Trends in hospitalization and death rates among patients with head and neck cancer in Spain, 2009 to 2019

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ABSTRACT

Background: Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer worldwide, and prevalence is still substantially higher in men than in women. Causative factors include smoking and alcohol use, while human papillomavirus (HPV) infection is causally related to a subset of oropharyngeal cancers. In this retrospective study, we aimed to provide estimates on the clinical and economic burden of HNSCC in Spain.

Methods: We used the discharge reports from the Spanish Minimum Basic Data Set (MBDS), to retrospectively analyze hospital discharge data in individuals with a diagnosis of HNSCC in any diagnostic position, based on the ICD coding system (ICD-9-CM and ICD10 CM), from 2009 to 2019.

Results: A total of 175,340 admissions and 14,498 deaths due to laryngeal, pharyngeal and oral cavity cancer were recorded in Spain, of which 85% occurred in men. The most prevalent diagnoses were laryngeal cancer in men (50.9%) and oral cavity cancer in women (49.1%). In general, the hospitalization and death rates for all major head and neck cancer sites decreased in men and increased or remained stable in women during the study period. However, the corresponding rates for tonsillar cancer, strongly associated with HPV infection, increased significantly in men. Overall, the economic burden of HNSCC during the study period was estimated at 100 million euros per year on average.

Conclusion: HNSCC still places an important clinical and economic burden on the health system in Spain. Prevention strategies should be prioritized, and vaccination programs against HPV in both sexes should be reinforced.

Introduction

Head and neck cancer is a heterogeneous group of malignancies that usually begin in the squamous cells that line the mucosal surfaces of the upper aerodigestive tract, most commonly the oral cavity, pharynx and larynx. These cancers are often referred to as head and neck squamous cell carcinomas (HNSCC).1,2 In 2020, HNSCC was the seventh most common cancer worldwide, accounting for 878,348 new cases (670,146 in men and 208,202 women) and 444,347 new deaths (340,360 in men and 103,987 in women).3 HNSCC is typically diagnosed in adult patients and, regardless of the etiology, men are at a substantially higher risk than women (2- to 4-fold) for developing all forms of HNSCC, especially laryngeal cancer.1,2

The most important risk factors for HNSCC are tobacco and alcohol consumption, the combined use of which has a synergistic effect that increases the risk of cancer development, particularly for oral cavity and laryngeal cancer.4 Notably, heavy users of both substances have a ≥35 times greater risk of developing HNSCC.5 However, growing evidence is showing that human papillomavirus (HPV) infection, predominantly type 16 (HPV-16), is causally related with a subset of oropharyngeal squamous cell carcinomas (OPSCC), especially in younger age groups.6 The association between HPV infection and HNSCC development is strongest for tonsillar cancer and weakest for oral cavity and laryngeal cancers.7 Interestingly, HPV-positive HNSCCs comprise a distinct molecular, clinical, and pathological disease entity in a patient demographic that differs substantially from those of HPV-negative HNSCC, along with a markedly improved prognosis.8-10 Individuals with HPV-positive HNSCC tend to be younger and healthier and have different risk factors related to sexual behavior.11

HNSCC associated with smoking and alcohol consumption has been decreasing in incidence in recent decades, particularly among men, due to the substantial reduction in the prevalence of tobacco and alcohol consumption.12,13 Conversely, the incidence of HPV-positive OPSCC has been rising exponentially in the same period, predominantly among younger people in North America and Europe14–16 reaching up to 2.5 times that of HPV-negative OPSCC, and it is currently being more common than HPV-driven cervical cancer.17 This increasing trend is likely to reflect the latency period of about 10 to 30 years after the onset of changes in sexual behaviors that are relevant to oral HPV exposure.18,19

In recent decades, HNSCC survival has improved only modestly. According to data from the Surveillance, Epidemiology and End Results Registry (SEER) in the United States, the overall 5-year relative survival rate increased from...
55% in 1992–1996 to 66% in 2002–2006 in all age groups and all anatomical sites. However, this improvement is thought to be partially attributable to the emergence of HPV-associated HNSCC, rather than to advances in therapeutic interventions per se.20

HNSCC is often preventable and can be cured when identified at early stages. Therefore, prevention strategies should be prioritized to help reduce the clinical burden of HNSCC, primarily by reducing or eliminating preventable risk factors, such as smoking and alcohol use, and secondly, by improving early detection of asymptomatic disease and subsequent interventions to prevent disease progression. Head and neck cancer screening programs have been hampered because many cancers appear de novo and HPV-related precancerous lesions are not well characterized.21 Various screening programmes have reported detection rates for confirmed malignancy or premalignant pathology of less than 3%.22 Notably, the involvement of HPV infection in the development of HNSCC has important implications in this regard.23 Prophylactic vaccination against HPV in both sexes holds great promise for reducing HPV-positive oropharyngeal cancers in the future, and efforts should be made to reinforce adherence to HPV vaccination programs.24 In addition to its dire impact on morbidity and mortality, HNSCC places a substantial economic burden on the public health system. Unfortunately, many patients are diagnosed and treated at a late stage of the disease, conferring a poor prognosis and increased direct costs.25,26

In this retrospective epidemiological study, we aimed to provide estimates on the clinical and economic burden of HNSCC in Spain during the period 2009–2019. Information on trends in HNSCC incidence and mortality and its economic impact, may be useful when prioritizing prevention and medical intervention strategies in Spain.

