). The Surveillance, Epidemiology and End Results (SEER) in USA shows that between 1992 and 2009, there was a decrease in oral cancer cases, and this was attributable to a great extent on a reduction of new LC cases (23, 24). Portugal, a neighbouring country to Spain, showed a decline in LC in the decade ending 2005 for both sexes, but interestingly, showed a rising incidence of LC during 2005–07 (25).

The objective of this study was to examine the trends in the pattern of occurrence of LC between 1990 and 2011 in the Autonomous Community of Madrid (CM), Spain.

## Materials and methods

The population-based sample comprises 881 patients diagnosed with LC between 1990 and 2011. Data were obtained from the Central Tumour Registry of Madrid (hospital-based registry), Cancer Data Interchange System (SIDC), to include the Autonomous Community of Madrid (CM), between 1990 and 2011. This registry processes the information provided by the public hospitals of the CM.

In the registry's classification of LC, malignant tumours are considered under CIE-O3 (25), C00 and its subsites by exact location (C00.0–00.9) as follows:

C00.0 Upper lip vermillion
C00.1 Lower lip vermillion
C00.2 Lip vermillion SAI
C00.3 Upper lip mucosa
C00.4 Lower lip mucosa
C00.5 Lip mucosa SAI
C00.6 Lip commissure
C00.8 Tumours that share limits with two or more subcategories
C00.9 Lip SAI (Sine alter indication)

Based on SEER criteria, this registry does not include tumours of the skin, nor carcinoma *in situ* (25, 27).

The population sample (881 patients) studied spanned across a 20-year period beginning in 1990 (whole period 1990–2011), as well as by dichotomy into two subperiods: first from 1991 to 2001 (477 new registrations), and a second period from 2002 to 2011 (404 new registrations) to study and compare the characteristics of the pattern of LC and trends over a 20-year period in this cohort of cases.

Variables provided by the registry were as follows: age, gender, tumour location, tumour histology, tumour extent (local, regional, disseminated) and multiple primary tumours (MPT) in patients previously diagnosed with LC. The definition of MPT used by the authors comes from the IARC recommendations (28, 29). Variables were operationally categorized by mean age (older/younger than 68 years), morphological location according to the affected tissue (mucosa, vermillion, commissure, others), anatomical location (upper, lower, commissure, whole), and tumour histology grouped by SCC, basal cell carcinoma (BCC) and others.

Descriptive epidemiology was performed using frequencies, percentages, means and standard deviation. The data were analysed using the chi-squared test and the exact test of Fisher, as appropriate. For trend analyses, following Czerninsky et al. (12), the authors included a polynomial regression trend line together with the regression scatter to exemplify the predicted incidence. The $R^2$ value was calculated to demonstrate the fraction of the variance in the data that is explained by the regression model. The statistical processing was conducted using SPSS 17.0 (30). The level of statistical significance was chosen as $P < 0.05$.

Throughout the data gathering and analysis, the existing rules of confidentiality prescribed by current legislation in Spain were respected (Sistema de Intercambio de datos de la comunidad de Madrid, 2002) (31).

## Results

*Trends*

During the period 1990–2011, the evolution of the number of patients, diagnosed triennially, was very variable ($P < 0.001$). As a result, performing regression with all the data from the whole period did not yield a function with an adequate $R^2$. At this point, we made an arbitrary division between the periods 1990–2001 and 2002–2011, which considerably improved the fit of the curve.

Owing to an increase in the number of cases registered until 2001 and an inflection point that can clearly be seen around 2001 and 2002, marking a decrease since 2002 (Fig. 1), an analysis was performed of data from both the complete duration of the study (1990–2011) and also for the two independent time periods (1990–2001 and 2002–2011).

*Age*

For the whole period (1990–2011), the mean age of patients diagnosed with LC was 67.8 ± 12.5 years (Table 1). This mean value was taken for further comparative analysis of data. Most LC cases were diagnosed in patients over 68 years (55.7%), and to a lesser extent among the younger patients (44.3%) ($P < 0.001$). The vast majority of cases diagnosed (160 cases, 18.2%) (Table 1) were registered in the age group 65–69 years.

The mean age of LC during the first period (1990–2001) was 66.3 ± 12.3 years. In the second period, however (2002–2011), the mean age shifted to the right almost by 3 years (69.7 ± 12.2), ($T = -4.066$) ($P < 0.001$) (Table 1).

