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Upper Gastrointestinal Cancer and Reflux Disease

Jin-Jo Kim

Division of Gastrointestinal Surgery, Department of Surgery, The Catholic University of Korea, Incheon St. Mary's Hospital, Incheon, Korea

There is a growing evidence that gastroesophageal reflux disease is related to several upper gastrointestinal cancers, mainly the esophageal adenocarcinoma and a certain type of gastric cardia adenocarcinoma. Currently, the incidence of gastroesophageal reflux disease is rapidly increasing in Korea. Therefore, there is a possibility of such increasing cancerous incidents, similar to the western worlds. In this article, the relationship between gastroesophageal reflux disease and several upper gastrointestinal cancers, the components of refluxate which has possible causal relationship with carcinogenesis, and the clinical implications of such relationship in the management of gastroesophageal reflux disease patients are discussed through the review of literature.

Key Words: Gastroesophageal reflux disease; Gastrointestinal cancer; Fundoplication

Introduction

Gastroesophageal reflux disease (GERD), a condition defined by troublesome and recurrent heartburn and regurgitation, has long been considered as an important risk factor of several upper gastrointestinal cancers by many investigators.[1-7] Barrett esophagus (BE), which is the consequence of long-term reflux of gastric acid, is known to be in the center of such carcinogenesis.[8,9] BE is columnar-lined epithelium in the tubular esophagus, which is from metaplastic change of squamous epithelium of the esophagus. The hallmark of BE is demonstration of 'specialized intestinal metaplasia', the presence of goblet cells, on histological examination of an endoscopic biopsy specimen.[10] It is postulated that a rise in the incidence of GERD in western countries has a strong relationship with a rise in the incidence of BE, and eventually with a rise of several upper gastrointestinal cancers, mainly esophageal adenocarcinoma (EAC) and some of gastric cardia cancer (GCC).[1-7] Recently, the incidence of GERD in Korea is rapidly rising from 3.5% in 2001 to 7.3% in 2008.[11] GERD is now becoming an important health issue in Korea and simultaneous rise in the incidence of EAC and GCC, which have been known very rare in this country, can be a future serious health issue like in other western countries, although some investigators advocate the importance of strong ethnic or genetic factors in the development of such cancers.[12]

The objective of this review is to seek the relationship between GERD and several upper gastrointestinal cancers, the component of refluxate which has a possible causal relationship with carcinogenesis, and the clinical implication of such relationship in the management of GERD patients.

Esophageal Cancer

Esophageal cancer is the eighth most common malignancy and the sixth leading cause of cancer mortality, worldwide.[13] It is an important worldwide health problem because of its poor prognosis and a relatively high incidence in some parts of the world. Despite the advances in surgical techniques, chemotherapy, and radiotherapy, the prognosis is still dismal. Most patients are diagnosed

Correspondence to: Jin-Jo Kim
Division of Gastrointestinal Surgery, Department of Surgery, The Catholic University of Korea, Incheon St. Mary's Hospital, 56 Dongsu-ro, Bupyeong-gu, Incheon 403-720, Korea
Tel: +82-32-280-5609, Fax: +82-32-280-5988
E-mail: kjj@catholic.ac.kr
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with late-stage disease and less than 20% survive for 5 years.[2] The large majority of esophageal tumors are accounted for esophageal squamous cell carcinoma (ESCC: 60~70%) or EAC (20~30%), whereas melanoma, leiomyosarcoma, carcinoid, and lymphoma are rarely diagnosed.[14] Trends towards rising incidence are observed for EAC in western countries and are associated with trends towards stabilizing or declining incidence for ESCC, suggesting that these tumors may be associated with distinct risk factors.[3] ESCC occurs most often in patients with histories of tobacco consumption or ethanol intake.[14] EAC, on the other hand, can complicate long-standing acid reflux, and the main condition predisposing to its onset is BE, an acquired disorder whose prevalence is rapidly increasing worldwide.[9] However, in eastern Asia including Korea and Japan, the incidence of BE and EAC are extremely low and ESCC is much more prevalent than EAC.[15]

