

RESEARCH ARTICLE

Head and Neck Squamous Cell Carcinoma in Iranian Patients and Risk Factors in Young Adults: a Fifteen-Year Study

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Abstract

Background: Head and neck squamous cell carcinoma (HNSCC) is the 8th most common cancer worldwide. Although older age, male gender, smoking and alcohol consumption are known risk factors, an increasing number of HNSCC patients are without typical risk factors. Our aim was to define demographics of HNSCC in Iran and the potential risk factors related to Iranian ethnicity and lifestyle. **Methods:** We conducted a cross-sectional analytical study on 262 patients with primary SCC of the larynx, hypopharynx or tongue referred to our pathology department during 1995-2010. Patients' demographics, tumor characteristics and risk factors such as smoking, alcohol consumption and anemia were analyzed and compared in two groups of patients: over 40 years (older group) and 40 years or less (young group); Chi-square and Mann-Whitney analytical tests were employed. **Results:** 5.7% of patients were young adults. The male to female ratio was 1.5 in the younger group and 5.6 in the older group. In young adults, 40% of tumors were located in larynx and 40% in the tongue. Age >40 was significantly associated with laryngeal location ($P < 0.001$). History of smoking and drinking was significantly associated with age >40 and SCC of larynx in both age groups. Cervical lymph node involvement was significantly correlated with SCC of tongue ($P < 0.001$), however, considering young adults only, SCC of hypopharynx was most frequently accompanied by lymph node involvement (60%). The most prevalent tumor among men was SCC of larynx whereas SCC of hypopharynx was the most prevalent tumor among women (61%), of whom 18.2% were ≤ 40 . **Conclusions:** The incidence of HNSCC among young adults seems to be higher in Iran compared to other countries. Reduction in exposure to known risk factors, especially tobacco smoking in forms of cigarettes and bubble pipes, and search for other causative agents of HNSCC in young population is recommended.

Keywords: Head and neck - squamous cell carcinoma - risk factors, smoking - young adults - Iran

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is the 8th most common cancer worldwide and it accounts for nearly 6% of all cancers (O'Regan et al., 2006; Westra, 2009). HNSCC is a major health problem, because of poor prognosis and little improvement in the five-year survival during the past four decades (Vokes et al., 1993).

Although HNSCC usually occurs in patients older than 60 years, during the past 50 years, younger age groups have been reported from different parts of the world, including United States of America, China, India and some European countries (Gupta, 1999; Llewellyn et al., 2001; Schantz & Yu, 2002; Llewellyn et al., 2003; Toner & O'Regan, 2009). The incidence rate of HNSCC has reached 0.4-3.6% in patients younger than 40 years which has drawn physicians' attention to the changing face of the disease (Llewellyn et al., 2001). On the other hand, recent studies have revealed differences of the risk factors and prognosis of HNSCC, in patients younger than

40 and the older patients, although controversy still exists regarding disease outcomes in young and old patients: some authors report a worse prognosis of the disease in the young compared to the old (Mallet et al., 2009; Kaminagakura et al., 2010; Soudry et al., 2010; Bachar et al., 2011; Kostrzewska-Poczekaj et al., 2012) while other studies have not found a significant clinical difference, or even a more favorable prognosis in younger patients (Luna-Ortiz et al., 2011). In fact, even if the tumors are histologically more mature and less malignant in younger patients compared to older ones, they are usually more advanced clinically at the time of diagnosis due to late referral of young patients to physicians (Shiboski et al., 2005; Gawecki et al., 2007; Sink et al., 2011). Another difference is that young adults most commonly develop primary tumor in oropharynx and oral cavity and less frequently in the larynx compared to older patients (Shiboski et al., 2005; Gawecki et al., 2007).

According to the previous reports, HNSCC has been strongly associated with the use of tobacco and alcohol

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(Blot et al., 1988; Tuyns et al., 1988; Lewin et al., 1998). However, there is a distinct group of young patients with HNSCC who reported little or no exposure to the major risk factors (McGregor et al., 1983; Tsukuda et al., 1993; Llewellyn et al., 2004; Dahlstrom et al., 2008). In addition, rising incidence of oropharyngeal carcinoma in the absence of a parallel rise in smoking and alcohol consumption suggests that other risk factors might also play a role (Shibosk et al., 2005; Westra et al., 2009).

