

HEAD AND NECK CANCER EPIDEMIOLOGY IN NORTH SARDINIA, ITALY

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ABSTRACT

The aim of this study was to analyze and describe the epidemiological characteristics and trends of head and neck cancer in North Sardinia, Italy, in the period 1992-2010. Data were obtained from the tumor registry of the province of Sassari which is part of a wider registry web, coordinated, today, by the Italian Association for Tumor Registries. The overall number of head and neck cancer cases registered was 1650. The male-to-female ratio was 5.1:1 and the mean age 62.1 years for males and 63.1 years for females. The standardized incidence rates were 30.2/100,000 and 5.1/100,000 and the standardized mortality rates 11.6/100,000 and 1.6/100,000 for males and females respectively. An increasing trend in incidence of head and neck cancer in women was evidenced. Conversely, incidence was found to slightly decrease in males. Relative survival at 5 years from diagnosis was 50% for males and 55.5% for females. Furthermore, an increase in mortality rates was observed in both sexes in the period under investigation. Our data showed an increasing trend in the incidence of head and neck cancer in women in North Sardinia in recent decades. Conversely, a slight reduction of incidence rates was observed in males. Furthermore, an increasing trend in mortality rates was observed in both sexes, suggesting the need to enhance surveillance policies and to improve diagnosis and treatment methods.

Key words: Head and neck cancer, squamous cell carcinoma, larynx, pharynx, oral cavity, HPV, screening, Sardinia, Italy.

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Introduction

Head and neck cancer (HNC) is the fifth most common neoplastic disease in the world⁽¹⁾ and the eighth most common cause of cancer death⁽²⁾. The term HNC includes a heterogeneous group of diseases that share a common anatomic origin. Although these malignancies may arise from any tissue in this region of the body, most of them develop from within the mucosa that lines the upper aero-digestive tract with the most prevalent site being the oral cavity, followed by the larynx and pharynx⁽³⁾. Approximately 90% of these cancers are squamous cell carcinomas (HNSCC), and grades can vary from well-differentiated keratinizing to undifferentiated non-keratinizing⁽⁴⁾. Considering world incidence rates, HNC ranks as the fifth most common malignancy in men, after lung, stomach, prostate, and colorectal cancers and the eighth most

common cancer in women, after breast, cervix uteri, colorectal, stomach, lung, ovarian and uterine corpus cancers⁽⁵⁾. Alcohol and tobacco abuse are common etiologic factors in cancers of the oral cavity, pharynx and larynx. Because the entire aero-digestive tract epithelium may be exposed to these carcinogens, patients with HNC are at risk of developing second primary neoplasms of the head and neck, lung, esophagus, and other sites that share these risk factors⁽⁶⁾. However the etiologic factors for HNC in individuals who have never used tobacco products are not well understood⁽⁷⁾. Additional environmental risk factors for HNC include poor dental hygiene, poor nutrition, prolonged exposure to ultraviolet light while genetic risk factors are family history or genetic predisposition to cancer^(8,9,10,11). Recently, the role of human papillomavirus (HPV) 16 in HNC, especially for oropharyngeal cancers, has been highlighted⁽¹²⁾.

A decrease in the overall incidence of HNC has been detected worldwide in the past two decades, largely due to a decline in the prevalence of smoking, which began approximately 40 years ago^(13,14). Public health efforts regarding tobacco control started to reduce the prevalence of cigarette smoking in many countries. However, an increase in the incidence of oropharyngeal cancer has been noted in the last 30 years, which is more pronounced in young adults in the USA and European countries^(13,14). Recent evidence suggests that an increasing proportion of these oropharyngeal cancers are caused by HPV. Changes in sexual behavior, leading to increased oral HPV infection, likely contribute to the increased incidence of oropharyngeal cancer⁽¹⁵⁾. The aim of this population-based study was to analyze and describe the epidemiological characteristics and trends of HNC in north Sardinia, Italy, in the period 1992-2010.