Methods

Study design and data sources

We used discharge reports from the Minimum Basic Data Set (MBDS), published annually by the Spanish Ministry of Health, to retrospectively analyze hospital discharge data containing a diagnosis of malignant neoplasm of the head and neck in any diagnostic position over a 11-year period, from 1 January 2009, to 31 December 2019. The MBDS includes demographic data (age, sex, place of residence, place of hospitalization), dates of admission and discharge, primary and secondary diagnoses, diagnostic and therapeutic procedures, destination and situation at discharge, clinical and hospital history codes, and financing of care. This database reports more than 90% of admissions to both public and private acute care hospitals in Spain and is validated for data quality and overall methodology by the Spanish Ministry of Health.27,28

For each MBDS discharge record, we retrieved up to 41 diagnoses coded on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9-CM, for cases collected between 2009 and 2015, and up to 45 diagnoses coded on the basis of the International Classification of Diseases, Tenth Revision, Clinical Modification, ICD-10-CM, for cases collected between 2016 and 2019. Records were grouped in oral cavity, pharynx, larynx, tonsils, base of tongue and other locations of oropharynx. For each record, the following variables were collected: diagnosis, sex, age, length of hospital stay, cost per hospital stay and outcome (discharge/death). Eligible malignant neoplasms of the head and neck are listed in Table 1.

Data analysis

The number of hospitalizations and deaths, examined by year, sex and age group, was expressed as absolute frequencies (n). The hospitalization rate, examined by anatomical site, year, sex and age group, and the death rate (defined as the ratio between in-hospital deaths and individuals in the Spanish population during the study period), examined by anatomical site, sex and age group, were expressed per 100,000 population and 95% confidence interval (CI). The fatality rate (defined as the number of deaths per inpatient population), examined by anatomical site, sex and age group, was expressed as percentage and 95% CI. Average hospital length of stay, examined by anatomical site and sex, was expressed in euros. We used the Chi-square test to assess significant differences in proportions, and analysis of variance (ANOVA) for multiple comparisons. To adjust statistical significance for multiple comparisons the post hoc Bonferroni correction was used. Poisson regression models were used to assess differences in the hospitalization and death rates between the study years and age groups. Corrected population data from municipal records, extracted from the Spanish National Institute of Statistics were used as the denominator for the hospitalization rates.29 We assumed that the age distribution of the population registered in the MBDS was equivalent to the general Spanish population. In all tests, the level of significance was set at p < 0.05. For the statistical analysis, we used IBM SPSS Statistics for Windows, Version 19.0 (Armonk, NY: IBM Corp).

