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# A Case-Control Study of Laiyngeal Cancer and Smoking


## Abstract

**The present study is to examine by case-control method the impact of smoking on laryngeal cancer. 60 hospitalized cases of the Ear Nose Throat (ENT) department, the National Taiwan University Hospital, diagnosed and pathologically confirmed laryngeal cancer in the period between 1 January 1988 and 31 December 1994 were selected for study. At the same time, 90 controls of the ENT department, the National Taiwan University Hospital, hospitalized in the same period for non-tumor diseases of the head and neck were selected.**

**One copy of a stnictured questionnaire was mailed to each of the subjects. The questionnaire contained items such as: social and demographic background of the subject, history of diseases of the ear, nose and throat, life style, smoking, amount of cigarettes consumed, and duration of smoking.**

**Cases and controls were not significantly different in sex, marital status, race, educational level, religious belief and area of residency (all p values larger than 0.05); though were significantly different in age distribution (p0.05). Age, smoking experience, total year of smoking, way of smoking and the total amount of smoking were statistically associated with laryngeal cancer (all p values smaller than 0.05). Age at first smoking, daily amount of smoking and mode of smoking (filtered or non-filtered cigarettes) were not found to be associated with laryngeal cancer (all p values larger than 0.05).**

**After being adjusted for age, the total amount of smoking was found to be strongly associated with laryngeal cancer ($p<0.001$).**


**Key Words: laryngeal cancer, smoking, case-control method**

## Introduction

Laryngeal cancer though accounts for only 2-5% of all malignant neoplasms, malignant neoplasms of the head and neck are the third leading cancer in Taiwan.

According to the 1991 DOH report of cancer registration[1], the crude incidence rate of laryngeal cancer for men was 2.44 per 100,000 population; and for women, 0.21. Compared to the incidence rates of laryngeal cancer in some developed countries in Europe and the US2, Taiwan is a low incidence country. In 1991, there were 29,592 cancer patients; of them, 4,198 were reported by medical care institutions as cancer patients of the respiratory system and thoracic organs (ICD 160-165). The number of cancer patients of the same sites reported by the National Taiwan University Hospital in the same year was 322. Of them, 21(6.5%) were patients of laryngeal cancer (ICD 161).

Laryngeal cancer is the disease of the elderly. The incidence reaches the peak at the age of 60 and above[3,4]. Prognosis is relatively fair, the five-year survival rate being more than 50%. If treated properly, the survival rate could reach as high as 85-90%[3]. Therefore, for early diagnosis and early treatment to improve survival rate, prevention is most essential. The pathogenic factors of laryngeal cancer should be understood and then removed from the lifestyle or the environment. The present study is to examine by case-control method[5] the impact of smoking on laryngeal cancer.

**Materials and Methods**

1. Subjects of study

60 hospitalized patients of the ENT department, the National Taiwan University Hospital, who had been, during the seven-year period between 1 January 1988 and 31 December 1994, diagnosed and pathologically confirmed laryngeal cancer were selected for study. At the same time, 90 patients of the ENT department, the National Taiwan University Hospital, who had been hospitalized for care in the same period for non-tumor diseases of the head and neck were selected as controls.

2. Study tool

The structured questionnaire used in the present study had been designed making reference to both domestic and international literature. The draft was first evaluated by experts, revised, and then pretested with laryngeal cancer patients in the hospital to rearrange the order and the wordings. The questionnaire contained items such as the social and demographic background of the subject, history of illnesses of the ear, nose and throat of relatives, lifestyle of the patient before hospitalization, smoking habit, and amount and duration of smoking.

One copy of the questionnaire was then mailed to each of the subjects. If they failed to return the questionnaires in time, they were followed-up by telephone. The returned questionnaires were checked. If responses to some questions were not clear or not complete, the subject was followed-up by telephone for further information to ensure the accuracy and reliability of responses.

3. Data processing and analysis

The information collected was keyed-in with Epi-info 6.0. Each variable was

verified of its accuracy. Corrections were made if data were found unreasonable. SAS 6.11 software was then used for single and multi-variable description and analysis. Description of single variables was made for frequency distribution, means and standard errors, median and ranges, or frequency and percentages. For statistical testings, either the Student's t-test or the Wilcoxon rank sum test was used for continuous variables, and Pearson's $X^2$-test or Fisher's exact test for analogical variables. For factors of statistical significance in the single-variable analysis, logistic regression analysis was conducted to examine their association with laryngeal cancer.

**Results**

1. The background information

   From demographic characteristics (see Table 1), it was found that the cases and the controls were not significantly different in sex, marital status, race, educational level, religious belief and area of residence (all p values larger than 0.05); though were different significantly in age distribution ($p<0.05$). There were more cases in the 60-69 and 50-59 age groups in both groups; the study group had more cases (16.7%) in the 70 and above group than the control group (3.4%); on the other hand, the control group had more cases (10.1%) in the 49 and under group than the study group (5.0%).