*Gender*

LC in this population occurred predominantly in men (749 cases, 85%, $X^2$: 432.1, $P < 0.001$). Women accounted for 15% of the total (132 cases). The male-to-female ratio was 5.6:1 and remained constant in both periods without significant variations ($X^2$: 0.07; $P = 0.781 > 0.05$).

During the whole period (1990–2011), the proportion of men remained practically constant in both age groups, while 71.9% of the total female population were over 68 years of age ($X^2$: 16.59; $P < 0.001$) (Table 1).

When comparing age at diagnosis in the two periods by gender, it was noted that in the first period, men are evenly distributed in the two age groups, while women are more numerous in the age group over 68 years. In the second period, the number of men less than 68 years decreased significantly. This contributed to an increase in the mean age of the total group (Table 1).

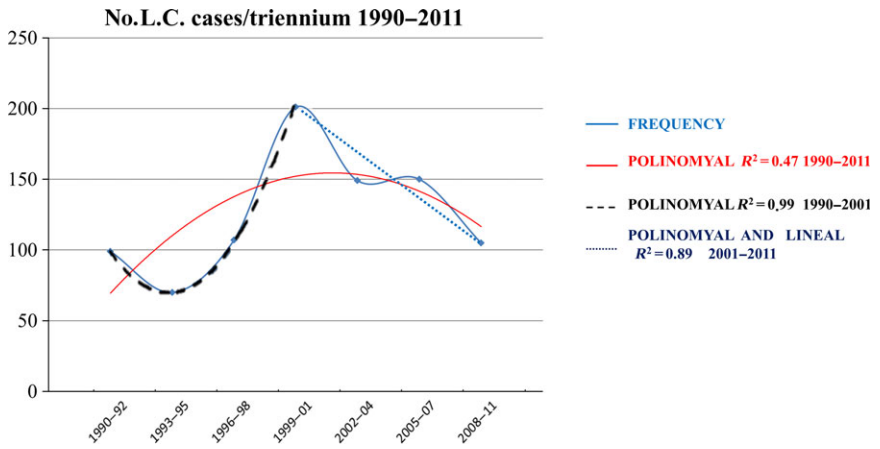


**Figure 1** L.C. Cases/Triennium. Period 1990–2011.

*Histology*

According to the reported pathological diagnoses (CIE-O-3), the most common histological type of LC was SCC (819 cases, 93%) (Table 1). SCC Not Otherwise Specified (NOS) stands out (782 cases, 87.4%). BCC was the second most frequent type of tumour (27 cases, 3.1%). Two cases of malignant melanoma were found, as well as a Kaposi's sarcoma and five salivary gland tumours affecting the lips. Distribution of the most frequent histological types in this anatomical region, SCC, BCC and others, is shown in Table 1.

On comparing the distribution of these histological groups in the periods studied, a significant increase in BCC cases was observed, from 2.1% in the first period to 4.7% in the second ($X^2$: 6.61; $P = 0.037 < 0.05$). The group of 'other histological types' decreased in proportion. The incidence of SCC remained constant (Table 1).

*Correlation of histology with age and gender*

The distribution of histological groups was not affected by age, and remained constant during the whole length of the study in both age groups; that is, more than 68 and less than 68 years.

When the whole period was considered, male cases were more frequent (87%M vs. 13%F) among those diagnosed with SCC; however, within the total of BCCs, the percentages were more evenly distributed between the two groups by gender (58.6%M vs. 41.4%F $P < 0.001$) (Table 1).

In the first period (until 2001), 80% of the BCCs were in women vs. 20% in men ($X^2$: 48.88, $P < 0.001$). In the second period, the numbers of men increased in the BCC group, although with no statistical significance (Fig. 2).

When the histological types were compared by gender, it was noted that the distribution between the two genders has become more equal, due to SCC increasing in frequency in women and BCCs decreasing in numbers. Among men, the frequency of BCC had risen (Fig. 3).

*Location*

LC was more frequently found in the lip vermillion compared with the mucosal side of the lip and the commissure ($X^2$: 901.89; $P < 0.001$) (Table 1). This location of the vermillion/mucosa has exhibited significant differences when comparing the two study periods. The tumours on the mucosal aspect of the lip (C00.3–00.5) had increased significantly and notably, the commissural cancers increased from 9 to 12 cases ($X^2$: 13.22; $P = 0.004$) (Table 1).

