Disparities in stage at diagnosis of head and neck tumours in Brazil: a comprehensive analysis of hospital-based cancer registries

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Summary

Background The advanced stage of cancer is a determining factor in poor prognosis. Head and neck squamous cell carcinomas (HNSCC) are highly incident in Brazil, but similarly to many Low and Middle-Income Countries, data is limited regarding the proportion of tumours diagnosed at advanced clinical stages and the main factors associated with it. Therefore, this study aimed to identify the factors associated with advanced stage of HNSCC in Brazil.

Methods Cross-sectional study based on secondary data collected from Hospital-based Cancer Registries (HBCR) between 2000 and 2017. Descriptive data analysis and Poisson regression with robust variance were performed to determine prevalence ratios (PRs).

Findings Among 145,365 HNSCC cases, 78.2% (90,267/115,371) were diagnosed at stages III or IV. The highest percentage of advanced-stage tumours were hypopharyngeal [91.3% (10,186/11,159)], followed by oropharyngeal [86.6% (28,578/32,991)], oral cavity [75.1% (27,121/36,120)], and laryngeal cancer [69.5% (24,382/35,101)]. We observed annual increase trends of 0.29% and 0.38% for oral cavity and oropharyngeal late-stage tumours, respectively. Patients younger than 50 years old, with a low education level, presenting a primary tumour located in the hypopharynx or oropharynx, and alcohol and tobacco consumers were positively associated with advanced stage. Furthermore, we observed a dose–response effect of a statistically significant reduction in the prevalence of cases diagnosed in advanced stages as the patients' age group or education level increased.

Interpretation Diagnosis of HNSCC at advanced clinical stages in Brazil was associated with age, primary tumour site, and socioeconomic factors that must be mitigated, allowing more universal and equitable access and diagnosis at earlier stages.

Funding No funding.

Keywords: Head and neck cancer; Socio-economic factors; Stage at diagnosis; Health care access

Introduction

Head and Neck Squamous Cell Carcinomas (HNSCC) are neoplasms affecting the upper aerodigestive tract mucosa, mainly comprising the oral cavity, pharynx, and larynx.[1] By 2020, approximately 750,000 new cases and more than 360,000 deaths from these tumours were estimated worldwide, with these neoplasms being the sixth most incident in the world.[2] In Brazil, these

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Disclaimer: This summary is available in Portuguese in the Supplementary Material.

Research in context

Evidence before this study

We searched PubMed, LILACS, Science Direct, and Google Scholar, for observational studies, conducted in Brazil, reporting determinants of advanced stage of head and neck squamous cell carcinoma at diagnosis using cancer registration data. We used the following search terms: ("squamous cell carcinoma" OR Cancer OR neoplasm) AND ("head and neck" OR "oral" OR "oral cavity" OR "mouth" OR "laryn*" OR "orophary*" OR "hypophary*") AND ("stage at diagnosis" OR "advanced staging" OR "TNM") AND ("cancer registry" OR "registry" OR "hospital-based") AND "Brazil". Our search was limited to observational studies among adults, which were published before June 1st, 2024, limited to Portuguese, Spanish, and English languages. No study conducted in Brazil investigating the determinants of advanced stages of head and neck squamous cell carcinoma at diagnosis was identified. Head and neck tumors are among the most common in the world, especially in developing countries. Health disparities have been associated with worse health outcomes, including advanced stage at diagnosis, which is one of the main determinants of poor prognosis. Previous studies have been published in Brazil with the aim of evaluating the sociodemographic factors associated with advanced-stage diagnoses of various other cancers. However, this is the first study to evaluate stage at diagnosis of head and neck tumors at the national level. There is, therefore, a need to better understand the factors associated with advanced staging at diagnosis of head and neck cancer in Brazil.

Added value of this study

We conducted a study with 145,365 individuals diagnosed in cancer care establishments, mostly public, distributed throughout Brazil. The use of data from 334 Hospital-Based Cancer Registries (HCR) as a data source is of great value for understanding the health conditions of cancer patients in the country, ensuring regional comparisons. The results of this study expose the regional social inequalities and provide knowledge of their impact on health, serving as a baseline to define actions to eliminate these differences.

Implications of all the available evidence

This study encourages comparisons between Brazilian regions. Based on this and other previous studies, which corroborate this, we identified that the referral and counter-referral flows of patients between the health system's care units need to be reviewed through actions supported by public policies.

tumours are among the ten most incident in men.[3] Alcohol and tobacco consumption are the main risk factors for HNSCC, and an independent and multiplicative effect is observed in concomitant consumption.[4] From a sociodemographic point of view, it is in the stratum of the most vulnerable population where the highest prevalence of alcohol and tobacco consumption is observed.[5] HPV infection is also an etiological factor for oropharyngeal tumours, especially among younger individuals, and in countries with a higher human development index (HDI). In patients diagnosed at the public health system in Brazil (SUS), the prevalence of HPV-positive oropharyngeal tumours is low.[6]

The stage of the disease at diagnosis is an essential prognostic factor. If detected in early stages, HNSCC generally have an overall five-year survival rate of 75%.[7] Furthermore, HNSCC early detection offers more conservative treatment options, resulting in a reduced functional and aesthetic impact, as well as less toxicity for patients. Despite advances in diagnosing and treating HNSCC, there has not been a significant change in survival rates in recent years.[8] This reserved prognosis is partially attributed to the diagnosis of the disease in advanced stages, which, according to some authors, occurs in more than half of the cases.[4,9] From a biological point of view, a disease with more aggressive characteristics may explain the advanced stage at the time of diagnosis.[10] However, demographic factors such as age, sex, race/ethnicity, socioeconomic status, type of health insurance, tumour location, smoking history, and access to care have been associated with detection at advanced stages.[11–13] In Brazil, there is a lack of literature on this topic. Regional studies, which often focus on a single anatomical site, have explored some aspects related to this.[4,14]

Therefore, this study aims to characterize patients with HNSCC treated at hospitals within Brazilian Hospital-based Cancer Registries (HBCR) and identify the demographic and clinical factors associated with the advanced stage of this disease in Brazil.

Methods

This is an observational, cross-sectional study using secondary data. Data were extracted from the Integrator of Brazilian Hospital Cancer Registries (IHCR), which gathers information in a standardised way on sociodemographic, clinical, and hospital care-related characteristics, compiling information from two different sources: Hospital Cancer Registries of São Paulo, coordinated by Fundação Oncocentro de São Paulo (FOSP) and the Integrator of Hospital Cancer Registries (IHCR), coordinated by the Brazilian National Cancer Institute. Currently, more than 300 hospital units in all Brazilian regions contribute with information.

Cases diagnosed with HNSCC were included according to the International Statistical Classification of

Diseases in Oncology, 3rd edition (ICD-O/3), specifically in the oral cavity sites (C00.3-5; C00.8; C02-C06) oropharynx (C01; C05.1, 2; C09-C10), hypopharynx (C12-C13), and larynx (C10.1; C32),[15] with cell carcinoma morphology scaly (M8000/3; M8010/3; M8051/3, 8052/3; M8070-M8076/3; M8082-M8084/3; M8560/3),[16] and recorded in the years 2000–2017. Cases under 18 years of age and over 100 years of age, without sex information, with unknown primary tumour site or histology, with missing stage and with previous diagnosis and treatment of cancer were excluded.

