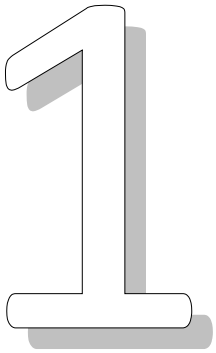
Epidemiological characteristics of a Spanish cohort of patients diagnosed with squamous cell carcinoma of head and neck: distribution of risk factors by tumor location



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Artículo 1: "Epidemiological characteristics of a Spanish cohort of patients diagnosed with squamous cell carcinoma of head and neck: distribution of risk factors by tumor location"

El carcinoma escamoso de cabeza y cuello es una enfermedad altamente heterogénea que engloba un alto número de tumores del área cérvico-facial. Los factores de riesgo clásicamente asociados con la enfermedad son el uso del tabaco y alcohol, aunque hay otros factores que tienen importancia en la etiología de este tumor. Estos factores varían según la población, existiendo datos escasos en la población española.

Con estos antecedentes, se planteó un estudio multicéntrico observacional y retrospectivo de CECC en la población española para determinar las características epidemiológicas de estos tumores así como la distribución de los factores de riesgo según la localización tumoral. Tras tres años de reclutamiento, se incluyeron 459 pacientes (75 carcinomas de cavidad oral, 167 carcinomas oro/hipofaríngeos y 217 carcinomas de la laringe).

La mayoría de pacientes fueron varones (88.4%), grandes fumadores y bebedores, diagnosticados en estadios avanzados de la enfermedad, con una media de 59 años. La distribución según la localización tumoral en varones fue similar a la incidencia global. Sin embargo, nuestro estudió mostró una proporción particularmente baja de mujeres con tumores en la laringe, predominando la presencia de tumores de oro/hipofaringe y cavidad oral ($p<0.01$). Estas localizaciones están asociadas a un mayor consumo de alcohol, observando en la muestra de mujeres un exceso de incidencia aún ajustado por la cantidad de alcohol consumido. Esto puede explicarse debido a una menor especificación del consumo de alcohol al no estar aceptado socialmente o al mayor efecto carcinogénico del alcohol en el sexo femenino.

La mayoría de los pacientes con carcinomas de cavidad oral o laringe provinieron de áreas urbanas, mientras que los tumores faríngeos fueron más comunes en áreas rurales, bien por la mayor exposición al tabaco en áreas rurales o por la infección vírica, debido a la diferencia en prácticas sexuales entre el modo de vida rural o urbana.

Respecto al nivel educacional, un alto porcentaje de nuestra muestra tuvo un bajo nivel (primaria o menor). Por otra parte, un tercio de los pacientes tuvieron historia familiar de cáncer (47% de ellos con CECC), sugiriendo un alto riesgo de desarrollar CECC en pacientes con historia familiar de la enfermedad, particularmente en aquellos con un familiar de primer grado. En cuanto a sus manifestaciones clínicas, los pacientes con cáncer laríngeo presentaron

disfonía, mientras que los tumores de faringe debutaron con masa en el cuello y en la cavidad oral lo más frecuente fueron las lesiones ulceradas presentes durante un tiempo prolongado. La pérdida de peso apareció en un tercio de los pacientes.

Observando los factores de riesgo clásicos, la mayoría de los pacientes incluidos en el estudio eran grandes fumadores con un inicio temprano, predominando el consumo de cigarrillos de tabaco negro, revelando el análisis bivariado una asociación entre aquellos pacientes que fuman más de 20 paquetes/año y una mayor proporción de tumores laríngeos que faríngeos. De modo similar, los sujetos eran grandes bebedores variando su consumo según la localización tumoral, asociándose un mayor consumo de alcohol en tumores de la faringe que de la laringe ($p<0.01$).

Aunque el estudio tiene ciertas limitaciones debido a su diseño retrospectivo, es el primer estudio de estas características en población española, describiendo las variables epidemiológicas de un amplio grupo de CECC en nuestro territorio.