*Correlation of location with gender and histology*

An increase in mucosal location was observed in both sexes, but proved to be significant only in men (Fig. 4). Regarding its location, LC mostly affected the vermillion of the lower lip, and no significant statistical differences were found between the two series ($X^2$: 4.79; $P = 0.18$) (Table 2).

Taking into account the number of tumours in the overall period, in both genders, the lower lip is the most frequently affected site, although the proportion is less in women. Upper lip location constitutes 22.7% of all female LC cases ($X^2$: 57.52; $P < 0.001$) (Table 2). These differences remained significant in both periods (1990–2001: $X^2$: 43.43, $P < 0.001$; 2002–2011: $X^2$: 16.61, $P > 0.001$). Continuing the analysis for the whole period, the following was found in each location with regard to the male-to-female ratio: upper/lower is almost equivalent (33/30), while in the lower lip is 8:1 towards men (596/81) ($P < 0.001$).

In all anatomical locations, the male-to-female ratio is higher, with the exception of the upper lip, where gender distribution was even (Table 2).

SCC mostly affected the lower lip, while BCC was predominantly detected in the upper lip and on the commissure ($X^2$: 195.91; $P < 0.001$). This distribution remained constant throughout the duration of the study (Fig. 5; Table 2).

*Tumour extent*

LC was mainly localized to lip at the time of diagnosis. In this cohort of cases, 811 cases (92%) were at a localized stage, 65 cases (7.4%) had regional metastasis, and only four cases were disseminated ($X^2$: 1376.6; $P < 0.001$). This distribution was not significantly associated with any other study variable (e.g. age and gender) and remained constant throughout the study period (Table 2).

*Multiple primary tumours*

A total of 51 MPTs (5.8%) associated with LC were found in the overall period; 34 were confirmed by biopsy and 17 secondary tumours were clinically diagnosed pending biopsy ($X^2$: 1469.77; $P < 0.001$) (Table 1).

**Table 1** Descriptive epidemiology: the distribution of variables by periods of study

| *Variable* | *Whole period (1990–2011)* | *Period 1990–2001* | P | *Period 2002–2011* |
|---|---|---|---|---|
| Freq (*n*) | 881 | 477 | | 404 |
| Mean age** | 67.8 ± 12.49 | 66.3 ± 12.3 | | 69.7 ± 12.2 |
| Average age** *N* (%) | | | | |
| Below 68 | 390 (44.3) | 251 (52.62) | ++ | 139 (34.41) |
| Over 68 | 491 (55.7) | 226 (47.38) | | 265 (65.59) |
| Gender** | | | | |
| Men | 749 (85) | 407 (85.3) | NS | 342 (84.7) |
| Women | 132 (15) | 70 (14.7) | | 62 (15.3) |

| | | | P = *0.005* | | | P = *0.003* | |
|---|---|---|---|---|---|---|---|
| | *<68 y.o* | *≥68 y.o* | *<68 y.o* | *≥68 y.o* | | *<68 y.o* | *≥68 y.o* |
| Gender/average age** | | | | | | | |
| M 100% | 353 (47.1) | 396 (52.8) | 225 (55.3) | 182 (44.7) | ++ | 128 (37.4) | 214 (62.6) |
| F 100% | 37 (28) | 95 (72) | 26 (37.1) | 44 (62.9) | + | 11 (17.7) | 51 (82.3) |
| Total | 749 (100) | 132 (100) | 407 (100) | 70 (100) | | 342 (100) | 62 (100) |
| Histologic subtypes** | | | | | | | |
| SCC | 819 (93) | | 445 (93.3) | | + | 374 (92.6) | |
| BCC | 29 (3.3) | | 10 (2.1) | | | 19 (4.7) | |
| Other | 33 (3.7) | | 22 (4.6) | | | 11 (2.7) | |
| Total | 881 (100) | | 477 (100) | | | 404 (100) | |