Results

Between 2009 and 2019, a total of 175,340 patients were hospitalized in Spain for malignant neoplasms of the head and neck. Of these, 84.7% were men. Among the major head and neck cancer sites, the most prevalent diagnosis in men was laryngeal cancer, which accounted for 50.9% of all hospitalizations, followed by pharyngeal cancer, 28.3% and oral cavity, 20.8%. In women, oral cavity cancer was the most prevalent malignancy, accounting for 49.1% of all hospitalizations, followed by pharyngeal cancer, 28.1% and laryngeal cancer, 22.9% (Table 2). The mean age at admission was 60.2 years (SD 12.2) for pharyngeal cancer (60.8 years [SD 11.5] in men and 57.0 years [SD 14.9] in women), 64.9 years (SD 10.7) for laryngeal cancer (65.2 years [SD 10.6] in men and 61.9 years [SD 12.0] in women), and 65.1 years (SD 13.2) for oral cavity cancer (64.0 years [SD 12.3] in men and 67.5 [SD 14.7] in women).
| Group                     | Subgroup                          | ICD-9-CM<sup>a</sup> | ICD-10-CM<sup>b</sup> | Diagnosis (ICD-10-CM coding system) |
|--------------------------|-----------------------------------|-----------------------|------------------------|-------------------------------------|
| Oral cavity              | Other oral cavity sites<sup>c</sup> | 143.0                 | C03.0                  | Upper gum                           |
|                          |                                   | 143.1                 | C03.1                  | Lower gum                           |
|                          |                                   | 143.8, 143.9          | C03.9                  | Gum, NOS                            |
|                          |                                   | 144.0                 | C04.0                  | Malignant neoplasm of anterior part of floor of mouth |
|                          |                                   | 144.1                 | C04.1                  | Malignant neoplasm of lateral part of floor of mouth |
|                          |                                   | 144.8                 | C04.8                  | Malignant neoplasm of other sites of floor of mouth |
|                          |                                   | 144.9                 | C04.9                  | Malignant neoplasm of floor of mouth, part unspecified |
|                          |                                   | 145.0                 | C06.0                  | Malignant neoplasm of cheek mucosa   |
|                          |                                   | 145.1                 | C06.1                  | Malignant neoplasm of vestibule of mouth |
|                          |                                   | 145.2                 | C05.0                  | Malignant neoplasm of hard palate   |
|                          |                                   | 145.6                 | C06.2                  | Malignant neoplasm of retromolar area |
|                          |                                   | 145.8                 | C06.8                  | Malignant neoplasm of other specified parts of mouth |
|                          |                                   | 145.9                 | C06.9                  | Malignant neoplasm of mouth, unspecified |
|                          | Lip                               | 140                   | C00                    | Malignant neoplasm of lip            |
|                          | Oral tongue<sup>d</sup>           | 141.1                 | C02.0                  | Malignant neoplasm of dorsal surface of tongue |
|                          |                                   | 141.2                 | C02.1                  | Malignant neoplasm of tip and lateral border of tongue |
|                          |                                   | 141.3                 | C02.2                  | Malignant neoplasm of ventral surface of tongue |
|                          |                                   | 141.4                 | C02.3                  | Malignant neoplasm of anterior two-thirds of tongue, part unspecified |
|                          |                                   | 141.9                 | C02.9                  | Malignant neoplasm of tongue, unspecified |
| Pharynx                  | Oropharynx<sup>e</sup>           | 145.3                 | C05.1                  | Malignant neoplasm of soft palate    |
|                          |                                   | 145.4                 | C05.2                  | Malignant neoplasm of uvula          |
|                          |                                   | 145.5                 | C05.8, C05.9           | Malignant neoplasm of palate, unspecified |
|                          |                                   | 146.3                 | C10.0                  | Vallecule                            |
|                          |                                   | 146.4                 | C10.1                  | Anterior surface of epiglottis       |
|                          |                                   | 146.7                 | C10.2                  | Posterior wall of oropharynx         |
|                          | Nasopharynx                       | 147                   | C11                    | Malignant neoplasm of nasopharynx    |
|                          | Hypopharynx                       | 148                   | C12, C13               | Malignant neoplasms of piriform sinus and hypopharynx |
| Larynx                   |                                   | 161.0                 | C32.0                  | Malignant neoplasm of glottis        |
|                          |                                   | 161.1                 | C32.1                  | Malignant neoplasm of supraglottis   |
|                          |                                   | 161.2                 | C32.2                  | Malignant neoplasm of subglottis     |
|                          |                                   | 161.3                 | C32.3                  | Malignant neoplasm of laryngeal cartilages |
|                          |                                   | 161.8                 | C32.8                  | Malignant neoplasm of other specified sites of larynx |
|                          |                                   | 161.9                 | C32.9                  | Malignant neoplasm of larynx unspecified |
|                          | Tonsil and Waldeyer’s ring        | 146.1                 | C09.0                  | Malignant neoplasm of tonsillar fossa |
|                          | Tonsil<sup>f</sup>               | 146.2                 | C09.1                  | Malignant neoplasm of tonsillar pillars |
|                          |                                   | 146.0                 | C09.8                  | Overlapping lesion of tonsil         |
|                          |                                   |                      | C09.9                  | Malignant neoplasm of tonsil unspecified |
|                          | Waldeyer’s ring                   | 149.1                 | C14.2                  | Malignant neoplasm of Waldeyer’s ring |
|                          | Base of tongue and lingual tonsil | 141.0                 | C01                    | Malignant neoplasm of base of tongue |
|                          |                                   | 141.6                 | C02.4                  | Malignant neoplasm of lingual tonsil |
|                          | Other parts of the oropharynx<sup>g</sup> | 141.5, 141.8          | C02.8                  | Malignant neoplasm of tongue junctional zone |
|                          |                                   | 146.6                 | C10.2                  | Malignant neoplasm of lateral wall or oropharynx |
|                          |                                   | 146.8                 | C10.4                  | Malignant neoplasm: Branchial cleft   |
|                          |                                   | 146.5                 | C10.8                  | Malignant neoplasm: Overlapping lesion of oropharynx |
|                          |                                   | 146.9                 | C10.9                  | Malignant neoplasm of oropharynx, unspecified |
|                          |                                   | 149.0                 | C14.0                  | Malignant neoplasm of pharynx, unspecified |
|                          |                                   | 149.8, 149.9          | C14.8                  | Overlapping lesion of lip, oral cavity and pharynx |

<sup>a</sup>ICD-9 CM codes were used for cases collected between 2009 and 2015; <sup>b</sup>ICD-10-CM codes were used for cases collected between 2016 and 2019; <sup>c</sup>Excluding tonsillar neoplasm: other parts of the oropharynx; <sup>d</sup>Excluding the base of tongue, lingual tonsil and tongue junctional zone; <sup>e</sup>Excluding those anatomical sites included in “other locations of oropharynx”; <sup>f</sup>Excluding Waldeyer’s ring; <sup>g</sup>Excluding other anatomical sites where HPV infection is most common.

Overall, the hospitalization rate for HNSCC during the study period was higher in men than in women. For laryngeal cancer, the mean annual hospitalization rate (per 100,000 population) was 29.96 (95% CI 29.76–30.17) in men and 2.36 (95% CI 2.3–2.42) in women. By age group, rates were highest among men aged 65–74 years and in women, among individuals aged 60–64 years. For pharyngeal cancer, hospitalization rates were 16.68 (95% CI 16.52–16.84) and 2.90 (95% CI 2.83–2.97), respectively, the highest rates being in men aged 60–69 years and in women aged 55–64 years. The corresponding rates for oral cavity cancer were 5.44 (95% CI 5.35–5.53) and 2.49 (2.43–2.55) per 100,000 population, respectively; in men, rates were highest in patients older than 60 years, while an age-dependent progressive increase, peaking at 8084 years, was observed in women (Table 2 and Figure 1).