Infection with human papilloma virus (HPV) type 16 has been established as a causative agent in up to 70% of oropharyngeal cancers especially in younger individuals without other risk factors (Koch et al., 1999; Dahlstrom et al., 2003; Shibosk et al., 2005; Westra et al., 2009; Van Monsjou et al., 2010; Kaminagakura et al., 2012).

Marijuana smoking is also associated with HNSCC, and some authors have suggested that the rising incidence of tongue cancer in young individuals could be explained by the rising trend of marijuana smoking (Schantz et al., 1989; Koch et al., 1999; Sturgis, 2004; Sturgis et al., 2004).

Other proposed risk factors for HNSCC are poor dental hygiene, poor diet, immunosuppression, sub-mucous fibrosis, gastrointestinal reflux, various inherited syndromes and chronic iron deficiency anemia (Maier et al., 1994; Sturgis & Wei, 2002; Llewellyn et al., 2004; Sturgis et al., 2004; Dahlstrom et al., 2008; Toner & O'Regan, 2009).

Genetic factors have also been studied vastly as a risk factor for developing HNSCC in young adults and as a prognosis determinant; while polymorphisms of DNA repair genes have not been established to be responsible for developing the disease in young adults (Gawecki et al., 2007; Kostrzewska et al., 2012), over-expression of p16(INK4a) has been found to be associated with favorable prognosis in young patients with SCCs of the oral tongue (Harris et al., 2011) and Pfeiffer et al. have found regions of DNA deletions (named germline loss of heterozygosity) that may contribute to genetic susceptibility for HNSCC in young adults and non-smokers (Pfeiffer et al., 2011).

Since HNSCC is affected by environmental factors like smoking, alcohol consumption, viral infections, dietary habits, medication use, life style, race and genetics, the disease pattern may vary in different countries (Sanderson & Ironside, 2002). Therefore, we aimed to define the demographics, potential risk factors and tumor characteristics of HNSCC in Iranian patients referring to our clinic; furthermore, we investigated significant differences in the above parameters between young adults (≤ 40 years) and patients over 40 years old.

Materials and Methods

We conducted a cross-sectional analytical study and enrolled all the patients who were diagnosed with HNSCC in Hazrat Rasoul Akram hospital from 1995 to 2010. All patients who had pathologically confirmed diagnosis of primary SCC of larynx, hypopharynx or tongue were included. Patients with the SCC of the other parts of the head and neck and those with other malignancies (including thyroid tumors, lymphomas and metastatic tumors) were excluded.

In this study, a young patient was defined as being 40 years old or younger. Patients were considered smoker or drinker if they had smoked cigarettes or drank alcohol habitually for at least one month in their life time. Anemia was defined as hemoglobin concentrations below 11.5 gr/dl for women and below 13.5 gr/dl for men. Staging of tumors was performed based on pathologic TNM staging system, suggested by union for international cancer control (UICC).

Tumor characteristics including grade, stage, location and cervical lymph nodes status in addition to sex, age, hematologic status, smoking and drinking history of patients were extracted from their medical records and analyzed using SPSS (version 15). The variables were analyzed using Chi-square and Mann-Whitney analytical tests. P value < 0.05 was considered statistically significant. The institutional review board approved the study.

Results

We analyzed medical records of 262 patients with HNSCC of whom 15 (5.7%) were 40 years old or younger. The mean age was 34 years (range: 23-40) in young adults and 62 years (range: 41-89) in patients above 40 years old. The male to female ratio was 1.5 in young adults and 5.6 in older group.

The most common location of HNSCC in patients over 40 was larynx (204/247=82.5%). This was significantly different from HNSCC location in our younger group that 6/15 (40%) occurred in larynx and 6/15 (40%) in the tongue. In men, HNSCC was most frequently observed in the larynx ($P < 0.05$) while in women, the most common sites for HNSCC were the larynx and the tongue (Table 1).

