Gastroesophageal reflux disease and non-esophageal cancer

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

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

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Herbella FAM, Neto SP, Santoro IL, Figueiredo LC. Gastroesophageal reflux disease and non-esophageal cancer. World J Gastroenterol 2015; 21(3): 815-819 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i3/815.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i3.815

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 $900000000 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[8]. More detailed molecular mechanisms are available in recent reviews[7,8].

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[9]. Fat tissue increases the release of proinflammatory molecules and induces insulin resistance, all of them linked to carcinogenesis[10,11]. 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[19], multichannel intraluminal impedance[20] and aerosolized reflux detection[21]. In fact, refluxate may reach up to the mouth and GERD is thought to cause tooth wearing[22].

GERD has long been considered a risk factor for laryngeal/pharyngeal cancer[23]. Few studies did not show GERD as an independent risk factor for cancer in multivariate analysis when tobacco and alcohol consumption are considered[24]; however, other studies, including a meta-analysis, do show GERD as an independent risk factor especially in non-smokers[25-27]. 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)[22].

The literature on oral cancer and GERD is scarce even though they also may be associated[28].

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[29]. GERD is associated with different lung diseases[30]; however, the association of GERD and lung cancer is unknown. A single preliminary report showed significant GERD in lung cancer patients irrespective of histology[31].

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[32-34], 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)[39-41] 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...
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, 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, similar to the example of the esophageal cancer with the exception of the female gender.

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 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 reflux disease.

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

REFERENCES

1. El-Seraf HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014; 63: 871-880 [PMID: 23853213 DOI: 10.1136/gutjnl-2012-304269]
2. Rubenstein JH, Chen JW. Epidemiology of gastroesophageal reflux disease. Gastroenterol Clin North Am 2014; 43: 1-14 [PMID: 24502335 DOI: 10.1016/j.gict.2013.11.006]
3. Sandler RS, Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C, Gemmen E, Shah S, Avdic A, Rubin R. The burden of selected digestive diseases in the United States. Gastroenterology 2002; 122: 1500-1511 [PMID: 11984534 DOI: 10.1016/S0016-5085(02)02978-5]
4. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bullisiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Rinal G, Kim HP, Dibonaventura MD, Carroll CF, Allen JK, Cook SF, Sandler RS, Kappelman MD, Shaheen NJ. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 2012; 143: 1179-1187.e1-e3 [PMID: 22885331 DOI: 10.1053/j.gastro.2012.08.002]
5. Oh DS, Demeester SR. Pathophysiology and treatment of Barrett’s esophagus. World J Gastroenterol 2010; 16: 3762-3772 [PMID: 20698038 DOI: 10.3748/wjg.v16.i30.3762]
6. Hur C, Miller M, Kong CY, Dowling EC, Nattinger KJ, Dunn M, Feuer E. Trends in esophageal adenocarcinoma incidence and mortality. Cancer 2013; 119: 1149-1158 [PMID: 23303625 DOI: 10.1002/cncr.27834]
7. Fang Y, Chen X, Bajpai M, Verma A, Das KM, Souza RF, Garman KS, Donohoe CL, O’Farrell NJ, Reynolds JV, Dvorak K. Cellular origins and molecular mechanisms of Barrett’s esophagus and esophageal adenocarcinoma. Ann N Y Acad Sci 2013; 1300: 187-199 [PMID: 24117642 DOI: 10.1111/nyas.12249]
8. Denlinger CE, Thompson RK. Molecular basis of esophageal cancer development and progression. Surg Clin North Am 2012; 92: 1089-1103 [PMID: 23026271 DOI: 10.1016/j.suc.2012.07.002]
9. Wang DH, Souza RF. Biology of Barrett’s esophagus and esophageal adenocarcinoma. Gastrointest Endosc Clin N Am 2011; 21: 25-38 [PMID: 21112495 DOI: 10.1016/j.gice.2010.09.011]
10. Donohoe CL, Pidgogon GP, Lysaght J, Reynolds JV. Obesity and gastrointestinal cancer. Br J Surg 2010; 97: 628-642 [PMID: 20306531 DOI: 10.1002/bjs.6709]
11. Alemán JO, Eusebi LH, Ricciardiello L, Patidar K, Sanyal AJ, Holt PR. Mechanisms of obesity-induced gastrointestinal neoplasia. Gastroenterology 2014; 146: 357-373 [PMID: 24315827 DOI: 10.1053/j.gastro.2013.11.051]
12. Fisichella PM, Patti MG. Gastroesophageal reflux disease and morbid obesity: is there a relation? World J Surg 2009; 33: 2034-2038 [PMID: 19404705 DOI: 10.1007/s00268-009-0404-z]
13. Herbella FA, Sweet MP, Tesedo P, Nipomnick I, Patti MG. Gastroesophageal reflux disease and obesity. Pathophysiology and implications for treatment. J Gastrointest Surg 2007; 11: 817
Gastroesophageal reflux and cancer