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RESEARCH ARTICLE

Epidemiological characteristics of a Spanish cohort of patients diagnosed with squamous cell carcinoma of head and neck: distribution of risk factors by tumor location

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Abstract
Purpose Head and neck cancer is a highly heterogeneous disease comprising a large number of tumors located in the cervicofacial area. This study aimed to determine the epidemiological characteristics of squamous-cell carcinomas of the head and neck in the Spanish population, and the distribution of risk factors based on tumor locations.
Methods/patients A cohort of 459 patients (75 oral cavity, 167 oro-/hypopharyngeal and 217 laryngeal cancers) recruited in 19 hospitals participating in the Spanish head and neck cancer cooperative group were included over 3 years (2012–2014). Epidemiological parameters and risk factors were obtained from a self-administered questionnaire, and tumor characteristics were obtained from clinical records. Multivariate multinomial logistic regression was used to assess factors associated with tumor location.
Results Most patients were males (88.4 %), smokers (95 %) and drinkers (76.5 %). Relative to laryngeal cancer, pharyngeal cancer and oral cancer were more common in women than men (OR 3.58, $p = 0.003$ and 4.33,

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$p = 0.001$, respectively); pharyngeal cancer was more associated with rural environment (OR 1.81, $p = 0.007$) and weekly alcohol intake (10–140 g: OR 2.53, $p = 0.012$; 141–280 g: OR 2.47, $p = 0.023$; >280 g: OR 3.20, $p = 0.001$) and less associated with pack-years of smoking (21–40 packs: OR 0.46, $p = 0.045$; 41–70 packs: OR 0.43, $p = 0.023$; ≥71 packs: OR 3.20, $p = 0.015$).

Conclusions The distribution of these tumors differs between the sexes, with a higher proportion of oral cavity and pharyngeal tumors in women than in men. Oro-/hypopharyngeal cancers were more strongly associated with rural areas and with alcohol consumption, although less strongly associated with smoking than laryngeal tumors.

Keywords Head and neck cancer · Squamous cell carcinoma · Epidemiological characteristics · Spain · Risk factors

Introduction

Head and neck cancer (HNC) includes a large number of tumors located in different anatomical regions of the cervicofacial area, which, taken together, represent one of the most common cancers in the developed world [1]. Most of them are squamous cell carcinomas diagnosed in locally advanced stages, the oral cavity, pharynx and larynx being the most frequent locations [2].

Clinical presentation of HNC varies significantly depending on the location of the primary tumor and the extent of the disease. Thus, the first sign of the disease could be a palpable mass or, alternatively, location-specific symptoms such as dysphonia in laryngeal cancer or dysphagia in oropharyngeal cancer [3].

Major geographical differences in the incidence and location of the primary tumor in HNC are a consequence of the diverse patterns of tobacco and alcohol consumption in the different regions, as well as genetic variation between populations [4, 5].

Several epidemiological studies have shown an association between tobacco and alcohol consumption and the risk of HNC. Alcohol potentiates the effects of tobacco, a very common risk factor for these tumors [6, 7]. Other studies have shown a protective effect of fruit and vegetable intake [8, 9]. Social factors such as low socioeconomic status and low levels of education also seem to be related to disease development [10] and they could be related to the exposures described above.

There is evidence that two viruses are involved in the development of HNC: the Epstein-Barr virus (EBV) and human papillomavirus (HPV). Other infectious agents may also act as risk factors, but confirmatory studies are needed [11].

Other conditions, such as gastroesophageal reflux, have been associated with laryngeal and pharyngeal cancer regardless of age, gender, or tobacco and alcohol consumption [12].

In general, occupational exposures play a limited role in HNC, but an increased risk of sinonasal tumors has been observed among metal, wood, textile and leather workers, as well as people working in refineries [11].

The exposure to radiation for diagnostic purposes has been linked to salivary gland cancer [13], as has the therapeutic irradiation of these areas with the development of sarcoma [14].

Besides environmental factors, several association studies have suggested that genetic predisposition may also play a role in these diseases, since there is a higher risk in those subjects with family history of HNC [15, 16].

The aim of this study was to determine the epidemiological characteristics of squamous-cell carcinomas of the head and neck (SCCHN) in Spain using a series of attended cases, as well as the distribution of risk factors based on the most frequent tumor locations (oral cavity, oro/hypopharynx and larynx). To our knowledge, this is the first study of its type conducted in Spain.