The distribution of missing stage cases was analysed, and we opted for a case-complete analysis.

Outcome

The outcome was the advanced clinical stage at diagnosis, according to the TNM classification. This variable was treated dichotomously as advanced (III and IV), and early (I and II) stages.

Variables

The IHCR collects more variables than FOSP, the variables present in both datasets are collected in a standardised way, from clinical records. The independent variables included in both datasets were: sex (male or female); age-group at the time of diagnosis (18–49 years old, 50–59 years old, 60–69 years old, 70–79 years old, and 80 years old or more); education level (none, incomplete, and complete elementary level, high school, and higher education) and location of the HCR. Additional variables included only in the IHCR dataset were: race/ethnicity (a self-reported variable collected from clinical records whose categories were combined for the analysis in white and non-white); marital status (with or without a partner, including single, widowed, and divorced, and with a partner, -married or in common-law union); alcohol consumption and smoking at the time of diagnosis (yes and no); type of referral to the hospital unit (public, private, or self-employed); and absence or presence of a secondary tumour.

The period from 2000 to 2017 was chosen based on the availability of the Brazilian HBCR databases. We considered this period due to the consolidation of the Brazilian HBCR databases, which began in 2000. At the time of downloading the public database, only the cases observed until 2017 were available.

The year of diagnosis was categorized into three six-year periods, 2000–2005; 2006–2011, and 2012–2017. This classification was based on the number of years analysed and the equal distribution of the number of years across the periods. The histological type was categorized into squamous cell carcinoma (SCC) and not otherwise specified (NOS).

Descriptive population analysis was performed using frequency distribution (%) for categorical variables. To evaluate the temporal trends of advanced stages prevalence, a Joinpoint regression analysis was carried out for each primary tumour site to obtain the Average Annual Percentage Change (AAPC).[17] The geographical distribution of the prevalence (%) of cases diagnosed in advanced clinical stages was plotted using maps, by primary tumour site. Due to the absence of information regarding the socioeconomic status of individuals, HBCR data from São Paulo was analysed separately. For comparison purposes, Pearson's $\chi 2$ test was performed between the independent and dependent variables of the study (advanced clinical stage), considering the value of $p < 0.05$ as significant. As the frequency of the outcome is greater than 10%, Poisson regression with robust variance was applied as a strategy to determine the association between the independent variables and the occurrence of advanced clinical stage (outcome).[18] According to the Wald test ($\alpha = 0.05$), variables with statistical significance or those with theoretical plausibility were kept in the final model. P trend test was applied to evaluate a dose–response effect of independent ordinal variables, which were included in the final model.

This study utilises publicly accessible secondary anonymized data and is exempt from requiring approval by an ethics committee. Access to public data was through the electronic address: https://irhc.inca.gov.br/RHCNet/.

All analyses were performed using the statistical program STATA/MP version 16.0 (Statistics/Data Analysis).

Role of the funding sources

This study did not have any funding.

Results

Between 2000 and 2017, 193,890 head and neck tumours were diagnosed and treated at the registered institutions. According to the eligibility criteria of this study, 145,365 cases were included, covering the 26 Federative Units (FU) of the country and the Federal District. Among these, 99,773 cases [68.6% (99,773/145,365)] were from 25 FU (data integrated by IHCR), and 45,592 [31.4% (45,592/145,365) were from São Paulo state (data integrated by FOSP). Oral cavity [31.7% (46,032/145,365)] and laryngeal cancer [31.4% (45,685/145,365)] were the most common HNSCC site-specific tumours diagnosed in Brazil, followed by oropharyngeal [27.7% (40,288/145,365)], and hypopharyngeal [9.2% (13,360/145,365) cancers.

The percentage of cases with missing clinical stage at diagnosis was similar among primary tumour sites within IHCR and FOSP (Supplementary Table S1). There were 28.1% (28,007/99,773) and 4.4% (1987/45,592) of cases without clinical stage at diagnosis found at IHCR and FOSP, respectively. The final analyses included 115,371 staged cases, including 71,766 from IHCR and 43,605 from FOSP (Fig. 1).

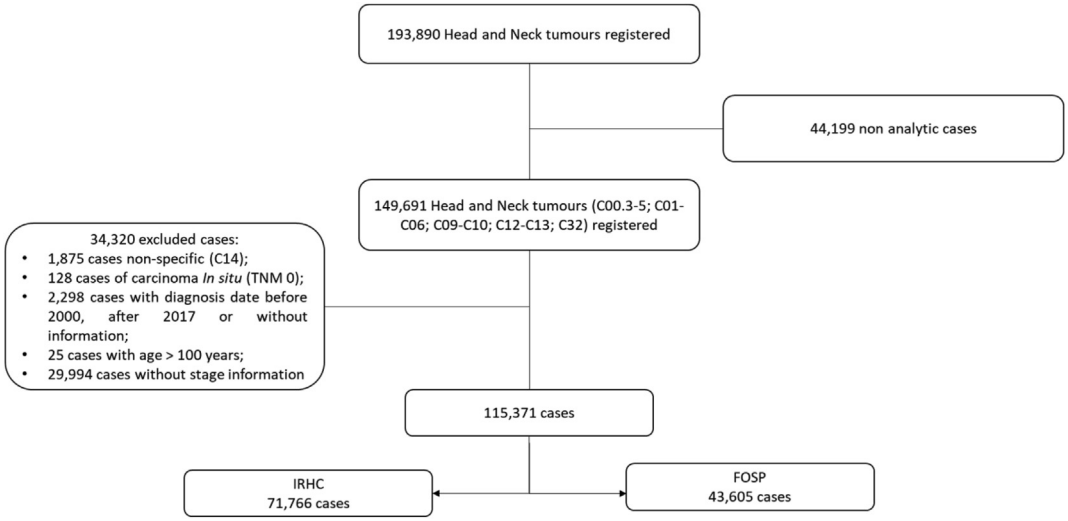

Fig. 1: The selection process flowchart of registered cases diagnosed with HNSCC in the HCR between 2000 and 2017.

Table 1 shows the distribution of cases by stage tumours concerning sociodemographic and clinical characteristics. We observed in IHCR that advanced-stage tumours were most frequently diagnosed in men [83.7% (47,534/56,800)]; aged between 18 and 59 years [53.7% (30,470/56,800); non-white [48.6% (27,610/56,800)]; without a partner [42.0% (23,866/56,800)]; with incomplete elementary education [42.1% (23,883/56,800)]; with a primary tumour located in the oropharynx [31.4%, (17,809/56,800)], or hypopharynx [10.7% (6105/56,800)]; diagnosed in the last periods of the study, from 2006 to 2017 [77.9% (44,290/56,800)]; being referred by the Brazilian Public Health System (SUS) [69.7% (39,584/56,800)]; without a second primary tumour [92.5% (52,544/56,800)]; current or former alcohol consumers [58.2% (33,070/56,800)]; and smokers [71.3% (40,470/56,800)]. At FOSP, we observed that advanced stages tumour cases were most frequently diagnosed among men [87.1% (29,143/33,467)]; aged less than 60 years [55.7% (18,634/33,467)]; with incomplete elementary education [38.6% (12,916/33,467)]; with primary tumours located in the oropharynx or oral cavity [32.2% (10,769/33,467) and 28.8% (9634/33,467), respectively]; and diagnosed in the last years of the study [71.5% (23,925/33,467)].

