

Laryngeal cancer: smoking is not the only risk factor

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Abstract. *Laryngeal cancer: smoking is not the only risk factor.* **Aim:** To investigate the role of smoking, alcohol, coffee consumption, demographic factors, toxic agents, and occupation in laryngeal carcinogenesis.

Materials/methods: A case-control study included 70 patients with histologically confirmed laryngeal cancer and 70 controls with non-neoplastic conditions unrelated to diet/smoking/alcohol. Relative risk, odds ratio (OR), and 95% confidence intervals were estimated using multiple logistic regression.

Results: Current smokers had 19.46 OR of laryngeal cancer compared to non-smokers ($p = 0.006$). The respective OR for alcohol consumption was 3.94 ($p = 0.006$). While the risk increased in heavy drinkers, there was no difference in duration of alcohol consumption. There was a strong and consistent relation between laryngeal cancer and the consumption of Greek/Turkish coffee cups/day ($p = 0.002$, OR = 1.77). Diesel exhaust fumes also seemed to increase the risk of laryngeal cancer, although the association was found to be no longer significant after analysis with logistic regression.

Conclusion: The present study confirmed the relation of smoking and alcohol with laryngeal cancer. However, other factors such as coffee and diesel exhaust fumes may play an important role in laryngeal carcinogenesis.

EBM Level: III

Introduction

Carcinoma of the larynx is the third most common cancer of the upper aerodigestive tract, and the 13th most common cancer in men.¹ However, its incidence varies significantly in different parts of the world. It is higher in Spain, France, Northern Italy, and Poland (20-40 cases/100 000/ year), and much lower in China, Japan, India, the Scandinavian countries, and the U.K. (1-10 cases/100 000/year).²

During the decades following World War II, the incidence of laryngeal cancer increased rather alarmingly, even in women. This has largely been attributed to changes in tobacco and alcohol consumption.² However, other factors associated with the modern lifestyle of developed countries may also play a significant role in laryngeal carcinogenesis.³ These

factors may include pollution, chemical toxic agents, different diets, coffee consumption, etc.

The aim of the present study was to investigate the role of smoking, alcohol and coffee consumption, as well as toxic agents, occupation, and demographic factors, in laryngeal carcinogenesis.

Materials and methods

A case-control study of laryngeal cancer was conducted in two tertiary university ENT departments. The study looked at 70 consecutive patients (65 men and 5 women), with histologically confirmed squamous cell carcinoma of the larynx (incident cases). The vast majority of patients were included in the study after the histological confirmation of the carcinoma, and a few days before curative surgery. Exclusion crite-

ria were: non-squamous cell carcinomas of the larynx, unrelated carcinoma/neoplasia in other organs, diabetes mellitus, renal insufficiency, and age younger than 40 years. Three patients refused to participate in the study.

Controls were selected during the same period from in-patients suffering from non-neoplastic conditions not related to diet, smoking or alcohol consumption. Controls were matched to cases in accordance with gender and age. They comprised 70 subjects (64 males/6 females) with the following diseases: eye disorders ($n = 47$), injuries ($n = 16$), abdominal hernia ($n = 2$), epistaxis ($n = 2$), tympanoplasty ($n = 2$), peritonsillar abscess ($n = 1$). Three controls did not meet the age criterion, and were excluded from the study. Three eligible controls refused to participate in the study.

The research protocol was submitted to the Ethics Committee of the University of Athens before data collection started and approval was given. Participants were asked to sign a consent form before being enrolled in the study. All participants (cases and controls) were personally interviewed by the first author. A structured questionnaire included personal history (age, weight at present and two years previously, residence, training, medical history, and family history), detailed history of tobacco smoking (number of cigarettes smoked per day, years of smoking, type of tobacco), detailed history of alcohol drinking (years of drinking, number of units per day or week, type of alcohol), detailed history of coffee drinking (type of coffee, number of cups per day), and complete occupational history including specific job titles, and exposure to different toxic agents.

SPSS, version 14.0, was used for the statistical analysis of the data. Chi-square statistical analysis was used to investigate the distributional differences of the categorical variables between cases and controls. Results were confirmed by logistic regression analysis. The forward stepwise method was used to select variables to be maintained in the final model. Statistical significance was set at 5%. The magnitude of association between cases and controls is stated as odds ratios (OR) followed by the 95% confidence intervals.