Patients and methods

Design and study population

The present work is an observational study, carried out in 19 hospitals from different areas of Spain (four each in Catalonia and Madrid, two each in Castile and Leon, the Balearic Islands, Aragon and the Valencian Community, and one each in Galicia, Castile-La Mancha and Andalusia) belonging to the Spanish Head and Neck Cancer Cooperative Group (TTCC). Cases with a histologically confirmed diagnosis of SCCHN in oral cavity, oro-/hypopharynx or larynx, treated in these hospitals were invited to participate. Nasopharyngeal tumors were not included in the study due to the different risk factors involved (namely, a greater involvement of the EBV). Patients whose primary tumor affected several locations ($n = 1$) and those for which there was no information about location ($n = 11$) were excluded from the final analysis. A total of 459 patients (75 oral cavity cancer-OC, 167 oro/hypopharyngeal cancer-OHPC, 217 laryngeal cancer-LC) over a period of 3 years (2012–2014) were included. Written informed consent was

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obtained from all study subjects and the protocol was approved by the Institutional Review Board of each hospital.

Variable information

At baseline, all participants completed a self-administered questionnaire, which included sociodemographic data, personal and familiar backgrounds, symptoms present at the onset of the disease, and the risk factors associated with HNC, including detailed information about alcohol consumption and smoking habits.

The variables included in the study are defined as follows:

- Age refers to the age at diagnosis.
- Gender: male or female.
- Area of origin: patients were divided into two groups according to the size of their area of habitual residence: "urban area" included cities with more than 100,000 inhabitants; "rural area" comprised all others.
- Family support: patients were considered to have family support if they did not live alone.
- Educational level: data were divided into two groups: at most primary education, and more than primary education.
- Family history of cancer refers to the existence of one or more family members of patients with any type of cancer.
- Family history of HNC refers to the existence of one or more family members of patients with an HNC.
- Degree of relationship: we considered patients' first-degree relatives (parents, siblings and children), and other relatives (uncles, aunts, nephews, nieces, cousins, grandparents and grandchildren).
- Clinical presentation refers to the signs and symptoms at the time of diagnosis.
- Time with symptoms is defined as the time from symptom onset to first specialist consultation.
- Weight loss refers to the amount of weight (kg) lost before the diagnosis of the disease.
- Gastroesophageal reflux was judged to occur if the patient had feelings of heartburn after meals or at bedtime.
- Tobacco consumption: we collected the following information: age of onset, type of tobacco smoked, and whether the patient usually found themselves in environments with smoke. The calculation of the package-years was performed using the following formula: (number of cigarettes a day × years smoking/20 cigarettes per pack).
- Alcohol consumption: we collected information about the specific consumption of wine, beer and other alcoholic drinks. We then calculated the amount of ethanol (in grams) consumed with reference to the Standard Drink Unit (SDU) in Spain, which is equivalent to consumption of a single wine or beer, or a half measure of spirits. One SDU corresponds to 10 g of pure ethanol [17].
- Anatomical regions (oral cavity, pharynx: oro- and hypopharynx, larynx), stage and grade: these data were recorded according to the definitions of the 7th edition of the Manual for Cancer Staging [18]. Medical charts were retrospectively reviewed to collect the data.

The different items were checked for missing values or inconsistent data, and problems with the information were resolved appropriately.

Statistical analysis

In descriptive analysis, categorical variables were expressed as frequencies or percentages and the differences between pairs of groups were tested with Chi square contingency tables. A P value <0.05 was taken to indicate statistical significance.

Multivariate multinomial logistic regression was used to estimate ORs and 95 % confidence intervals with respect to tumor location. Laryngeal tumors were used as the reference group. The final model included those variables that proved to be statistically significant in bivariate analyses and well-established risk factors (tobacco and alcohol consumption).

Statistical analyses were performed using the Stata version 12.0 (Stata Corp, College Station, TX, USA).

Results

The characteristics of the population with HNSCC included in this study (n = 459) are summarized in Table 1. Median age at diagnosis was 59 years (range 37.5–87.3 years) and the distribution of patients by age groups was similar across all tumor locations. Most patients were men. However, the proportion of women was particularly low in the case of laryngeal cancer. The majority of patients with OCC or LC lived in areas with more than 100,000 inhabitants. Most patients had family support and tended to have a lower educational level (primary or no education), with no significant differences among specific locations. One hundred sixty-six patients had a family history of cancer, 47 % of them with head and neck cancer. Of the family members with head and neck cancer, 62.8 % were a first-degree relative of the patient. The majority of patients diagnosed with laryngeal cancer presented clinically with dysphonia. In the case of pharyngeal cancer the most frequent sign was the presence of a