| | | | P < *0.001* | | | P > *0.05* | |
|---|---|---|---|---|---|---|---|
| | *Men* | *Women* | *Men* | *Women* | | *Men* | *Women* |
| Histologic subtypes/Gender** | | | | | | | |
| SCC 100% | 709 (86.5) | 110 (13.4) | 392 (88.1) | 53 (11.9) | NS | 317 (84.8) | 57 (15.2) |
| BCC 100% | 17 (58.6) | 12 (41.4) | 2 (20) | 8 (80) | + | 15 (78.9) | 4 (21.1) |
| Other 100% | 23 (69.7) | 10 (30.3) | 13 (59.1) | 9 (40.9) | NS | 10 (90.9) | 1 (9.1) |
| Total | 749 | 132 | 407 | 70 | | 342 | 62 |
| Location** | | | | | | | |
| Vermilion | 596 (66.7) | | 323 (67.7) | | + | 273 (67.57) | |
| Mucosa | 165 (18.7) | | 77 (16.1) | | | 88 (21.78) | |
| Commissure | 21 (2.4) | | 9 (1.89) | | | 12 (2.97) | |
| All | 99 (11.2) | | 68 (14.26) | | | 31 (7.67) | |
| Total | 881 (100) | | 477 | | | 404 | |
| MPT** | | | | | | | |
| No | 830 (94.2) | | 440 (92.2) | | + | 390 (96.5) | |
| Yes | 51 (5.8) | | 37 (7.8) | | | 14 (3.5) | |

| | *No* | *Yes* | *No* | *Yes* | | *No* | *Yes* |
|---|---|---|---|---|---|---|---|
| TPM/Histology** | | | | | | | |
| SCC (100) | 776 (94.7) | 43 (5.3) | 415 (93.3) | 30 (6.7) | + | 361 (96.5) | 13 (3.5) |
| BCC (100) | 28 (96.6) | 1 (3.4) | 9 (90) | 1 (10) | NS | 19 (100) | 0 |
| Other (100) | 26 (78.8) | 7 (21.2) | 16 (72.7) | 6 (27.3) | NS | 10 (90.9) | 1 (9.1) |
| Total | 830 | 51 | 440 | 37 | | 390 | 14 |

'*P*-value' Period 1990–2011: (*) $P < 0.05$; (**) $P < 0.001$.
'*P*-value' between periods 90-01/02-11: (+) $P < 0.05$; (++) $P < 0.001$.

Throughout the study period, a significant decrease of MPTs was observed ($X^2$: 7.42; $P = 0.02 < 0.05$).

SCCs were associated with MPTs in 5.3% of the cases in the overall period ($P < 0.001$), although this number decreases significantly from the first period to the second ($X^2$: 4.35; $P = 0.03 < 0.05$).

BCC is least associated with MPTs, and only one case was registered during the first period.

## Discussion

The lip shares common characteristics with the skin and the oral mucosa (32) and is classified by the ICD-10 code as C00 (26). Despite this designation with a unique ICD code, the definition and classification of LC appears ambiguous and lacks uniformity (33). This definition reflects an anatomic designation of disease, but not a specific histopathology. LC is often grouped together with oral cavity cancers in the literature on global epidemiology (4, 34).

The Central Register of Tumours (CRT) of the CM is a hospital-based registry that has been active since 1989. All patients enrolled in this study had a histological diagnosis and have completed their treatment. Hospital and population-based registries have independent systems of registering data, designed with different objectives and methodology, but they are complementary to each other (35). Their strategic purpose goes beyond providing pure