The prevalence of advanced stage HNSCC was high in Brazil [78.2% (90,267/115,371)] and the percentage of cases at Stage IV increased over the years, from 47.5% (1661/3495) in 2000 to 58.9% (3139/5326) in 2017 (Fig. 2).

Temporal trends of advanced stage prevalence were significantly increasing for oral cavity cancer and the AAPC was 0.29% (95% CI 0.12%, 0.46%) as well as for oropharyngeal cancer (AAPC = 0.38%; 95% CI 0.20%, 0.56%) (Fig. 3). For hypopharynx and larynx, the AAPC were not significant.

The spatial distribution of HNSCC advanced stages, by primary tumour site, is shown in Fig. 4. Between 75 and 89% of the individuals with oral cavity cancer were diagnosed at an advanced stage in the majority of FU (15 of 24 FU with data), the remaining FU had proportions ranging from 50.0 to 74.0%. More than 90% of oropharyngeal cancers were diagnosed at advanced stages in five of six FU from the North Region, whereas in the rest of the country, the proportion of individuals with advanced stages was between 75.0 and 89.0%. More than 90.0% of hypopharyngeal cancers were diagnosed at advanced stages in 17 of 24 Brazilian FU with data. Between 50.0 and 74.0% of laryngeal cancer cases presented with advanced stages in most FU. These proportions are presented in detail, by state, in Supplementary Table S2.

When calculating the proportions of cases presenting at advanced clinical stages by primary tumour site, hypopharyngeal cancer exhibited the highest percentage of tumours in advanced stages [(91.3% 10,186/11,159), followed by oropharyngeal [86.6% (28,578/32,991), oral cavity [75.1% (27,121/36,120)], and laryngeal cancer [69.5% (24,382/35,101) (Table 2).

Table 2 also shows the results of the multivariate analysis of both datasets, revealing that some of the factors associated with advanced stage at diagnosis had similar magnitude of association. Being younger than 50 years was associated with advanced stage (for IHCR, PR = 1.04; 95% CI 1.03–1.05; and for FOSP, PR = 1.08; 95% CI 1.06–1.09) compared to those aged 60–69. Additionally, having a low education level was associated with advanced clinical stage both in IHCR and FOSP datasets (for IHCR, PR = 1.13; 95% CI 1.09–1.16; and for FOSP, PR = 1.24; 95% CI 1.19–1.29) compared to those with college-level education. Furthermore,

IHCR n = 71,766/115,371 (62.2%)				FOSP n = 43,605/115,371 (37.8%)			
Variables	Stage at diagnosis		p value	Variables	Stage at diagnosis		p value
	I-II	III-IV			I-II	III-IV	
	14,966/71,766 (20.9%)	56,800/71,766 (79.1%)			10,138/43,605 (23.2%)	33,467/43,605 (76.8%)	
Sex				Sex			
Male	11,771/14,966 (78.7)	47.534/56,800 (83.7)	<0.0001	Male	8324/10,138 (82.1)	29,143/33,467 (87.1)	<0.0001
Female	3195/14,966 (21.4)	9266/56,800 (16.3)		Female	1814/10,138 (17.9)	4324/33,467 (12.9)	
Age group (years)				Age group (years)			
18–49	2187/14,966 (14.6)	11,000/56,800 (19.4)	<0.0001	18–49	1557/10,138 (15.4)	6469/33,467 (19.3)	<0.0001
50–59	4206/14,966 (28.1)	19,470/56,800 (34.3)		50–59	2957/10,138 (29.2)	12,165/33,467 (36.4)	
60–69	4553/14,966 (30.4)	15,619/56,800 (27.5)		60–69	3163/10,138 (31.2)	9418/33,467 (28.1)	
70–79	2868/14,966 (19.2)	7953/56,800 (14.0)		70–79	1859/10,138 (18.3)	4253/33,467 (12.7)	
80+	1152/14,966 (7.7)	2758/56,800 (4.9)		80+	602/10,138 (5.9)	1162/33,467 (3.5)	
Race/ethnicity				Race/ethnicity			
White	7134/14,966 (47.7)	25,654/56,800 (45.2)	<0.0001	White	–	–	–
Non-white	6827/14,966 (45.6)	27,610/56,800 (48.6)		Non-white			
Missing data	1005/14,966 (6.7)	3536/56,800 (6.2)		Missing data			
Marital status				Marital status			
With partner	8443/14,966 (56.4)	27,984/56,800 (49.3)	<0.0001	With partner			
Without partner	5206/14,966 (34.8)	23,866/56,800 (42.0)		Without partner	–	–	–
Missing data	1317/14,966 (8.8)	4950/56,800 (8.7)		Missing data			
Education				Education			
None	1894/14,966 (12.7)	7657/56,800 (13.5)	<0.0001	None	606/10,138 (6.0)	2229/33,467 (6.7)	<0.0001
Not finished elementary	5915/14,966 (39.5)	23,883/56,800 (42.1)		Not finished elementary	3526/10,138 (34.8)	12,916/33,467 (38.6)	
Finished elementary	1960/14,966 (13.1)	7547/56,800 (13.3)		Finished elementary	1963/10,138 (19.4)	6537/33,467 (19.5)	
High school	1606/14,966 (10.7)	4558/56,800 (8.0)		High school	1019/10,138 (10.1)	2860/33,467 (8.6)	
Some college	522/14,966 (3.5)	1140/56,800 (2.0)		Some college	500/10,138 (4.9)	854/33,467 (2.6)	
Missing data	3069/14,966 (20.5)	12,015/56,800 (21.2)		Missing data	2524/10,138 (24.9)	8071/33,467 (24.1)	
Origin				Origin			
North	485/14,966 (3.2)	2074/56,800 (3.7)	<0.0001	North	50/10,138 (0.5)	162/33,467 (0.5)	<0.0001
Northeast	5164/14,966 (34.5)	15,847/56,800 (27.9)		Northeast	43/10,138 (0.4)	100/33,467 (0.3)	
Southeast	5557/14,966 (37.1)	22,499/56,800 (39.6)		Southeast	9.830/10,138 (97.0)	32.457/33,467 (97.0)	
South	3392/14,966 (22.7)	14,793/56,800 (26.0)		South	32/10,138 (0.3)	41/33,467 (0.1)	
Midwest	262/14,966 (1.8)	1359/56,800 (2.4)		Midwest	179/10,138 (1.8)	696/33,467 (2.1)	
Missing data	106/14,966 (0.7)	228/56,800 (0.4)		Missing data	4/10,138 (0.0)	11/33,467 (0.0)	
IHCR n = 71,766 (62.2%)				**FOSP n = 43,605 (37.8%)**			
Variables	Stage at diagnosis		p value	Variables	Stage at diagnosis		p value
	I-II	III-IV			I-II	III-IV	
	n = 14,966 (20.9%)	n = 56,800 (79.1%)			n = 10,138 (23.2%)	n = 33,467 (76.8%)	
Primary tumour site				Primary tumour site			
Oral cavity	5095/14,966 (34.0)	17,487/56,800 (30.8)	<0.0001	Oral cavity	3904/10,138 (38.5)	9634/33,467 (28.8)	<0.0001
Oropharynx	2523/14,966 (16.9)	17,809/56,800 (31.4)		Oropharynx	1890/10,138 (18.6)	10,769/33,467 (32.2)	
Hypopharynx	533/14,966 (3.6)	6105/56,800 (10.7)		Hypopharynx	440/10,138 (4.3)	4081/33,467 (12.2)	
Larynx	6815/14,966 (45.5)	15,399 (27.1)		Larynx	3904/10,138 (38.5)	8983/33,467 (26.8)	
Hospital Unit Area				Hospital Unit Area			
North	472/14,966 (3.2)	2.049/56,800 (3.6)	<0.0001	North			
Northeast	5149/14,966 (34.4)	15,726/56,800 (27.7)		Northeast			
Southeast	5593/14,966 (37.4)	22,601/56,800 (39.8)		Southeast	–	–	–
South	3474/14,966 (23.2)	15,027/56,800 (26.5)		South			
Midwest	278/14,966 (1.9)	1397/56,800 (2.5)		Midwest			
Diagnosis period				Diagnosis period			
2000–2005	3866/14,966 (25.8)	12,510/56,800 (22.0)	<0.0001	2000–2005	3059/10,138 (30.2)	9542/33,467 (28.5)	0.002
2006–2011	5288/14,966 (35.3)	21,204/56,800 (37.3)		2006–2011	3474/10,138 (34.3)	11,988/33,467 (35.8)	
2012–2017	5812/14,966 (38.8)	23,086/56,800 (40.6)		2012–2017	3605/10,138 (35.6)	11,937/33,467 (35.7)	