2. Smoking habit and laryngeal cancer

   It can be noted from Table 2 that the percentages of current smokers and ever-smokers were higher in the study group (25 current smokers, 4 1.7%; and 22 ever-smokers, 36.7%) than in the control group (22 current smokers, 24.4%; and 18 ever-smokers, 20.0%). The percentage distributions of smoking experience in both groups were significantly different ($p<0.05$).

   Most of the smokers consumed cigarettes. Of the 47 smokers (both current and ever-smokers) in the study group, 45 (95.8%) smoked domestic cigarettes; of the 40 smokers in the control group, 39 (97.5%) did so. For domestic cigarettes, the Long Life and the New Paradise were the most popular brands; some smoked the Double Happiness, the Golden Dragon and the President. For imported cigarettes, the State Express was the most popular; some smoked the Mild Seven, and Japanese or Philippine cigarettes. No statistical difference was found between domestic and imported cigarettes ($p>0.05$).

   Most of the smokers smoked filtered cigarettes. 29 (61.7%) in the study group and 29 (72.5%) in the control group smoked filtered cigarettes; whereas 12 (25.5%) in the study group and 5 (12.5%) in the control group smoked non-filtered cigarettes. No statistical difference was found in the mode of smoking between the two groups ($p>0.05$). When smoking, 28 (59.6%) in the study group and 19 (47.5%) in the control group practiced shallow-inhaling; 11(27.5%) in the study group and 15 (3 1.9%) in the control group practiced deep-inhaling; and 10 (25.0%) in the study group and 4 (8.5%) in the control group did not inhale. The median age at first smoking for both groups was quite

close, 20 years for the study group and 21 years for the control group. The youngest age at first smoking was 11 years for the study group and 14 years for the control group. The latest age at first smoking was 55 years for the study group and 30 years for the control group. The mode of smoking, ways of smoking and age at first smoking were not found statistically to be associated with laryngeal cancer (all p values larger than 0.05).

The average total years of smoking was 37.1 years for the study group and 31.9 years for the control group with statistically significant difference ($p<0.05$). The median daily amount of cigarettes consumed was 20 for the study group and 15 for the control group. The largest amount consumed per day was 60 for the study group and 40 for the control group. The median total amount of cigarettes consumed calculated by multiplying the total years of smoking by the daily amount of cigarettes consumed was twice as high (14,281 packs) for the study group than the control group (7,665 packs). The difference was statistically significant ($p<0.05$).

Table 3 uses logistic regression analysis to examine the association between either single factor or multiple factors and laryngeal cancer. Individually, variables such as age at first smoking, daily amount of cigarettes consumed, and mode of smoking were not found statistically to be associated with laryngeal cancer (all p values larger than 0.05); whereas smoking experience, total years of smoking, ways of smoking and the total amount of cigarettes consumed were found to be associated with laryngeal cancer (p values less than 0.05). Multi-variable analysis, however, showed that only the total amount of smoking was associated with laryngeal cancer ($p<0.05$). However, as the age distributions of the two groups were different, they should be considered as confounders and added to the logistic regression analysis to control their impact on the association between the total amount of smoking and laryngeal cancer.

**Discussion and Conclusion**

By demographic characteristics, with the exception of age, the two groups were not significantly different in sex, marital status, race, educational level, religious belief and area of residence (all p values larger than 0.05). The male to female ratio of laryngeal cancer was 19:1. This was similar to the 18:1 ratio of laryngeal cancer patients of the National Taiwan University Hospital in the period between 1971 and 1981, and was in the range of the 6:1 and 32:1 male-female ratios reported either locally or internationally.[3,46-8] The median age of laryngeal cancer patients was 64 years, and 75% (45/60) of them were above 60 years. As reported by Lee HY[3] and Wei et al.[4], laryngeal cancer was the disease of the elderly and the incidence reached a peak after 60 years. By race, native Taiwanese had higher odds. This could be due to the fact that there were in Taiwan more native Taiwanese than people of other provinces. Laryngeal cancer occurred more often in people of lower educational levels. This finding corresponded to the findings of Wei et al.[4] in a study of the Chinese population in Shanghai. People of lower educational levels

would have more exposures to risk factors. They were less aware of any preventive measures, either.

