Journal of Surgery and Trauma 2016; 4(1-2): 17-23.

www.jsurgery.bums.ac.ir

ORIGINAL ARTICLE

Evaluation of the results of direct laryngoscopy of patients with larynx and hypopharynx signs and lesions in ENT specialized medical centers of Birjand city

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Received: April 19, 2017 ***Revised: May 20, 2017*** ***Accepted: May 30, 2017***

Abstract

Introduction: Laryngeal and hypopharyngeal lesions areamong common head-and-neck diseases. Evaluating them with direct laryngoscope provides information about the kinds and regions of the lesions, whichalong with the clinical signs helps to diagnose and determine the treatment plans. The aim of this study is to evaluatethe frequency distribution of different types of laryngeal and hypopharyngeal lesions viadirect laryngoscopyofthe patients referred to the medical centers of Birjand city.

Methods: This cross-sectionalstudy wasperformed on 165 patients referred to all ENT specialized medical centers of Birjand city who,according to the primary clinical diagnosis, were in need of direct laryngoscopy. Patients with bronchial or lower lesions were omitted from the study. The necessary information including age, sex, residence, primary complaint, risk factors,type and region of the lesion was collected with the patient's consent. Data were analyzed in SPSS 18 software usingKruskal-Wallis and Chi-Square tests. The significance level was set at $P<0.05$.

Results: The mean age of the participants was 43.76±23.66 years, and 53.3% were male. The most frequent primary complaint was dysphonia,the most frequent types of lesion were foreign object and neoplasm, the most involved regions were glottis and hypopharynx, and the most frequent risk factors were opium and smoking.The results showed a significant correlation between the type of lesions and the variables of age, residence, risk factors and region of legions.

Conclusions: The results showed that dysphonia was the most frequent primary complaint. The majority of neoplastic lesions,which had a significant correlation with smoking, opium consumption and bad nutritional habits, were seen in men,indicating the necessity to inform people about the primary signsof these lesions in order to diagnose timely and decrease tobacco use.

Key Words: Laryngoscopy; Laryngeal Neoplasms; Hypopharyngeal Neoplasms

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Introduction

Laryngeal and hypopharyngeallesions are amongst commondiseases of head and neck and upper airway, which appear with different symptoms (1). These lesions include benign and malignant lesions and foreign objects, the appearance of which varies depending on the type and region of the lesion (2, 3). With a wide geographical distribution, the malignant laryngeal cancers are among the most common types of cancer comprising7.1% of the known cancers (4, 5).

As the most common malignancy of the upper airway routes in adults, squamous cell carcinoma of larynx and hypopharynxaccount for30 to 40 percent of all cancers of thehead-and-neck region and 1 to 5.2 percent of all cancers (6). This type of malignancy is responsible for more than 90% of all malignant neoplasms of larynx and is of a higher prevalence in men than womenso much so that it is typically known as the disease of adult malesmokers (5, 7). Hypopharynx squamous cell carcinomasare less prevalent in comparison to other regions of head and neck (8). Diagnosis of the lesion in the context is an important step to the treatment of head-and-neck cancers. Moreover, some benign lesions need to have a biopsy too (9). One of the diagnostic procedures for these lesions is laryngoscopy which is an easy way with fewcomplicationsand is accessible to most medical centers. Even in rare cases such as LaryngealParaganglioma, useful clinical results could be obtained with laryngoscopy (10). Direct laryngoscopy confirms the diagnosis and stage of the disease in the context before treatment plan initiates (11). Examining the lesions of larynx and hypopharynx with direct laryngoscopy provides both the possibility of touching, biopsy and surgical interventions and the adequate information about the type, region, and expansion of lesions. Along with these advantages, there are disadvantages such as the difficulty of endurance by the patient, inadequate vision in some regionslike pyriform sinus and infraglottis, spasms, reduced movement of the vocal cords, and dependence on equipment for magnifyingand simultaneous imaging when using direct laryngoscopy. However, the results obtained from this procedure, besides the clinicalsymptoms of the patient, will contributeconsiderablyto the diagnosis and ultimatedetermination of the treatment plan; and even in some cases, diagnosis and treatment can be performed simultaneously (1). In terms of examining the prevalence of different types of lesions in the region of head and neck, larynx and hypopharynx, several studies have been performed on the relevant patients and in different parts of the country (1, 8, 12). Given the significance of proper diagnosis and treatment of lesions of the larynx and hypopharynx and even the criticalnessof the diagnosis and treatment of some of them and the lack of precise and detailed statistical information in this regard in Birjand, we were prompted to examinedifferent types of laryngeal and hypopharyngiallesions in the patients referred to the treatment centers of Birjand city by using direct laryngoscopy as a valuable and useful endoscopictechnique of diagnosis and treatment.

