

## GASTROESOPHAGEAL REFLUX DISEASE: IS IT A CAUSATIVE FACTOR IN LARYNGEAL CANCER?

### *GASTROÖZOFAJEAL REFLÜ HASTALIĞI: LARENKS KANSERİNDE ETKEN BİR FAKTÖR MÜDÜR?*

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#### ABSTRACT

Gastroesophageal reflux disease is an extremely common disorder and has seen an explosion in interest from both scientific communities and the general public, resulting in an abundance of misleading and even conflicting information. Previously published reports suggested that gastroesophageal reflux disease is associated with laryngeal cancer, but today there are many publications which do not support this argument. However, gastroesophageal reflux disease may lead to esophageal and upper respiratory epithelial destruction causing Barrett's esophagus and esophageal adenocarcinoma, laryngitis, pharyngitis, eustachian tube abnormalities, chronic sinusitis, pneumonia and asthma. In this review, the link between the gastroesophageal reflux disease and laryngeal cancer is investigated.

**Key words:** Gastroesophageal reflux disease, laryngeal cancer, etiology

#### ÖZET

Gastroözofajeal reflü hastalığı oldukça sık karşılaşılan bir rahatsızlık olması nedeniyle hem bilimsel camiada hem de halk arasında giderek artan bir ilgiye neden olmaktadır. Ancak bu ilgi aynı zamanda oldukça fazla miktarda yanlış hatta çelişkili bilgilerin ortaya çıkmasına neden olmuştur. Başlangıçtaki yayınlar gastroözofajeal reflü hastalığını larenks kanseri ile ilişkilendirirken, son dönemlerde yapılan çalışmalar bu bağlantıyı desteklememektedir. Ancak gastroözofajeal reflü hastalığı özefagus ve üst solunum yolu epitelinde destrüksiyona yol açarak Barrett özefajitine, özefagus adenokarsinomuna, larenjit, farenjit, östaki tüpü fonksiyon bozukluklarına, kronik sinüzite, pnömoni ve astıma neden olabilir. Bu derlemede gastroözofajeal reflü hastalığı ile larengeal kanser arasındaki ilişki araştırılmıştır.

**Anahtar kelimeler:** Gastroözofajeal reflü hastalığı, larenks kanseri, etyoloji

#### INTRODUCTION

Following skin cancers, laryngeal cancer is the second-most common malignancy in the head and neck region and the eleventh most common form of cancer among men worldwide (7). Tobacco use is the predominant risk factor for laryngeal carcinoma because the larynx is the most vulnerable organ to the carcinogenic effect of tobacco smoke (Hashibe, Brennan). Alcohol use is another risk factor which also acts in synergy with tobacco (33). Approximately 75% to 80% of head and neck squamous cell carcinomas are caused by tobacco exposure and alcohol consumption. Although infection with the human papilloma virus has been etiologically linked with the remaining 20% to 25% of all head and neck cancers, in case of laryngeal cancer, the prevalence of HPV DNA has been reported to range between 3% and 47% (11,21). Other etiological factors include carcinogens such as asbestos, nickel, wood dust, paint, diesel fume and glass-wool (27).

Gastroesophageal reflux disease (GERD), on the other hand, is an extremely common disorder. Heartburn is the most common manifestation of GERD, with 7% of adults having this symptom daily and 35% monthly (17). In addition to other factors, tobacco and alcohol induce reflux by a number of physiologic mechanisms, and reflux, in turn, causes esophageal and upper airway mucosal damage resulting esophagitis and Barrett's esophagus, laryngitis, pharyngitis, eustachian tube abnormalities, chronic sinusitis, pneumonia and asthma (16,19). The connection between GERD and squamous cell carcinoma of the upper aerodigestive tract was suggested for the first time by Gabriel and Jones in 1960 (14). Henceforth many studies about the relationship between GERD and laryngeal cancer development have been published. Although GERD is strongly associated with adenocarcinoma of the esophagus, the link between reflux and squamous cell carcinoma of the esophagus is

Date received/Dergiye geldiği tarih: 06.02.2011 - Dergiye kabul edildiği tarih: 28.06.2011

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carcinoma of the esophagus is yet to be proven (22).

It is well known that the mucosal inflammation secondary to GERD can be reversed by treatment. Consequently, if GERD is a definite carcinogenic factor for the upper airway, active treatment of GERD may reduce the incidence of laryngeal cancer. If the patients with GERD are kept under close supervision, the malignant changes in the larynx may be promptly diagnosed.