(Table 1 continues on next page)

IHCR n = 71,766 (62.2%)				FOSP n = 43,605 (37.8%)			
Variables	Stage at diagnosis		p value	Variables	Stage at diagnosis		p value
	I-II	III-IV			I-II	III-IV	
	n = 14,966 (20.9%)	n = 56,800 (79.1%)			n = 10,138 (23.2%)	n = 33,467 (76.8%)	
(Continued from previous page)							
Access to health services				Access to health services			
SUS	9360/14,966 (62.5)	39,584/56,800 (69.7)	<0.0001	SUS			
Not-SUS	2264/14,966 (15.1)	5819/56,800 (10.2)		Not-SUS	–	–	–
Came on its own	541/14,966 (3.6)	1541/56,800 (2.7)		Came on its own			
Missing data	2801/14,966 (18.7)	9856/56,800 (17.4)		Missing data			
Another primary tumor				Another primary tumor			
No	13,489/14,966 (90.1)	52,544/56,800 (92.5)	<0.0001	No			
Yes	885/14,966 (5.9)	2217/56,800 (3.9)		Yes	–	–	–
Uncertain	22/14,966 (0.2)	228/56,800 (0.4)		Uncertain			
Missing data	570/14,966 (3.8)	1811/56,800 (3.2)		Missing data			
Alcohol consumption				Alcohol consumption			
Never	3778/14,966 (25.2)	10,620/56,800 (18.7)	<0.0001	Never			
Former	1574/14,966 (10.5)	8230/56,800 (14.5)		Former	–	–	–
Current	5279/14,966 (35.3)	24,840/56,800 (43.7)		Current			
Missing data	4335/14,966 (29.0)	13,110/56,800 (23.1)		Missing data			
Smoke				Smoke			
Never	2348/14,966 (15.7)	5718/56,800 (10.1)	<0.0001	Never			
Former	1884/14,966 (12.6)	7458/56,800 (13.1)		Former	–	–	–
Current	7392/14,966 (49.4)	33,012/56,800 (58.1)		Current			
Missing data	3342/14,966 (22.3)	10,612/56,800 (18.7)		Missing data			

In the IRHC dataset, these variables include sex, age group, race/skin colour, education, marital status, access to health services, diagnosis period, primary tumour site, presence of another primary tumour, origin, alcohol consumption, and smoking status. In the FOSP dataset, the available variables were sex, age group, education, diagnosis period, primary tumour site, and origin.

Table 1: **Absolute and relative frequencies (percentages of independent variables per column) of advanced stage cases according to demographic, clinical, and lifestyle variables (n = 115,371).**

presenting a primary tumour located in the hypopharynx (for IHCR, PR = 1.16; 95% CI 1.15–1.18; and for FOSP, PR = 1.25; 95% CI 1.23–1.27), or oropharynx (for IHCR, PR = 1.11; 95% CI 1.10–1.12; and for FOSP, PR = 1.18; 95% CI 1.16–1.19) were associated with advanced stage at diagnosis compared to the oral cavity. In the IHCR dataset analysis, we observed a significant dose–response decreasing effect in the prevalence of cases diagnosed in advanced stages as the patient's age group or education level increased. In the IHCR dataset, having consumed alcohol (PR = 1.06; 95% CI 1.04–1.08) and being a smoker (PR = 1.09; 95% CI 1.07–1.10), or a former smoker (PR = 1.07; 95% CI 1.05–1.09) were also positively associated with advanced stage at diagnosis, compared to non-drinkers and non-smokers, respectively. Whereas identifying a second primary tumour at the time of diagnosis of HNSCC presented a negative association of 11% (PR = 0.89; 95% CI 0.87–0.91) for advanced stages.

Discussion

To our knowledge, this is the first comprehensive Brazilian study evaluating and identifying factors associated with HNSCC advanced clinical stage at diagnosis. This study showed that 78.2% of HNSCC cases in Brazil between 2000 and 2017 were diagnosed at stages III or IV. Younger individuals with low education levels, pharyngeal tumours, and without a second primary tumour at diagnosis were more likely to be diagnosed at an advanced clinical stage. The strongest association of a sociodemographic variable observed in this study was between lower education level, a proxy for socioeconomic status, and advanced clinical stages at diagnosis.