Results

Cases and controls did not differ statistically in terms of gender, medical history, weight or years of education. However, the mean age

Table 1
Demographic characteristics of study participants

| Variable | | Controls | | Cases | | P |
|-----------|--------|----------|------|-------|-------|-------|
| | | N | % | N | % | |
| Gender | Male | 64 | 91.4 | 65 | 92.86 | 1.000 |
| | Female | 6 | 8.6 | 5 | 7.14 | |
| Age | < 65 | 19 | 27.1 | 34 | 48.57 | 0.015 |
| | ≥ 65 | 51 | 72.9 | 36 | 51.43 | |
| Residence | Urban | 41 | 58.6 | 25 | 35.71 | 0.011 |
| | Rural | 29 | 41.4 | 45 | 64.29 | |

of cancer cases was significantly lower than the controls: approximately five years (64.3 ± 8.8 vs. 69.7 ± 10.9 , $p = 0.001$). In order to adjust the difference of the age distribution between the two groups, case and controls were further categorised using the cut-off value of 65 years, which represented the median value.

A higher number of cancer cases than controls were resident in rural areas ($p = 0.01$) (Table 1).

A higher number of laryngeal cancer cases than controls reported alcohol consumption in the present study and this difference was found to be statistically significant ($p < 0.0001$, OR = 4.0, 95% CI = 1.89-8.46). The relation remained statistically significant, even after the age adjustments mentioned above, in both age groups. Furthermore, cancer cases reported a higher number of consumed alcohol units than controls, and the number of heavy drinkers was higher in the cancer group ($p < 0.0001$). There was no difference in the duration of consumption between cases and controls. A higher percentage of cancer cases reported higher consumption of beer ($p = 0.001$, OR = 6, 95% CI = 2-17.7), whisky ($p = 0.004$, OR = 8.5, 95% CI = 1.8-39.1) and ouzo ($p = 0.02$, OR = 3.1, 95% CI = 1.2-7.6). A higher

consumption of brandy was also reported by cancer cases, but this did not prove to be statistically significant, most probably due to the limited number of brandy consumers. The consumption of wine was not found to be a statistically significant risk factor for laryngeal cancer. The duration of consumption of beer, ouzo and whisky did not differ significantly between cases and controls (p value = 0.3).

A strong association between tobacco smoking and laryngeal cancer was also found, as cancer patients were more often smokers than controls ($p < 0.0001$) (Table 2). The positive relation between smoking and cases and controls remained constant in both age groups. When all the smokers in both case and control samples were analysed further, the cancer cases smoked more cigarettes a day, but the difference with the controls was not statistically significant ($p = 0.07$).

A higher number of laryngeal cancer cases compared to controls reported coffee consumption, and this difference proved statistically significant (p value = 0.002). However, the duration of consumption did not differ between cases and controls. Further data analysis revealed that the difference was attributable to Greek/Turkish coffee

Table 2
Risk factors for laryngeal cancer

| Risk factor | | Controls | | Cases | | P |
|--------------------------|-----|----------|------|-------|-------|----------|
| | | N | % | N | % | |
| Alcohol consumption | No | 35 | 50 | 14 | 20 | < 0.0001 |
| | Yes | 35 | 50 | 56 | 80 | |
| Smoking* | No | 25 | 35,7 | 1 | 1.43 | < 0.0001 |
| | Yes | 21 | 30,0 | 51 | 72.86 | |
| Coffee consumption | No | 13 | 18,6 | 1 | 1.43 | 0.001 |
| | Yes | 57 | 81,4 | 69 | 98.57 | |
| Exposure to toxic agents | No | 47 | 67,1 | 31 | 44.29 | 0.011 |
| | Yes | 23 | 32,9 | 39 | 55.71 | |

*24 patients in the control group and 18 patients in the study group had been smokers in the past.

consumption (p value = 0.01). The relation was not statistically significant for instant coffee, while a positive relation with a statistically significant difference was found when the two types of coffee were combined (p value = 0.001). Following the age adjustment, the results did not change with regard to total coffee consumption (cups per day), while there was a difference related to the type of coffee. When looking at Greek/Turkish coffee consumption (cups per day) in particular, the difference between cancer cases and controls remained statistically significant in both age groups; in the case of instant coffee consumption (cups per day) the difference was only statistically significant in patients younger than 65 years of age.