Methods

This study was performed on the patients referred to the specializedENT centers in Birjand city (Vali-e-Asr Hospital, Imam Reza Hospital, and private clinics), who were in need of diagnostic endoscopy of the larynx and hypopharynx based on the initial diagnosis in the years of 2011-2012. The primary diagnostic procedurewas direct laryngoscopy, whichgiven the case, was performed on an outpatient basis with local anesthesia or hospitalization with general anesthesia. However, in the case of the spread of the lesions to lower regions, esophagus or trachea were also examined. However,when the lesion was primarily in the bronchus or lower points,the patientwas referred to a relevant specialist tocontinue the specialized treatment, and then s/he was excluded from the study. Biopsies were taken from the lesions and examined pathologically.Overall,165 patients were included in the study and relevant data including age, gender, residence, original complaints of the patients, risk factors, andregion and type of lesionwere collected after acquiring the consent of the patients. This study was confirmed with the ethics code of IR.BUMS.REC.1394.176 on 1.11.2016fromthe Ethics Committee of Birjand University of Medical Sciences. Quantitative variables are shown as mean ± standard deviation and qualitative variables as frequency (percentage). Data were analyzed in SPSS software (version 18)using Kruskal-Wallis and chi-square tests. The significance level was considered at $P<0.05$.

Results

Of the165 patients with a mean age of 43.76 ± 23.66, 88 patients (53.3%) were men and 77 patients (46.7%) were female. Also, 85 patients (51.5%) were residents ofcities and 80 patients (48.5%) lived in rural areas. Results of the patients' original complaints showed that dysphonia was the most common primary symptom, while otalgiahad the lowest frequency (Chart 1). The frequency distribution of the studied patients on the basis of the region of the lesions indicated that the highest frequency was in glottis and hypopharynx (Table 1). The most common types of lesion in this study were foreign object, neoplasm, and vocal cord nodules and the least common type of lesion was posterior laryngitis (Table 1). The most common risk factor among the studied patients was opium abuse and smoking(Table 1).

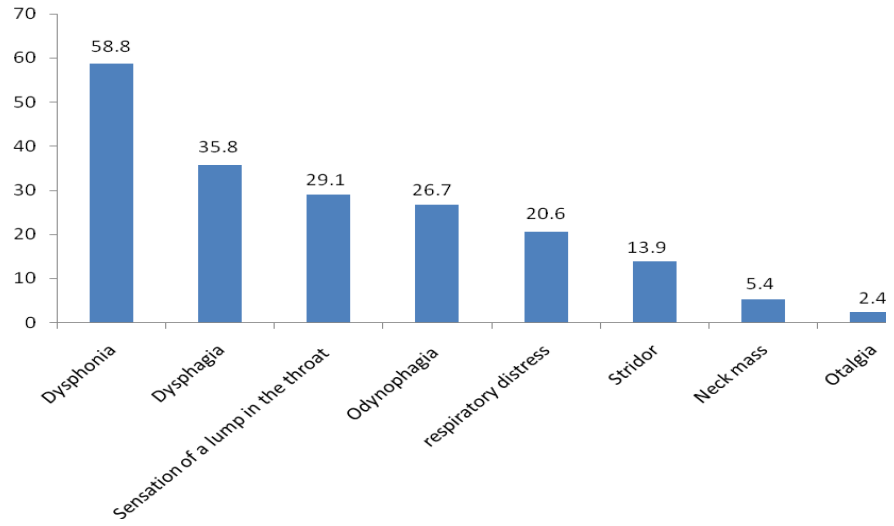

Chart 1: Frequency distribution of participants according to initial complaints

Table 1: Frequency distribution of patients according to lesion location, lesion type, and risk factors