#### **The association between GERD and laryngeal cancer**

The incidence of laryngeal cancer has increased in spite of declining numbers of people who smoke (6). Then again GERD and its associated complications such as Barrett's esophagus and esophageal adenocarcinoma have also increased, due to alimentary changes during the past decades (5,31). It is well known that reflux causes laryngeal mucosal damage secondary to irritant effects resulting in chronic inflammation (17). Consequently, some authors anticipated that continuous laryngeal irritation secondary to GERD could have a carcinogenic effect, which may explain why the laryngeal cancer group also contains nonsmokers and nondrinkers (26,37). Several epidemiological observations reporting a high prevalence of GERD in patients with diagnosed laryngeal carcinoma supported this theory (4,8,13,20,23). Following the first statement about the correlation between GERD and squamous cell carcinoma of the upper aerodigestive tract of Gabriel and Jones in 1960, Glanz and Kleinsasser reported 35 cases of chronic hypertrophic laryngitis that developed into laryngeal carcinomas, where chronic hypertrophic laryngitis was an otolaryngologic manifestation of GERD (15). Smit found pathological GERD in 82% of total laryngectomized patients using doubleprobe 24-hour monitoring (34). Koufman performed a double-probe pH measurement in a group of patients with laryngeal carcinoma and in 58% of cases found a pathological laryngopharyngeal reflux (20). Similarly, in Biacabe's study the incidence of silent GERD was 37% in 72 patients treated for laryngopharyngeal cancer (4). Other authors also observed similar rates in their studies; Copper's 16 of 24 head and neck cancer patients (67%) had pathological gastroesophageal reflux (8), Price diagnosed GERD in 68% of his laryngeal cancer patients (30) and Qadeer found nearly twofold higher GERD prevalence in patients with laryngeal carcinoma (50–80%) than the general population (20–40%) (32). Despite the increasing number of studies linking the association between GERD and laryngeal carcinoma, the mechanism of carcinogenic action is not understood. However, there is some experimental evidence for the damaging potential of reflux material on laryngeal tissues. The first experimental report was published in 1968 by Delahunty and Cherry; they created vocal granulomas in a canine larynx by applying gastric juice (9). Adams study on hamsters demonstrated the considerable cocarcinogenic potential of gastric acid and pepsin, supporting GERD may be a potential carcinogen on laryngeal tissues (1). Adhami has worked on the effect of acid and pepsin on larynxes of adult beagles (2). In spite of such animal studies, the molecular pathway of carcinogenic mechanism is still not explained.

Today the proponents of the view "GERD is a laryngeal carcinogenic" believe that GERD accentuates the carcinogenic effect of smoking and alcohol on human larynxes. This is based on the fact that smokers are 15 to 20 times more likely to develop laryngeal cancer than nonsmokers, and the risk increases in case of alcohol consumers three to four times (38,39). Tobacco and alcohol decrease lower esophageal sphincter pressure, cause abnormal esophageal motility, delay gastric emptying, and increase gastric secretion (10,35,36). As a result, smoke and alcohol induced laryngeal mucosal damage is aggravated by gastric acid and pepsin. Locke's population based study reported that smokers and alcohol consumers are 1.6 and 1.9 times more likely to have GERD than nonsmokers and nondrinkers, respectively (24). In addition, Smit et al reported that reflux duration measured by ambulatory 24-hour pH monitoring was significantly higher in the distal and proximal esophagus of 15 subjects during a smoking period compared with a nonsmoking period (28). Based on these findings, a great number of studies conclude that GERD has a fundamental role in laryngeal cancer development, however, the majority of these studies are uncontrolled case series and do not have control groups. An exceptional one is El-Serag's controlled retrospective study (13). The study consists of 17520 laryngeal cancer cases and 70080 controls, in a multivariable logistic regression analysis that was controlled for age, gender, ethnicity, smoking, and alcohol. They found that the risk of laryngeal cancer may be higher in the presence of both reflux and smoking/alcohol compared with smoking/alcohol alone: GERD patients were 2.31 times more likely to develop cancer; smoking increased the risk by 2.60 times, but in the presence of both smoking and GERD, the risk increased by 2.79 times. According to this they concluded that, the risk for laryngeal or pharyngeal cancers is modestly increased in the presence of GERD and smoking and GERD may act synergistically in laryngeal carcinogenesis.

Following the reports supporting carcinogenic effect, theories refuting the connection between GERD and laryngeal cancer have also emerged. Ozer states that stress can have both a short and long-term influence on the function of the gastrointestinal tract and plays an important role in the process of GERD, so the life threatening laryngeal cancer diagnosis by itself could be the reason for the increased incidence of GERD in this group of patients (3,29). On the other hand, some authors established that GERD is associated with the adenocarcinoma of the esophagus, not with squamous cell carcinoma of the esophagus (12,18,25). Therefore cancers of the larynx and pharynx are almost exclusively of the squamous cell histologic type and since the larynx and pharynx are exposed to gastroesophageal reflux to a lesser extent than the esophagus, it is biologically unlikely that the carcinogen effect was overlooked (28).

## CONCLUSION

The association of GERD and laryngeal cancer is still a dilemma for the otolaryngologist and additional prospective and case-controlled studies are required. From today's perspective, "GERD as a potential carcinogen for laryngeal cancer" seems to be more likely. We still don't know whether we should treat GERD aggressively as a potential carcinogen. On the other hand, if GERD is only a co-carcinogen, controlling smoking and alcohol abuse is sufficient to reduce the incidence and severity of GERD, so no additional effort is necessary.

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