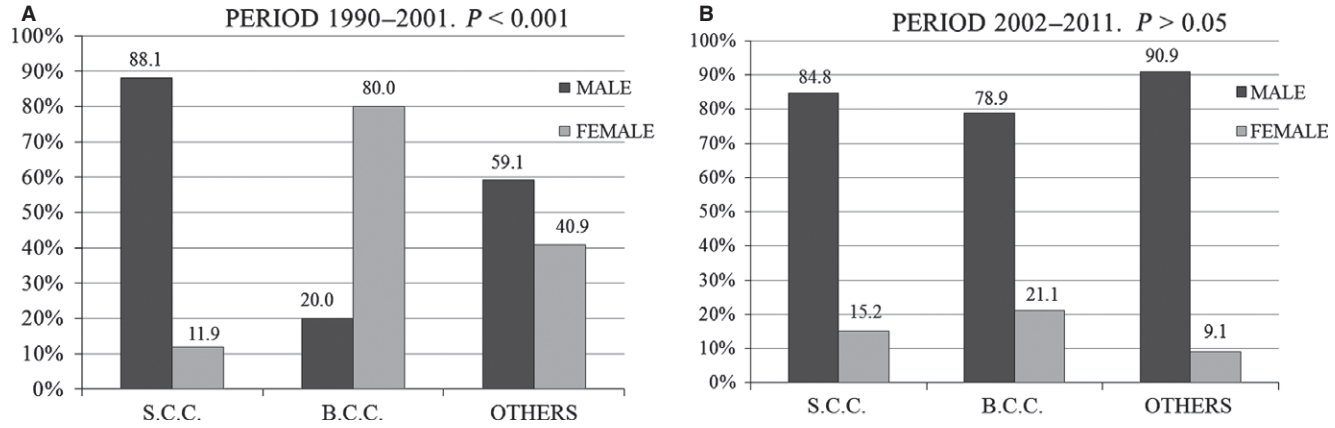


**Figure 2** Gender distribution of each histological type of LC. (A) Period 1990–2001. (B) Period 2002–2011.

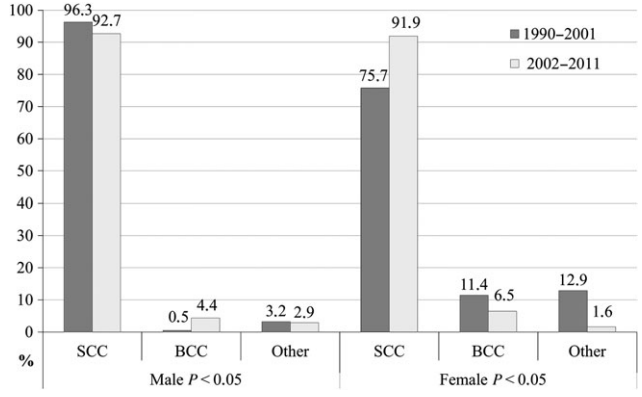


**Figure 3** Comparison between time periods of the distribution of histological types by gender.

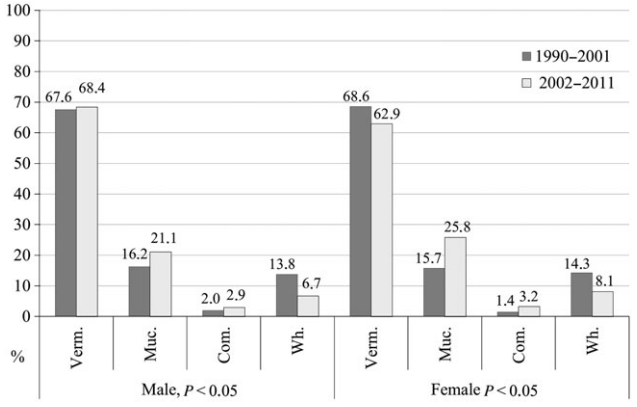


**Figure 4** Location distribution of LC in each gender by time period.

descriptive statistics by geographic region (36). The hospital-based registry serves mainly to assess any improvement in patient care, professional education or administrative information, and supports the needed clinical investigations (27). As a result of the Registry being hospital-based, the disease incidence cannot be estimated and the authors acknowledge that there could be a selection bias of patients (10). However, the inherent validity of this study is not affected.

The subsidiary hospitals of the CRT broadly cover the population under surveillance. Tumours that are treated outside of hospitals are not recorded, but in Madrid, this is unlikely to be a significant factor affecting data synthesis. Therefore, all cases of LC in the CM have been ascertained. Despite this, at all times, the terminology 'number of diagnosed cases' is used in this publication, rather than 'cancer incidence'; although in practice, they can be considered as equivalent for purposes of estimation of incidence figures. Compared to published studies (11, 37–40), the series consisting of 881 patients and over 20 years of observation is extensive to allow an accurate depiction of the pattern of lip cancer in the CM, as well as for the detection of any possible variations. Our population sample in the whole period (1990–2011) shows complete consistency with the classical pattern of LC previously reported; lip cancer increases with age (our mean age was 68 years ± 12.4) (39, 41, 42). As stated in the literature, the male-to-female ratio leans towards men (5.6:1); it is of interest to compare the male-to-female ratio in our series with published studies in Brazil, 5:1 (43), Mexico 1:1 (44), Israel 1.2:1 (12),Western Australia 3:1 (4) and Portugal 4:1 (11, 17, 45). LC in Madrid mostly affects the lower lip, and SCC is the most prevalent histological type as described previously (12, 13, 17, 22, 44, 46–48).

BCC develops predominantly on the upper lip and the commissure, and our data are consistent with the findings reported by Czerninsky in Israel (12). In a systematic review, Kyrgidis et al. (49) discuss the host factors that may make people susceptible to BCC. Retrospective studies like ours unfortunately do not allow a detailed analysis of such factors.