Variable		Frequency (Percentage)
Lesion location	Hypopharynx	49 (29.7)
	Esophagus	26 (15.8)
	Larynx*	28 (17)
	Supraglottic	90 (54.5)
	Glottic	63 (38.2)
	Infraglotic	6 (3.6)
		5 (3)
Lesion type	transglottic	51 (30.9)
	Neoplasm	48 (29.1)
	Vocal cord nodule	35 (21.2)
	Inflammation and edema	13 (7.9)
	Vocal cord paralysis	15 (9.1)
	Posterior laryngitis	3 (1.8)
Risk factors	Opium	43 (26.1)
	Smoking	33 (20)
	Bad food habits	29 (17.5)
	Hot food	22 (13.3)
	Spicy food	7 (4.2)
	Acid reflux into the esophagus	22 (13.3)
	Vocal abuse	18 (10.9)

* Some patients had more than one involvement in their larynx.

Table 2: Correlation between lesion type and other variables in the study

Variable			Lesion type Foreign body	Neoplasm	Vocal cord nodule	Other	Significance level
Age s(year)			29.73±26.38	60.44±13.73	37.71±12.36	47.84±24.34	<0.001
Sex	Male		29 (33)	28 (31.8)	15 (17)	16 (18.2)	0.509
	Female		22 (28.6)	20 (26)	20 (26)	15 (19.5)	
Residence	Urban		33 (83.8)	18 (21.2)	21 (24.7)	13 (15.3)	0.24
	Rural		18 (22.5)	30 (37.5)	14 (17.5)	18 (22.5)	
Risk factors							
	Opium	Yes	3 (7)	32 (74.4)	1 (2.3)	7 (16.3)	<0.001
		No	48 (39.3)	16 (13.1)	34 (27.9)	24 (19.7)	
	Smoking	Yes	3 (9.1)	20 (60.6)	2 (6.1)	8 (24.2)	<0.001
		No	48 (36.4)	28 (21.2)	25 (33)	23 (17.4)	
	Bad food habits	Yes	1 (4.3)	9 (39.1)	5 (21.7)	8 (34.8)	0.014
		No	50 (35.2)	39 (27.5)	30 (21.1)	23 (16.2)	
	Acid reflux into the esophagus	Yes	2 (9.1)	4 (18.2)	9 (40.9)	7 (31.8)	0.008
		No	49 (34.3)	44 (30.8)	26 (18.2)	24 (16.8)	
	Vocal abuse	Yes	1 (5.6)	0 (0)	15 (83.3)	2 (11.1)	<0.001
		No	50 (34)	48 (32.7)	20 (13.6)	29 (19.7)	
Lesion location	Hypopharynx		23 (46.9)	18 (36.7)	1 (2)	7 (14.3)	<0.001
	Esophagus		12 (13.3)	23 (25.6)	34 (37.8)	21 (23.3)	
	Larynx		16 (61.5)	7 (26.9)	0 (0)	3 (11.5)	

The results showed that there is a significant relationship between the type of lesion and the variables of age, place of residence, risk factors, and the lesion region, but no significant relationship was found between type of lesion and gender. The most common type of lesion in hypopharynx and esophagus was foreign object and inthe larynx, it was vocal cord nodules (Table 2). The number of patients with neoplasm was highest in the larynx such that the frequency distribution of the neoplasm lesion was 22.9% in supraglottis, 27.1% in glottis, 2.1% in infraglottis, and 8.3% intransglottis. Based on the findings of this study, the consumption of opium in rural residents was higher than in the urban population (36.2%vs. 16.5%), with the difference being statistically significant (p=0.004). However, theplace of residencedid not show a significantrelationship with other risk factors. Furthermore, smoking among men with 34.1% frequency was significantly higher than in women with 3.9% frequency (p<0.0001). Gender had no significant relationship with other risk factors.

