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# Investigation of the Influence of Serum Selenium Levels on the Risk of Laryngeal Cancer

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**ABSTRACT**

**Introduction:** Cancers of the upper aerodigestive tract are relatively common, with laryngeal malignancies ranking second in prevalence. Selenium is an essential trace element whose biological functions in human cells remain incompletely elucidated. While moderate selenium levels may provide protective antioxidant effects, both deficiency and excess have been associated with carcinogenic processes. The present study aimed to evaluate the relationship between serum selenium concentration and the likelihood of laryngeal cancer development.

**Methods:** We conducted a case–control study involving 30 untreated patients with laryngeal cancer and 30 disease-free individuals, recruited from Ghaem and Imam Reza Hospitals in Mashhad, Iran. The two groups were matched for age, sex, cigarette exposure (pack-years), duration of opium consumption, symptoms of gastroesophageal reflux, and occupational dust exposure. Venous blood samples were collected before treatment to measure serum selenium levels, and mean values were statistically compared between cases and controls.

**Results:** Across all 60 participants, the mean serum selenium level was 96.37 ± 20.13 µg/L. Patients in the cancer group exhibited higher concentrations (102.89 ± 19.40 µg/L) than those in the control group (89.85 ± 18.98 µg/L). This difference was statistically significant ($p = 0.011$).

**Conclusion:** This study indicated that elevated serum selenium levels may be linked with an increased probability of laryngeal cancer.

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## Introduction

Laryngeal cancer is the second most common malignancy of the upper aerodigestive tract, with squamous cell carcinoma (SCC) representing the predominant histological type, accounting for approximately 85%–95% of all laryngeal tumors. A large-scale review of nearly 160,000 laryngeal SCC cases in the United States showed that the glottis was the primary site in 51% of patients, the supraglottis in 33%, and the subglottis in 2%, while in 14% of cases the exact location could not be determined. The overall male-to-female incidence ratio for laryngeal carcinoma is estimated at 3.9:1 (1, 2).

Tobacco use and alcohol consumption remain the most significant risk factors for the development of laryngeal malignancies (3), with risk increasing in proportion to both the duration and intensity of exposure. Chronic laryngeal irritation has also been proposed as a potential etiological factor, particularly among individuals without a history of smoking or alcohol use (4). Occupational exposure

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to hazardous substances constitutes another critical contributor. Incidence rates are higher among manual laborers who not only consume greater amounts of tobacco and alcohol but are also frequently exposed to toxic agents. Reported occupational hazards include diesel fumes, asbestos, organic solvents, sulfuric acid, mustard gas, mineral oils, metal dusts, asphalt, wood and stone dust, mineral wool, and cement particles. However, establishing a causal relationship between any specific toxin and laryngeal cancer has been challenging due to small sample sizes and multiple confounding variables in most studies (5).
Human papillomavirus (HPV) is a well-established causative factor in cervical cancer and is increasingly recognized as a key etiological agent in oropharyngeal squamous cell carcinoma (SCC) (6). Moreover, genetic predisposition to laryngeal SCC should not be overlooked (7). Evidence from a cohort study reported a relative risk of 3.79 for head and neck SCC among individuals with a positive family history of these malignancies (2). Dietary patterns also influence risk; adherence to a diet rich in fruits and vegetables and lower in meat and fat has been associated with a decreased incidence of head and neck cancers (8).
Selenium is an essential trace element involved in multiple biological processes, including antioxidant defense and immune regulation, and is incorporated into at least 30 selenoproteins (9). These proteins contribute to maintaining redox homeostasis and preserving DNA integrity, and some studies suggest that they may exhibit anti-carcinogenic properties (10). Selenium also helps neutralize the toxic effects of heavy metals and other harmful agents. Clinical evidence has indicated that selenium supplementation may reduce the risk of certain cancers. Notably, both selenium deficiency and excessive intake have been associated with an increased incidence of malignancies such as lung, laryngeal, colorectal, and prostate cancers (11, 12).
This case–control study aims to compare serum selenium levels between patients with laryngeal cancer and a matched control group to assess whether selenium status is associated with the risk of developing laryngeal cancer.