Table 1 Characteristics of cases: overall and by subtypes of squamous head and neck cancer

Head and neck cancer cases	Overall		Subtypes						P^b
			OCC[a]		OHPC[a]		LC[a]		
Variables and potential confounders	(*N* = 459)	%	(*N* = 75)	%	(*N* = 167)	%	(*N* = 217)	%	
Age at diagnosis									
<50	69	15.03	15	20.00	29	17.37	25	11.52	0.277
50–65	270	58.82	42	56.00	99	59.28	129	59.45	
>65	116	25.27	18	24.00	37	22.16	61	28.11	
Missing	4	0.87	0	0	2	1.20	2	0.92	
Gender									
Male	406	88.45	58	77.33	144	86.23	204	94.01	<0.001*
Female	53	11.55	17	22.67	23	13.77	13	5.99	
Area									
≤100,000 inhabitants	176	38.34	20	26.67	82	49.10	74	34.10	<0.001*
>100,000 inhabitants	268	58.39	49	65.33	79	47.31	140	64.52	
Missing	15	3.27	6	8.00	6	3.59	3	1.38	
Familiar support									
No	73	15.90	12	16.00	29	17.37	32	14.75	0.728
Yes	384	83.66	63	84.00	137	82.04	184	84.79	
Missing	2	0.44	0	0	1	0.60	1	0.46	
Level of education									
Primary or lower	296	64.49	43	57.33	112	67.07	141	64.98	0.336
Higher than primary	163	35.51	32	42.67	55	32.93	76	35.02	
Family history of cancer									
Yes	166	36.17	29	38.67	58	34.73	79	36.41	0.871
No	291	63.40	46	61.33	107	64.07	138	63.59	
Missing	2	0.44	0	0	2	1.20	0	0	
Family history of head-neck cancer									
Yes	78	16.99	13	17.33	31	18.56	34	15.67	0.723
No	379	82.57	62	82.67	134	80.24	183	84.33	
Missing	2	0.44	0	0	2	1.20	0	0	
Relative with head-neck cancer									
No	379	82.57	62	82.67	134	80.24	183	84.33	0.720
First-degree	49	10.68	10	13.33	20	11.98	19	8.76	
Second-degree	26	5.66	3	4.00	9	5.39	14	6.45	
Other	3	0.65	0	0	2	1.20	1	0.46	
Missing	2	0.44	0	0	2	1.20	0	0	
Symptoms									
Dysphonia	141	30.72	1	1.33	18	10.78	122	56.22	<0.001*
Dysphagia	38	8.28	6	8.00	22	13.17	10	4.61	
Bulk	62	13.51	9	12.00	35	20.96	18	8.29	
Ulcer	58	12.64	40	53.33	16	9.58	2	0.92	
Pain	66	14.38	15	20.00	33	19.76	18	8.29	
Other	27	5.88	1	1.33	12	7.19	14	6.45	
Various	51	11.11	2	2.67	24	14.37	25	11.52	
Missing	16	3.49	1	1.33	7	4.19	8	3.69	
Time with symptoms									
≤2 months	225	49.02	41	54.67	84	50.30	100	46.08	0.313
>2 months	223	48.58	32	42.67	77	46.11	114	52.53	
Missing	11	2.40	2	2.67	6	3.59	3	1.38	

Table 1 continued

Head and neck cancer cases	Overall		Subtypes						P^b
			OCC[a]		OHPC[a]		LC[a]		
Variables and potential confounders	(*N* = 459)	%	(*N* = 75)	%	(*N* = 167)	%	(*N* = 217)	%	
Weight loss									
Yes	141	30.72	24	32.00	60	35.93	57	26.27	0.107
No	312	67.97	50	66.67	104	62.28	158	72.81	
Missing	6	1.31	1	1.33	3	1.80	2	0.92	
Gastroesophageal reflux									
Yes	160	34.86	24	32.00	57	34.13	79	36.41	0.738
No	292	63.62	51	68.00	106	63.47	135	62.21	
Missing	7	1.53	0	0	4	2.40	3	1.38	

* Statistically significant results

[a] *OCC* oral cavity cancer; *OHPC* oro-/hypopharyngeal cancer; *LC* laryngeal cancer. [b] *P* values were calculated excluding missing values

mass in the neck, followed by pain. Finally, the presence of ulcerated lesions was the most frequent sign in the case of the oral cavity neoplasm. About half of the patients had symptoms for more than 2 months before diagnosis and 30.7 % suffered weight loss. Thirty-five percent of these patients had symptoms suggestive of gastroesophageal reflux, there being no significant differences for the different tumor locations.

