

Gastroesophageal reflux disease and non-esophageal cancer

Fernando AM Herbella, Sebastião Pannocchia Neto, Ilka Lopes Santoro, Licia Caldas Figueiredo

Fernando AM Herbella, Sebastião Pannocchia Neto, Department of Surgery, Federal University of Sao Paulo, Sao Paulo 04037-003, Brazil

Ilka Lopes Santoro, Licia Caldas Figueiredo, Pneumology Division, Department of Medicine, Federal University of Sao Paulo, Sao Paulo 04037-003, Brazil

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Correspondence to: Fernando AM Herbella, MD, Department of Surgery, Federal University of Sao Paulo, Rua Diogo de Faria 1087 cj 301, Sao Paulo 04037-003, Brazil. herbella.dcir@epm.br
Telephone: +55-11-99922824

Fax: +55-11-99922824

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Abstract

The association of gastroesophageal reflux disease (GERD) and esophageal cancer is well known. The carcinogenic properties of the gastroduodenal contents may also lead to cancer in target organs for GERD especially considering that they do not have intrinsic protective mechanisms as found in the esophagus. This review focuses on the putative relation between GERD and non-esophageal cancer. Most of the papers reviewed are far from ideal to prove the relationship of extra-esophageal cancer and GERD since a small number of

patients is presented, most do not control cases based on tobacco usage and obesity, and the diagnosis of GERD is variable, not always from an objective measurement such as pH monitoring but relying on symptoms in most reports. Nevertheless, head and neck and lung cancer have a growing incidence parallel to GERD and a shift towards non-smoking, female gender and adenocarcinoma (compared to squamous cell carcinoma) is arising, similar to the example of esophageal cancer with the exception of the female gender.

Key words: Gastroesophageal reflux; Cancer; Pharynx; Larynx; Trachea; Lung

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Core tip: Gastroesophageal reflux disease (GERD) is a very prevalent disease with a rising incidence. The disease is certainly linked to the pathogenesis of esophageal adenocarcinoma originated in the Barrett's esophagus. The carcinogenic properties of the gastroduodenal contents may also lead to cancer in target organs for GERD, especially considering that they do not have intrinsic protective mechanisms as found in the esophagus. Although strong conclusions cannot be drawn due to lack of good quality published studies, GERD may also be linked to the pathogenesis of head and neck and lung cancers.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a very prevalent disease, affecting 18%-27% of the population

in North America, 9%-25% in Europe, 2%-8% in East Asia, 9%-33% in the Middle East, 11% in Australia and 23% in South America^[1]. Moreover, the incidence of GERD seems to be increasing with time^[2]. It accounts for almost 9000000 outpatient visits, 65000 hospitalizations and costs of over US \$9000000000 per year only in the United States^[3,4]. The association of GERD and esophageal cancer is well known, with a metaplasia-dysplasia-carcinoma sequence leading ultimately to esophageal adenocarcinoma^[5]. Esophageal adenocarcinoma also showed a significant increase in incidence in the last decades^[6].

Virtually all adjacent organs to the esophagus may be affected by the gastric refluxate and new discoveries are made on a regular basis showing that even distant organs may be affected by GERD. It seems logical that the carcinogenic properties of the gastroduodenal contents may also lead to cancer in target organs for GERD especially considering that they do not have intrinsic protective mechanisms as found in the esophagus.

This review focuses on the putative relation between GERD and non-esophageal cancer.

MECHANISM OF GERD-INDUCED CARCINOGENESIS

Esophageal adenocarcinoma originated in a Barrett's esophagus is the most studied cancer linked to GERD; however, its cellular origins and molecular mechanisms are still not fully understood^[7]. GERD induces esophageal inflammation and consequent oxidative stress leading to DNA damage. Both acid and bile are active on oncogenic pathways. Acid induces DNA damage, decreases proliferation, and increases apoptosis. Bile salts induce DNA damage, affect proliferation in a pH-dependent manner, and cause resistance to apoptosis^[7,8]. More detailed molecular mechanisms are available in recent reviews^[7-9].

Apart from the direct effect of gastric refluxate, other variables link GERD and cancer. Obesity is a risk factor for different cancers, including esophageal adenocarcinoma^[10]. Fat tissue increases the release of proinflammatory molecules and induces insulin resistance, all of them linked to carcinogenesis^[7,11]. GERD is strongly associated to obesity as well^[12]. It has been shown that for each 5-point increase in body mass index, the DeMeester GERD score increases by 3 units^[13]. Parallel to GERD, the prevalence of obesity more than doubled between 1980 and 2009 in the United States, as indicated by Centers for Disease Control and Prevention Surveys.

Smoking is also linked to esophageal^[14], head and neck^[15] and lung cancer^[16] and, again, is a risk factor for GERD^[17].

ORAL/LARYNX/PHARYNX CANCER

Gastric contents reach the larynx/pharynx in healthy volunteers and in patients with GERD^[18]. This has been

proven by different methods, such as dual probe pH monitoring^[18], multichannel intraluminal impedance^[19], and aerosolized reflux detection^[20]. In fact, refluxate may reach up to the mouth and GERD is thought to cause tooth wearing^[21].

GERD has long been considered a risk factor for laryngeal/pharyngeal cancer^[22]. Few studies did not show GERD as an independent risk factor for cancer in multivariate analysis when tobacco and alcohol consumption are considered^[23]; however, other studies, including a meta-analysis, do show GERD as an independent risk factor especially in non-smokers^[24-27]. Also, the incidence of these tumors is increasing parallel to GERD.

