

Cigarette Smoking and Progression of Laryngeal Lesions

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ABSTRACT

The association between cigarette smoking and an increased risk of laryngeal carcinoma has been demonstrated in numerous studies. The aim of the present study was to assess the prevalence of smoking habit in patients with different laryngeal pathologies. The prevalence of cigarette smoking was compared between patients with laryngeal tumors and those with nonmalignant laryngeal lesions. Data on all patients with indications for direct microlaryngoscopy at the Clinic for Otorhinolaryngology of the University Hospital Center Split, during a five-year period were analyzed. The study included 562 patients with various laryngeal pathologies, divided into three groups as follows: group 1, benign lesions; group 2, precancerous lesions; and group 3, tumors. The majority of patients (82.92%) had a long history of smoking. The proportion of smokers was lowest in benign lesion group (72.13%), higher in precancerous lesion group (81.48%) and highest in malignant lesion group (97.14%). There was a statistically significant difference in the prevalence of cigarette smoking between patients with laryngeal tumors and those with benign or precancerous lesions ($p < 0.001$). The mean number of cigarettes per day was 20.54 ± 14.80 , and was lowest in benign lesion group (15.67 ± 13.41) and highest in malignant lesion group (26.33 ± 12.70). The mean length of smoking habit was 26.44 ± 16.92 years, ranging from 19.57 ± 16.03 years in benign lesion group to 35.20 ± 12.12 years in malignant lesion group. Study results clearly pointed to the increased prevalence of laryngeal diseases in smokers, with a significant difference between patients with benign laryngeal lesions and those with laryngeal tumors.

Key words: cigarette smoking, precancerous lesion, laryngeal tumor

Introduction

Cigarette smoking is a major factor of laryngeal carcinogenesis¹⁻⁶. In smokers, the relative risk of laryngeal tumor development is 5- to 30-fold risk recorded in nonsmokers⁴⁻⁹, increases with early onset of smoking habit and depends on the length of smoking habit as well as association with other risk factors. Maier et al. report 96.5% of patients with squamous cells carcinoma of the larynx to be smokers, with a 5.6 relative risk of carcinoma in smokers⁸. DeStefani et al. found 97.2% of smokers and a relative risk of 14.7². Wunder et al. report on a 13.5 and 34.4 relative risk of tumor development in subjects smoking up to 20 and more than 20 cigarettes daily, respectively⁵. In the study by Falk et al., the relative risk of squamous cell carcinoma was 6.0 in subjects smoking up to 30 cigarettes and 19.2 in those smoking more than 30 cigarettes daily. The risk tended to decrease in former smokers with at least 5-year history of nonsmoking, to reach the level observed in nonsmokers after 15 years⁶.

Krajina found 97.6% of laryngeal tumor patients to smoke 30 cigarettes daily on an average¹.

In Croatia, 27.4% of the population over 18 years of age smoke on a daily basis. The high prevalence of smoking habit among young individuals aged 18–29 is a cause for concern, with special reference to Eastern Croatia where the prevalence rises to as high as 46%¹⁰. Statistical data show a male predominance of smoking (34% male vs. 22% of female). Surveys performed in Istria revealed adolescents in Istria County to start smoking as early as age 12–13 (32.09%); the habit of cigarette smoking was more regularly practiced by female adolescents (35.72%)¹¹.

Some 30% of the world population, 47% of men and 12% of women, are smokers. About 3.5 million individuals per year die from diseases caused by smoking in the world. Cigarette smoking is the cause of death in 36% of male and 13% of female individuals worldwide. In Croa-

tia, 397 patients, 370 (93%) male and 27 (7%) female, were newly diagnosed with laryngeal carcinoma in 2005¹².

The association between cigarette smoking and an increased risk of laryngeal carcinoma has been definitely demonstrated in numerous studies; however, tobacco smoke causes laryngeal mucosa lesions, thus certainly favoring the development of other laryngeal diseases as well. Therefore, the aim of the present study was to assess the prevalence of smoking habit in patients with different laryngeal pathologies. The prevalence of cigarette smoking was compared between patients with laryngeal tumors and those with nonmalignant laryngeal lesions.