Many experts[4,6-14] pointed out that smoking was the major pathogenic factor of laryngeal cancer. The present study also found that smoking experience had a strong association with laryngeal cancer ($p<0.001$, Tables 2 and 3). Though age at first smoking, daily amount of cigarettes consumed, and mode of smoking were not associated with laryngeal cancer (all p values larger than 0.05), total years of smoking ways of smoking and total amount of smoking were associated with laryngeal cancer (p values less than 0.05). Herity et al.[7] in a study in Ireland examined the associations between smoking, lung cancer and laryngeal cancer. They found that smoking was highly associated with either lung cancer or laryngeal cancer. The relative odds ratios were 10.3 for heavy smoker than non-heavy smokers to contract lung cancer, and 4.9 to contract laryngeal cancer. Falk et al.[12] in a study at the Bay Area of Texas, USA, showed that current smokers had the highest odds; that heavy smokers (more than two packs a day) had 2.5 times more chances than light smokers (1.5 packs a day) and 10.0 times more than non-smokers to contract laryngeal cancer. One who had smoked for more than 45 years had 17.0 more chances than nonsmokers to contract laryngeal cancer. Smoking non-filtered cigarettes was more dangerous than filtered ones.

Muscat et al.[10] in their study in the US pointed out that smoking had a dosage effect on laryngeal cancer; and that, in both heavy and light smokers, smoking was found to be more carcinogenic to the upper part of glottis than the glottis itself. Hedberg et al.[14] found that the relative odds ratio of contracting laryngeal cancer for smokers (40 cigarettes a day) was 23.1 times higher than that of non-smokers. Peng[15] developed the concept of smoking index, which was the number of cigarettes consumed each day multiplied by the years of smoking. Chances of contracting cancers were higher when the smoking index exceeded 400 cigarettes per year. The more cigarettes one smoked, the chances of contracting cancers became higher. Smoking pipe tobacco or cigars though induced less hazards to human body, the fumes produced by pipe tobacco or cigars were mostly alkaline. They were absorbed in the oral cavity and were more likely to induce cancer of the oral cavity or esophagus.

The present study showed a strong association between the total amount of cigarettes consumed and laryngeal cancer ($p<0.00l$, Tables 2 and 3); though, the daily amount of cigarettes consumed was not found to be associated with laryngeal cancer. Falk[12], Herity[17], Hedberg[14] and Lo[16] reported that heavy smokers had 5.0-23.1 times more chances of contracting laryngeal cancer than non-heavy smokers (including non-smokers and light smokers). Muscat[10] maintained that chances of contracting laryngeal cancer were the same for either heavy or light smokers. The average amount of cigarettes consumed in the present study exceeded 400 cigarettes per year ($14,281 \div 365 \times 20 = 783$ for the study group, and $7,665 \div 365 \times 20 = 420$ for the control group). The chances of contracting cancer were higher. When the amount of cigarettes that one consumed exceeded 400 per year, chances

increased. By adjusting for age, the findings in the present study (Table 3) suggested that the total amount of cigarettes consumed was the only risk factor of laryngeal cancer.

**Limitations of Study**

Many studies suggested the association between the concentration of cigarettes and laryngeal cancer. Stefani et al.[17] found that smokers of dark or black tobacco had 2.5 times more chances than smokers of light tobacco and 35.0 times more chances than non-smokers of contracting laryngeal cancer. Munoz et al.[18] maintained that the carcinogenicity of dark or black tobacco was higher than light tobacco. Chou[19], by examining the contents of both domestic and imported cigarettes, found that the tar in cigarettes was carcinogenic; whereas nicotine, though addictive, could not be proved carcinogenic. With a few exceptions, most cases in the present study smoked domestic cigarettes. No information on the contents of these cigarettes was collected. An examination of the association between the concentration of cigarettes and laryngeal cancer was therefore not possible.

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## Table 1. Demographic Characteristics of Study Subjects

| Variables | Cases No. (%) | Controls No. (%) | p Value |
|---|---|---|---|
| Sex: | | | 0.5270* |
| Male | 57(95.0) | 82(91.1) | |
| Female | 3(5.0) | 8(8.9) | |
| Marital status: | | | 0.5790** |
| Unmarried/divorced/widowed | 7(11.7) | 8(8.9) | |
| Married/living together | 53(88.3) | 82(91.1) | |
| Race: | | | 0.5780** |
| Taiwanese | 33(55.0) | 56(62.2) | |
| Hakka | 6(10.0) | 6(6.7) | |
| Fukien/Kwangtong | 8(13.3) | 7(7.8) | |
| Other provinces | 13(21.7) | 21(23.3) | |
| Educational level: | | | 0.2120** |
| Illiterate/primary school | 19(31.6) | 20(22.2) | |
| Junior high | 9(15.0) | 18(20.0) | |
| Senior high | 16(26.7) | 17(18.9) | |
| Junior college | 10(16.7) | 15(16.7) | |
| University and above | 6(10.0) | 20(22.2) | |
| Religious belief: | | | 0.4940** |
| No religion | 8(14.0) | 19(21.1) | |
| Confucianism/Buddhism | 42(73.7) | 63(70.0) | |
| Christianity | 7(12.3) | 8 (8.9) | |
| Place of residence: | | | 0.2427* |
| Northern Taiwan | 41(68.3) | 74(82.2) | |
| Central Taiwan | 12(20.0) | 10(11.0) | |
| Southern Taiwan | 4(6.7) | 4(4.4) | |
| Eastern Taiwan | 3(5.0) | 2(2.2) | |
| Age (years)## | | | 0.0054# |
| 30-39 | 0(0.0) | 4(4.5) | |
| 40-49 | 3(5.0) | 5(5.6) | |
| 50-59 | 12(20.0) | 28(31.4) | |
| 60-69 | 35(58.3) | 49(55.1) | |
| 70+ | 10(16.7) | 3(3.4) | |