Most patients were heavy smokers (Table 2) and many of them had begun smoking at an early age (10–15 years). Black tobacco or a mixture of black and blonde tobacco were the forms most frequently consumed. Some patients (14.4 %) smoked a pipe and/or cigars in addition to cigarettes and are included in the "others" category in Table 2. Most patients were heavy drinkers (Table 2) and had been drinking for an average of 30 years. The grams of ethanol consumed weekly differed significantly between tumor locations, with higher consumption being noted in patients diagnosed with pharyngeal and laryngeal tumors.

Tumor characteristics are listed in Table 3. Most of them were diagnosed in locally advanced stages. Tumors of the pharynx had a larger locoregional extension (stage IVa–b) and were more undifferentiated (histological grade 3) at the time of diagnosis.

Taking laryngeal tumors as the reference group, Table 4 shows the association of sociodemographic characteristics and tobacco and alcohol consumption, the main well-established risk factors, with specific locations. A higher proportion of women were noted in the oro-/hypopharyngeal and oral cavity tumor groups than in the laryngeal cancer group. OHPCs were more strongly associated with rural areas and with alcohol consumption, although less strongly associated with smoking. There were no statistically significant differences in these variables in OCCs with respect to LCs.

Discussion

Head and neck cancer is a very heterogeneous disease that comprises a large number of tumors with clinically and etiologically different characteristics. This study shows the epidemiological characteristics of a Spanish cohort of patients diagnosed with squamous cell carcinoma of oral cavity, pharynx (excluding nasopharynx) and larynx, overall and by tumor location.

Most of the patients were diagnosed at advanced stages and were men aged 50–65 years. There was a higher proportion of women in the group of patients with oral cavity and pharyngeal cancer than with laryngeal cancer. These data are consistent with previously published findings [2, 19]. The lower incidence of HNSCC in women compared with men is explained by differences in the patterns of tobacco and alcohol consumption. In recent decades the number of cases in women has been increasing due to a change in these patterns [19]. Nevertheless, it is not known why women develop oral cavity and pharyngeal cancer more frequently than laryngeal cancer. The two cancers are more frequently linked to alcohol consumption than is laryngeal cancer because of the direct exposure of these locations to alcohol beverages. However, we found a statistically significant excess of women even after adjusting for alcohol consumption. A possible explanation could be that women under-reported their consumption of alcohol, since it is considered less socially acceptable for women to drink. Moreover, women's possible lower consumption of alcohol would have been offset by the well-known stronger carcinogenic effects of alcohol on women than on men [20].

Considering the area of origin of the patients treated at the different hospitals revealed statistically significant differences with respect to primary tumor location, whereby a higher percentage of patients with pharyngeal

Table 2 Tobacco and alcohol consumption: overall and by subtypes of squamous head and neck cancer