Materials and methods

The epidemiological data presented in this article were obtained from the "Registry of tumors of the Province of Sassari". This registry was created in 1992 by the local health agency for the epidemiological surveillance of tumors in the province. In 1999 it became part of a wider web of tumor registries, coordinated today by the Italian Association for Tumor Registries (Associazione Italiana Registri Tumori, AIRTUM). The association coordinates 34 registries in the country, collects and publishes data, and collaborates with international organizations in the field. Every registry collects data on neoplastic diseases affecting inhabitants in the territory of jurisdiction through the local hospitals and health care services, as with other registries (e.g., death registries). Demographic, clinical, pathological and prognostic data are collected for each case of cancer and are registered in a digital database. This database was the data source for the present population-based report as well as other recent reports on cancer epidemiology in the area^(16,17,18,19,20).

The demographic characteristics of the patients affected by HNC were collected. Crude incidence and mortality rates per 100,000 inhabitants per year were calculated, as were standardized rates adjusted for European age-population standards. A comparison between incidence and mortality in the province of Sassari and those in other Italian provinces was performed. Additionally, the

cumulative risk of developing the disease and of dying between zero and 74 years of age was estimated. The age class distribution and time trends of incidence, mortality, as well as histology were evaluated. Finally, relative 5-year survival was calculated by the Hakulinen method.

Results

The overall number of cases of HNC registered in the period under investigation was 1650. Diagnosis was obtained by histological or cytological reports in 1571 cases (95.3%) and using other information sources (clinical reports, radiological referrals, death certifications, etc) in 75 cases (4.5%). The modality of diagnosis was not known in 4 cases (0.2%). Among the 1650 individuals registered, 1380 were males and 270 females, with a male-to-female ratio of 5.1:1. The mean age was 62.1 years for males and 63.1 years for females. The cumulative risk of developing the disease was 2.62% for males and 0.4% for females. As regards the anatomical distribution of the tumors, 36.2% were sited in the oral cavity, 30.2% in the larynx, 12.1% in the oropharynx, 10.2% in the salivary glands, 4.5% in the hypopharynx, 4% in the nasal cavity and paranasal sinuses, and 2.8% in the nasopharynx. Among the 1571 tumors that had histological or cytological diagnosis, 1358 (86.4%) were squamous cell carcinomas, 92 (5.9%) were adenocarcinomas, 92 (5.9%) were other histotypes, while in the remaining 29 (1.8%) cases the exact histologic type was not specified. The crude incidence of HNC in the period under investigation was 33.6/100,000 for men and 6.4/100,000 for women. Standardized incidence rates were 30.2/100,000 for males and 5.1/100,000 for females.

Age class	Males	Females
0-14	0.07	0.37
15-29	0	0.74
30-44	6.6	8.52
45-59	35	34.07
60-74	43.55	31.11
75+	14.78	25.19

Table 1: Age-class incidence distribution.

Table 1 shows the distribution of incidence in relation to age in percentages, while Table 2 shows the distribution of incidence rates in relation to age. Peak incidence rates occurred at 70-74 years for males and over 85 years for females. Incidence

rates were also calculated from 1992 to 2010. There was a slight decrease in incidence rates in males, from 33.2/100,000 in 1992, to 31.5/100,000 in 2010. The corresponding figures for females were 4/100,000 and 8/100,000, respectively (Figure 1). A constant increase in incidence occurred between 1992 and 2010 in women. Analysis of the trend of mean age at disease onset for the same periods of time did not reveal any relevant changes. Table 3 shows the comparison of the incidence and mortality in the province of Sassari with those in other Italian provinces.

