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Editorial

Increased Subsequent Risk of Head and Neck Cancer for Men With Gastroesophageal Reflux Disease: New Evidence from Nationwide Cohort Study

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We have read with great interest the recently published article, entitled "*Acid Reflux and Head and Neck Cancer Risk: A Nationwide Registry over 13 Years*."[1] This study reveals a significant association between gastroesophageal reflux disease (GERD) and oropharyngeal and hypopharyngeal cancers. GERD causes gastric content to reflux up toward esophagus, such reflux material (e.g. hydrochloric acid, pepsin and bile acids) has been suggested to exert its potential carcinogenicity through prolonged exposure to mucosa. Structurally, hypopharynx and oropharynx area is the only and necessary bridge to all extra-esophageal subsites; located in such a dependent part of upper aerodigestive tract for acid accumulation making hypopharynx and oropharynx area particularly vulnerable to mucosal irritation caused by gastric reflux. The persistent mucosal damage and irritation might contribute to subsequent cancer developments by mutagenicity due to DNA breaking.

In a nationwide cohort study, it is identified that males have a higher risk of head and neck cancer (HNC) following GERD diagnosis, in particular oropharyngeal and hypopharyngeal cancers. A delineated mechanism has not been established to explain such a gender difference. However, a higher prevalence of obstructive sleep apnea (OSA) in males might play a critical role. There is a link between OSA and its subsequent effect on oropharyngeal and hypopharyngeal cancers. The upper aerodigestive tract in OSA patients is anatomically prone to collapse at the level of the pharynx, especially during sleep. This results to acid accumulation in oro- and hypo-pharynx area; the exposure to gastric material irritates and damages the mucosa, which might facilitate the development of subsequent cancer by mutagenicity from DNA breaking.

The relationship between GERD and cancer of hypopharynx or oropharynx is far from established.[2,3] In this study, the link between these two entities has been identified, providing the evidence-based information that may influence clinical practice. First, GERD can masquerade as a wide variety of otolaryngologic presentations after damaging pharynx. These symptoms can overlap early manifestations of pharyngeal cancer, such as sore throat, odynophagia, dysphagia, pharyngeal tightness, globus pharyngeus and throat clearing.[4-6] Similar symptomatology may result in patients being mistakenly diagnosed with GERD. Additionally, it has been reported that less than 50% of patients with throat discomfort due to GERD have abnormal otolaryngologic findings,[5] making the early diagnosis of cancer much more unachievable. Missing the golden time for tumor detection and treatment delays may jeopardize survivals. Therefore, for patients initially diagnosed with GERD as the cause of laryngopharyngeal signs but did not respond symptomatically to aggressive acid suppression, an otolaryn-

gologic referral may be appropriate for detailed extra-esophageal examinations to exclude the possibility of oropharyngeal or hypopharyngeal cancer.

Gastric acid may reflux superior to the esophagus, causing supra-esophageal pathologies, such as sinusitis, otitis media and tongue base hypertrophy.[7,8] The refluxed material (e.g. hydrochloric acid, pepsin and bile acids) has also been suggested to exert its potential carcinogenicity via chronic mucosal irritation.[7,9-13] However, most research on the link between GERD and extra-esophageal structures exclusively focused on cancers of larynx alone or laryngopharynx.[2,3,7,10,13,14] This study first revealed evidence-based information on what types of HNC were most likely to develop subsequent to GERD. Except for oropharyngeal and hypopharyngeal cancers, there was no significant association between GERD and other types of HNC. This can be explained from the anatomic proximity of the pharynx to the esophagus and stomach (Figure 1). There is no guarantee that gastric contents can successfully reach and damage all the subsites of head and neck in each occasion, hypopharynx and oropharynx, however, is the only and necessary bridge to all extra-esophageal subsites, making it particularly vulnerable to GERD. Moreover, during 7-8 hours of sleep, hypopharynx and oropharynx became the most dependent part of upper aerodigestive tract for acid accumulation. The persistent mucosal irritation and damaging may be associated with subsequent cancer development by mutagenicity due to DNA breaking.[12]