It is assumed that the development of EAC follows a stepwise progression from no reflux disease to reflux disease, from reflux disease to BE, and from BE to EAC. Pohl et al.[16] reported in their case-control study among consecutive patients undergoing a standard upper endoscopy that hiatal hernia was the only risk factor to be strongly associated with the development of GERD, and for GERD patients, male gender, age, an increased body mass index (BMI), duration of reflux symptoms, and presence of hiatal hernia were all associated with the development of BE, and finally, the development EAC/high grade dysplasia among patients with BE was associated with male gender, smoking, decreased fruit and vegetable intake, and a long segment of BE, but not with age, BMI, or a hiatal hernia. There are also several population-based studies suggesting the .association between GERD and EAC.[1,17,18] GERD is a strong and dose-dependent risk factor for EAC, which was established in the late 1990s, although 40% of patients did not have symptomatic reflux.[1] A recent meta-analysis about this subject showed that compared with individuals without reflux symptoms, experiencing symptoms at least weekly increased the odds of developing EAC 5-fold (odds ratio [OR], 4.9; 95% confidence interval [95% CI], 3.9~6.2), while daily symptoms increased the odds more than 7-fold (OR, 7.4; 95% CI, 4.9~11.1). Regarding the duration of symptom, less than 10~15 years of reflux symptoms increased the odds 3-folds (OR, 3.05; 95% CI, 1.53~6.08), while symptoms of at least 20 years increased the odds 5-folds (OR, 5.41; 95% CI 2.45~11.9), although the results were very heterogeneous.[19] Because of this kind of dose-dependent relationship between GERD and EAC, recommendations have been made to screen white men older than 50 years with longstanding and severe symptoms of GERD for BE, the known precursor of EAC.[20] Despite these recommendations, 95% of patients who develop EAC have not received endoscopic screening or being diagnosed as having BE, prior to the diagnosis of EAC.[21] Nason et al.[22] reported in their cross sectional study of 769 patients with GERD who underwent scheduled upper endoscopy that an increasing number of severe GERD symptoms correlated positively with endoscopic findings of esophagitis (OR, 1.05; 95% CI, 1.01~1.09). Whereas an increasing number of GERD symptoms were associated with decreased odds of adenocarcinogenesis (OR, 0.94; 95% CI, 0.89~0.98), especially in patents taking proton pump inhibitors (PPI). They concluded that medically treated patients with mild or absent GERD symptoms have significantly higher odds of adenocarcinogenesis compared with medically treated patients with severe GERD symptoms. Although the acid suppressive therapy with PPI effectively eliminates GERD symptoms, the reflux events of weakly acidic refluxate do not decrease effectively, especially in patients with BE.[23] Therefore, the current nearly epidemic use of PPI may permit occult disease progression to EAC in severe GERD patients with or without BE, without a perception of symptoms for a long period.

Helicobacter pylori (HP), a known causative organism of gastric cancer, has a certain linkage with the relationship between GERD and EAC. In an Australian population-based, case-control study, HP infection was associated with significantly reduced risks of EAC (OR, 0.45; 95% CI, 0.30~0.67) and GCC (OR, 0.41; 95% CI, 0.27~0.60) but not ESCC (OR, 1.04; 95% CI, 0.71~1.50).[24] Possible explanations for this inverse correlation between HP infection and EAC development is hypochlorhydria which was induced by chronic atrophic gastritis, having resulted from the infection, thereby reducing acid reflux from the stomach.[25,26] A progressively declining infection rate of HP has been observed with simultaneous declining incidence of gastric cancer over the course of 20th century in western countries. On the contrary, the incidence of EAC has markedly risen since 1970s. It can be said that the disappearance of HP may be fueling the increase of EAC incidence in the western world.[25] Unlike the relationship between HP infection and EAC, the results of studies regarding the relationship between HP infection and ESCC are much conflicting. There is substantial heterogeneity among studies with statistically significant association in both directions.[27]