The anatomical site of the primary tumour was identified as a determinant of the disease's stage at diagnosis. In this study, the highest percentage of tumours with advanced stage were diagnosed at hypopharynx (91.2%), followed by oropharynx (86.9%), oral cavity (75.0%), and larynx (69.5%). These results agree with those of other authors who associate the same tumour sites at the time of diagnosis with a worse prognosis.[19] Clinical signs and symptoms are indicators for seeking medical care, making diagnosis possible in the early stages of the disease. Areas that are difficult to access clinically, such as the back of the oral cavity, may present more frequently in advanced stages at diagnosis. In laryngeal cancer, particularly in tumours located in

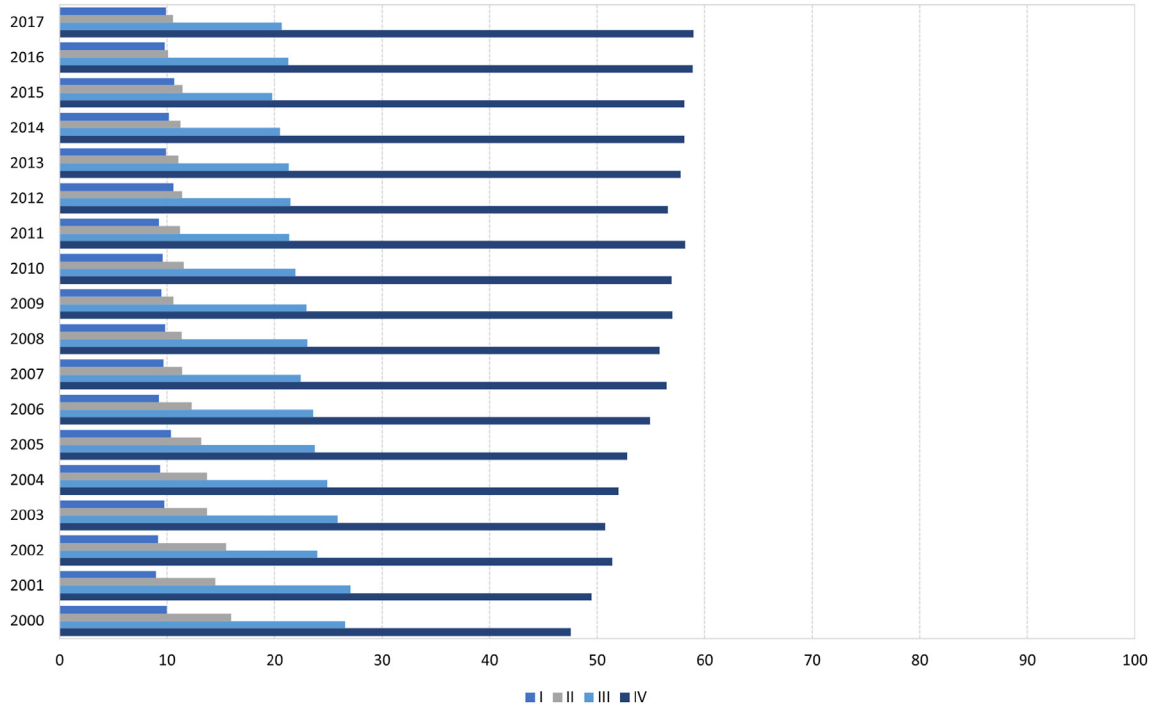

Fig. 2: Distribution of Head and Neck Squamous Cell Carcinoma (HNSCC) cases diagnosed during the study period (2000–2017) by clinical stage (n = 115,371).

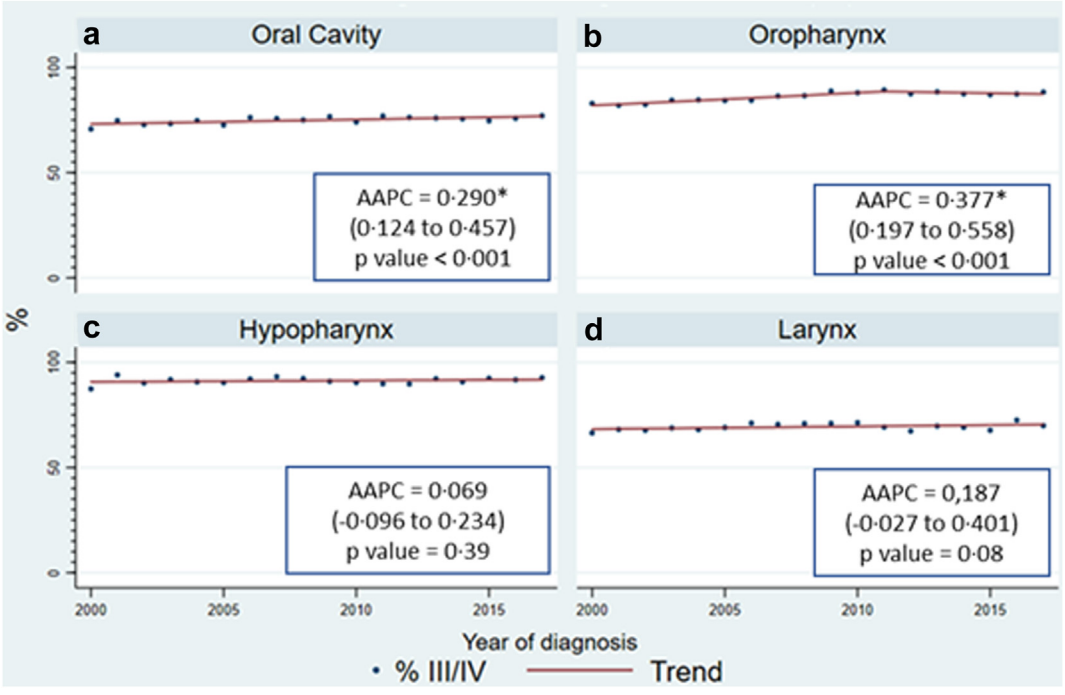

Fig. 3: Average Annual Percentage Change (AAPC) and Confidence Interval (95%) for advanced stage by each tumour site of the Head and Neck: **(a)** oral cavity; **(b)** oropharynx; **(c)** hypopharynx; and **(d)** larynx.