Age class	Incidence		Mortality	
	Males	Females	Males	Females
0-4	0	0	0	0
5-9	0	0	0	0
10-14	0.4	0.5	0	0
15-19	0	0	0	0
20-24	0	0.4	0	0
25-29	0	0.3	0	0
30-34	2.3	1.2	0.3	0
35-39	5.7	2.1	0.9	0.9
40-44	20.2	3.8	4.4	0.6
45-49	37	10.2	14.6	2
50-54	56.9	9.5	21.1	1.5
55-59	89	14	25.1	4.3
60-64	104.5	12.1	40.1	5.8
65-69	98.2	12.7	45.8	2.3
70-74	117.4	14.2	45	5.8
75-79	102.9	17.4	46.9	6
80-84	80.8	18.7	56.3	13.1
85+	71.1	23.8	53.3	15.2

Table 2: Age-class incidence and mortality rates.

There were 636 deaths in the period under investigation (543 males and 93 females). Crude overall mortality was 13.2/100,000 for males and 2.2/100,000 for females. Mean age at death was 64.7 years in males and 69 years in females. Standardized mortality rates were 11.6/100,000 for males and 1.6/100,000 for females. The cumulative risk of death was 0.98% for males and 0.12% for females. There was a notable increase in mortality rates after the sixth decade of life in men and after the eighth decade in women. Figure 1 shows the time trend of mortality between 1992 and 2010: a significant increase in mortality in both sexes was registered. Finally, relative survival at 5 years from diagnosis was 53.5% (50% for males and 55.5% for females).

Province	Males		Females	
	Incidence	Mortality	Incidence	Mortality
Alto Adige	36.4	15.6	5.8	1.6
Biella	32.1	17.4	5.4	2
Ferrara	26	11.6	4.2	1.9
Firenze	20.2	7.8	3.4	1.5
Friuli VG	37.7	17.6	6	1.8
Genova	29.1	12.8	4.6	1.5
Macerata	16.4	3.9	1.9	1
Modena	19.8	7.5	3.2	1.2
Napoli	25.1	8.9	4.1	1.6
Parma	25.6	10.8	4.2	1.4
Ragusa	12.1	7.2	1.5	0.6
Reggio E	22.1	7.5	3.8	1.4
Romagna	20.3	6.5	3.6	1.5
Salerno	18.6	8.6	2.7	1.1
Sassari	30.2	11.6	5.1	1.6
Torino	26.5	10.9	4.6	1.5
Trento	38.3	20.4	6.5	2.5
Umbria	18.9	8.3	3.1	1.3
Varese	27	12.8	4.4	1.5
Veneto	35.7	15.4	5.6	2.4

Table 3: Comparison with incidence and mortality rates of other Italian provinces.

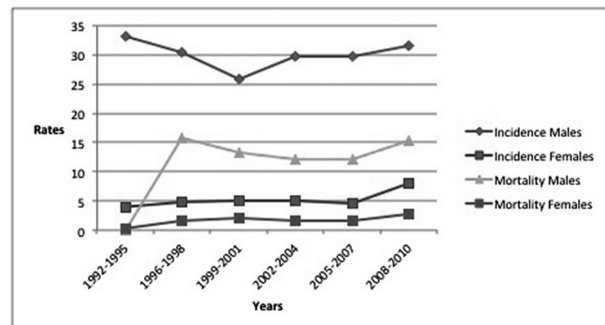


Fig. 1: Incidence and mortality rates trends.

Discussion

HNC is one of the 10 most frequent neoplastic diseases in the world with an estimated annual burden of 563,826 incident cases (including 274,850 oral cavity cancers, 159,363 laryngeal cancers, and 52,100 oropharyngeal cancers) and 301,408 deaths⁽²¹⁾. The incidence rates in the world are higher in the most developed countries being about 4.0-6.8 per 100,000 in males and 0.8-4.5 per 100,000 in females⁽³⁾. The male to female ratio reported by large epidemiological studies and national cancer registries varies from 2:1 to 15:1

depending on the site of disease and geographic region⁽²²⁾. The incidence of cancers of the head and neck increases with age. In Europe, 98% and 50% of patients diagnosed are over 40 and 60 years of age, respectively⁽²²⁾.