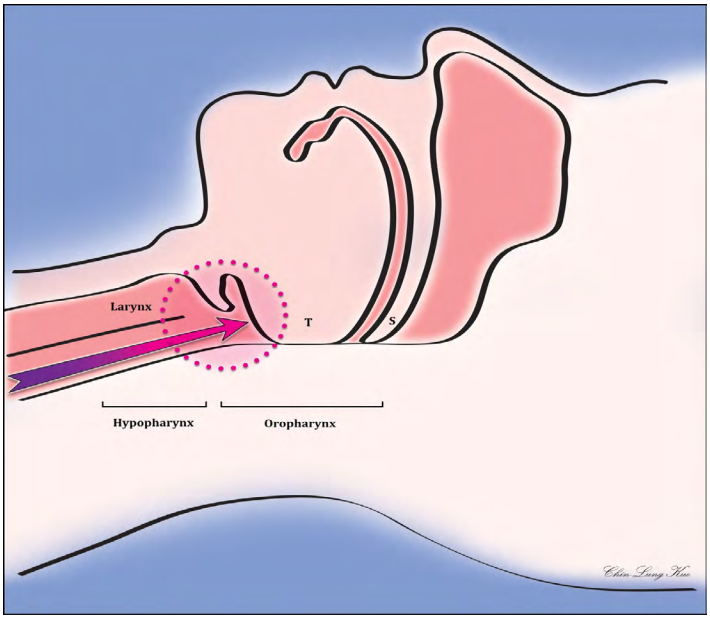

Figure 1. Acid accumulation and irritation in pharynx. Oro- and hypo-pharynx is the necessary bridge to all supra-esophageal subsites. During sleep, it becomes the most dependent part of upper aerodigestive tract for acid accumulation (red dotted circle). The accumulation may be more prominent in patients with obstructive sleep apnea because the upper aerodigestive tract may be obstructed at the level of oro- and hypo-phayrnx by such structures as elongated soft palate (S) and hypertrophied tongue base (T).

Regarding the effects of gender, males were identified as having a higher risk of HNC following GERD diagnosis, in particular oropharyngeal and hypopharyngeal cancers, as compared with the general population. The underlying mechanisms explaining the gender difference in cancer risk are not clearly delineated. Nevertheless, a biological plausibility exists. First, hypopharynx and oropharynx are most vulnerable to GERD due to anatomic proximity to esophagus and stomach. Second, inherent gender differences in the prevalence of OSA might play a critical role. In most population-based studies, a 2- to 3-fold higher risk of OSA for males compared with females has been reported.[15,16] The upper aerodigestive tract in OSA patients is anatomically prone to collapse at the level of the pharynx, especially during sleep, causing acid accumulation in oro- and hypo-pharynx (Figure 1). The persistent mucosal irritation and damaging may cause mutagenicity by breaking DNA, contributing to subsequent cancer development.[12] The above theoretical mechanism may partially explain the gender difference in cancer risk in GERD patients, but this issue needs to be further clarified with studies investigating the association between OSA and cancers of oropharynx and hypopharynx.

The study found that GERD patients younger than 60 years of age were at higher risk of developing HNC than the general population, whereas those older were not. An important contributing factor to the difference might be altered esophageal pain perception to acid in elderly.[17,18] Elderly often present with less severe heartburn and acid regurgitation despite increased acid exposure and more severe mucosal injury. The perplexing phenomenon may adversely influence healthcare-seeking behavior. There may be a time delay from presentation until progression to advanced disease, making prevalence of GERD underestimated in elderly population. The underlying underestimation of GERD has been a source of speculation on equivalent risks of cancer development between the elderly with GERD and the general population. Duration of GERD had also been found to be a factor associated with cancer development in GERD patients. Patients diagnosed with GERD for more than 5 years were not at significantly higher risk of cancer compared with the general population. The possible explanation was the limitation of follow-up in the study, with a range of 1.5 to 4.9 years. A longer follow-up may be necessary to determine the true risk of cancer in patients with a diagnosis of GERD for more than 5 years.

This study contributes to emerging findings regarding the association between GERD and subsequent HNC. After taking confounding factors into consideration, a prospective link was confirmed between males and subsequent cancer development of oropharynx and hypopharynx within the first 5 years

following GERD diagnosis. The study may allow for the specific targeting of follow-up strategy to high-risk individuals after a diagnosis of GERD.

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