Herbella FAM et al. Gastroesophageal reflux and cancer

value of gastroesophageal reflux disease (GERD) symptoms and detection of pepsin and bile acids in bronchoalveolar lavage fluid and exhaled breath condensate for identifying lung transplantation patients with GERD-induced aspiration. Surg Endosc 2018; 22: 1794-1800 [PMID: 24414458 DOI: 10.1007/s00464-013-3388-3]

Sweet MP, Patti MG, Hoopes C, Hays SR, Golden JA. Gastro-oesophageal reflux and aspiration in patients with advanced lung disease. Thorax 2009; 64: 167-173 [PMID: 19176842 DOI: 10.1136/thx.2007.07219]

Vereczek A, Horvath OP, Varga G, Molnar TF. Gastroesophageal reflux disease and non-small cell lung cancer. Results of a pilot study. Dis Esophagus 2008; 21: 457-460 [PMID: 19125801 DOI: 10.1111/j.1442-2050.2007.00976.x]

Etzel CJ, Lu M, Merrimian K, Liu M, Vapoorcyan A, Spitz MR. An epidemiologic study of early onset lung cancer. Lung Cancer 2006; 52: 129-134 [PMID: 16564601 DOI: 10.1016/j.lungcan.2005.11.018]

Liam CK, Pang YK, Leow CH, Poosparajah S, Menon A. Changes in the distribution of lung cancer cell types and patient demography in a developing multicultural Asian country: experience of a university teaching hospital. Lung Cancer 2006; 53: 23-30 [PMID: 16690159 DOI: 10.1016/j.lungcan.2006.03.009]

Couraud S, Zalcmann G, Milleron B, Morin F, Souquet PJ. Lung cancer in never smokers—a review. Eur J Cancer 2012; 48: 1299-1311 [PMID: 22464348 DOI: 10.1016/j.ejca.2012.03.007]

Yang Y, Fujita J, Tokuda M, Bandoth S, Ishida T. Lung cancer associated with several connective tissue diseases: with a review of literature. Rheumatol Int 2001; 21: 106-111 [PMID: 11765223 DOI: 10.1002/2001-0141-3]

Patti MG, Gasper WJ, Fischella PM, Nipomnick I, Palazzo F. Gastroesophageal reflux disease and connective tissue disorders: pathophysiology and implications for treatment. J Gastrointest Surg 2008; 12: 1900-1906 [PMID: 18766408 DOI: 10.1016/s1165-008-0674-9]

Fukui T, Shakhivirkev R, Agosto-Perez F, Mezey JG, Downey RJ, Travis WD, Crystal RG. Lung adenocarcinoma subtypes based on expression of human airway basal cell genes. Eur Respir J 2013; 42: 1332-1344 [PMID: 23645403 DOI: 10.1183/09031936.00441812]

Goh KL. Gastroesophageal reflux disease in Asia: A historical perspective and present challenges. J Gastroenterol Hepatol 2011; 26 Suppl 1: 2-10 [PMID: 21199509 DOI: 10.1111/j.1440-1746.2010.06534.x]

Bhatia SJ, Reddy DN, Ghoshal UC, Jayanthi V, Abraham P, Choudhuri GC, Christensen BC, McClean MD, Kelsey KT. Gastric reflux is an independent risk factor for laryngopharyngeal cancer. Cancer Epidemiol Biomarkers Prev 2013; 22: 1061-1068 [PMID: 23703970 DOI: 10.1158/1055-9965.EPI-13-0183]

Qadeer MA, Colabianchi N, Vaezi MF. Is GERD a risk factor for laryngeal cancer? Laryngoscope 2005; 115: 486-491 [PMID: 15744163 DOI: 10.1097/01.lary.0000157851.24272.41]

Vaezi MF, Qadeer MA, Lopez R, Colabianchi N. Laryngeal cancer and gastroesophageal reflux disease: a case-control study. Am J Med 2006; 119: 768-776 [PMID: 16945612 DOI: 10.1016/j.amjmed.2006.01.019]

Bacci A, Mercante G, Ingoglia N, Ferri T, Muzzetto P, Leandro G, Di Mario F, Bacci S. Effects of gastroesophageal reflux disease in laryngeal cancer. Clin Otolaryngol Allied Sci 2004; 29: 545-548 [PMID: 15373871 DOI: 10.1111/j.1365-2273.2004.00851.x]

Chong YH. Clinical significance of heterotopic gastric mucosal patch of the proximal esophagus. World J Gastroenterol 2013; 19: 331-338 [PMID: 23272354 DOI: 10.3748/wjg.v19.i3.331]

Mercante G, Bacci A, Ferri T, Bacci S. Gastroesophageal reflux as a possible co-promoting factor in the development of the squamous-cell carcinoma of the oral cavity, of the larynx and of the pharynx. Acta Otorhinolaryngol Belg 2003; 57: 113-117 [PMID: 12864467]

Roder NP, Davis CS, Kovacs EJ, Fischella PM. The diagnostic