In Europe, the crude incidence rates of HNC were 36/100,000/year in the male population and 7/100,000/year for females in 2002, while the corresponding mortality rates were 18 and 3/100,000/year. On the European scale, HNC accounts for 139,000 new cases per year⁽²³⁾. In Europe, a high incidence of oral and oropharyngeal cancers occurs among men in France, Spain, Slovakia, and Slovenia⁽²⁴⁾.

In Italy, in the period between 1998-2002, HNC represented 4.1% of all cancers among males and 1.1% among females; there were on yearly average 32.5 HNC every 100,000 males and 6.5 every 100,000 females. The yearly estimated number of new HNC cases in Italy was 10,432 for males and 1,980 for females; as regards mortality, there were 3,614 deaths in males and 762 in females in 2002. The cumulative risk (0-74 years) was 2.3% among males (1 case every 44 men) and 0.4% among women (1 case every 274 females). The risk of dying was 0.9% in males and 0.1% in females. Incidence rates vary across Italy and the ratio between highest (in northern Italy) and lowest rates (in the South) is about 3 in males and 4 in females. As regards time trends, incidence and mortality are decreasing among males, while among females incidence is increasing and mortality decreasing. The decrease in incidence among males is due to a decrease in larynx cancer incidence. The overall increase of incidence among females is due to the increase of oral cavity and pharynx cancers while larynx cancers are stable⁽²⁵⁾.

Standardized incidence rates in the province of Sassari were similar to those estimated by AIRTUM for northern Italian regions. Comparisons of the incidence rates with those of other Italian provinces place our province near those with high incidence rates, like Trento, Friuli Venezia Giulia and Alto Adige (Table 3). Indeed, among southern Italian regions, such as Ragusa, Salerno and Napoli, Sassari was the one with highest incidence rates.

Concerning histology, our data evidenced a prevalence of squamous cell carcinomas (HNSCC) over adenocarcinomas and other subtypes. Furthermore, a slight increase in incidence of squamous cell carcinomas was evidenced, between 1992 and 2010. Squamous cell carcinoma is the most fre-

quently observed histotype in the head and neck. The most important risk factors are tobacco use and alcohol intake. In a pooled analysis, the proportion of the incidence due to tobacco and alcohol use was estimated at 72% for HNC, of which 4% was due to alcohol alone, 33% was due to tobacco alone and 35% was due to tobacco and alcohol combined⁽²⁶⁾. Although, a decline in the prevalence of smoking has occurred in recent decades, HNSCC incidence rates still remain high in some anatomical sites (oropharynx) and geographic regions and this is thought to be a consequence of persistent infection of high-risk HPV⁽²⁷⁾. These patients are more likely to be male, white, non-smokers, non-drinkers, younger in age and have a higher socioeconomic status. In contrast, the incidence rates of non-HPV related HNSCC have remained stable or decreased among men in Europe and the USA, whilst rates among females have increased; trends which largely reflect changes in gender specific smoking rates⁽²⁷⁾.

The time trends analysis showed a steady increase in the incidence of HNC in females in the province of Sassari in the period under investigation. Conversely, a slight reduction in the incidence rates was observed in males. These trends are common to numerous national and international geographical areas, and may reflect the increasing diffusion of tobacco smoking in women as opposed to the reduction of smoking incidence in men.

At present, primary prevention addressing tobacco, alcohol abuse and dietary habits represents the major tool for controlling risk factors in the general population⁽²⁸⁾. After pooling more than 50,000 sets of individual-level data from case-control studies, the International Head And Neck Cancer Epidemiology Consortium (INHANCE) estimated that quitting tobacco smoking for one to four years reduces the risk of developing HNC, with further risk reduction at 20 years or more, at which time the risk is similar to that of people who have never smoked^(22,29). For alcohol use, a beneficial effect was seen only after 20 years or more of quitting^(22,30). At present, screening programs for these tumors have not been proved to be effective; however, prevention could occur – for oral sites – through a dental or an otorhinolaryngological examination, which is clinically advisable, in particular, for heavy smokers and drinkers. However, it remains difficult to involve this high risk category in prevention programs⁽²⁸⁾.