Another piece of evidence that links GERD and laryngeal/pharyngeal cancer is the putative higher risk in patients with heterotopic acid-producing gastric mucosa in the proximal esophagus (inlet patch)^[28].

The literature on oral cancer and GERD is scarce even though they also may be associated^[29].

LUNG

Similar to the proximal respiratory organs, duodenogastric contents may also reflux to the lungs. Pepsin and biliary salts can be recovered from the lungs in patients with end-stage pulmonary diseases^[30]. GERD is associated with different lung diseases^[31]; however, the association of GERD and lung cancer is unknown. A single preliminary report showed significant GERD in lung cancer patients irrespective of histology^[32].

The link between GERD and lung cancer seems plausible based on the following facts: (1) Lung adenocarcinoma has a growing incidence with a trend to surpass squamous cell carcinoma^[33,34], similar to esophageal cancer; (2) Lung adenocarcinoma is the most frequent histologic type in non-smokers and a clear risk factor has not been attributed to it^[35]; (3) Connective tissue diseases are common risk factors for lung adenocarcinoma^[36] and GERD^[37]; and (4) Centrally located lung adenocarcinoma (area of the lung closer to the esophagus and more prone to aspirate gastroduodenal refluxate) is likely to arise from the glandular epithelium (superficial layer more susceptible to contact with refluxate). In contrast, peripheral adenocarcinoma is likely to originate in type II pneumocytes and Clara cells^[38].

CONCLUSION

GERD is a common and costly disease; however, despite great achievements in the understanding of the pathophysiology and treatment of the disease, medicine is not winning the battle against GERD. The incidence of GERD is escalating (Figure 1)^[39-59] and, even though old complications attributed to this illness, such as esophageal stenosis and ulceration, have almost disappeared, a new spectrum of the disease is surging with extra-esophageal manifestations and cancer. Thus, esophageal cancer

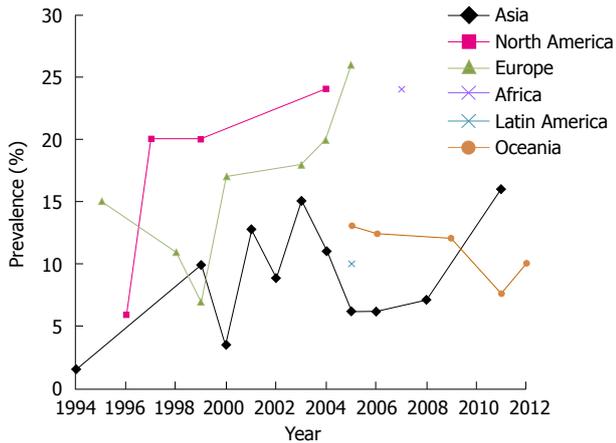


Figure 1 Worldwide prevalence of gastroesophageal reflux disease^[39-59]. Gastroesophageal reflux disease defined by symptoms with a weekly frequency or according to the author's definition.

should also be added to the burden of GERD and probably head and neck and lung cancers as well.

Head and neck and lung cancer both have smoking as the main etiologic factor. Even though the prevalence of smokers is decreasing^[60], the incidence of the aforementioned tumors is not (Figure 2). Obviously, a proportional increase in the incidences of two separate diseases does not necessarily indicate an etiological relationship but more than that, a shift towards non-smoking, female gender and adenocarcinoma (compared to squamous cell carcinoma) is arising^[61], similar to the example of the esophageal cancer with the exception of the female gender^[62-64].

It must be said that most of the papers reviewed are far from ideal to prove the relationship of extra-esophageal cancer and GERD. A single study addressed the association of lung cancer and GERD. Not all studies showed a relationship between GERD and head and neck cancer, and even in studies showing positive association this is not too strong. Some present with a small number of patients, most do not control cases based on tobacco usage and obesity. Moreover, the diagnosis of GERD is variable, not always from an objective measurement such as pH monitoring but relying on symptoms that has been shown not to be a trustworthy method for correct GERD diagnosis. Different previous publications showed that symptoms are unreliable for the diagnosis of GERD^[65,66] although the labeling of patients as refluxers based on symptom questionnaires is still a common practice, in spite of the fact that most of these questionnaires were not validated in comparison to esophageal ambulatory pH monitoring^[67].

In conclusion, laryngeal and pharyngeal tumors are highly associated to GERD. Oral and lung cancers probably are also connected to GERD.

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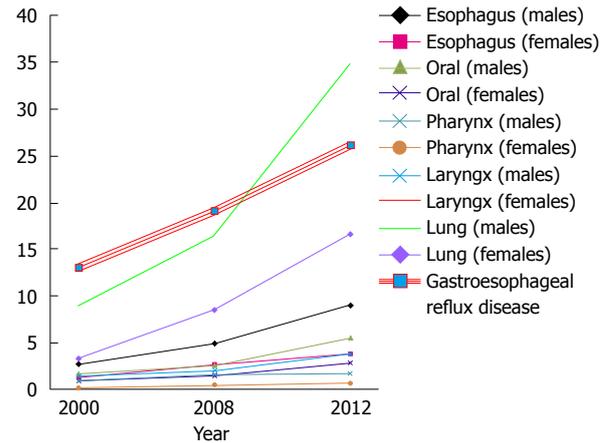


Figure 2 Worldwide incidence of cancers putatively associated to gastroesophageal reflux disease^[62-64].

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