Patients and Methods

Data on all patients (N=562) undergoing direct microlaryngoscopy at the Clinic for Otorhinolaryngology of the University Hospital Center Split, over a five-year period were collected and analyzed. Results were processed by standard statistical methods.

Results

The study included 562 patients with different laryngeal pathologies, divided into three groups according to histopathologic diagnosis as follows: 244 (43.4%) patients with benign laryngeal lesions (e.g., polyps, cysts, hemangiomas, etc.) including patients with normal his-

topathology findings; 108 (19.2%) patients with precancerous laryngeal lesions, including laryngeal papilloma; and 210 (37.4%) patients with malignant lesions of the larynx (Table 1).

Patient distribution according to gender and histopathologic diagnosis is presented in Table 2. Whereas benign lesion group showed an equal gender distribution, male patients were predominant in group of patients with precancerous lesion and malignant lesion ($\chi^2=34.8$; $p<0.001$). Overall, there were 408 (72.6%) male and 154 (27.4%) female patients.

Patient distribution according to age (age range 19–81; mean age 53.53 ± 14.21 years) is shown in Table 3. Duncan test following analysis of variance at the level of significance revealed malignant lesion patients group to be statistically significantly older than benign and precancerous lesion patients group ($F=15$; $p<0.001$).

Most study patients (82.92%) had a long history of cigarette smoking (Table 4). The proportion of smokers was lowest in benign lesion group (72.13%) and highest in malignant lesion group (97.14%). There was a statistically significant difference in the prevalence of smoking habit between patients with laryngeal tumors and those with benign or precancerous laryngeal lesions ($\chi^2=68.5$; $p<0.001$).

The mean number of cigarettes daily was 20.54 ± 14.80 ; it was lowest in benign lesion group (15.67 ± 13.41 cigarettes) and highest in malignant lesion group (26.33 ± 12.70

TABLE 1
PATIENT DISTRIBUTION ACCORDING TO HISTOPATHOLOGIC DIAGNOSIS

	Histopathologic diagnosis	n (%)	n (%)
Benign lesion group	Benign	244 (43.4)	244 (43.4)
Precancerous lesion group	Leukoplakia	40 (7.1)	108 (19.2)
	Dysplasio gradus I	32 (5.7)	
	Dysplasio gradus II	20 (3.6)	
	Dysplasio gradus III	12 (2.1)	
	Papilloma	4 (0.7)	
Malignant lesion group	Carcinoma in situ	16 (2.9)	210 (37.4)
	Plasmocytoma	2 (0.3)	
	Chondrosarcoma	2 (0.3)	
	T-lymphoma	2 (0.3)	
	Squamous cell carcinoma	188 (33.6)	
	Total	562 (100)	562 (100)

TABLE 2
GENDER DISTRIBUTION OF STUDY PATIENTS

Gender	Histopathologic diagnosis			
	Benign lesion group	Precancerous lesion group	Malignant lesion group	Total
Male, n (%)	116 (20.6)	94 (16.7)	198 (35.3)	408 (72.6)
Female, n (%)	128 (22.8)	14 (2.5)	12 (2.1)	154 (27.4)
Total, N (%)	244 (43.4)	108 (19.2)	210 (37.4)	562 (100)

TABLE 3
AGE DISTRIBUTION OF STUDY PATIENTS

Histopathologic diagnosis				
Age (yrs)	Benign lesion group	Precancerous lesion group	Malignant lesion group	Total
$\bar{X}\pm SD$	48.14±14.09	53.13±14.81	61.41±10.08	53.53±14.21
Total	122 (43.4%)	54 (19.2%)	105 (37.4%)	281 (100%)

TABLE 4
PATIENT DISTRIBUTION ACCORDING TO CIGARETTE SMOKING, NUMBER OF CIGARETTES PER DAY AND LENGTH OF SMOKING HABIT

Histopathologic diagnosis				
Benign lesion group	Precancerous lesion group	Malignant lesion group	Total	
Smokers, n (%)	88/122 (72.13)	44/54 (81.48)	102/105 (97.14)	233/281 (82.92)
Cigarettes per day, mean±SD	15.67±13.41	23.04±18.20	26.33±12.70	20.54±14.80
Length of smoking (yrs), mean±SD	19.57±16.03	28.70±19.61	35.20±12.12	26.44±16.93

cigarettes). The mean length of smoking was 26.44±16.93 years; it was also shortest in benign lesion group (19.57± 16.03 years) and longest in malignant lesion group (35.20±12.12 years).