Of 185 patients who were smoker, 177 (95.6%) were men and 8 (4.3%) were women. History of cigarettes smoking was correlated with male gender and age > 40 years ($P < 0.05$). The most prevalent site for HNSCC among smokers was the larynx so that among patients with SCC of larynx, 66.6% (4/6) of young patients and 81.3% (166/204) of older group with the SCC of larynx had positive history of smoking. The relative frequency of smoking in young adults was greatest in the SCC of hypopharynx (1/18=5.5%). None of the young adults with SCC of the tongue were smoker (Table 2).

All 45/262 (17.2%) of patients who had ever drunk alcohol were men over 40 years. Drinking was significantly correlated with male gender and age over 40 years. None of the young adults or patients with tongue SCC had ever drunk alcohol. Drinking was mostly prevalent among patients with SCC of larynx (Table 3).

Lower tumor stages were more frequently observed in older patients and in women. However, most tumors were of low-grade in both age groups and both genders, and there was no significant correlations between tumor grade and any age groups.

Of 76 patients with positive lymph nodes, 59 (77.6%) were men and 17 (22.3%) were women. Only 8/76 (10.5%) of patients with positive lymph nodes were young adults. None of sex or age groups differed significantly in lymph nodes status. Involvement of cervical lymph nodes was

Table 1. Characteristics of Patients and Tumors Based on Patients' Age and Gender

Characteristic	Patients ≤ 40 years N/ Total (%)		Patients > 40 years N/ Total (%)		P value*	
	Male (n=9)	Female (n=6)	Male (n=210)	Female (n=37)		
Smoking history:	Positive	5 /185 (2.7)	0	172 /185(92.9)	8 /185 (4.3)	<0.05
	Negative	4 /72 (5.5)	6 /72 (8.3)	35 /72(48.6)	27 /72 (37.5)	
	Missing	0	0	3	2	
Alcohol consumption:	Positive	0	0	45 /45(100)	0	<0.05
	Negative	8 /206 (3.8)	5 /206(2.4)	158 /206(76.7)	35 /206(17.0)	
	Missing	1	1	7	2	
Tumor Site:	Larynx	4 /210 (1.9)	2 /210(0.9)	190 /210(90.5)	14 /210 (6.6)	<0.001
	Hypopharynx	1 /18 (5.5)	2 /18 (11.1)	6 /18(33.3)	9 /18 (50)	
	Tongue	4 /34 (11.8)	2 /34 (5.8)	14 /34(41.1)	14 /34 (41.1)	
Tumor Stage:	T1	0	2 /83 (2.4)	73 /83(87.9)	8 /83 (9.6)	0.399
	T2	1 /44 (2.2)	1 /44 (2.2)	35 /44(79.5)	7 /44 (15.9)	
	T3	1 /46 (2.1)	0	41 /46(89.1)	4 /46 (8.7)	
	T4	1 /50 (2.0)	2/50 (4.0)	41 /50(82.0)	6 /50 (12.0)	
	Missing	6	1	20	12	
Tumor grade:	Well	6 /107 (5.6)	1 /107(0.9)	83 /107(77.6)	17 /107(15.9)	0.82
	Moderately	2 (3.3)	3 (5.0)	48 (80)	7 (11.7)	
	Poorly	0	1 (11.1)	7 (77.8)	1 (11.1)	
	Missing	1	1	72	12	
Lymph node involvement:	Positive	4 /76 (5.2)	4 /76 (5.2)	55 /76(72.3)	13 /76 (17.1)	≥0.05
	Negative	4 /160 (2.5)	1 /160(0.6)	136 /160(85.0)	19 /160(11.9)	
	Missing	1	1	19	5	
Anemia:	Present	4 /94 (4.2)	4 /94 (4.2)	67 /94(71.2)	19 /94 (20.2)	0.08
	Absent	5 /164 (3.0)	2 /164(1.2)	141 /164(85.9)	16 /164 (9.7)	
	Missing	0	0	2	2	

*Study variables were analyzed using Chi-square and Mann-Whitney analytical tests. P-values refer to comparison between young adults and patients over 40 years old.

