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ORIGINAL ARTICLE

Non-smoking and non-drinking patients with head and neck squamous cell carcinoma: a distinct population

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OBJECTIVE: To recognize specific clinicopathological characteristics of non-smoking and non-drinking (NSND) head and neck squamous cell carcinoma (HNSCC) patients. This can increase our knowledge regarding a potentially different carcinogenesis in these patients.
STUDY DESIGN/METHODS: Retrospective analysis of data for 195 NSND patients with HNSCC and comparison with data for patients with HNSCC obtained from the Netherlands Cancer Registry.
RESULTS: Compared with all HNSCC patients in the Netherlands, our NSND patients with HNSCC were typically female (*n* = 142; 73% *vs* 26%), old at disease presentation (mean 73 years *vs* 64 years), and had tumors mainly of the oral cavity (*n* = 130; 66% *vs* 25%). Most tumors were stage I (*n* = 67; 34%) and stage IVA (*n* = 59; 30%). The incidence of second primary tumors (SPTs) was high (*n* = 32; 16%), mainly occurring in the oral cavity (*n* = 26; 13%).
DISCUSSION/CONCLUSION: Our study confirms that NSND HNSCC patients have different clinicopathological characteristics from those of the overall HNSCC population; however, the frequency of SPTs is as high in NSND patients as in patients who smoke and drink alcohol. More research, and particularly molecular data are needed to obtain a better understanding of head and neck cancer in NSND patients.
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Keywords: head and neck squamous cell carcinoma; non-smoking; non-drinking; tobacco; alcohol; second primary tumors; epidemiology

Introduction

Head and neck squamous cell carcinomas (HNSCCs) are malignant tumors arising from the mucosal membranes of the upper aerodigestive tract. HNSCC is a common malignancy, accounting for 5% of all newly diagnosed cancer cases worldwide. Despite significant improvements in treatment modalities, overall survival rates of HNSCC patients have only moderately improved (Vokes *et al*, 1993). This lack of progress in prognosis is mainly due to two factors. First, a high locoregional recurrence and distant metastases rate (10–30%) and second, the high occurrence of second primary tumors (SPTs) often located in the same or adjacent anatomical region. These SPTs occur at a constant rate of 2–3% per year for more than 10 years (Licciardello *et al*, 1989).

The association between tobacco smoking and alcohol consumption and the development of cancer of the head and neck has been established in many studies. These substances are independent risk factors but exert a synergistic effect when combined (Andre *et al*, 1995; Jaber *et al*, 1999). Individuals who smoke more than 20 cigarettes a day and use more than 100 g of alcohol a day have a 200 times increased risk of developing head and neck cancer (Andre *et al*, 1995). There is, however, a small population of HNSCC patients without these major risk factors. These non-smoking and non-drinking (NSND) patients are an interesting subgroup of HNSCC, but they have rarely been studied, or only in small numbers (Constantinides *et al*, 1992; Agudelo *et al*, 1997; Wiseman *et al*, 2003).

Analysis of this distinct group of HNSCC patients may shed light on several important issues: (i) specific clinicopathologic features (i.e., gender, age, tumor localization and tumor stage at disease presentation and the occurrence of SPT), (ii) additional risk factors, and (iii) possible changes in the non-neoplastic normal epithelium of these patients.

In the present study, we retrospectively described several clinicopathologic characteristics of 195 NSND patients with HNSCC at our center. These data were compared with the same characteristics in all HNSCC patients in the Netherlands Cancer Registry (NCR).

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Patients and methods

All newly diagnosed patients with head and neck cancer at the University Medical Center Utrecht (UMCU) have been prospectively registered in a database since 1980. This database contains information on patient characteristics, risk factors, and tumor classification, including development of recurrences and SPTs. During the period 1980–2003, 4404 patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx were registered. Smoking and drinking habits were recorded. Smoking was categorized as no smoking (i.e., no history of smoking), quit smoking >2 years, quit smoking >1 year, quit smoking <1 year, and as 0–20 cigarettes per day or 20–40 cigarettes per day, and alcohol consumption was categorized as no alcohol consumption (i.e., no history of alcohol consumption), no daily alcohol consumption, 1 consumption per day, 2–4 consumptions per day, 5–9 consumptions per day, and >9 consumptions per day.