Gastric Cancer

Gastric cancer is still a serious health problem in Korea, because it is second most prevalent cancer and its cancer-related death rate is third highest among other cancers in Korea.[28] Gastric cancers are

classified as gastric non-cardia cancer (GNCC) and GCC according to its anatomical location. GNCC, which is the more prevalent type of gastric cancer in Korea, is associated with chronic atrophic gastritis which is the consequence of *HP* infection whether it is intestinal or diffuse histological subtype.[29-32] The incidence of GNCC has been declining in western countries as the *HP* infection rate has decreased.[33] On the other hand, a steady increase in the incidence of GCC has been observed over the past three decades.[25] At present, GCC accounts for nearly half of all gastric cancers among men from USA.[34] The current rise in the incidence of GCC in the western world was explained by many investigators with rising incidence of GERD and obesity.[18,25,26,34] However, the prevalence of GCC in Korea is only 7.2% in 2012[35] and this shows very different situation, in comparison with that of western countries, that only a small increase in the incidence has been observed from 6.2% in early 1990s,[36] even though a substantial rise in the incidence of GERD has been observed during that period.[11,37] The role of ethnic or genetic factors in the development of this cancer can be a possible explanation for this phenomenon.[12]

Derakhshan et al.[5] reported in their case-control study dealing with 138 upper gastrointestinal cancer patients that GNCC was associated with gastric atrophy but not with GERD symptoms, EAC was associated with GERD symptoms but not with gastric atrophy. GCC was positively associated with both gastric atrophy (OR, 3.92; 95% CI, 1.77~8.67) and with GERD symptoms (OR, 10.08; 95% CI, 2.29~44.36), although the latter was only apparent in the non-atrophic subgroup and in the intestinal subtype. The association of GCC with gastric atrophy was stronger for the diffuse versus intestinal subtype and this was the converse of the association observed with GNCC. They concluded that there are two distinct etiologies of GCC, one arising from gastric atrophy and being of intestinal or diffuse subtype, similar to GNCC, and one related to GERD and intestinal in subtype, similar to EAC. These findings were supported by several reports from other investigators.[4,6,7,38] From these findings, it is certain that some of GCC, mainly the intestinal subtype, share common pathogenesis with EAC, in which the reflux of gastric acid plays the major role.

Which Component of Refluxate to Be Blamed More?

There is a body of literature which indicates gastric acid plays a very important role in the development of EAC, in a dose dependent manner, through the development of BE.[1,16,23,39-42] However, abnormal esophageal bilirubin exposure is more frequently observed along with the severity of esophageal mucosal damage, and mixed reflux of gastric and duodenal contents is more frequently observed than reflux of gastric contents alone in GERD patients with BE, a synonym of the extreme consequence of mucosal damage in GERD. Moreover, the vast majority of duodenal reflux occurs at a pH range of 4 to 7, at which bile acids, the major component of duodenal juice, are capable of damaging the esophageal mucosa.[43] Therefore, the concept that not the reflux of gastric acid alone but the duodenogastroesophageal reflux (DGER) plays a central role in the carcinogenesis of EAC is gaining an acceptance.[44] Several experimental studies have supported this theory[45-52] and many investigators have focused on the importance of DGER.[53-59] Direct toxic effects of bile acids to the squamous epithelial cell of the esophagus in a weakly acidic environment have widely been investigated.[43,60-63] If human bile is acidified below pH 2, irreversible precipitation of bile acids occurs. The clinical implications of this finding may be: (1) regurgitated bile acids may precipitate and become inactivated within an acidic gastric environment and, (2) given a more alkaline environment, such as after gastrectomy or with acid suppressive therapy with PPI, bile acids may remain in solution and can reflux into the esophagus causing esophageal mucosal injury. It is impossible or impractical to consistently alkalinize gastric juice with PPI above pH 7, in which most of the bile acids exist in ionized, hydrophilic form which cannot penetrate the mucosal cell membrane, a portion of the bile acids remains soluble in its unionized, lipophilic form, which is capable of crossing the mucosal cell membrane and damaging the mitochondria.[44] Consequently, a gastric juice of pH <2 or >7 is less injurious than a pH between 2 to 7, in which bilirubin exposure is most frequently observed in GERD patients.[43] These findings together may suggest that bile acids are more harmful to the esophageal squamous epithelial cell than gastric acid and cause more severe mucosal damage, ultimately Barrett's metaplasia, especially when it is combined with weakly acidic environment than gastric acid does. In DGER, bile acids and gastric acid may act in synergism in damaging the mucosal cell.