Among men, hospitalization rates showed a decreasing trend over the study period for all diagnoses except for tonsil cancer, while an increasing trend was observed in women. In men, the mean annual hospitalization rate (per 100,000 population) due to oral cavity cancer significantly decreased 2 fold from 2009 to 2019 (15.41 vs. 7.66, p < 0.001); for cancers in other locations of oropharynx, rates decreased 1.5 fold, from 6.15 to 4.19 (p < 0.001), and for laryngeal, pharyngeal and base of tongue cancers, rates decreased 1.3 fold (from 34.03 to 27.06 [p < 0.001]), 1.1 fold (from 18.19 to 15.89 [p < 0.001]), and 1.2 fold (from 3.25 to 2.65 [p = 0.018]), respectively. In contrast, hospitalization rates due to tonsil cancer increased 1.1 fold from 2.34 to 2.6 (p = 0.012). In women, hospitalization rates for oral cavity and laryngeal cancer increased significantly by 1.4 fold, from 5.88 to 7.98 and from 1.97 to 2.76, respectively.
Table 2. Hospitalization rate, fatality rate, death rate, length of stay and direct cost associated with HNSCC in Spain by anatomical site and sex between 2009 and 2019.

| Anatomical site        | N                      | Hospitalization rate | In-hospital deaths | Fatality rate | Death rate | Length of stay | Direct cost |
|------------------------|------------------------|----------------------|--------------------|---------------|------------|----------------|-------------|
|                        | Men        | Women     | Men        | Women     | Men        | Women     | Men        | Women     | Men        | Women     | Men        | Women     | Men        | Women     | Men        | Women     | Men        | Women     |
| Oral cavity            | 30,821     | 13,172    | 5.44      | 2.49      | 1541      | 660       | 11.23     | 10.18     | 0.59       | 0.25       | 7 (11)    | 7 (10)    | 7486      | 6984      |
| Lip                    | 4470       | 1205      | 1.7       | 0.46      | 218       | 63        | 4.88      | 5.23      | 0.08       | 0.02       | 4 (5)     | 3 (5)     | 5106      | 4745      |
| Tongue                 | 14,547     | 7723      | 5.77      | 2.97      | 1574      | 654       | 10.82     | 8.47      | 0.6        | 0.25       | 7 (10)    | 6 (7)     | 8019      | 8111      |
| Gum                    | 19,799     | 9834      | 7.85      | 3.78      | 2223      | 939       | 11.23     | 9.55      | 0.85       | 0.36       | 7 (12)    | 7 (10)    | 7822      | 7495      |
| Pharynx                | 42,082     | 7540      | 16.68     | 2.9       | 5143      | 787       | 12.22     | 10.44     | 1.97       | 0.3        | 6 (10)    | 6 (8)     | 5955      | 5541      |
| Oropharynx             | 16,879     | 3305      | 6.69      | 1.27      | 2200      | 383       | 13.03     | 11.59     | 0.84       | 0.15       | 6 (9)     | 6 (9)     | 5895      | 5951      |
| Nasopharynx            | 8182       | 2780      | 3.24      | 1.07      | 820       | 246       | 10.02     | 8.85      | 0.31       | 0.09       | 5 (7)     | 5 (6)     | 4755      | 4412      |
| Hypopharynx            | 17,263     | 1486      | 6.84      | 0.57      | 2154      | 161       | 12.48     | 10.83     | 0.83       | 0.06       | 7 (12)    | 7 (10)    | 6583      | 6769      |
| Waldeyer’s ring        | 6          | 5         | 0.002     | 0.000     | 2         | 0         | 33.33     | 0.00      | 0.00       | 0.00       | 5 (3)     | 5 (3)     | 4448      | 5205      |
| Larynx                 | 75,583     | 6142      | 29.96     | 2.36      | 5991      | 376       | 7.93      | 6.12      | 2.30       | 0.14       | 6 (12)    | 5 (12)    | 7066      | 7118      |
| Tonsil                 | 5930       | 1424      | 2.35      | 0.55      | 672       | 106       | 11.33     | 7.44      | 0.26       | 0.04       | 6 (8)     | 5 (7)     | 5850      | 5959      |
| Base of tongue and lingual tonsil | 6992 | 1413 | 2.77 | 0.54 | 902 | 159 | 12.9 | 11.25 | 0.35 | 0.06 | 7 (11) | 6 (10) | 6705 | 6570 |
| Other locations of oropharynx | 15,044 | 2737 | 5.96 | 1.05 | 2185 | 379 | 14.52 | 13.85 | 0.84 | 0.15 | 7 (10) | 7 (10) | 5883 | 5896 |

*Mean annual hospitalization and death rates expressed per 100,000 population (95% CI); †Fatality rate expressed as percentage of deaths per inpatient population (95% CI); ‡Median length of stay expressed in days (interquartile range, IQR); ‡Direct cost expressed in euros.
Figure 1. Mean annual hospitalization rate (per 100,000 population) in men (A) and women (B) by anatomical site and age group in the general population of Spain between 2009 and 2019.