Discussion

In the group of patients with malignant laryngeal tumors, the prevalence of cigarette smoking was 97.14%, which is consistent with literature data. In Croatia, the prevalence of smoking among women has increased in recent years. The mean rate of smoking habit in women worldwide is 12%, whereas in Croatia it reaches 22% or even more in particular areas. In Istria County, 35.72% of female high school students smoke regularly *vs.* 34.26% of their male counterparts¹¹. However, the marked increase in the rate of cigarette smoking in female population does not appear to be associated with an increased prevalence of laryngeal tumors in this population group. In the present study, a total of 12/210 (5%) malignant tumors were diagnosed in female patients, out of which only one was nonsmoker. Other factors (e.g., hormonal, lower number of cigarettes daily, etc.) must also be involved in carcinogenesis in women¹³.

In benign lesion group, there were 72.13% of smokers, yielding a statistically significant difference from malignant lesion group with 97.14% of smokers ($\chi^2=68.5$; $p<0.001$). Polls taken at the national level show the mean rate of smoking habit in Croatia to be 27.4%; accordingly, the number of smokers in benign and malignant lesion group was 2.6-fold and 3.5-fold mean rate recorded in Croatia.

Comparison of benign and malignant lesion group of patients revealed the latter to be characterized by a significantly older age (48.14 *vs.* 61.41 years), greater number of cigarettes daily (15.67 *vs.* 26.33 cigarettes), and longer history of smoking (15.67 *vs.* 35.20 years).

A number of factors have been implicated in the increased prevalence of laryngeal tumors in smokers. Some fifty compounds with known carcinogenic effects have been isolated from tobacco smoke. These mostly include tar substances (e.g., polycyclic aromatic hydrocarbons), and many other carcinogens such as toluidine, urethane, polonium, naphthylamine, vinyl chloride, etc. One of the adverse tobacco smoke compounds is carbon monoxide (CO), which binds to hemoglobin 200 times faster than oxygen. In smokers, 10% to 15% of hemoglobin can be bound to CO, thus considerably reducing the body oxygen supply, which may pose great risk in individuals with heart diseases, angina pectoris in particular. In addition, the vascular wall permeability for cholesterol increases, thus favoring the atherosclerotic plaque formation.

It should also be noted that certain conditions additionally stimulate the action of these carcinogenic compounds. A part of malignant tumors originate from a single malignantly altered cell, so-called monoclonal malignant cell, whereas others arise from precancerous lesions^{14,15}. This is demonstrated by dysplastic changes of variable grade frequently found along tumor margins. Dysplastic changes always arise from the basal layer of stratified squamous epithelial cells. Epithelial thickness decreases with aging and the basal layer of stratified epithelial cells is closer to the surface, thus being exposed to the action of tobacco compounds. In young individuals, epithelial thickness is about 50 microns, whereas in the elderly it is only 29.9 microns¹⁶. In addition, in elderly individuals mitotic index is twofold that in children (1.72 *vs.* 0.88).

On the other hand, the area of stratified squamous epithelium expands to the areas of stratified columnar epithelium, which can be excellently visualized by contact endoscopy¹⁷. Therefore, laryngeal tumors are rarely found before age 30 and then are mostly associated with irradiation therapy for laryngeal papilloma in childhood.

The expansion of stratified squamous epithelium influences the mucociliary transport, thus slowing down the elimination of nicotine compounds from the mucosal surface while protracting and accumulating their action.

Conclusion

Study results pointed to the increased prevalence of laryngeal diseases in smokers and a statistically significant difference in the prevalence of smoking habit between patients with benign laryngeal lesions and those

with laryngeal tumor. The greater number of cigarettes daily and longer history of smoking contributed significantly to the increased prevalence of laryngeal carcinoma.

Quitting smoking results in marked regression of the initial pathologic lesions of the larynx, regeneration of the stratified columnar epithelium and mucociliary transport, while frequent cough and throat dryness disappear, strongly suggesting that stopping smoking is the only favorable decision to make.