*Fisher's exact test **Pearson's $X^2$-test
#Wilcoxon rank sum test ##$p<0.05$

## Table 2. Smoking Experience of Cases and Controls

| Variables | Cases No. (%) | Controls No. (%) | p Value |
|---|---|---|---|
| Smoking experience: | | | 0.000* ## |
| Never smoke | 13(21.6) | 50(55.6) | |
| Ever smoked | 22(36.7) | 18(20.0) | |
| Currently smoking | 25(41.7) | 22(24.4) | |
| Brand smoked: | | | 0.2752* |
| Domestic | 45(100.0) | 39(100.0) | |
| Long Life | 31(68.9) | 34(89.4) | |
| New Paradise | 9(20.0) | 2(5.1) | |
| Others | 5(11.1) | 3(7.5) | |
| Imported | 8(100 0) | 12(100.0) | |
| State Express | 5(62.5) | 7(58.3) | |
| Others | 3(37.5) | 5(41 7) | |
| Mode of smoking: | | | 0.3110* |
| Non-filtered | 12(25.5) | 5(12.5) | |
| Filtered | 29(61.7) | 29(72.5) | |
| Both | 6(12.8) | 6(15 0) | |
| Way of smoking: | | | 0.1120* |
| No inhale | 4 (8 5) | 10(25.0) | |
| Shallow-inhale | 28(59.6) | 19(47.5) | |
| Deep-inhale | 15(31.9) | 11(27.5) | |
| Age at first smoking (years): | | | 0 7209** |
| Maximum | 55 | 30 | |
| Median | 20 | 21 | |
| Minimum | 11 | 14 | |
| Daily amount (cigarettes): | | | 0.1057** |
| Maximum | 60 | 40 | |
| Median | 20 | 15 | |
| Minimum | 1 | 4 | |
| Total year of smoking (years): | | | 0.0400# ## |
| Mean | 37.1 | 31.9 | |
| Standard deviation | 12.3 | 10 7 | |
| Total amount (packs): | | | 0.0001** ## |
| Maximum | 43,800 | 25,733 | |
| Median | 14,281 | 7,665 | |
| Minimum | 91 | 821 | |

*Pearson's $X^2$-test **Wilcoxon rank sum test
#Student's t-test ## $p<0.05$

**Table 3. Single and Multiple Factors Related to Laryngeal Cancer**

| Variables | Regression coefficient (SE) | Odds Ratio | 95% CI |
|---|---|---|---|
| Single-Variable Analysis | | | |
| Age* # | 0.0638 (0.0239) | 1.066 | (1 0171 , 1.1170) |
| Smoking experience# | | | |
| Ever smoker/non-smoker | 1.4749 (0.4271) | 4.371 | (1.8923 , 10.0948) |
| Current smoker/non-smoker | 1.5477 (0.4449) | 4.701 | (1.9654 , 11.2425) |
| Age at first smoking | 0.0038 (0.0369) | 1.004 | (0.9338 , 1.0791) |
| Daily amount | 0.0443 (0.0229) | 1.045 | (0.9994 , 1.0933) |
| Total years of smoking## | 0.0394 (0.0196) | 1.040 | (1.0010 , 1.0809) |
| Mode of smoking | 0.8755 (0.5835) | 2.400 | (0.7648 , 7.5320) |
| Way of smoking# | | | |
| Shallow/non-inhale | 1.6489 (0.4048) | 5.201 | (2.3525 , 11.4996) |
| Deep/non-inhale | 1.5713 (0.4828) | 4.813 | (1.8683 , 12.3987) |
| Total amount (packs)# | $1.04x10^{-4}$ ($0.24x10^{-4}$) | 1.00001 | (1.0001 , 1.0002) |
| Multi-Variable Analysis | | | |
| Age* | 0.0464 (0.4048) | 1.0475 | (0.4738 , 2.3159) |
| Total amount (packs)## | $0.66x10^{-4}$ ($0.53x10^{-4}$) | 1.00007 | (1.0000 , 1.0002) |

Note: Figures are obtained by logistic regression analysis.
*Age is treated as a confounder.
#p<0.001 ##p<0.05