More patients than controls had been exposed to a toxic agent and this difference was statistically significant (p = 0.01, OR = 2.57, 95% CI = 1.29-5.11). Exposure to diesel exhaust fumes seems to be closely related to an increased risk of laryngeal cancer (p = 0.001, OR = 1.39, 95% CI = 1.14-1.7). The duration of exposure did

not differ between cases and controls. Moreover, no difference was observed regarding exposure to asbestos, perithrine, solvents, wood, cotton and metal dust between cases and controls.

This study also looked at the possible relation between tobacco smoking and alcohol consumption and the specific localisation of laryngeal cancer. We did not find any statistically significant association.

Logistic regression analysis

The relation between residence in rural areas and laryngeal cancer did not remain significant after the logistic regression analysis in the present study. Moreover, this result did not change in the stratified analysis that was performed according to the place of residence. This association was therefore considered to be random.

The association between alcohol consumption and laryngeal cancer remained statistically significant after the logistic regression analysis. Current drinkers were at more risk of laryngeal cancer than non-drinkers and this

difference was statistically significant (p = 0.006, OR = 3.943, 95% CI = 1.47-10.53). Ex-drinkers had a borderline higher risk of laryngeal cancer than people who had never been drinkers (p value = 0.05).

The positive association between tobacco smoking and laryngeal cancer also remained statistically important when logistic regression analysis was performed. Current smokers were at more risk of the disease than people who had never smoked (p = 0.006, OR = 19.46, 95% [CI = 2.3-164.7]). By contrast, ex-smokers versus never smokers did not differ regarding the risk of laryngeal cancer (p > 0.05).

The relation between laryngeal cancer and coffee consumption also remained significant after the logistic regression analysis. Cancer cases consumed a significantly higher number of cups per day of Greek/Turkish coffee than controls (p = 0.002 OR = 1.767, 95% CI = [1.242-2.515]).

The results of exposure to different toxic agents, especially to diesel exhaust fumes, did not prove consistent in the present

study. After the logistic regression, the difference between cases and controls did not remain statistically significant.

Discussion

The results of the present study concur with other studies in the literature about the role of alcohol and smoking as significant risk factors for laryngeal cancer.^{4,6} Tobacco smoking was confirmed as the most important risk factor in laryngeal carcinogenesis. The OR for current smokers, compared with people who had never smoked, was 19.46 (95% CI: 2.3-164.66). The relation between tobacco smoking and laryngeal cancer is the strongest and most constant association in the present study.

Patients with laryngeal cancer were found to consume more alcohol than controls (p value = 0.006, OR = 3.943, 95% CI = 1.47-10.53). Furthermore, the risk of laryngeal cancer was higher for heavy drinkers and this confirmed studies conducted during the past decade.^{4,5} No difference associated with the consumption of beer or spirits was found. While there was a positive relation between the risk of laryngeal cancer and the consumption of beer, whisky, ouzo and brandy, the consumption of wine was not found to be a statistically significant risk factor for laryngeal cancer. Taking into account the widespread distribution of wine consumption worldwide, this finding can be considered very important, especially in view of the existing controversy in the literature. Indeed, while some authors suggest that beer and spirits are the most dangerous beverages for laryngeal cancer,^{5,7} Barra *et al.*⁸ claim that wine contributes

to a higher risk of laryngeal cancer. Finally, Kjaerheim *et al.*⁹ suggest that cancer risk is independent of the type of alcohol, and that the most prominent drink will tend to give the highest RRs.

Another important and new finding in the present study is the positive relation between laryngeal cancer and coffee consumption. There is a strong and constant association in the statistical analysis, even after the adjustment of coffee consumption with tobacco and alcohol consumption. This finding cannot therefore be seen as a confounding habitual action of smokers without any direct link with laryngeal cancer. The observed relation was mainly due to Greek/Turkish coffee consumption – OR = 1.767 (95% CI: 1.242-2.515) – and there was also a dose-related association here (p value < 0.0001). With regard to instant coffee (cups per day), the association was statistically significant in patients younger than 65. The fact that younger people usually consume more instant coffee than traditional Greek/Turkish coffee may explain this finding. Since the association between coffee consumption and laryngeal cancer has only recently started to be acknowledged in the literature, it was felt that the association of coffee consumption with other cancers had to be explored.