(p < 0.001 for both comparisons); for base of tongue cancer, rates increased 1.3fold, from 0.48 to 0.62, \( p = 0.027 \). Hospitalization rates for cancers of the pharynx, other locations of oropharynx and tonsils did not vary significantly throughout the study period (Figure 2 and Supplemental Table S1).

A total of 14,498 head and neck cancer-related in-hospital deaths were reported in Spain from 2009 to 2019, of which 87.4% occurred in men and 12.6% in women. Most deaths occurred in patients older than 35 years. Among men, 47.3% of all deaths were due to laryngeal cancer, with maximum figures recorded in patients aged 65–69 years, 40.6% due to pharyngeal cancer, with maximum figures recorded in patients aged 60–64 years, and only 12.2% due to oral cavity cancer, almost half of which occurred in men aged 55–69 years. In women, 43.2% of deaths were due to pharyngeal cancer, with maximum figures recorded in patients aged 55–59 years, 36.2% due to oral cavity cancer, 50% of which occurred in women older than 75 years, and 20.6% due to laryngeal cancer, more than half among patients aged 50–69 years (Tables 2, 3 and Tables 4).

The estimated mean annual death rates (per 100,000 population) in men were 2.30 (95% CI 2.24–2.36) for laryngeal cancer, with the highest rates recorded in patients aged 75–79 years, 1.97 (95% CI 1.92–2.02) for pharyngeal cancer, with the highest rates recorded in patients aged 65–69 years, and 0.59 (95% CI 0.56–0.62) for oral cavity cancer, with the highest rates recorded in patients older than 80 years. Among women, the corresponding rates were 0.25 (95% CI 0.23–0.27) for oral cavity cancer, the highest rates being in patients older than 85 years, 0.30 (95% CI 0.28–0.32) for pharyngeal cancer, with the highest rates recorded in women aged 75–79 years, and 0.14 (95% CI 0.13–0.15) for laryngeal cancer, with the highest rates found in women older than 85 years (Tables 2, 3 and Tables 4). The annual death rate for oral cavity cancer decreased significantly during the study period both in men, from 1.49 in 2009 to 0.84 in 2019, and in women, from 0.47 to 0.31 (\( p < 0.001 \) for both sexes). In men, death rates due to laryngeal cancer and cancers in other locations of oropharynx also decreased significantly, from 2.67 to 2.20, and from 0.79 to 0.68, respectively,
(p < 0.001 for both comparisons). In contrast, the corresponding rates for tonsil cancer increased significantly from 0.23 to 0.32 (p = 0.001) (Figure 3).

Fatality rates for pharyngeal cancer were estimated at 12.22% (95% CI 11.91–12.53) and 10.44% (95% CI 9.75–11.13) in men and women, respectively, 7.93% (95% CI 7.74–8.12) and 6.12% (95% CI 5.52–6.72) for laryngeal cancer, respectively, and 11.23% (95% CI 10.7–11.76) and 10.18% (95% CI 9.44–10.92) for oral cavity cancer, respectively (Table 2). In men, fatality rates showed a slight but significant increasing trend over the study period for all diagnoses except for base of tongue cancer: from 9.73% to 10.93% for oral cavity cancer (p = 0.037); from 10.83% to 13.36% for pharyngeal cancer (p < 0.0001); from 7.91% to 8.14% for laryngeal cancer (p = 0.015); from 9.87% to 12.25% for tonsil cancer (p = 0.019), and from 12.97% to 16.15% for cancers in other locations of oropharynx (p = 0.034). In women, no significant changes in the fatality rate were observed (Supplemental Table S2).

The median length of hospital stay for inpatients with pharyngeal cancer was 6 (IQR 10) days for men and 6 (IQR 8) days for women, with an estimated cost of 5,955 and 5,541 euros per patient, respectively, and a total cost of 29.2 million euros per year on average; for inpatients with laryngeal cancer, median length of stay were 6 (IQR 12) and 5 (IQR 12) days, with an estimated cost of 7,066 and 7,118 euros per patient, respectively, and a total cost of 57.8 million euros per year on average; for inpatients with oral cavity cancer, median length of stay were 7 (IQR 11) and 7 (IQR 10) days, with an estimated cost of 7,486 and 6,984 euros per patient, respectively, and a total cost of 14.8 million euros per year on average. The total cost of the
hospitalizations for HNSCC during the 11-year study period was estimated to be around 101.8 million dollars per year on average (Table 2).

**Discussion**

This retrospective nationwide study provides data on the burden of hospitalizations and mortality due to head and neck malignant neoplasms in the general population in Spain from 2009 to 2019. More than 175,000 admissions for laryngeal, pharyngeal and oral cavity cancer, and almost 15,000 related in-hospital deaths were recorded during the 11-year period analyzed, representing a substantial clinical and economic burden for both patients and the health care system. The mean age of patients at admission was 63 years, and around 85% of them were men, corresponding to an overall male to female incidence and death rate ratio of approximately 6:1. These figures are similar to those reported in other studies conducted in Spain and in other countries.