Table 2. Frequency of HNSCC

	Age	Smoker		Non-smoker	
		N/Total (%)	N/Total (%)	N/Total (%)	N/Total (%)
Frequency of HNSCC according to age, smoking history and site of tumor					
Tumor location:					
Larynx	≤40 years	4/210	(1.9)	2/210	(0.9)
	>40 years	166/210	(79.0)	38/210	(18.0)
Hypopharynx	≤40 years	1/18	(5.5)	2/18	(11.1)
	>40 years	5/18	(27.7)	10/18	(55.5)
Tongue	≤40 years	0		6/34	(17.6)
	>40 years	9/34	(26.4)	19/34	(55.8)
Frequency of HNSCC in young adults based on smoking history and site of the tumor					
Tumor Site:					
Larynx		4/6	(66.6)	2/6	(33.3)
Hypopharynx		1/3	(33.3)	2	(66.6)
Tongue		0		6/6	(100)
Sum		5/15	(33.3)	10/15	(66.6)

significantly more prevalent (65%) in SCCs of the tongue (P<0.001) and 11.8% of patients with tongue tumor were younger than 40 years. In young adults, 60.0% of hypopharynx SCCs had lymph node involvement.

According to hemoglobin concentration at the time of surgery, 36.5% of patients were anemic, of whom 75.5% were male and 24.5% were female. Anemia was most frequently observed in patients with SCC of the hypopharynx (61.1%), of whom 9.1% were 40 years or below (Table 4). Comparing the relative frequency of anemia in young adults with the elderly, tumors of tongue had the most relative frequency (21.4%) in young adults. There were no significant differences in anemia between

Table 3. Frequency of HNSCC

Tumor Site:	Age ≤40 years N/Total (%)	Age >40 years N/Total (%)
Frequency of HNSCC in patients with history of drinking according to age and site of tumor		
Larynx	0	44/44 (100)
Hypopharynx	0	1/1 (100)
Tongue	0	0
Sum	0	45/45 (100)
Frequency of HNSCC in anemic patients according to age and site of tumor		
Larynx	4/69 (5.7)	65 /69(94.2)
Hypopharynx	1/11 (9.0)	10/11 (90.9)
Tongue	3/14 (21.4)	11/14 (78.5)
Sum	8/94 (8.5)	86/94 (91.4)

age (P=0.08) and sex groups (P=0.4).

Site of the tumor was significantly correlated with patients' age (P<0.001), gender (P<0.001), smoking history (P<0.001), alcohol consumption (P=0.007) and lymph node status (P=0.001). SCC of the larynx was more prevalent among men (92%) and its prevalence among men ≤ 40 years was 2.1%. SCC of the hypopharynx was more common among women (61%) of whom 18.2% were younger than 40 years. Prevalence of tongue SCC was the same in both genders and 17.6% of patients with tongue SCCs were young adults.

Tumor grade was significantly correlated with cervical lymph nodes involvement (P=0.036); on the other hand, 77.8% of patients with positive lymph nodes had high-grade tumors. Although 14.3% of these patients were young adults, we did not find significant differences in tumor grade between patients younger than 40 and other patients (P=0.82). Similarly, tumor grade was not

significantly correlated with gender, smoking status, alcohol consumption and anemia of the patients.

Regarding the stage of the tumor, higher tumor stages were significantly correlated with positive lymph node involvement ($P=0.001$) and anemia ($P=0.012$). Anemia was most commonly present in patients with higher stages of the disease (50%), of whom 12% were young adults. Tumor stage was not correlated with age, gender, smoking or drinking status of the patients.

Discussion

HNSCC usually affects middle-aged or elderly men and has a strong association with smoking and alcohol consumption (Blot et al., 1988; Vokes et al., 1993). Although recent studies have shown increased incidence of HNSCC among young adults, the incidence of HNSCC in young people is still lower than the elderly (Schantz et al., 2002; Llewellyn et al., 2003). According to our data, only 5.7% of patients with HNSCC were ≤ 40 years old. The percentage of HNSCC in patients with younger age varies in different studies, depending greatly on the cut-off age chosen. When "young" was defined as below 45 years, the relative frequency of HNSCC in young individuals was 6.7%, compared to 0.4-3.6% when age was defined as younger than 40 (Llewellyn et al., 2001). The frequency of HNSCC in young patients (≤ 40 years old) in our study and previous reports from Iran (7.5%) was slightly more than other countries (Andisheh-Tadbir et al., 2008). However, the significance and explanation of this correlation needs further investigations.