Tumors were classified according to the International Classification of Diseases for Oncology and the TNM classification (according to the criteria of the International Union Against Cancer). An SPT was defined according to the criteria of Warren and Gates (1932): (i) each of the tumors must present a definite picture of malignancy, (ii) each must be distinct, and (iii) the probability of one being a metastasis of the other must be excluded. Local recurrence was defined as occurring less than 1.5 or 2 cm from the index tumor and within 3 years of detection of the index tumor.

Patient and tumor characteristics were compared with those of patients with HNSCC included in the NCR. This population-based database, which has full coverage since 1989, contains information derived from the national computerized pathology databank and the hospital discharge databank, to which all Dutch hospitals annually provide information on the discharge diagnosis of admitted patients. Data on diagnosis, treatment, and follow-up for 6 months after cancer diagnosis are retrieved from patients' medical records.

Statistical analysis was performed using nonparametric chi-square test for comparison of disease localization in the two groups of patients (national database patients with HNSCC and the NSND patients with HNSCC). Student's *t*-test was used for statistical analysis of age and gender.

Inclusion criteria

All HNSCC patients (oral cavity, oropharynx, hypopharynx, lip, and larynx) who had no history of smoking or drinking were included in our study.

Results

Of the 4404 patients referred to the UMCU for cancer of the oral cavity, oropharynx, hypopharynx, or larynx in the period 1980–2003, 195 (4.4%) were eligible for inclusion in our study. Most patients were women ($n = 142$; 73%). The mean age at initial diagnosis was 73 years (median 76, range 20–97). Sixteen patients (8%) had a history of another primary tumor other than HNSCC. These tumors were located in the breast ($n = 7$), uterus ($n = 3$), skin ($n = 2$), thyroid gland ($n = 1$), abdomen ($n = 1$), bladder ($n = 1$), and pancreas ($n = 1$). Sixty-two patients (32%) reported malignancy in first- or second-degree relatives, 10 of whom had head and neck malignancy (5%).

Table 1 shows tumor distribution according to pathological TNM classification and site. A substantial percentage of the tumors were located in the oral cavity ($n = 130$; 67%). Most of the tumors were stage I ($n = 67$; 34%) and stage IVA ($n = 59$; 30%). Fifty patients (26%) had cervical lymph node metastases. Four patients (2%) had metastatic disease located in the lung and liver. Thirty-two patients (16%) developed SPTs (Table 2); 26 of these tumors were localized in the oral cavity. Three patients had a third primary tumor, one patient a fourth, one patient a sixth, and one patient a seventh. These tumors were all in the oral cavity.

National data on HNSCC obtained from the NCR for the period 1989–2003 showed a male preponderance (74%) of the disease, with patients being, on average, 63.5 years old at initial diagnosis (Table 3). Most tumors were localized in the larynx (39%). The differences in gender, age and tumor localization between the two groups were statistically significant.

Table 1 Pathological TNM classification by tumor site

	Oral cavity (n = 130)	*Lip (n = 3)*	*Oropharynx (n = 17)*	*Hypopharynx (n = 10)*	*Larynx (n = 35)*	*Total (n = 195)*
T1	45 (35)	1 (33)	5 (28)	0 (0)	18 (51)	69 (35)
T2	43 (33)	0 (0)	4 (24)	1 (10)	8 (23)	56 (29)
T3	8 (6)	1 (33)	4 (24)	2 (20)	4 (12)	19 (10)
T4	34 (26)	1 (33)	4 (24)	7 (70)	5 (14)	51 (26)
N0	97 (75)	2 (67)	7 (41)	5 (50)	34 (97)	145 (74)
N1	18 (14)	0 (0)	2 (12)	2 (20)	0 (0)	22 (11)
N2	12 (9)	0 (0)	8 (47)	2 (20)	1 (3)	23 (12)
N3	3 (2)	1 (33)	0 (0)	1 (10)	0 (0)	5 (3)
M0	127 (98)	3 (100)	16 (94)	10 (100)	35 (100)	191 (98)
M1	3 (2)	0 (0)	1 (6)	0 (0)	0 (0)	4 (2)

Values are expressed as *n* (%).