In 1991, the International Agency for Cancer Research (IARC) classified coffee as being “possibly carcinogenic in bladder cancer”.¹⁰ However, Sala *et al.*¹¹ were unable to find such an association, whilst it was claimed that coffee consumption is related to a lower risk of bowel and colorectal cancer. Most studies state that the strong antioxidant properties of several coffee compounds (i.e.

caffeic and chlorogenic acid, catechins, flavonoids and diterpenes) plays a protective role in carcinogenesis. Despite this fact, a direct and significant association between coffee drinking and cancer has recently been reported for the gastric cardia.¹²

An inverse association (albeit potentially weak) between coffee consumption and oesophageal, oral, and pharyngeal cancer has been reported in some cohort studies involving the head and neck.¹³⁻¹⁵ On the other hand, Baker *et al.*¹⁶ found an increased risk of lung cancer in participants who consumed 2-3 cups of regular coffee a day. By contrast, decaffeinated coffee drinking was associated with decreased risk, both for participants who consumed ≤ 1 cup/day, and those who consumed ≥ 2 cups of coffee/day in the latter study. Such results suggest that any chemo-protective effect of the phyto-chemicals contained in coffee may be annulled by the elevated risk associated with caffeine.

A number of studies have reported on the effect of coffee consumption in laryngeal carcinogenesis in particular. However, the results appear controversial. While Pintos *et al.*¹⁷ and La Vecchia *et al.*¹⁸ did not find any relation between coffee consumption and the risk of cancer in the upper aerodigestive tract (including laryngeal cancer), Zvrko *et al.*¹⁹ found a positive relation between coffee consumption (more than 5 cups /day) and laryngeal cancer (OR = 4.5). A recent meta-analysis by Galeone *et al.*²⁰ did not confirm the latter results, and was not suggestive of any association between caffeinated coffee drinking and cancer of the larynx. However, it is interesting to note that most of the studies

analysed had inadequate information regarding the chemical composition of coffee beverages (i.e. Arabica or Robusta variety), or their preparation.

Even though the type of bean also determines the levels of active ingredients in coffee preparations (with the Arabica variety having half the caffeine and twice the diterpenes of Robusta), it appears that the brewing method is a major determinant of the ultimate diterpene levels remaining in the beverage after preparation.²¹ The finding of a positive dose-related association between laryngeal cancer and the consumption of traditional, slowly-boiled, hot Greek/Turkish coffee reported in the present study should therefore be viewed in the light of recent evidence, which suggests that the brewing method may indeed be relevant to the effect of coffee for a given cancer type.²¹

The present study found a statistically significant higher exposure to diesel exhaust fumes in laryngeal cancer cases compared to controls. Although the relation was no longer found to be significant after the logistic regression analysis, it can certainly justify further research in this area, especially since diesel exhaust fumes have also been found to be mutagenic in both laboratory and animal studies.²² It is interesting to note that Soll-Johanning *et al.*²³ suggested that bus and tram drivers have higher risk of laryngeal cancer due to a high exposure to diesel exhaust fumes. Similar findings were also reported in other studies.^{24,25}

The strengths of the present study include the almost complete participation of both cancer cases and controls, and the robust statistical analysis. Recurrences were

excluded in order to eliminate the possibility of confounding lifestyle habits before and after the first diagnosis of laryngeal cancer.

Our study also had some weaknesses. A recent cancer diagnosis may influence patient reporting. The level of awareness about intake may be different in heavy smokers and drinkers than in controls. In addition, life habits in hospital controls may be different from those in the general population, and associated with the reasons for their hospitalisation. To eliminate this factor, we excluded any controls suffering from neoplastic diseases, and other diseases related to diet, smoking or alcohol consumption.

Conclusion

The present study confirmed the relation between smoking, alcohol and laryngeal cancer. It also identified a positive relation between laryngeal cancer and the consumption of traditional Greek/Turkish coffee in a dose-related manner. Finally, the significantly higher level exposure to diesel exhaust fumes in laryngeal cancer cases compared to controls seems to justify further research in the area.

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