When comparing the two periods (1990–2001 and 2002–2011) into which our data has been dichotomized, subtle differences of note appear to be significant. Consistent with the findings of Maruccia (48) and Warnakulasuriya (50), a shift of 3 years to the right of the mean age at presentation has been observed, possibly owing to an ageing population and longevity (4).

With regard to gender, several studies (4, 12, 45, 51) reported over similar time periods, showed that occurrence

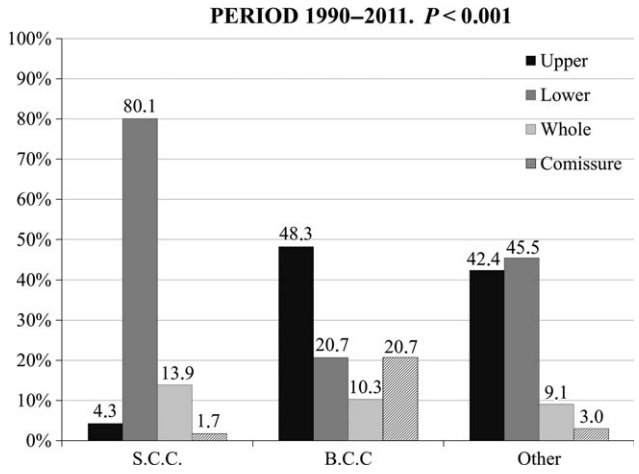


**Figure 5** Location distribution of LC for each histological type.

**Table 2** Distribution of other variables (location of tumour, gender, histology and extent) that are unaffected by trends

| Variable | Period 1990–2011 | | | |
|---|---|---|---|---|
| Location (Upper/Lower)** | | Gender** | | |
| *N* (%) | | Men | Women | Ratio |
| Upper | 63 (7.2) | 33 (4.40) | 30 (22.70) | 1.1:1 |
| Lower | 677 (76.8) | 596 (79.60) | 81 (61.40) | 8:1 |
| All | 120 (13.6) | 102 (13.60) | 18 (13.60) | 5.6:1 |
| Commissure | 21 (2.4) | 18 (2.40) | 3 (2.30) | 6:1 |
| Total | 881 (100) | 749 (100) | 132 (100) | |

| Histology** | SCC | BCC | Other | Extent** | |
|---|---|---|---|---|---|
| Upper | 35 (4.3) | 14 (48.3) | 14 (42.4) | Localized | 811 (92.1) |
| Lower | 80.1 (656) | 6 (20.7) | 15 (45.5) | Regional | 65 (7.4) |
| All | 114 (11.9) | 3 (10.3) | 3 (9.1) | Disseminated | 4 (0.5) |
| Commissure | 1.7 (14) | 6 (20.7) | 1 (3) | Unknown | 1 (0.1) |
| Total | 819 (100) | 29 (100) | 33 (100) | Total | 881 (100) |

'*P*-value' Period 1990–2011: $*P < 0.05$; $**P < 0.001$.

of LC in men is decreasing and they also found a slight increase in women (4, 52). The present study shows a similar trend, although the findings are not statistically significant. This trend has been observed since the early 90s in Scotland (53). Alho et al. (41) reported the same numbers in men/women in the north of Finland, in the period 1983–1997, which is not reflected in the authors' data until a decade later. De Visscher et al. (54) reported that the increase in LC incidence in women is owing to an increase in tobacco consumption, prolonged and unprotected exposure to the sun (which is becoming more popular), as well as certain unknown factors. Monteiro et al. (25) in Portugal also demonstrated a decrease in the incidence of LC until 2005; this trend is recorded in both genders, although much more marked in men. However, a study reported from the USA (55) has not showed these trends.

With regard to histological presentation of LC, during the overall period (1990–2011), the authors of the present study calculated an increase in the total number of BCCs, from 2.1% in the first period (1990–2001) to 4.7% in the second period (2002–2011), which is consistent with Czerninsky et al. (12). They reported a slightly increasing trend but only in female cases. Among skin cancers too, an increase in the total number of BCCs has been described (49, 56, 57), the risk factors of which are consistent with LC.