Epidemiologic studies on cancer over decades have shown considerable differences between male and female subpopulations in terms of cancer incidence and mortality, with higher rates in males relative to females for most cancer types. Cancers of the lip, larynx, hypopharynx, tonsil and...
Table 4. Death and fatality rates in women by anatomical location and age group in Spain from 2009 to 2019.

| Age group | Oral cavity | Pharynx | Larynx | Tonsil | Base of tongue | Lingual tonsil | Other locations of oropharynx |
|-----------|-------------|---------|--------|--------|----------------|---------------|-----------------------------|
| 0–4 yr    | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 5–9 yr    | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 10–14 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 15–19 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 20–24 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 25–29 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 30–34 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 35–39 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 40–44 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 45–49 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 50–54 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 55–59 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 60–64 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 65–69 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 70–74 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 75–79 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| 80–84 yr  | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |
| >85 yr    | 0           | 0       | 0      | 0      | 0              | 0             | 0                           |

Yr; years; FR; fatality rate; DR; death rate.

*Fatality rate expressed as percentage of deaths in inpatient population (95% CI); *Death rate expressed as in-hospital deaths per 100,000 population (95% CI).

Oropharynx, in particular, have been reported to be among the 10 types of cancers with the largest male-to-female incidence rate ratio. Male to female hospitalization and death rate ratios were particularly high for laryngeal (13:1 and 16:1) and hypopharyngeal cancer (12:1 and 14:1), while more modest rates were found for oral cavity cancer (2:1 for both). Cancer development at these sites is strongly related to tobacco exposure and to excessive alcohol intake. Although smoking prevalence in Spain has decreased significantly in the last decades, even more drastically in men than in women (–42% and –10%, respectively, from 1993 to 2017), it remains high among the population aged 15 years or more (22%), and is still higher in men than in women, 26% and 19%, respectively. This sex disparity is even more pronounced when only heavy smokers are considered, 6% vs 3%, respectively. Comparable figures have been reported across the 27 EU member countries, estimated at 18% (22% in men and 15% in women) and 6.0% (9% in men and 3% in women), respectively. Regular alcohol consumption is also higher in men than in women, 49% vs 25%, respectively, as is binge drinking, at 12% vs 4%, respectively. Alcohol consumption in the WHO European Region has decreased by about 11% in the last 25 years, particularly in the Mediterranean countries, which have recorded a decline of up to 34%. 33, 34 The greater prevalence of tobacco and...
alcohol consumption in men, together with the latency period between exposure and cancer development, results in the currently higher tobacco- and alcohol-related head and neck cancer incidence in men than in women. A recently published systematic review of population-based studies representing 18 countries and spanning almost fifty years showed that, in men, incidence trends for non-HPV-related head and neck cancers declined in all countries except Taiwan and England, while in women, incidence trends increased in both HPV-related and non-HPV-related cancers in different geographical areas, especially in Asian and European countries.

Compared with previous data for the period 1997–2008, the sex disparity in HNSCC hospitalization and death rates in Spain during the period 2009,2019 has narrowed by half, with the male to female ratios dropping from 13:1 and 14:1 to 6:1 and 7:1, respectively. The narrowing sex differential reflects the overall decreasing trend in the hospitalization and death rates from all the major anatomic sites in men, along with a parallel upward or stable trend in women. We found that between 2009 and 2019, hospitalization rates for all major anatomic sites decreased significantly in men, −50% for oral cavity, −20% for laryngeal, and −12% for pharyngeal cancer, as did the death rates for oral cavity (−44%) and laryngeal cancer (−18%). In women, conversely, the hospitalization rates for these two major anatomic sites increased significantly, by 36% for oral cavity and 40% for laryngeal cancer. However, the death rate from oral cavity cancer decreased by 34%, particularly in the last 5 years of the study period, with no significant changes in the other major anatomic sites. The observed trends in hospitalization and death rates are consistent with those reported in this same population for the period 1997–2008, with generalized decreases in both rates in men and increases in women. Compared to the continuous upward trend in oral cancer death rate in women reported

Figure 3. Trend over time of mean annual death rate (per 100,000 population) in men (A) and women (B) by anatomical site in the general population in Spain between 2009 and 2019.
for the entire period 1997–2008, the abrupt change in the trend from the middle of the 2009–2019 period is striking. Although we cannot rule out the contribution of other potential causal relationships, e.g., clinical or epidemiological, it is likely that the transition from ICD-9-CM to ICD-10-CM coding, starting in 2016, has had an effect on the apparent trend in the hospitalization and death rates during the study period.47–49