Regarding the gender of the patients, previous studies have shown a decrease of male to female ratio in sex distribution of young patients (Toner & O'Regan, 2009) and Patel et al. reported that SCC of the oral cavity, specifically oral tongue, is increasing among young white individuals and that the increasing trend was significantly greater in young white women compared with that of young white men (Patel et al., 2011); this change in the incidence can be due to increased trends of smoking and/or drinking in women and the greater prevalence in men can be caused by their more exposure to occupational carcinogens, toxins and other risk factors like marijuana compared to women (Dahlstrom et al., 2008). In our study only 43/262 (16.4%) of the patients were females, possibly reflecting the existing difference in prevalence of smoking or drinking between Iranian men and women. The male: female ratio in our young group was close to that of Irish patients (1.7%) (O'Regan et al., 2006) and to the previous reports from Iran (1.4%) (Andisheh-Tadbir et al., 2008). In studies where the cut-off age was set to 30 years, a female predominance was observed in HNSCC patients younger than 30 years (Byers, 1975; McGregor et al., 1983). The male: female ratio in our elderly group was in accordance to other studies that reported the rate of HNSCC in men over 40 years is 2-15 times more than women in the same age spectrum (Gawecki et al., 2007).

Similar to previous reports, our study shows that SCC of larynx is significantly more prevalent in the elderly compared to young patients, and larynx is the most common site of HNSCC in all patients (Gawecki

et al., 2007, Andisheh-Tadbir et al., 2008). Other studies indicated that tongue was the most common location of HNSCC among young adults; for example, 76% of Irish patients younger than 40 and 19% of those older than 40 had SCC of tongue, while pharynx and larynx together were the most common site of tumor in the older age group (O'Regan et al., 2006). In our study and another report from Iran (Andisheh-Tadbir et al., 2008), SCC of the larynx was more prevalent in men than women. We found SCC of the tongue and hypopharynx to be more frequent among women compared to men. Considering SCC of tongue alone, 52% of patients were male and 48% were female. These figures were 52.2% for women and 47.6% for men with SCC of tongue in a similar report from Southern Iran (Andisheh-Tadbir et al., 2008).

Smoking is known as one of the major risk factors for HNSCC. About 41% of HNSCCs in men are related to smoking (O'Regan et al., 2006). In our study, 81.7% of patients with SCC of larynx had history of smoking. Smoking was the least prevalent among patients with SCC of the tongue (26.4%). None of the young adults with SCC of tongue in our study were ever smoker (Table 5). Drinking was most commonly observed among patients with SCC of the larynx (Table 3) whereas none of the patients with SCC of the tongue had ever drunk alcohol. In this study, 10/15 (66.6%) of young adults had negative history of smoking and 13/15 (86.6%) had negative history for drinking. Excluding two patients with unknown drinking history, 53.3% were negative for both smoking and drinking. Previous reports have also declared a group of never smoking and never drinking patients with HNSCC, the majority of them being young women with SCC of oral cavity and the oropharynx as the primary site of the tumor (Muscat et al., 1996; Llewellyn et al., 2004; Goldstein & Irish, 2005; Dahlstrom et al., 2008). Mackenzie et al. (2000) reported 109 young patients with HNSCC, of whom 32% had never smoked tobacco or drank alcohol habitually and 37% had only one of these risk factors. In the study of Irish patients with HNSCC by O'Regan et al. (2006), 17% of young adults and none of the patients younger than 30 years had ever smoked cigarettes. Absence of conventional risk factors such as alcohol consumption and smoking in these patients proposes the presence of other possible risk factors in developing HNSCC especially in young patients (O'Regan et al., 2006; Toner & O'Regan, 2009). The suggested risk factors include certain types of viral infections such as HPV, poor diet, immunosuppression, marijuana exposure, poor dental hygiene, gastrointestinal reflux and genetic predisposition (Llewellyn et al., 2004; Dahlstrom et al., 2008; Westra, 2009; Rutt et al., 2010).

Lymph node involvement was present in 32.2% of our cases, while in another report from Iran 50% of HNSCC patients with lymph node biopsy showed lymph node metastasis (Andisheh-Tadbir et al., 2008). Like the Irish study (O'Regan et al., 2006), lymph node status did not differ significantly in our young adults.