With regard to the lip, it is debatable whether the BCCs are primary lip cancers or just extensions of cutaneous BCCs (48). Therefore, the increase noted in occurrence of lip BCCs could be considered as a consequence of the increase of cutaneous BCCs. Czerninsky et al. (12) reported a much higher percentage of BCCs (40%) than found by others. Of interest, the proportion of BCCs on the upper lip (78%) reported by them is much higher than in our study (48%). In the present study, BCCs on the upper lip appeared more frequent in women, while on the facial skin, they are more prevalent in men (15). The present data demonstrate an equal gender distribution of BCCs at the upper lip location, in contrast to other series where gender ratio leans more towards men. This would lead us to explore in a prospective study the exact origin of lip cancers in Madrid with reference to their primary anatomical location and any gender difference.

In Australia, Abreu et al. (4) attributed the higher rates of lip cancer in men to sun exposure and actinic radiation (8–9 h of average daily sunshine and 18–21 MJ/m$^2$/day). In the CM region, the AEMET (Spanish Bureau of Meteorology) recorded a radiation dose of 17.6–26 MJ/m$^2$/day [period 1983–2005 (58, 59)] and an average of 7.6 h of sun/day [period 1971–2000 (57)]. Both UVA and UVB have been implicated in cellular DNA changes and in the development of LC (4, 12, 60). Actinic keratosis (AK) or solar cheilosis is a precursor for the development of LC (61), and affected individuals require surveillance and appropriate advice to prevent development of LC. Considering the high incidence of LP in certain regions of Spain, it is worthwhile to consider the follow-up of dysplastic lesions of AK to report on their evolution.

The potential protective properties of women's use of lipstick and the working indoors do not explain the increase in the number of female cases. This increase may be attributed to a change in male and female habits regarding tobacco use and alcohol consumption (4). These two risk factors are clearly associated with oral cancer, but play a debatable role in LC development, with the exception of pipe smoking (particularly with a hot stem), which is seldom associated with women. The present study demonstrates that tumours of the (inner) lip mucosa have experienced the highest increase, showing similarities to oral cavity cancers, in which tobacco clearly pays a determinant role. Therefore, it is clear that there is a stronger association between tobacco use and the aforementioned increase.

In recent times, there has been a decrease in tobacco consumption in Europe. This reduction has been considerably smaller and slower in women (62), according to the typical stages of the tobacco epidemic (63, 64). In Spain, women start consuming alcohol and tobacco in later years than in the rest of Europe. The rising trend in female tobacco use in Spain had its peak in the 1980s and could be related to the increase in LC in the period studied among women of 65 years of age or older. In contrast, men's consumption decreased over the same time period. The

study data demonstrate that the distribution by gender became more equal, with SCC increasing its frequency in women and BCC decreasing. In men, however, BCC is increasing. Geraud et al. (16) earlier demonstrated these differences in the gender and the histological distributions.

It must be taken into consideration that the incidence of oral cavity and pharynx tumours is increasing in some countries in Europe (25, 45, 65). Additional risk factors associated with oral and oropharyngeal cancers, such as human papillomavirus (HPV) infection (66) could be implicated for their increase. According to Blomberg et al. (45), a thick layer of keratin found on the vermillion lip can justify the lack of association with HPV, and therefore the low prevalence of HPV-associated lip cancers.

With regard to MPTs, patients with oral cancer have a high risk of developing MPTs, especially in the upper part of aero-digestive tract (67–72). Our study data demonstrate MPT in 5.8% of patients with LC. In Italy, in a population study with oral cancer where the lip was included, Cianfriglia et al. (72) showed a rate of 4.5% for MPTs, while in the Netherlands registry, in oral cancer patients, the rate of MPTs was 10.7% in the upper part of the aero-digestive tract, and lower in for the rest of the body (7%). Both authors demonstrated that the rates obtained from the hospital-based registries are higher than population-based rates (73). This would justify the need to identify the profile of the patient with LC with a greater risk of developing MPTs. It is necessary to continue to monitor patients diagnosed with LC in order to confirm or reject these observations.

So, we can summarize that, in the population 1990–2011, LC is a condition mostly affecting older men (male-to-female ratio 5.6:1; with the exception of the upper lip, where gender is evenly distributed). SCC is the most common histological type, followed by BCC. LC mostly affects the lower lip (76.8%) and its histology may be different when comparing lower with upper lip.

In the other hand, when comparing periods 1990–01 and 2002–11, we can infer that the pattern of LC in public hospitals in Madrid is changing. An inflection point can clearly be seen around 2001 and 2002, showing a decline of LC thereafter. The number of BCC cases has increased during recent years and histological differences by gender are disappearing, with increasing cases of SCC in women and BCC in men. Furthermore, patients are older on average by 3 years.

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## Conflict of interest

None.