Head and neck cancer cases	Overall		Subtypes						P^a
			OCC		OHPC		LC		
Variables and potential confounders	(*N* = 459)	%	(*N* = 75)	%	(*N* = 167)	%	(*N* = 217)	%	
Starting smoking age									
Never smokers	22	4.79	7	9.33	8	4.79	7	3.23	0.078
10–15 years old	227	49.46	28	37.33	80	47.90	119	54.84	
15–20 years old	160	34.86	29	38.67	64	38.32	67	30.88	
>20 years old	43	9.37	9	12.00	12	7.19	22	10.14	
Missing	7	1.53	2	2.67	3	1.80	2	0.92	
Active smokers									
Yes	436	94.99	68	90.67	159	95.21	209	96.31	0.104
No	22	4.79	7	9.33	8	4.79	7	3.23	
Missing	1	0.22	0	0	0	0	1	0.46	
Kind of tobacco									
Never smokers	22	4.79	7	9.33	8	4.79	7	3.23	0.085
Black	176	38.34	25	33.33	56	33.53	95	43.78	
Blond	94	20.48	21	28.00	34	20.36	39	17.97	
Mix	93	20.26	15	20.00	38	22.75	40	18.43	
Others	66	14.38	6	8.00	28	16.77	32	14.75	
Missing	8	1.74	1	1.33	3	1.80	4	1.84	
Pack-years of smoking									
≤20	84	18.30	19	25.33	38	22.75	27	12.44	0.120
21–40	72	15.69	11	14.67	26	15.57	35	16.13	
41–70	139	30.28	21	28.00	46	27.54	72	33.18	
≥71	150	32.68	22	29.33	51	30.54	77	35.48	
Missing	14	3.05	2	2.67	6	3.59	6	2.76	
Environmental smoke									
Yes	335	72.98	50	66.67	121	72.46	164	75.58	0.336
No	117	25.49	24	32.00	42	25.15	51	23.50	
Missing	7	1.53	1	1.33	4	2.40	2	0.92	
Alcohol consumers									
Yes	351	76.47	49	65.33	138	82.63	164	75.58	0.005*
No	104	22.66	26	34.67	26	15.57	52	23.96	
Missing	4	0.87	0	0	3	1.80	1	0.46	
Grams ethanol per week									
<10	104	22.66	25	33.33	26	15.57	53	24.42	0.025*
10–140	98	21.35	18	24.00	35	20.96	45	20.74	
141–280	80	17.43	16	21.33	26	15.57	38	17.51	
>280	164	35.73	16	21.33	69	41.32	79	36.41	
Missing	13	2.83	0	0	11	6.59	2	0.92	

OCC oral cavity cancer, *OHPC* oro-/hypopharyngeal cancer, *LC* laryngeal cancer

* Statistically significant results

[a] *P* values were calculated excluding missing values

cancer were from rural areas (<100,000 inhabitants). In the multivariate analysis, the area of origin remained independently significant, irrespective of cigarette and alcohol consumption. This could be due to different patterns of tobacco consumption, whereby there was greater exposure of the pharynx than the larynx to tobacco smoke in patients from areas with fewer than 100,000 inhabitants. Moreover, considering that a high percentage of oropharyngeal tumors (57–72 %, depending on the context) [21] is caused by HPV infection and that this infection is associated with an

Table 3 Tumor characteristics: overall and by subtypes of squamous head and neck cancer

Head and neck cancer cases	Overall		Subtypes						P^a
			OCC		OHPC		LC		
Variables and potential confounders	(*N* = 459)	%	(*N* = 75)	%	(*N* = 167)	%	(*N* = 217)	%	
Stage									
Ca in situ	3	0.65	0	0	1	0.60	2	0.92	<0.001*
I	24	5.23	9	12.00	2	1.20	13	5.99	
II	33	7.19	8	10.67	4	2.40	21	9.68	
III	96	20.92	10	13.33	20	11.98	66	30.41	
IV	258	56.21	43	57.33	131	78.44	84	38.71	
Metastases	9	1.96	1	1.33	4	2.40	4	1.84	
Missing	36	7.84	4	5.33	5	2.99	27	12.44	
Grade									
1	73	15.90	25	33.33	16	9.58	32	14.75	0.001*
2	160	34.86	27	36.00	48	28.74	85	39.17	
3	60	13.07	8	10.67	29	17.37	23	10.60	
Unknown	166	36.17	15	20.00	74	44.31	77	35.48	

OCC oral cavity cancer, *OHPC* oro-/hypopharyngeal cancer, *LC* laryngeal cancer

* Statistically significant results

[a] *P* value were calculated excluding missing values

Table 4 Multivariable multinomial logistic regression model, taking laryngeal tumors as reference, assessing factors associated with location of HNSCC