REFERENCES

1. KRAJINA Z, KULČAR Ž, KONIĆ-CORNELLETTI V, Lijec Vjesn, 97 (1975) 89. — 2. DESTEFANI E, CORRERA P, OREGGIA F, Cancer, 60 (1987) 3087. — 3. SUGAR J, VERECZKEY I, TOTH J, J Environ Pathol Toxicol Oncol, 15 (1996) 195. — 4. MUSCAT J, WYNDER E, Cancer, 69 (1992) 2244. — 5. WUNDER E, COVEY L, MABUCHI K, Cancer, 38 (1976) 1591. — 6. FALK R, PICKLE L, BROWN L, Cancer Res, 49 (1989) 4024. — 7. OLSEN J, SABREO S, FASTING U, J Epidemiol Commun Health, 39 (1985) 165. — 8. MAIER H, GEWELKE U, DIETZ A, Otolaryngol Head Neck Surg, 107 (1992) 577. — 9. AHRENS W, JOCKEL E, PATZAK W, ELSNER G, Am J Ind Med, 20 (1991) 477. — 10. KUZMAN M,

MAYER D, Hrvatski časopis za javno zdravstvo, 3 (2007) 11. — 11. BLAREŽINA K, SUTLIĆ V, Hrvatski časopis za javno zdravstvo, 1 (2005) 3. — 12. CROATIAN NATIONAL INSTITUTE FOR PUBLIC HEALTH, Incidencija raka u Hrvatskoj (Hrvatski zavod za javno zdravstvo, Zagreb, 2005). — 13. REINER Z, CVRTILA D, PETRIC V, Arch Otorhinolaryngol, 245 (1988) 47. — 14. KASSIS J, LAUFFENBURGER DA, TURNER T, WELLS A, Semin Cancer Biol, 11 (2001) 105. — 15. SEZER O, JAKOB C, NIEMOLLER K, J Clin Oncol, 19 (2001) 3299. — 16. SHANTZ SP, BYERS RM, GOEPFERT H, Cancer, 62 (1988) 1374. — 17. CIKOJEVIĆ D, GLUNČIĆ I, PEŠUTIĆ-PISAC V, J Laryngol Otol, 122 (2008) 836.

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PUŠENJE CIGARETA I LARINGEALNE PROMJENE

SAŽETAK

Brojni radovi pokazuju jasnu vezu pušenja i povećanog rizika za nastanak tumora grla, ali duhanski dim oštećenjem sluznice larinksa zasigurno pogoduje nastanku i drugih oboljenja larinksa. Stoga smo u radu nastojali prikazati učestalost pušenja u bolesnika s različitim oboljenjima larinksa. U radu smo analizirali sve bolesnike u kojih je bila indicirana direktne mikrolaringoskopija na ORL odjelu KB Split u periodu od pet godina. Radom su obuhvaćena 562 bolesnika, koje smo svrstali u tri grupe: grupa 1 – benigne promjene, grupa 2 – prekancerozne promjene, grupa 3 – tumori. Većina bolesnika su dugogodišnji pušači (82,92%). Najmanje pušača bilo je u grupi 1 (72,13%), u grupi 2 (81,48%), a najviše u grupi 3 (97,14%). Postoji statistički značajna razlika u učestalosti pušenja bolesnika s tumorom larinksa i bolesnika s benignom ili prekanceroznom promjenom ($\chi^2=68,5$, $p<0,001$). Dnevno su u prosjeku pušili $20,54\pm 14,80$ cigareta, najmanje u grupi 1 ($15,67\pm 13,41$), a najviše u grupi 3 ($26,33\pm 12,70$) cigareta. Bolesnici su prosječno pušili $26,44\pm 16,93$ godine, najduže u grupi 3 ($35,20\pm 12,12$) godina, a najkraće u grupi 1 ($19,57\pm 16,03$) godina. Prikazani rezultati jasno ukazuju na povećanu učestalost oboljenja larinksa u pušača, ali i značajnu statističku razliku o učestalosti pušenja u bolesnika s benignim promjenama larinksa u odnosu na bolesnike s tumorom larinksa.