Table 2 Incidence of subsequent head and neck squamous cell carcinoma

Primary tumor	*Second primary tumor*	*Third primary tumor*	*Fourth primary tumor*	*Sixth primary tumor*	*Seventh primary tumor*
Oral cavity (n = 130)	Oral cavity (n = 23) Oropharynx (n = 3)	Oral cavity (n = 3)	Oral cavity (n = 1)	Oral cavity (n = 1)	Oral cavity (n = 1)
Lip (n = 3)	0	0	0	0	0
Oropharynx (n = 17)	Oral cavity (n = 2)				
Hypopharynx (n = 10)	0	0	0	0	0
Larynx (n = 35)	Oral cavity (n = 1) Oropharynx (n = 1) Hypopharynx (n = 2)				
Total (n = 195)	32 (16%)	3 (2%)	1 (1%)	1 (1%)	1 (1%)

Table 3 National HNSCC data (NCR) *vs* NSND HNSCC patients

	NSND, n (%)	*NCR, n* (%)	*P*
Gender			
Male	53 (27)	14 128 (74)	< 0.001
Female	142 (73)	4837 (26)	
Total	195 (100)	18 965 (100)	
Age			
Mean	72.7	63.5	< 0.001
Median	75.6	64	
Site			
Oral cavity	130 (66)	4773 (25)	< 0.001
Lip	3 (2	2046 (11)	
Oropharynx	17 (9)	3180 (17)	
Hypopharynx	10 (5)	1498 (8)	
Larynx	35 (18)	7468 (39)	
Total	195 (100)	18 965 (100)	

HNSCC, head and neck squamous cell carcinoma; NCR, National Cancer Registry; NSND, non-smoking and non-drinking.

Discussion

The NSND HNSCC patients represented 4.4% of all patients with head and neck cancer treated at our center. This proportion is consistent with a reported incidence of 2.4–3.9% (Constantinides *et al*, 1992; Agudelo *et al*, 1997; Wiseman *et al*, 2003). Compared with all HNSCC patients in the Netherlands, our NSND patients with HNSCC were mainly female (73% *vs* 26%), were older (73 years *vs* 64 years), and had tumors mainly of the oral cavity (66% *vs* 25%).

Our study outcomes were consistent with those in the existing literature, although relatively few studies have evaluated NSND patients with HNSCC. Wiseman *et al* (2003) conducted a case series investigation of 40 NSND patients with HNSCC with a high percentage of older women (75%, mean age 60). Seventy-five percent of the tumors were in the oral cavity. Twenty-four percent of the patients developed an SPT.

Agudelo *et al* (1997) retrospectively reviewed 933 patients with squamous cell carcinoma of the larynx, of whom 31 (3.3%) had no history of tobacco or alcohol use. Comparison of the NSND patients with their smoking and drinking counterparts showed that the NSND patients were, on average, 10 years older, that there was no male predominance, and that the lesions were mainly located in the glottis, which permitted early diagnosis and a better survival. None of the patients developed SPTs.

Constantinides *et al* (1992) described a cohort of 10 NSND elderly patients (inclusion criteria was age > 59 years), nine of whom were women. Their median age was 75 years (range 60–87). Lesions were confined to the oral cavity (n = 6), oropharynx (n = 3), and larynx (n = 1). Three patients developed disease recurrence and two patients developed SPTs. de Boer *et al* (1997) examined 125 NSND women older than 40 years. These patients were 15 years older than their drinking and smoking counterparts, with most tumors localized in the oral cavity (73%).

Our findings and the current literature show that there are different populations of patients with HNSCC. NSND patients are mostly female, older, have more oral cavity tumors, and have a high incidence of SPTs. This suggests that carcinogenesis is possibly different in these two patient populations and that other tumorigenic factors may be relevant, such as human papilloma virus (HPV), gastrointestinal reflux disease, oral lichen planus, poor diet, and familial predisposition.

Human papilloma virus has been implicated in the development of oropharyngeal-localized neoplastic lesions (Mineta *et al*, 1998; Wilczynski *et al*, 1998; Gillison *et al*, 1999). HPV infection rate in our NSND population was not known. Gastrointestinal reflux disease and chronic voice abuse have been suggested as possible etiologic factors for laryngeal squamous cell carcinoma (Morrison, 1988; Freije *et al*, 1996), but not for oral cavity HNSCC as in the majority of our patients. A causal link between oral lichen planus and HNSCC has not been established, though some studies describe the transition of lichen planus to oral squamous cell carcinoma. The reported incidence of these tumors varies between 0.4% and 2.5% (Kaplan and Barnes, 1985; Katz *et al*, 1990). We do not know whether patients in our study suffered from oral lichen planus. The possible association between nutritional deficiencies and HNSCC remains controversial, but a number of case–control studies have consistently shown patients with oral cancers to have a poor diet (Winn *et al*, 1984; Rossing *et al*, 1989). Our patients' nutritional status was not available.