The significant increase in hospitalization and/or death rates observed in both men and women for tumors arising from squamous cells in the oropharynx (i.e., tonsil and base of tongue cancer) suggest that other risk factors apart from smoking and alcohol consumption, are involved in the current epidemiological pattern of this subset of head and neck cancers. There is enough evidence of the etiological role of HPV infection (mainly HPV 16) in oropharyngeal cancer, particularly for tumors arising from the tonsil, base of tongue and other oropharyngeal sites.50 In recent decades, an increase in the proportion of HPV-positive oropharyngeal cancers (i.e., tonsil and base of tongue cancers) was reported in several economically developed countries, most notably among white, male, middle-aged individuals who often do not have a history of tobacco or alcohol use.14,51–54 This growing trend might reflect changes in sexual behaviors relevant to oral HPV exposure (e.g., oral sex and multiple sex partners).18,19 Data on the prevalence of HPV-related head and neck cancer vary widely depending on the geographic distribution and the subsets of the oropharyngeal tissues. The highest prevalence of HPV-positive oropharyngeal cancer has been reported for United States and Canada (50–60%).55 While in Europe, it has been reported to range from 24% to 57% in southern and northern countries, respectively.56,57 In Spain, several studies have also reported an increase in the prevalence of HPV-positive oropharyngeal cancers in recent decades. Rodrigo et al. reported a nonsignificant but increasing prevalence from 1.8% in the period 1990–1999 to 6.1% in 2000–2009 in northern Spain.58 Another retrospective cohort study showed an increasing risk of HPV-related oropharyngeal cancer from 1991 to 2016 among people in the north-eastern region of Spain (5-year period increase of 30%; 31% for tonsil cancer, and 66% for base of tongue cancer), which was highest in the last 5 years of the study (2012 to 2016).59 Previous results from our group for the period 1997–2008 showed that the hospitalization and death rates for tonsil cancer in Spain still showed a favorable downward trend in men, while in women, the rates for base of tongue cancer already showed a significant upward trend.51

Many studies have suggested that the increasing incidence of HPV-positive oropharyngeal cancers is found almost exclusively among middle-aged individuals, but recent evidence suggests that HPV-positive cancers in elderly patients may be more common in current clinical practice than previously believed.50,51 In our study, the mean age at admission of patients with tonsil cancer was 61 years (61 for men and 60 for women) and for those with base of tongue cancer, 62 years (62 for men and 63 for women). Compared with previous results for the period 1997–2008, the mean age at admission of patients with oropharyngeal cancer—potentially associated with HPV infection—has increased by around 5% in men and 7% in women,31 suggesting that the patient demographics of the disease may be changing, as previously observed in other studies.62–64 Using novel age-period-cohort projection methods, Tota et al. predicted that oropharyngeal cancer incidence rates will probably continue to increase in the near future in the United States, primarily in older (≥65 years) white individuals.61 Although HPV-related oropharyngeal cancers are associated with a much better prognosis and survival than HPV-unrelated cancers (hazard ratios for overall survival and disease free survival, 0.7 and 0.5, respectively), preventive strategies in the near future will be of radical importance, especially considering the highrisk profile of older patients.65 Prophylactic vaccination against HPV in both sexes holds great promise for reducing HPV-positive oropharyngeal cancers in the vaccine-eligible birth cohorts.24 Although differences in the underlying molecular mechanisms are not expected, epidemiological differences such as age and gender distributions might suggest that the efficacy of the HPV vaccine shown in genital cancers may not be directly translatable to oropharyngeal cancer.66 Promising evidence of the potential utility of HPV vaccination in the prevention of oral HPV infection has been published. A recent systematic review including 9 studies and almost 49,000 participants showed the significant and stable effectiveness of HPV vaccines on vaccine-type oral and oropharyngeal HPV infection, regardless of study design. The average relative prevention rate among all the studies was 83%. Furthermore, a significant percentage of participants developed IgG antibodies in oral fluids against vaccine-targeted HPV after vaccination, which could represent an alternative surrogate marker for vaccine effectiveness.67 However, individuals who are currently experiencing an increasing incidence of oropharyngeal cancer (i.e., those born before 1970) are unlikely to benefit from vaccination in coming decades. According to the projections of a recently published population-based age-period-cohort study, the association of HPV vaccination with overall oropharyngeal cancer incidence through 2045 will remain modest (no vaccination vs vaccination: 14.3 vs 13.8 per 100,000 population in 2045), although reductions should occur among young and middle-aged adults.68

In an important step forward in preventing HPV-related head and neck cancer, on 12 June 2020, the US Food and Drug Administration approved an expanded indication for the HPV 9-valent vaccine (Gardasil 9/Merck) to include the prevention of oropharyngeal and other cancers of the head and neck cancer caused by HPV, with the postmarketing requirement/commitment of demonstrating the efficacy of the vaccine in preventing oral persistent infection (i.e., > 6 months) with oncogenic HPV types in men aged 2045 years.69,70 The European Parliament insists that a gender-neutral and publicly-financed HPV vaccination programme be implemented in the Member States in order to ensure the elimination of all HPV-related cancers.71,72 In Spain, however, HPV vaccination has not yet been expanded to boys. The HPV 9-valent vaccine extends coverage for both genders.73

Results from a recently published study showed that the cost of vaccinating a healthy individual throughout his entire life and in full compliance with national vaccination calendars in Spain ranges from 626 euros in men to 726 euros in women; the majority of this cost (67%) corresponds to vaccination
during childhood and adolescence. In the case of people with underlying conditions, the cost ranges from 983 to 1,815 euros. The only difference in the vaccination schedule between men and women in this study was the HPV vaccine, which costs an estimated total of around 100 euros per healthy person for the 3 doses (29.16 euros per dose). Comparable results have been reported for other Western European countries.