## Materials

### *Patients and Methods*

This case–control study was conducted from December 2022 to April 2023 on 30 newly diagnosed patients with laryngeal cancer from the ENT departments of Imam Reza and Ghaem Hospitals, along with a matched group of 30 healthy controls. The two groups were comparable based on age, sex, and smoking status. Participation required written informed consent; individuals who declined were not enrolled.
The case group included patients with a recent histopathological diagnosis of laryngeal cancer who were enrolled before the initiation of any treatment. The control group consisted of individuals with no history of malignancy and no use of selenium supplements within the month before enrollment. Given the high prevalence of smoking and opium use among patients with laryngeal cancer, controls were selected through convenient non-random sampling from patients admitted to the cardiopulmonary wards of Imam Reza and Ghaem Hospitals who reported a history of smoking.
Exclusion criteria included withdrawal from participation, a prior diagnosis of malignancy, recurrent disease, or selenium supplementation during the study period. For all patients, the diagnosis was confirmed histopathologically, and tumor mapping was performed to determine the histological subtype. Baseline demographic and clinical information was collected using a structured questionnaire and included variables such as age, sex, tobacco and alcohol use, symptoms of gastric reflux, family history of cervical cancer, degree of familial relation, occupation, and exposure to stone or wood dust.
Following data collection, 3 mL of venous blood was drawn from each participant. Serum specimens were then processed and analyzed using a graphite furnace atomic absorption spectrophotometer with selenium-specific wavelengths. Calibration was performed using standard selenium solutions, and quality control samples were run alongside each batch to ensure accuracy and precision. The measured absorbance values were converted to selenium concentrations according to the calibration curve. Selenium levels were subsequently compared between cases and controls. All data were analyzed using SPSS software.

### *Statistical Analysis*

Data were analyzed using SPSS version 20. Sample size was estimated with PASS version 15 using a two-sample t-test assuming unequal variances. A minimum of 28 participants per group was required with a significance level (α) of 0.05 and a power (1–β) of 90%; therefore, 30 individuals were included in each group.
Continuous variables were summarized as mean ± standard deviation. The normality of the data

distribution was assessed using the Kolmogorov–Smirnov test. Depending on the distribution, group comparisons for quantitative variables were performed using the independent t-test. Categorical variables were presented as frequencies and percentages and analyzed using the chi-square test or Fisher's exact test, as appropriate. A p-value of less than 0.05 was considered statistically significant.

## Results

In this case–control study, 60 participants were enrolled. The case group consisted of 30 patients diagnosed with laryngeal squamous cell carcinoma who were evaluated before receiving any treatment (chemoradiotherapy or surgery). The control group included 30 individuals without laryngeal cancer who were matched to the cases based on gender, age, and the extent of smoking and opium consumption.

The mean age of participants in the control group was 59.86 ± 11.67 years, whereas in the case group it was 57.80 ± 9.93 years. There was no significant difference in age between the two groups ($p \geq 0.05$). According to the Kolmogorov–Smirnov test, the data for serum selenium levels and age followed a normal distribution.

Among the 60 participants, each group consisted of 28 men (93.3%) and two women (6.7%). In both groups, 27 individuals were smokers and 3 were non-smokers. Regarding opium consumption, 26 patients in the case group (86.7%) and 23 patients in the control group (76.7%) reported opium use, with no significant difference between the groups ($p = 0.506$; $p \geq 0.05$). None of the participants had a history of alcohol consumption.

All patients were asked about symptoms of esophageal reflux, and no significant difference was observed between the two groups ($p = 0.299$; $p \geq 0.05$). Regarding occupation, 73.3% of participants in both groups were manual laborers (including construction and agricultural workers), with no significant difference between the groups ($p > 0.9$) (Table 1).

**Table 1.** Number and percentage of subjects with a history of contact with dust and GERD (Gastro Esophageal Reflux Disease) in the case and control groups

| | | | Control group | Laryngeal cancer group | P-value* |
|---|---|---|---|---|---|
| **Contact with dust** | No | Number | **8** | **8** | **>0.9** |
| | | Percent | **26.7%** | **26.7%** | |
| | Yes | Number | **22** | **22** | |
| | | Percent | **73.3%** | **73.3%** | |
| **GERD** | No | Number | **19** | **14** | **0.299** |
| | | Percentage | **63.3%** | **46.7%** | |
| | Yes | Number | **11** | **16** | |
| | | Percentage | **36.7%** | **53.3%** | |
| **Total** | | Number | **30** | **30** | |

Chi-Square test*

We classified all 30 patients in the laryngeal cancer group by tumor stage into early-stage (T1, T2) and advanced-stage (T3, T4) disease. In addition, the tumor anatomical subsite was categorized into three subtypes: supraglottic, glottic, and transglottic tumors (Figure 1). Analyses using the Pearson correlation test showed no significant relationship between tumor characteristics and serum selenium levels.