Discussion

In this study, among the primary complaints of the patients at the time of admittance, dysphonia was the most common primary complaint with 58.8%. The most common symptoms were dysphagia with 35.8%, feeling a lump in the throat with 29.1%, and odynophagia with 26.7%. Comparison of the symptoms in this study was closely consistent with the study by Ghahremani et al, in which the investigation of 146 patients showed that dysphonia was the most common complaint (77%), while the most common symptomswere dysphagia (38%), respiratory distress (36%), and feeling a lump in the throat (27%) (1). The study by Myziara et alon 108 cases of larynx cancerreported dysphonia with 85.2% frequencyto be the most common symptom (13). In the study by Hashemi et al, which was performed with the aim of investigating the effects of foreign objects in upper respiratory tract, dysphagia was the most common complaint (12). In the report of the second largest source of browsing data from 1985 to 1992, as a comprehensive document of hospital data by Hoffmann et al.,which was performed on a large sample of patients withhypopharynx cancer,the highest distribution of the patients' symptoms were dysphagia (48%), throat mass (45%), sore throat (43%), hoarseness (35.6%) and otalgia(17.5%). This distribution is somewhat similar to the results of the present study, and the existing differences are due to their exclusive investigation from hypopharynx cancer, which usually causes no respiratory symptoms. Thus, in this report, dysphonia has not been subject to the common symptoms of patients (14).

Foreign object,based on the results of this study, was the most frequent type of lesionfollowed byneoplasms, vocal cord nodules and their paralysis,respectively. These results of the frequency of neoplasmsis similar to those of the study by Ghahremani et al in whereneoplasm (51%) was the most common finding,and SCC was also the most common neoplasm.However, in their study, foreign objectswere not covered (1). Some

studies have reported laryngomalacia or nasal adenoid hypertrophy to be the most common lesions, or haveintroduced 95% of all hypopharynx tumors to be SCC.These differences, due to different age groups or the exclusiveness of the type oflesion assessment, are in contrast with findings in the present study(14, 15).

The statistical analysis of the data of this study showed a significant relationship between the type of lesionand the mean age of the patients so that the highest mean age was observed in patients with neoplasms and lowest mean age in patients with foreign objects. Meanwhile,there was no significant relationship between type of lesion and gender thoughthe ratio of men was higher than women in all cases except in vocal cord nodules. Some studies have considered both age and gender relevant to the foreign object lesion and have known both youth and adults as the category that is subject to injury.However, in some studies, this frequencywas higher in children under 10 years of age. Kamatet alreported the higher incidence of the foreign object in adults due to the presence of fish as themain food regime, but there was no significant difference between gender and foreign object in theirfindings (3).

Based on the significance of the relationship between type of lesionand its region in this study, the most common type of lesionin hypopharynx and esophaguswas foreign object and the most common type of lesion in the larynx was vocal cord nodule. Themost frequent neoplasm in different regions of laryngopharynxin our study was larynx and then hypopharynx, and in different regions of the larynx, glottis was the most common site for neoplasm followed bysupraglottis, transglottis, and Infraglottis, respectively. Also, the study by Ghahremani et al showed the most prevalent regions of neoplasm to be larynx followed byhypopharynx, but they stated that the most common regions of involvement for larynx were supraglottis, glottis, transglottis, and infraglottis, respectively. The study by Shahidi et al declared the cases of hospitalized cancer to be higher in the larynx (8).Neoplasm of glottis in this study had a prevalence of1.1 times higher than that of neoplasm of supraglottis, but this differs in different studies and populations. The ratio of supraglottic cancer to glottis is 4 to 1 in the study by Ghahremani.In the United States, glottis cancer is more common with a ratio of 2 to 1, but in France it is 1 to 2. In Finland two third of larynx cancers weresupraglottic, while nonetheless some recent studieshave reported the glottic type to be higher (1, 7, 16, 17). Several studies have introduced larynx cancers as the disease related to the middle age and above so much so that the peak of its incidence isat the age of 60 to 80. The ratio of these cancers has been reported to be higher in men than in women. However, women are more involvedat lower ages than men (5, 18-20). Theproportion of this cancer in men to women in the European countriesis varied ranging from 10-30times (21).