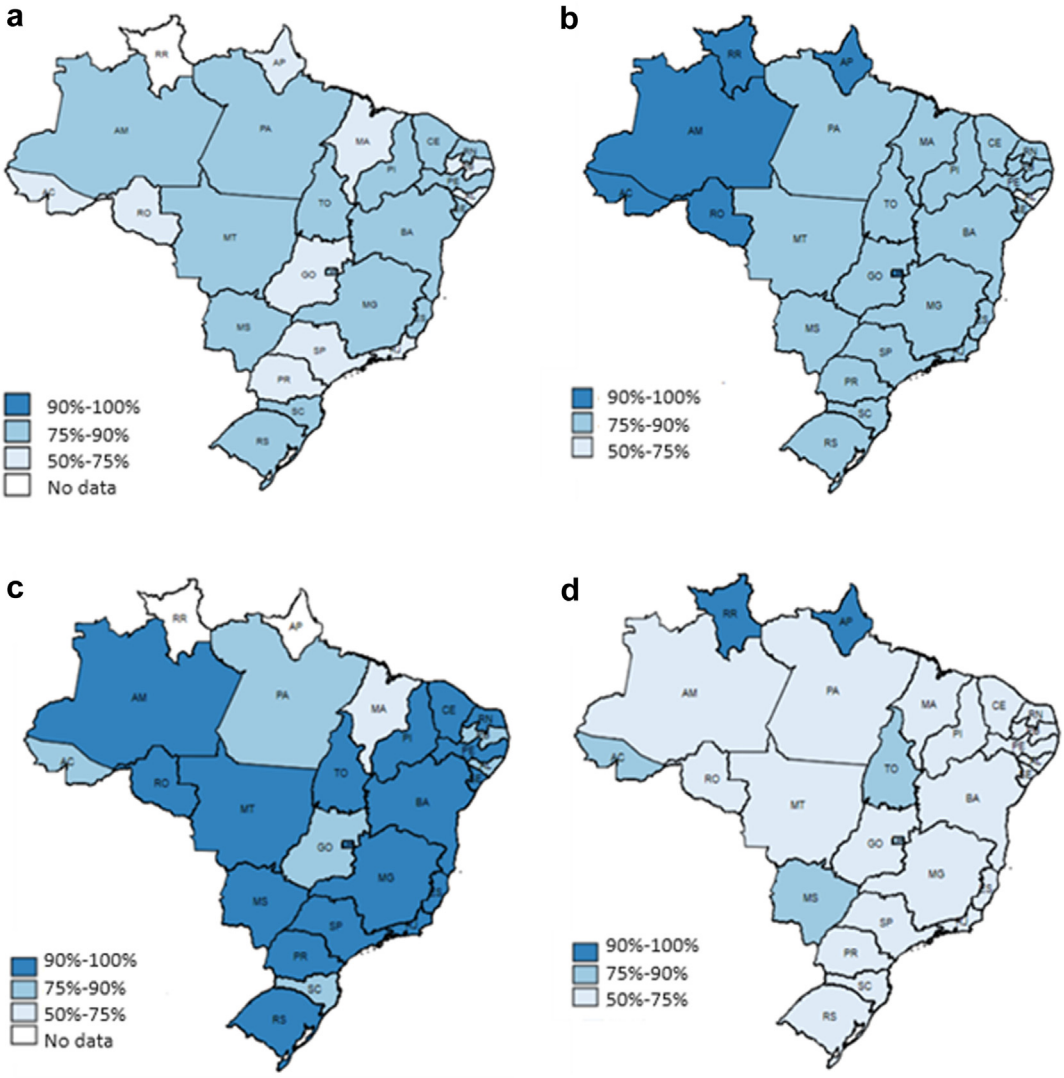

Fig. 4: Percentage (%) of advanced clinical stage cases of Head and Neck Squamous Cell Carcinoma in Brazilian states, 2000–2017, by tumour site, including: **(a)** oral cavity; **(b)** oropharynx; **(c)** hypopharynx; and **(d)** larynx.

the glottis, where vocal changes occur early in the natural course of the disease, diagnosis is possible in the early stages.[12] By comparison, hypopharynx tumours are among the last to show clinical signs and, therefore, are most often diagnosed in advanced stages.[19] The high prevalence of advanced disease at diagnosis in the oropharynx can be explained by the difficulty of clinical access and the increased frequency of HPV-positive tumours. Although detected with small tumour size, these present a large volume in cervical lymph nodes, increasing the clinical stage. Nevertheless, the percentage of HPV-positive oropharyngeal cancer among patients diagnosed at the Brazilian Public Health System (SUS) cancer hospitals is only 6%.[6]

There was a slight increase in the prevalence of cases of stage IV disease over the study period. We detected significant increasing prevalence trends for advanced clinical stage diagnosis with AAPC of 0.29% and 0.38% for oral cavity and oropharyngeal tumours, respectively. Carvalho and colleagues,[20] in study utilising a population-based database, with records spanning from 1973 to 1999, also noted a rise in the incidence of advanced tumours, with the involvement of regional and distant disease, and a reduction in the number of cases in early stages. Our results show increasing prevalence trends of advanced stages, for oral cavity SCC overtime. This phenomenon has been previously[21] observed. The main cause of detection of oral tumours at advanced stages is the delay in diagnosis, which involves several actors and circumstances, such as health professionals, health services, and patient awareness.[21,22] In Brazil, the municipalities with the highest number of cases of