Anemia was more common in our patients compared to Irish patients (36.5% against 15%), but similar to their results, there was no significant association between anemia and age or sex (O'Regan et al., 2006). In our

study, 75.5% of the anemic patients were males and 24.5% were females, possibly reflecting the difference in the number of women and men included in the study. Anemia can develop in a patient with cancer for a number of reasons including defective production of erythropoietin, infiltration or necrosis of bone marrow and loss of RBCs through hemorrhage or hemolysis. In addition, patients with malignancies usually suffer from nutritional deficiencies including iron and folic acid deficiency, which is particularly more common among patients with large tumors (O'Regan et al., 2006). Although it is not fully understood whether anemia can increase the risk of HNSCC, it has been suggested that chronic iron deficiency anemia can cause atrophy of mucosa and increase susceptibility to carcinogens. It has also been reported that the incidence of tongue tumor is increased in iron deficient animals (Prime et al., 1983). In our study 61.1% of patients with SCC of hypopharynx were anemic, compared to 41.2% of patients with SCC of the tongue and 32.9% of those with SCC of the larynx. However, when we evaluated the relation between anemia and tumor location in two age groups, anemia had the highest relative frequency in tongue carcinoma, among young adults (21.4%).

In this study, tumor grade was significantly correlated with cervical lymph nodes involvement and patients with positive lymph nodes had higher tumor grades. This can be explained by the aggressive behavior of high grade tumors. Although there was not a significant difference in tumor grade between our young and older patients, other studies reported a strong association between more mature HNSCCs and the young adults group (Gawecki et al., 2007). O'Regan et al. (2006) stated that a higher proportion of their young patients had well-differentiated tumors. However, similar to our study, the correlation was not significant.

Higher tumor stages were significantly correlated with lymph node involvement and anemia. The latter correlation can be partly explained by the fact that anemia was most commonly present in patients with higher stages of the disease and a patient with a high-stage tumor is more prone to conditions which can lead to anemia. Tumor stage did not differ significantly in our young patients. In a similar study in Irish patients, although trend towards lower tumor stages at the time of diagnosis was reported, no significant relation was found between age and tumor stage (O'Regan et al., 2006). Gawecki et al. (2007) stated that tumors in young adults were clinically more advanced than in older patients, because young adults tend to delay the visit to physician, in spite of evident clinical symptoms.

Considering other risk factors, case-control studies have demonstrated that regular consumption of vegetables, citrus fruits, fish, and vegetable oils play an important role in the prevention of cancer of the oral cavity and pharynx and a diet deficit in the aforementioned nutrients is frequently observed in patients with HNSCCs (Macfarlane et al., 1995). We were not able to assess dietary habits of our patients because of the large amount of missing data in our patient records.

In general, limitations of our study include:

retrospective nature of the study resulting in some missing data on the assessed risk factors in medical records of the patients, small number of patients aged ≤ 40 years, and lack of data on certain risk factors in our medical records such as dietary habits, history of marijuana smoking and infection with human papilloma virus. Thus, further studies are needed to evaluate the risk factors in patients with HNSCC, especially young adults. Prospective case-control and multicentric studies in Iranian patients will be of greater value in this respect.

In conclusion, smoking and drinking are two major risk factors for SCC of the head and neck. Since the incidence of HNSCC among young adults seems to be higher in Iran than other countries, it is mandatory to reduce these risk factors especially tobacco smoking in the forms of cigarettes and bubble pipes in the young Iranians as well as in the rest of the population. However, there has been increasing number of HNSCC patients, especially young adults, without typical risk factors. In these patients, other causes such as diet, oncogenic viruses and genetic predisposition have been considered as risk factors. It has also been suggested that the biology of SCC of the head and neck in young people may differ from that of the older people, so that the cancer in these patients can be a distinct form of the disease. In conclusion, the reason for the development of SCC of the head and neck in young patients without typical risk factors still remains unclear, while there are worldwide reports of increasing numbers of young people developing this disease. Therefore, search for causative agents for the development of HNSCC in the young population should be continued. In addition, because of the overall trend for decreasing age profile in oropharyngeal HNSCCs, clinicians must consider it in differential diagnosis of any lesion in the young, so that early detection of these cancers can improve their prognosis.

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