In addition, several studies have considered smoking and alcoholas the most important risk factors for larynx cancers so that the intensity, duration and type of smoking and the amount of the alcohol consumed, have a direct correlation with laryngeal cancer. Also,alcohol consumption has been known an important factor in the etiology of the supraglotticlarynx cancer compared to Glottictype (5, 22-25). In this study, although there was no significant relationship between the type of lesion and gender, the ratio of neoplasm in men was higher than in women, which could be due to greatersmokingin men, as smoking in men is significantly higher than in women.Opium and smoking were found the most prevalent factors in the studied patients and there was a significant relationship between the type of lesion and the risk factors.It should be noted that the results of studies in different communities have known smoking as the main cause of laryngeal cancer even among women. On the basis of a case-control study in the American society, the relative risk of affliction (of larynx cancer) in women who consumed more than 20 cigarettes per day was 28.2greater than non-smokers(24). In addition, studies in Italy emphasize the strong relationship between the consumption of alcohol and especially tobacco with larynx cancer in women (26, 27). Also, one of the largest investigations of larynx cancer in women, highlights the importance of smoking and, in a weaker way, alcohol abuse as the increasing risk factors among them.

Nevertheless, it shows notable results in terms of the relation of a dietary plan including vegetables, fresh fruits, and olive oil with larynx cancer so that the chances of developing cancer are significantly lower in cases of individuals with alcohol abuse or smoking (28). The results of other studies carried out in the past years, also, indicate the role of dietary habits and the important link between the type of diet and development of larynx and hypopharynx cancers(23, 29). In this study, we did not evaluate the diet of the patients; however,the examination of the poor dietary habits, including the consumption of hot or spicy foods, showed that the most common type of lesion in the people with poor dietary habits was neoplasm.

The relationship between risk factors including type of occupational activity and exposure to some factors like asbestos, strong mineral acids like sulfuric acid, or the work related to plastic industry on the one handand development of the larynx and hypopharynx cancershave been examined in a number of studies (30, 31). Bofta et al (2003) found significant associationsbetween risks oflarynx and hypopharynxcancersand industrial businesses related to construction, metals, textiles, ceramics, railroad transport, and food industry. The associations were also partially significant as related to construction, pottery-making, butchery, hairdressing, with jobs in timber and lumber construction as at risk groups (32).

Possible associations between thediets and jobs of the individuals andhead and neck lesions and cancers in our studied population are in need of further research.Type of lesion and place of residence were also among the significant issuesin the present study, which can be justified by greater opium consumption among rural people than urban residents. This indicates an important point towards the need to providemore information and to developa kind ofculture in these areas, as other studies have also emphasized the impact of social and cultural factors in this regard (23, 32).

Conclusions

Based on the findings of this study, dysphonia was the most common initial presentationin the patients, while foreign object and neoplasm were the most frequent lesions, andglottis andhypopharynx werethe most involved regions, which indicatesthe necessity to inform people about the primary symptoms for the early diagnosis of the lesions of thisanatomic region. The significantfrequency of opium, smoking, and poor dietary habits,as well as the higher incidence of neoplasm in men than in women, in rural areas than urban areas, and the higher proportion of opium consumption among rural residents is a warning concerning the need for serious programs to reduce the consumption of tobacco and to inform people, thus overall, elevate cultural level of the region.

Acknowledgements

In the end, it is necessary to thank all the personnel ofENT of Vali-Asr and Imam RezaHospitals who helped us complete this project.Also, the authors are grateful to Mr. HashemHooshyar who played an important role in the data analysis.