Our results clearly show the substantial economic burden associated with HNSCC, with a total direct cost estimated at around 100 million euros per year on average during the 11-year study period. Compared with previous data for the period 1997–2008, the average hospitalization length of stay throughout the study period decreased by about 20% in men, while it increased by 20% in women. However, the estimated mean cost per hospitalized patient slightly decreased by around 10% in both men (from 7,053 to 6,275 euros) and women (from 6,905 to 6,212 euros), resulting in lower total health expenditure during the period.

The total direct costs of cancer in Spain have increased from 4.1 billion euros in 2009 (90 euros per capita) to 5.2 billion euros in 2018 (112 euros per capita). According to these estimates, the direct costs of HNSCC care would account for a small, but still considerable, proportion of the total cancer care expenditure in Spain. As in other countries such as the United States and France, direct and indirect costs in Spain contribute similarly to the overall societal cost of HNSCC, although direct costs are slightly higher than indirect costs, at around 55% and 45%, respectively. The economic impact of head and neck cancers is poorly documented and varies significantly according to national policies and healthcare strategies, making it very difficult to make reliable comparisons. However, our estimated average cost per patient of 6,692 euros is similar to that of other European countries such as France, which reported an estimated average cost per patient of 5,365 euros in 2007 (range 2,764 to 7,673 euros), or the UK, where the estimated average cost per patient in the period between 2003 and 2009 was 4,287 GBP. In north-eastern Italy, however, the average cost per patient in the period between 2007 and 2010 was somewhat higher, estimated at 10,092 euros.

Our study has several strengths. Its main advantage is derived from the use of the MBDS database, which, due to its large sample size, provides high statistical power and representativeness when analyzing clinical variables such as in-hospital mortality. Additionally, the MBDS is subject to a high-quality data audit process at the state level. Our study also has some limitations. The most important limitation of using the MBDS database is the potential undercoding of clinical variables, due, on the one hand, to the intrinsic characteristics of the system (limited number of coding for secondary diagnoses), and, on the other, to deficiencies in the preparation of hospital discharge reports (e.g., failure to include all diagnoses or procedures performed). Another important limitation is that some variables of interest for specific studies may be missing, such as the functional status of the patients, laboratory or treatment variables, or, in the case of this study, information on smoking or alcohol use or HPV infection. The MBDS encodes hospital admissions, so there can potentially be data redundancy for patients who have been hospitalized more than once during the period analyzed. This potential redundancy could affect the point estimates of the prevalence (overestimation) and lethality (underestimation) of the disease. However, due to the large number of records in the database, it is unlikely that a certain percentage of redundant data could alter the general trends in hospitalization and death rates in the long term. Despite this limitation, the MBDS is currently one of the most valuable tools available for clinical and epidemiological research. Head and neck cancer death rates were probably underestimated, since only in-hospital deaths are recorded in the MBDS database. The MBDS database uses the coding scheme of the International Classification of Diseases. The transition from ICD-9-CM to ICD-10-CM coding, starting in 2016, probably had some impact on the epidemiological analysis, affecting the apparent hospitalization and mortality trends during the study period, although it is difficult to assess. A recent narrative literature review found significant gaps that limited the ability to draw reliable conclusions about the overall impact, positive or negative, of moving from ICD-9 to ICD-10 coding in the United States. It may be necessary to wait for longer-term epidemiological data to assess the true dimension of this transition.

In summary, our results show that, despite the slightly decreasing trend in the incidence and death rates of HNSCC in Spain in the last few decades, mainly due to the substantial reduction in the prevalence of smoking and alcohol use, HNSCC is still a clinical and economic burden on the Spanish health system. Although sex differences in hospitalization and death rates are gradually decreasing, trends in women remain stable or moderate compared to trends in men. On the other hand, the generalized increase in the incidence and death rates of head and neck cancer originating in anatomical sites more related to HPV infection, mainly oropharyngeal cancer, not only in young adults but also in older adults, is a cause for concern. In general, HNSCC survival has improved only modestly in the last decades. Prevention strategies should therefore be prioritized by discouraging smoking and alcohol use, reinforcing HPV vaccination programs, and improving early detection and treatment of asymptomatic disease to prevent disease progression.

Acknowledgements

The authors thank the Subdirección General del Instituto de Información Sanitaria for providing the information on which this study is based and Noelia López-Malpartida for critically reading the manuscript and her comments and suggestions. The authors received medical writing support in the preparation of this manuscript from Luis F. García-Fernández, PhD.

Data availability statement

All datasets underlying the current study are available on the Spanish National Health System (CMDB) website at: https://www.mscbs.gob.es/en/estadEstudios/estadisticas/cmbdhome.htm. The information contained in this repository is in the public domain and can be accessed without the need for any administrative permissions.

Disclosure statement

No potential conflict of interest was reported by the author(s).
Ethical considerations

All data included in this study were obtained as part of routine clinical activity and were evaluated retrospectively and anonymously, in strict compliance with the current Spanish and European legislation. For this reason, the Research Ethics Committee of the Rey Juan Carlos University ruled that no formal ethics approval was required for this study.

Funding

This study is part of the research activities of the ”Cathedral in Vaccines Research from Rey Juan Carlos University”, sponsored by Sanoﬁ.

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