IHCR n = 56,800/71,766 (79.2%)							FOSP n = 33,467/43,605 (76.8%)					
Variables	N (%)[a]	Bivariate		Multivariate		p trend	N (%)[a]	Bivariate		Multivariate		p trend
		Crude PR (CI 95%)	p value[b]	Adjusted PR (CI 95%)	p value			Crude PR (CI 95%)	p value[b]	Adjusted PR (CI 95%)	p value	
Sex												
Male	47,534/59,305 (80.2)	1.08 (1.07–1.09)	<0.0001	1.04 (1.03–1.05)	<0.0001	–	29,143/37,467 (77.9)	1.10 (1.09–1.12)	<0.0001	1.06 (1.04–1.08)	<0.0001	–
Female	9266/12,461 (74.4)	1.00 ref		1.00 ref			4324/6138 (70.5)	1.00 ref		1.00 ref		
Age group												
18 a 49	11,000/13,187 (83.4)	1.08 (1.07–1.09)	<0.0001	1.04 (1.03–1.05)	<0.0001	<0.0001	6469/8026 (80.6)	1.08 (1.06–1.09)	<0.0001	1.08 (1.06–1.09)	<0.0001	<0.0001
50 a 59	19,470/23,676 (82.2)	1.06 (1.05–1.07)		1.04 (1.03–1.05)			12,165/15,122 (80.5)	1.07 (1.06–1.09)		1.07 (1.06–1.08)		
60 a 69	15,619/20,172 (77.4)	1.00 ref		1.00 ref			9418/12,581 (74.9)	1.00 ref		1.00 ref		
70 a 79	7953/10,821 (73.5)	0.95 (0.94–0.96)		0.97 (0.95–0.98)			4253/6112 (69.6)	0.93 (0.91–0.95)		0.94 (0.92–0.96)		
80+	2758/3910 (70.5)	0.91 (0.89–0.93)		0.94 (0.92–0.96)			1162/1764 (65.9)	0.88 (0.85–0.91)		0.90 (0.87–0.94)		
Race/ethnicity												
White	25,654/32,788 (78.2)	1.00 ref	<0.0001	1.00 ref	<0.0001	–	–	–	–	–	–	–
Non-white	27,610/34,437 (80.2)	1.02 (1.02–1.03)		1.04 (1.03–1.05)								
Missing data	3536/4541 (77.9)	1.00 (0.98–1.01)		1.01 (0.99–1.02)								
Education												
None or not finished elementary	31,540/39,349 (80.2)	1.17 (1.13–1.21)	<0.0001	1.13 (1.09–1.16)	<0.0001	0.19	15,145/19,277 (78.6)	1.25 (1.20–1.30)	<0.0001	1.24 (1.19–1.29)	<0.0001	<0.0001
Finished elementary	7547/9507 (79.4)	1.16 (1.12–1.20)		1.10 (1.07–1.14)			6537/8500 (76.9)	1.22 (1.17–1.27)		1.21 (1.16–1.26)		
High school	4558/6164 (74.0)	1.08 (1.04–1.12)		1.05 (1.01–1.08)			2860/3879 (73.7)	1.17 (1.12–1.22)		1.15 (1.10–1.20)		
Some college	1140/1662 (68.6)	1.00 ref		1.00 ref			854/1354 (63.1)	1.00 ref		1.00 ref		
Missing data	12,015/15,084 (79.7)	1.16 (1.12–1.20)		1.13 (1.10–1.17)			8071/10,595 (76.2)	1.21 (1.16–1.26)		1.20 (1.16–1.25)		
Marital status												
With partner	27,984/36,427 (76.8)	1.00 ref	<0.0001	1.00 ref	<0.0001	–	–	–	–	–	–	–
Without partner	23,866/29,072 (82.1)	1.07 (1.06–1.08)		1.05 (1.05–1.06)								
Missing data	4950/6267 (79.0)	1.03 (1.01–1.04)		1.04 (1.02–1.05)								
Access to health services												
Not SUS	7360/10,165 (72.4)	1.00 ref	<0.0001	1.00 ref	<0.0001	–	–	–	–	–	–	–
SUS	39,584/48,944 (80.9)	1.12 (1.10–1.13)		1.07 (1.06–1.08)								
Missing data	9856/12,657 (77.9)	1.08 (1.06–1.09)		1.05 (1.03–1.07)								
Diagnosis period												
2000–2005	12,510/16,376 (76.4)	1.00 ref	<0.0001	1.00 ref	<0.0001	0.0001	9542/12,601 (75.7)	1.00 ref	0.002	1.00 ref	0.002	<0.0001
2006–2011	21,204/26,492 (80.0)	1.05 (1.04–1.06)		1.04 (1.03–1.05)			11,988/15,462 (77.5)	1.02 (1.01–1.04)		1.02 (1.01–1.03)		
2012–2017	23,086/28,898 (79.9)	1.05 (1.04–1.06)		1.03 (1.02–1.04)			11,937/15,542 (76.8)	1.01 (1.00–1.03)		1.02 (1.01–1.03)		
Primary tumour site												
Oral cavity	17,487/22,582 (77.4)	1.00 ref	<0.0001	1.00 ref	<0.0001	–	9634/13,538 (71.2)	1.00 ref	<0.0001	1.00 ref	<0.0001	–
Oropharynx	17,809/20,332 (87.6)	1.13 (1.12–1.14)		1.11 (1.10–1.12)			10,769/12,659 (85.1)	1.20 (1.18–1.21)		1.18 (1.16–1.19)		
Hipopharynx	6105/6638 (92.0)	1.19 (1.18–1.20)		1.16 (1.15–1.18)			4081/4521 (90.3)	1.27 (1.25–1.29)		1.25 (1.23–1.27)		
Larynx	15,399/22,214 (69.3)	0.90 (0.89–0.91)		0.90 (0.89–0.91)			8983/12,887 (69.7)	0.98 (0.96–0.99)		0.98 (0.96–0.99)		
Another primary tumour												
No	52,544/66,033 (79.6)	1.00 ref	<0.0001	1.00 ref	<0.0001	–	–	–	–	–	–	–
Yes	2217/3102 (71.5)	0.90 (0.88–0.92)		0.89 (0.87–0.91)								
Missing data	2039/2631 (77.5)	0.97 (0.95–0.99)		0.99 (0.96–1.01)								

(Table 2 continues on next page)

Variables	IHCR n = 56,800/71,766 (79.2%)					FOSP n = 33,467/43,605 (76.8%)					
	N (%)[a]	Bivariate		Multivariate		p trend	N (%)[a]	Bivariate		Multivariate		p trend
		Crude PR (CI 95%)	p value[b]	Adjusted PR (CI 95%)	p value			Crude PR (CI 95%)	p value[b]	Adjusted PR (CI 95%)	p value	
(Continued from previous page)												
Origin												
Southeast	22,499/28,056 (80.2)	1.00 ref	<0.0001	1.00 ref	<0.0001	–	32,457/42,287 (76.8)	1.00 ref	0.006	–	–	–
North	2074/2559 (81.1)	1.01 (0.99–1.03)		1.04 (1.02–1.06)			162/212 (76.4)	1.00 (0.92–1.07)				
Northeast	15,847/21,011 (75.4)	0.94 (0.93–0.95)		0.96 (0.95–0.97)			100/143 (69.9)	0.91 (0.82–1.01)				
South	14,793/18,185 (81.4)	1.01 (1.01–1.02)		1.03 (1.02–1.04)			41/73 (56.2)	0.73 (0.60–0.90)				
Midwest	1359/1621 (83.8)	1.05 (1.02–1.07)		1.05 (1.03–1.07)			696/875 (79.5)	1.04 (1.00–1.07)				
Missing data	228/334 (68.3)	0.85 (0.79–0.92)		0.88 (0.82–0.94)			11/15 (73.3)	0.96 (0.70–1.30)				
Alcohol consumption												
Never	10,620/14,398 (73.8)	1.00 ref	<0.0001	1.00 ref	<0.0001	–	–	–	–	–	–	–
Former	8230/9804 (84.0)	1.14 (1.12–1.15)		1.06 (1.04–1.08)								
Current	24,840/30,119 (82.5)	1.12 (1.11–1.13)		1.04 (1.03–1.05)								
Missing data	13,110/17,445 (75.2)	1.02 (1.01–1.03)		0.96 (0.94–0.98)								
Smoke												
Never	5718/8066 (70.9)	1.00 ref	<0.0001	1.00 ref	<0.0001	–	–	–	–	–	–	–
Former	7458/9342 (79.8)	1.13 (1.11–1.15)		1.07 (1.05–1.09)								
Current	33,012/40,404 (81.7)	1.15 (1.14–1.17)		1.09 (1.07–1.10)								
Missing data	10,612/13,954 (76.1)	1.07 (1.05–1.09)		1.10 (1.07–1.12)								

[a]The percentages correspond to advanced stage cases by category of variables. In the iRHC dataset, these variables include sex, age group, race/skin colour, education, marital status, access to health services, diagnosis period, primary tumour site, presence of another primary tumour, origin, alcohol consumption, and smoking status. In the FOSP dataset, the available variables were sex, age group, education, diagnosis period, primary tumour site, and origin. [b]Wald test p value.