To date, no screening programs for HNC are active in North Sardinia, as opposed to numerous smoking control campaigns.

HPV-associated oropharyngeal cancer represents a distinct clinical and biological entity with many unresolved issues that will be studied in future translational, clinical research⁽³¹⁾. The potential for clinical intervention into the natural history of HPV-positive oropharyngeal cancer is unknown at this time. HPV testing has recently been incorporated into screening programs for cervical cancer. This practice raises the question of whether analogous screening for HPV in the oral cavity or development of an "oral Pap smear" might lead to early diagnosis and treatment⁽³²⁾. Although detection of oral HPV DNA is associated with oropharyngeal cancer, its utility as a mechanism for secondary cancer prevention through screening is unknown⁽³³⁾.

Another possibility for prevention of HPV-associated HNSCC lies in HPV-vaccination programs⁽³²⁾. With the advent of widespread HPV vaccination programs, it is anticipated that the incidence of HPV-positive tumors (of both the cervix and oropharynx) will decrease in years to come; however, in the meantime it will be crucial to gain a full understanding of the molecular characteristics of HPV-positive and negative tumors, in order to benefit both subgroups of patients⁽²⁷⁾. HPV related oropharyngeal cancer may theoretically be prevented by vaccination against HPV-16, although no strong evidence is available to support this. Currently, most national HPV vaccination programs include only girls, because several health economics assessments did not support the cost effectiveness of including boys⁽³⁴⁾. However the rapid increase in HPV-related oropharyngeal cancer has led some health professionals to call for a reassessment of the cost effectiveness of including boys in such programs^(22,35). This vaccination, together with tobacco control, could have a decisive effect in the prevention of HNC⁽³⁶⁾.

Concerning mortality, 636 (543 males and 93 females) deaths occurred in the 18-year period we studied. Standardized mortality rates were considerably inferior in women. Considering the age-class mortality trend, a natural increase in relation to age was observed in both sexes, with peaks after the eighth decade of life and with a slight increase between 1992 and 2010 (Table 2). Standardized mortality rates increased in the province of Sassari

in the years under investigation. Finally, relative survival at 5 years from diagnosis was slightly higher in women than in men.

Mortality varies throughout the world, being influenced by incidence of disease as well as survival rates after diagnosis⁽⁵⁾. In the United States the 5-year relative age-adjusted survival rate for these head and neck sites was 58% between 1973 and 2002 (58% for males and 60% for females), and have remained unchanged for more than 3 decades⁽³⁷⁾. In Europe, survival data is available from the EURO CARE project. For patients diagnosed in 2000–2002, the survival rate was 72, 44 and 36% at 1, 5 and 10 years, respectively⁽³⁸⁾. Five-year survival was higher in women (51%) than men (39%), as occurred in our study⁽²³⁾. These numbers show the tremendous impact on survival in this patient cohort not only according to the late stage of diagnosis of the primary tumor, but also in terms of high frequency of recurrence, second primary tumors and comorbidities^(37,38).

Conclusions

Little data is available on HNC epidemiology, most comes from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) programme of the United States (US) registers, with lesser data coming from the cancer registers of European countries. Our data showed an increasing trend in the incidence of HNC in women in North Sardinia in recent decades. Conversely, a slight reduction of incidence rates was observed in males. These trends are similar to those observed in other geographical areas throughout the world.

A slightly increasing trend in mortality rates was observed in both sexes in our region, suggesting the need to enhance smoking control strategies, as cessation before the age of 50 reduces HNC mortality by 50%. Furthermore, considering the adoption of effective surveillance policies and the improvement of diagnosis and treatment methods may be necessary.

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