Variables	LC (*N* = 217)		OHPC (*N* = 167)		OR	95 % CI[c]	P^b	OCC (*N* = 75)		OR	95 % CI	P^c
Gender												
Male	204	94.01 %	144	86.23 %	Reference			58	77.33 %		Reference	
Female	13	5.99 %	23	13.77 %	3.58	1.55–8.27	0.003*	17	22.67 %	4.33	1.78–10.50	0.001*
Area[e]												
>100,000 inh.	140	64.52 %	79	47.31 %	Reference			49	65.33 %		Reference	
≤100,000 inh.	74	34.10 %	82	49.10 %	1.81	1.17–2.81	0.007*	20	26.67 %	0.80	0.44–1.47	0.482
Pack-years of smoking[f]												
≤20	27	12.44 %	38	22.75 %		Reference		19	25.33 %		Reference	
21–40	35	16.13 %	26	15.57 %	0.46	0.21–0.98	0.045*	11	14.67 %	0.56	0.22–1.44	0.228
41–70	72	33.18 %	46	27.54 %	0.43	0.22–0.84	0.013*	21	28.00 %	0.52	0.23–1.19	0.125
≥71	77	35.48 %	51	30.54 %	0.43	0.22–0.85	0.015*	22	29.33 %	0.58	0.25–1.34	0.202
Grams ethanol per week[f]												
<10	53	24.42 %	26	15.57 %	Reference			25	33.33 %		Reference	
10–140	45	20.74 %	35	20.96 %	2.53	1.22–5.24	0.012*	18	24.00 %	1.27	0.57–2.84	0.554
141–280	38	17.51 %	26	15.57 %	2.47	1.13–5.38	0.023*	16	21.33 %	1.51	0.64–3.55	0.341
>280	79	36.41 %	69	41.32 %	3.20	1.61–6.37	0.001*	16	21.33 %	0.81	0.36–1.86	0.626

LC laryngeal cancer, *OHPC* oro-/hypopharyngeal cancer, *OCC* oral cavity cancer, *OR* odds ratio, *CI* confidence interval

* Statistically significant results

[a] *P* values were calculated by multinomial logistic regression using multivariable analysis

[b] Missing values are described in Table 1

[c] Missing values are described in Table 2

earlier sexual debut and more sexual partners [22], it could also be due to differences in sexual practices between rural and urban populations.

The bivariate analysis revealed no statistically significant differences in cigarette consumption by tumor location. However, in the multivariate analysis we observed a significantly higher proportion of LCs than OHPCs in those patients who had smoked more than 20 pack-years.

In the case of alcohol we identified a higher risk of developing pharyngeal than laryngeal cancer in patients with high alcohol consumption. The development of pharyngeal and oral cavity cancers has been associated with alcohol consumption [20]. Our study did not find a higher risk of developing oral compared with laryngeal cancer among those who consumed alcohol. This may be due to a lack of statistical power, since this is the least-represented location among our sample of patients. Moreover, there was a notable percentage of women diagnosed with oral cavity cancer amongst whom, as discussed above, alcohol consumption may have been underestimated.

A high percentage of patients had family support regardless of tumor location. Family support is a common feature in Mediterranean countries. In Spain, the percentage of men over 65 who live alone is small (22.7 %), their partner being the care provider should this be necessary [23].

Head and neck cancer has been associated with low levels of education in previous studies [10]. Most of the patients in our study had a low educational level (64.5 % of participants had no education or only primary school education).

In most of the cases in our study with a family history of HNC, the affected family member was a first-degree relative (62.8 %). This figure is consistent with those of previous studies, suggesting that there is a higher risk of developing HNC in subjects with a family history of the disease, particularly in those with a first-degree relative with HNC [15, 16].

The clinical appearance of the disease matches the habitually discussed signs and symptoms [3]. Thus, the most common signs of laryngeal, oral cavity and pharyngeal cancers are, respectively, dysphonia, ulcers, and a mass in the neck.

We recognize that our study is limited by the retrospective nature of the design, which makes it susceptible to bias. Moreover, most of the information was obtained via self-administered questionnaires. Thus, in the case of surveys, even though they are accepted as being the best available method of learning about patterns of alcohol consumption [24], they are well known to underestimate a drinkers' risks, either due to recall bias and/or deliberate underreporting. Finally, we had no information about HPV infection, which is an important risk factor for some of these tumors.

In this study we describe the epidemiological characteristics of a group of Spanish patients diagnosed with head and neck cancer. We found a higher proportion of women with oral cavity and pharynx than with laryngeal cancer that could not be ascribed to the gender-based differences in consumption of tobacco and alcohol. We also noted a higher risk of developing pharyngeal cancer in patients who consumed alcohol beverages in great quantities, as has been reported previously by other groups. We demonstrated a higher risk of pharyngeal cancer in areas with fewer than 100,000 inhabitants regardless of cigarette and alcohol consumption consistent with differences between urban and rural areas with respect to tobacco consumption and/or sexual habits. In this context, it would be useful to develop prevention programs in the urban setting and extend them to rural areas.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures performed in this study were in accordance with the ethical standards of the institutional research committees and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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