Table 2: **Bivariate and adjusted Poisson regression analyses between cases with advanced stage (III and IV) according to demographic and clinical characteristics (percentage per line).**

hospitalisation for oral cavity cancer are those that have low coverage of the oral health program. This program aims to provide free and comprehensive oral health care to the Brazilian population, through the Brazilian Public Health System (SUS).[23]

The trends towards an increase in the prevalence of cases of oropharyngeal neoplasms diagnosed at advanced stages in Brazil has been previously reported.[24] For the oral cavity cancer, despite the increase in the number of biopsies due to the expansion of oral health programs, the rise in the percentage of cases diagnosed at advanced stage may be attributed to delays in referrals from primary care services to specialized care.[25]

The North and Northeast regions stood out with the highest percentages of the advanced stage of HNSCC. These findings corroborate those of other recently published authors who analysed SCC of the oral cavity and oropharynx.[4] These are the most unequal regions, having the highest Gini Index, with insufficient coverage of oral health in primary care and unequal distribution of health care units.[23]

Diagnoses in advanced stages are frequent in head and neck tumours, especially in developing countries. In Asian countries and Brazil, for example, the prevalence has been reported to range from 70.0% to 85.0%.[1,26]

In our study, the youngest were diagnosed at more advanced stages. Mohideen and collaborators[27] reported a worse prognosis in younger groups, but without finding a statistically significant difference in the distribution of advanced-stage tumours between young and elderly adults. In the present study, the prevalence of smokers and individuals who reported consuming alcohol at the time of diagnosis was higher among those diagnosed with advanced stages. In fact, according to some authors, smoking is identified as one of the determinants of the advanced stage of oral cavity cancer, with alcohol consumption being a modifier effect, which significantly increases the prevalence of advanced clinical stages.[4] These risk behaviours may be associated with other health outcomes after the cancer diagnosis. Smoking is associated with a worse prognosis, comorbidities, low therapeutic effectiveness, and treatment complications. Furthermore, due to changes in the mucosa, exposure to tobacco and/or alcohol increases the risk of a second primary tumour.[1]

Despite advances in diagnostic methods in recent years, the high number of cases diagnosed at advanced clinical stages reflects inequalities in access to health services. In recent years, socioeconomic status has been frequently described in the scientific literature as a predictor of advanced disease at diagnosis in several types of cancer.[12] There is a multifactorial relationship between head and neck cancer outcomes and socioeconomic status that includes conditions such as education, access to health care services, environmental exposures, dietary conditions, and the prevalence of tobacco and alcohol consumption. Education level is a determining

factor in detecting the disease at an advanced stage.[4,8,9,12] This is a characteristic that is reflected in the patient's delay in looking for a specialist, in the primary care professional's difficulty in identifying suspicious signs and symptoms, and in the mistaken reference to professionals from other specialties, which consequently leads to an increase in time to diagnosis.[10] According to some authors, individuals with low income, low education levels, and more precarious occupations are less likely to be screened for cancer.[12] Although a study done in France did not observe this association, the authors justified that this discrepancy was mitigated by equal access to health services in France.[28]

Black race has been identified in the literature as a predictor of advanced stage at diagnosis and worse overall survival in individuals with HNSCC.[13] In Brazil, Black and brown individuals tend to have lower family income and education levels, and less access to health care compared to their white counterparts, characterising socioeconomic level as a confounding or mediating factor in the association between race/ethnicity and poor head and neck outcomes.[29] In elucidating these racial disparities, Figueiredo Lebre Martins[29] acknowledges colonialism as a significant factor, substantiated by elevated levels of poverty and access barriers experienced by Black populations, contributing to the exacerbation of adverse head and neck cancer (HNC) outcomes in Brazil. Nevertheless, our study did not identify a strong correlation between non-white individuals and advanced clinical stages at diagnosis. This is likely due to the tumours included in this study, as they are related to more vulnerable populations. Moreover, HBCR data includes patients treated in public hospitals, who tend to be more deprived than those attending private hospitals.[11]

The access and frequency of demand for specialised services, with the identification of pre-malignant lesions, can favour the adoption of surveillance procedures, enabling diagnosis in the early stages of the disease. More than 28.0% of oral cavity cancer cases had precursor lesions of the neoplasm, which led to a higher frequency of consultations and, consequently, to early diagnosis.[30] Therefore, we can observe that clinical events, individual behaviours, and the social conditions of patients can be determinants of advanced clinical stages of head and neck cancer.

The study shows, for the first time in Brazil, the proportion of patients diagnosed with advanced stage head and neck cancer and the associated factors. Brazilian guidelines recommend early detection through early diagnosis of oral cavity suspicious lesions. For the other sites, no national guidelines are available.[10] Considering the low prevalence of HPV identified in head and neck tumours in the country, efforts should be directed towards intersectoral actions for tobacco control and public education policies. Additionally, the care pathway for head and neck cancer needs to be better organized within oncological care networks. These networks still face difficulties in referring patients from primary care to more complex specialised services. Organising these processes could reduce the proportion of patients diagnosed at advanced stages. Furthermore, broad actions for primary prevention and early detection of tumours sharing the same risk factors are needed. Brazil's tobacco control program is an example of this. In recent decades, there has been a reduction in tobacco use prevalence due to actions of this program, such as the prohibition of advertising tobacco products and the use of warning images about tobacco-related health damages on manufactured cigarette packs.

This should be interpreted in light of its strengths and limitations. As a secondary analysis, the results may be influenced by individuals' access to hospital services. Nevertheless, the high prevalence of the disease at late stages aligns with previous findings, including those from population-based studies.[4] One strength of this study is the inclusion of numerous cases from various cancer treatment centres nationwide, allowing for data stratification during analysis.

The high prevalence of advanced stages at diagnosis reflects unequal access to the health system. Although Brazil is the country with the largest population with a universal healthcare system, improvements in the flow of patients' access to specialised care are necessary, especially for the most vulnerable strata of the population. Head and neck sites that are more difficult to access clinically are more likely to present in more advanced stages of the disease. In addition, factors associated with socioeconomic status, such as educational level and race/ethnicity, are associated with this outcome, either because of the individual's misperception of the lesion's severity or the barriers to reaching the health care network. Brazil has the largest universal health system in the world, with primary care based on the family health strategy. Community health workers visit the households and potentially can identify hard-to-reach high-risk individuals. Once identified these individuals can be informed of their risk and actively followed up. The results presented here describe a critical scenario of patients reaching health services with advanced-stage lesions and should serve as baseline data to guide the improvement of linkage to care, development of awareness programs, and screening of high-risk patients. These initiatives are crucial for enhancing early detection and ultimately improving patient outcomes.

Contributors

FNC, MCC and LFRP participated in the design and conceptualisation of the study. FNC and MCC were responsible for the data curation. FNC, MCC and LFRP conducted the formal analysis. FNC wrote the original draft. DLBS was responsible for the conceptualization of the study and contributed to the interpretation. LMC participated in some figures and visualization. LFLM participated in data curation and interpretation. FLD contributed to the interpretation. All authors revised and edited the manuscript and approved the final version of the manuscript.

Data sharing statement

All datasets are publicly available online and are de-identified. We describe the data sources in the manuscript.

Declaration of generative AI and AI-assisted technologies in the writing process

AI and AI-assisted technologies, specifically ChatGPT/OpenAI, were employed in the refinement of this manuscript to enhance clarity and the textual structure. Following the use of these tools, the authors meticulously reviewed and edited the content, assuming full responsibility for the final publication. OpenAI's GPT-3.5 language model was used on June 10, 2024.

Editor note

The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

Declaration of interests

All authors declared no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100986.

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