The mean serum selenium level among all 60 participants was 96.37 ± 20.13 µg/L, while the normal laboratory reference range is 87–154 µg/L. A comparison of mean serum selenium levels between the laryngeal cancer group (before treatment) and the control group is presented in Figure 2. The mean serum selenium level was 102.89 ± 19.40 µg/L in the laryngeal cancer group and 89.85 ± 18.98 µg/L in the control group. The findings indicated that serum selenium levels were significantly higher in the laryngeal cancer group compared with the control group ($p= 0.011$; $p<0.05$).

## Discussion

The findings of this case–control study, which compared 30 patients with laryngeal cancer with 30 matched hospital-based controls, showed no significant association between age or tumor stage and serum selenium levels. Notably, higher serum selenium levels were associated with a higher risk of laryngeal cancer.

To our knowledge, only a limited number of studies have investigated selenium status in relation to laryngeal cancer progression or clinical outcomes,

and the available evidence remains inconsistent. Such discrepancies may reflect the dual biological roles of selenium in normal and malignant cells. For example, sodium selenite has been shown to promote apoptosis in lung cancer cell lines (13), whereas other studies have suggested a potential protective effect against the development of aggressive tumors (14).

Consistent with our findings, Narod et al conducted a case–control study in Poland titled *"Evaluation of serum selenium levels and cancer risk."* The study included 97 women with various types of cancer and 184 cancer-free controls at baseline. Using mass spectroscopy, the authors defined normal serum selenium levels as 70–90 µg/L. Selenium levels above 90 µg/L were associated with an increased overall cancer risk, although this association did not reach statistical significance. Their findings indicated a non-linear relationship between selenium status and cancer susceptibility (15-16). Similarly, Krystal et al evaluated selenium exposure using nail samples from more than 3,000 American men to examine prostate cancer risk. Their findings indicated that selenium supplementation did not confer protection among men with low baseline selenium levels; however, higher selenium status was associated with an increased likelihood of high-grade prostate cancer in men with elevated selenium levels (16).

Comparable findings were also reported in Iran by Shahriari et al, who investigated soil selenium levels in Golestan Province. Selenium concentrations were measured across 135 soil blocks, yielding an average value of 1.61 ± 3.7 mg/kg. Higher selenium levels were observed in high-risk regions for esophageal cancer (4.13 mg/kg) compared with lower-risk areas (3.39 mg/kg). The authors concluded that soil selenium levels may directly contribute to the regional burden of esophageal cancer (17).

Conversely, Jaworska et al reported differing findings in their Polish case–control study titled *"Low selenium level is associated with laryngeal cancer."* The study included 95 patients with lung cancer, 113 patients with laryngeal cancer, and matched healthy controls. Selenium levels were lower in both cancer groups compared with their respective control groups. Specifically, the mean selenium concentration was 63.2 µg/L in lung cancer patients versus 74.6 µg/L in controls, and 64.8 µg/L in laryngeal cancer patients versus 77.1 µg/L in their matched controls. The authors proposed that selenium concentrations below 60 µg/L may increase the risk of both lung and laryngeal cancer (18).

In contrast, our results showed higher mean selenium levels in both groups: 102.89 ± 19.40 µg/L in patients and 89.85 ± 18.98 µg/L in controls. These values exceed those reported by Jaworska et al., suggesting that participants in our study were not, on average, selenium-deficient. This discrepancy may partly account for the differences observed between our findings and theirs.

Furthermore, selenium status varies geographically. For instance, the mean selenium intake is generally higher in North America than in many European countries. Large randomized controlled trials conducted in populations with adequate baseline selenium intake, such as those in the United States and Canada, have not demonstrated a clear reduction in cancer incidence or mortality with selenium supplementation. In contrast, studies from regions with relatively low selenium status, including Poland and Sweden, have suggested that higher selenium levels may improve survival in certain cancers, such as breast cancer.

## Conclusions

We concluded that studies reporting an inverse relationship between serum selenium levels and cancer risk were predominantly conducted in countries with relatively low normal selenium levels. In contrast, the present study and similar investigations conducted in Iran indicate that our population has comparatively high average selenium levels. Therefore, given this higher baseline status, the hypothesis that selenium deficiency contributes to the development of laryngeal cancer was not supported by our findings.

## Ethics approval and consent to participate

The present study was approved by Research Council of Mashhad University of Medical Sciences and the ethics committee approval code number is (IR.MUMS.MEDICAL.REC.1401.561). The written informed consent forms were signed by all patients before initiation of the study.

## Consent for publication

Complete written informed consent was obtained from the patient for the publication of this study

## Availability of data and materials

The dataset supporting this article's conclusions is confidential and cannot be made publicly available.

However, data may be available upon reasonable request and with permission of the original data providers, subject to compliance with applicable confidentiality agreements and data protection laws, via contact through the corresponding author.

## Competing interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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## Authors' contributions

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