Conflict of interest

The authors declare no conflict of interest.

References

1. Ghahramani A, Mokhtari N. Usage of direct laryngoscopy in patients with laryngopharyngeal lesions. Iranian Journal of Otorhinolaryngology. 2007:185-90.

2. García JJ, Richardson MS. Common Lesions of the Larynx and Hypopharynx. Surgical pathology clinics. 2011 Dec 31;4(4):1153-75.

3. Kamath P, Bhojwani KM, Prasannaraj T, Abhijith K. Foreign bodies in the aerodigestive tract a clinical study of cases in the coastal belt of South India. American journal of otolaryngology. 2006 Dec 31;27(6):373-7.

4. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. International journal of cancer. 1999 Mar 15;80(6):827-41.

5. Raitiola H. Epidemiology, Clinical Characteristics and Treatment Outcome of Laryngeal Cancer. Academic Dissertation. University of Tampere. Medical School. Finland. Acta Electronica Universitatis Tamperensis. 2000;38.

6. Iype EM, Kumar SS, Varghese BT, Jose JC. Clinicopathological Factors of Cervical Nodal Metastasis and the Concept of Selective Lateral Neck Dissection in the Surgical Management of Carcinoma Larynx and Hypopharynx and Its Outcome. Indian Journal of Surgical Oncology.2017 May 9:1-4.

7. Teppo H. Incidence, survival, diagnostic delays and prognostic factors in laryngeal cancer. Oulun yliopisto. 2003 May:25(5):389-394.

8. Shahidi n, khorsandi am. The prevalence of occult neck metastasis in patients with no neck disease in squamouse cell carcinoma of upper aerodigestive tract.SID.2007:29(2).

9. Lippert D, Hoffman MR, Dang P, McCulloch TM, Hartig GK, Dailey SH. In-office biopsy of upper airway lesions: Safety, tolerance, and effect on time to treatment. The Laryngoscope. 2015 Apr 1;125(4):919-23.

10. Myssiorek D. Treatment of laryngeal paraganglioma. Operative Techniques in Otolaryngology-Head and Neck Surgery. 2016 Mar 31;27(1):36-40.

11.Smith A, Grady A, Vieira F, Sebelik M. Ultrasound-Guided Needle Biopsy for Diagnosis of Advanced-Stage Malignancies of the Upper Aerodigestive Tract. OTO Open. 2017 Feb;1(1):2473974X17690132.

12. Hashemi BS, Gandomi B, Hesamzade L. Evaluation of the Incidence and Complications of Foreign Body Ingestion in the Patients Referred to Shiraz Khalili Hospital. Armaghane danesh. 2004 Jan 15;8(4):41-9.

13. Miziara ID, Cahali MB, Murakami MS, Figueiredo LA, Guimaraes JR. Cancer of the larynx: correlation of clinical characteristics, site of origin, stage, histology and diagnostic delay. Revue de laryngologie-otologie-rhinologie. 1997 Dec;119(2):101-4.

14.Hoffman HT, Karnell LH, Shah JP, Ariyan S, Brown GS, Fee WE, Glass AG, Goepfert H, Ossoff RH, Fremgen AM. Hypopharyngeal cancer patient care evaluation. The Laryngoscope. 1997 Aug 1;107(8):1005-17.

15. Chen WT, Soong WJ, Lee YS, Jeng MJ, Chang HL, Hwang B. The safety of aerodigestive tract flexible endoscopy as an outpatient procedure in young children. Journal of the Chinese Medical Association. 2008 Mar 1;71(3):128-34.

16.Liu B, Ren Z. Contrast analysis of clinical and pathological staging of supraglottic carcinomas. Lin chuang er bi yan hou ke za zhi= Journal of clinical otorhinolaryngology. 1997 Dec;11(12):537-9.

17. Virtaniemi, Pasi P. Hirvikoski, Eero J. Kumpulainen, Risto T. Johansson, Eero Pukkala, Veli-Matti Kosma JA. Is the subsite distribution of laryngeal cancer related to smoking habits?. Acta Oncologica. 2000 Jan 1;39(1):77-9.