Only a few studies have evaluated the role of familial predisposition in HNSCC (Goldstein *et al*, 1994; Copper *et al*, 1995). One study showed the incidence of HNSCC in first-degree relatives of patients with new HNSCC to be significantly higher than in a control group (Copper *et al*, 1995). In this study, most of the

relatives of patients with oral and pharyngeal cancer had tumors of the upper digestive tract and most of the relatives of patients with laryngeal cancer had lung cancer. All patients and relatives had been exposed to the traditional HNSCC risk factors, namely tobacco and alcohol. To our knowledge, there are no studies of familial predisposition in NSND patients with HNSCC.

The absence of any known potential risk factor suggests that specific molecular and genetic mechanisms may be involved in the tumorigenesis of head and neck cancer in our population. Sorensen *et al* (1997) found no p53 mutations in six NSND patients younger than 40 years. Koch *et al* (1999) found a lower p53 mutation rate and a higher HPV infection rate in a non-smoking HNSCC population. They also found that non-smokers were likely to have less loss of heterozygosity at chromosomes 3p, 4q, and 11q13, and a lower overall percentage of microsatellite alterations. Singh *et al* (2002) also reported that gains of 1p and amplification of 3q were significantly less common in NSND patients. These genetic differences in NSND patients indeed suggest a different pathogenesis. Further studies are needed to clarify this issue.

Strikingly, SPTs occurred in 16% of our NSND patients with HNSCC, which is approximately the same percentage as in HNSCC patients who smoke tobacco and drink alcohol (Licciardello *et al*, 1989; Panosetti *et al*, 1989). Two theories have been advanced to explain the pathogenesis of multiple HNSCC tumors. The first theory is based on the concept of field cancerization, proposed by Slaughter *et al* (1953), which states that a large area of the aerodigestive tract mucosa is affected by long-term exposure to carcinogens, leading to multiple, independently developing lesions. van Oijen *et al* (1998) studied this concept by investigating the proliferation index of epithelium from adjacent, histologically normal mucosa taken from smoking and non-smoking HNSCC patients. They observed a significantly increased proliferation index in epithelia from smoking patients, but not in epithelia from the non-smoking patients. The authors concluded that multiple tumors might be the result of continuous exposure to tobacco; however, this does not explain the high frequency of SPTs in NSND patients.

The second theory proposes that at least a proportion of multiple HNSCCs arise from one clonal cell population. Genetically altered fields containing the p53 mutation similar to that observed in the index tumor have been detected in macroscopically normal mucosa surrounding the tumor and in some cases even extending beyond the surgical margins (Bedi *et al*, 1996; Tabor *et al*, 2001). Partridge *et al* (2001) examined a cohort of 11 patients with multiple HNSCC – including nine NSND patients – and found some identical novel microsatellite alleles indicating early genetic aberrations and a common clonal origin. They suggested that multiple lesions in these patients arise due to lateral spread from a common precursor and thus are clonally related. Thus it appears that in NSND patients, HNSCCs arise from clonal spread and not independently.

Despite the lack of exposure to tobacco and alcohol and for reasons not yet understood, the upper airway mucosa of NSND patients seems to have the same tendency to develop more than one tumor. To date, p53 mutations or an increased proliferation index, which are indicative of genetic alterations, have not been found, which suggests that other mechanisms must be responsible for this phenomenon. Future studies are needed to determine why the epithelium – although not exposed to known carcinogens – is still prone to develop multiple neoplastic lesions.

In conclusion, our study confirms the distinct clinicopathologic characteristics of NSND patients with HNSCC. These patients are older, mainly female, and their tumors are predominantly localized in the oral cavity. Surprisingly, the rate of SPT development is similar in patients with HNSCC who smoke and drink and in NSND patients with HNSCC. More knowledge of head and neck cancer in NSND patients is required to elucidate the mechanisms of their proneness to develop multiple tumors.

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