Cancer Prevention Strategy and the Possible Role of Antireflux Surgery

Debates are ongoing on whether acid suppressive therapy with drugs or antireflux surgery in GERD patients may also inhibit disease progression to BE or EAC, as well as control symptoms. There is little randomized controlled trial (RCT) dealing with this subject. Spechler et al.[64] conducted RCT for the comparison of the results of medical or surgical treatment in 247 complicated GERD

patients (77 continuous medical treatment group, 88 symptomatic medical treatment group, and 82 surgical treatment group) in 1986 and published its long term results. Five patients developed EAC during the mean 7.1 years of follow-up, and there was no significant difference in the rate of EAC development between the medical and surgical group. However, the sample size was too small to have sufficient statistical power, as they mentioned in their article. There is one large population-based cohort study from Sweden about this subject.[65] This study was conducted using the Swedish Inpatient Register and 85,526 patients who were discharged with at least 1 in-hospital diagnosis of heartburn, hiatal hernia or reflux esophagitis from 1965 to 1997 were enrolled into this study. Among them, 13,198 patients underwent at least 1 antireflux surgery. They estimated 'standardized incidence ratio' (SIR) which was defined by the ratio of the observed number of cancers to the expected number of cancers, the cancer incidence rates in the entire Swedish population multiplied by the person-years of follow-up, in order to estimate the cancer risk of the patients in comparison with the risk of general population in Sweden. SIR of EAC in the patients who did not have antireflux surgery was 6.3 (95% CI, 4.5~8.7) and 14.1 (95% CI, 8.0~22.8) in the patients who had antireflux surgery. However, the risk of EAC development significantly increased as the follow-up period was getting longer in the patients without antireflux surgery (P=0.03; the P-value for trend), and remained stable in the patients with antireflux surgery (P=0.32). SIR at more than 10 years of follow-up was 10.9 in the patients without antireflux surgery and 7.7 in the patients with antireflux surgery. This shows a long-term protective effect, although it may be small, of surgery.[66] There are some reports indicating regression of BE or dysplasia in BE, and normalization or stabilization of biomarkers associated with BE and EAC after antireflux surgery, even though these are small-numbered case series.[67-71]

Several experimental studies using combined esophageal pH-impedance monitoring revealed that PPI therapy did not affect the total number of reflux episodes or their duration. Instead, it could only decrease the acidity of the refluxate.[72-74] Stein et al.[75] reported exponential increase of esophageal bilirubin exposure from normal volunteer to early EAC patients as the degree of esophageal pathology related to GERD becomes more severe. They also noted a complete suppression of bilirubin exposure after Nissen fundoplication compared to no suppression after PPI use. Getting these together, antireflux surgery may have, at least, a theoretical advantage over PPI in preventing EAC development in GERD patients. However, a large-scaled RCT is needed to prove this theory.

Despite the current rapid rise in the incidence of GERD in Korea, antireflux surgery is rarely performed and there has been only one report of case series.[76] Recently, Korean Antireflux Surgery Study Group (KARS) was organized and the data regarding the antireflux surgery in Korea is now being collected. A nationwide data about the current status of antireflux surgery in Korea will soon be available, and the rise of the number of antireflux surgery is anticipated in the near future.

Conclusion

The prevalence of GERD in Korea is rising and associated rise in the incidence of EAC and GCC is anticipated. EAC and some of GCC are associated with GERD. DGER has an important role in the development such cancers. PPI may have some limitations in controlling DGER. Therefore, antireflux surgery may have a certain role in the prevention of such cancers.

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