18. Robin PE, Reid A, Powell DJ, McConkey CC. The incidence of cancer of the larynx. Clinical Otolaryngology. 1991 Apr 1;16(2):198-201.

19. ROTHMAN KJ, CANN CI, FLANDERS D, FRIED MP. Epidemiology of laryngeal cancer. Epidemiologic reviews. 1980 Jan 1;2(1):195-209.

20. Stephenson WT, Barnes DE, Holmes FF. Gender influences subsite of origin of laryngeal carcinoma. Archives of Otolaryngology–Head & Neck Surgery. 1991 Jul 1;117(7):774-8.

21.Levi F, La Vecchia C, Lucchini F, Negri E. Trends in cancer mortality sex ratios in Europe, 1950-1989. World health statistics quarterly. Rapport trimestriel de statistiques sanitaires mondiales. 1991 Dec;45(1):117-64.

22. Muscat JE, Wynder EL. Tobacco, alcohol, asbestos, and occupational risk factors for laryngeal cancer. Cancer. 1992 May 1;69(9):2244-51.

23. Tuyns AJ, Esteve J, Raymond L, Berrino F, Benhamou E, Blanchet F, Boffetta P, Crosignani P, Moral AD, Lehmann W, Merletti F. Cancer of the larynx/hypopharynx, tobacco and alcohol: Iarc international case-control study in Turin and Varese (Italy), Zaragoza and Navarra (Spain), Geneva (Switzerland) and Calvados (France). International journal of cancer. 1988 Apr 15;41(4):483-91.

24. MLWIINSKI M. Environmental factors in cancer of the larynx A second look. Cancer. 1976 Oct;38:1591-601.

25. Zheng W, Blot WJ, Shu XO, Gao YT, Ji BT, Ziegler RG, Fraumeni JF. Diet and other risk factors for laryngeal cancer in Shanghai, China. American Journal of Epidemiology. 1992 Jul 15;136(2):178-91.

26. Franceschi S, Bidoli E, Negri E, Barbone F, La Vecchia C. Alcohol and cancers of the upper aerodigestive tract in men and women. Cancer Epidemiology and Prevention Biomarkers. 1994 Jun 1;3(4):299-304.

27. Tavani A, Negri E, Franceschi S, Barbone F, La Vecchia C. Attributable risk for laryngeal cancer in northern Italy. Cancer Epidemiology and Prevention Biomarkers. 1994 Mar 1;3(2):121-5.

28. Gallus S, Bosetti C, Franceschi S, Levi F, Simonato L, Negri E, La Vecchia C. Oesophageal cancer in women: tobacco, alcohol, nutritional and hormonal factors. British journal of cancer. 2001 Aug;85(3):341.

29. Estève J, Riboli E, Péquignot G, Terracini B, Merletti F, Crosignani P, Ascunce N, Zubiri L, Blanchet F, Raymond L, Repetto F. Diet and cancers of the larynx and hypopharynx: the IARC multi-center study in southwestern Europe. Cancer Causes & Control. 1996 Mar 1;7(2):240-52.

30. International Agency for Research on Cancer. Occupational exposures to mists and vapours from strong inorganic acids; and other industrial chemicals. IARC Monographs on the evaluation of the carcinogenic risks of chemicals in humans. 1992;54.

31. Kogevinas M, Sala M, Boffetta P, Kazerouni N, Kromhout H, Hoar-Zahm S. Cancer risk in the rubber industry: a review of the recent epidemiological evidence. Occupational and Environmental Medicine. 1998 Jan 1;55(1):1-2.

32. Boffetta P, Richiardi L, Berrino F, Estéve J, Pisani P, Crosignani P, Raymond L, Zubiri L, Del Moral A, Lehmann W, Donato F. Occupation and larynx and hypopharynx cancer: an international case–control study in France, Italy, Spain, and Switzerland. Cancer Causes & Control. 2003 Apr 1;14(3):203-12.