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BRIEF ARTICLE

Atrophic gastritis: Risk factor for esophageal squamous cell carcinoma in a Latin-American population

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Abstract

AIM: To study the association between atrophic gastritis (AG) and esophageal squamous cell carcinoma (ESCC) in a Latin-America population.

METHODS: A case-control study was performed at two reference Brazilian hospitals including patients diagnosed with advanced ESCC and dyspeptic patients who had been subjected to upper gastrointestinal endoscopy, with biopsies of the gastric antrum and body. All cases with ESCC were reviewed by a single pathologist, who applied standard criteria for the diagnosis of mucosal atrophy, intestinal metaplasia, and dysplasia, all classified as AG. The data on the patients' age, sex, smoking status, and alcohol consumption were collected from clinical records, and any missing information was completed by telephone interview. The association between AG and ESCC was assessed by means of univariate and multiple conditional logistic regressions.

RESULTS: Most patients were male, and the median age was 59 years (range: 37-79 years) in both the ESCC and control groups. Univariate analysis showed that an intake of ethanol greater than 32 g/d was an independent risk factor that increased the odds of ESCC 7.57 times (P = 0.014); upon multiple analysis, alcohol intake of ethanol greater than 32 g/d exhibited a risk of 4.54 (P = 0.081), as adjusted for AG and smoking. Smoking was shown to be an independent risk factor that increased the odds of ESCC 14.55 times (P = 0.011) for individuals who smoked 0 to 51 packs/year and 21.40 times (P = 0.006) for those who smoked more than 51 packs/year. Upon multiple analyses, those who smoked up to 51 packs/year exhibited a risk of 7.85 (P = 0.058), and those who smoked more than 51 packs/year had a risk 11.57 times higher (P = 0.04), as adjusted for AG and alcohol consumption. AG proved to be a risk factor that increased the odds of ESCC 5.33 times (95%CI: 1.55-18.30, P = 0.008) according to the results of univariate conditional logistic regression.

CONCLUSION: There was an association by univariate conditional logistic regression between AG and ECSS in this sample of Latin-American population.

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Key words: Atrophic gastritis; Esophagus; Squamous cell carcinoma; Risk factor; Alcohol; Tobacco

INTRODUCTION

Esophageal cancer (EC) is the eighth most common cancer worldwide with 481 000 new cases (3.8% of all cancers) estimated in 2008, and is the sixth most common cause of death from cancer with 406 000 deaths (5.4%)[1]. The two main histological types of EC are adenocarcinoma and esophageal squamous cell carcinoma (ESCC), which differ regarding their risk factors and demographic distributions. Although adenocarcinoma has been the most frequent subtype among white males in the United States since the beginning of the 90s[2], ESCC remains as the most frequent subtype worldwide, corresponding to more than 80% of all cases[3]. The highest mortality rates of ESCC are found in East Asia, Southern and Eastern Africa[1]. In Brazil, which is the largest Latin-American country, ESCC represents 96% of all cases[4]. The main risk factors for ESCC in the West are alcohol consumption and smoking[5,6]. An increased risk of ESCC was initially reported among patients with pernicious anemia[7], and more recently, patients with atrophic gastritis (AG) were also found to be more susceptible[8]. This hypothesis was strengthened by a Swedish study that assessed the association among *Helicobacter pylori* (*H. pylori*) infection, gastric mucosal atrophy, and ESCC. These researchers discovered that an infection by cytotoxin-associated gene A (CagA)-positive *H. pylori* was associated with a higher risk of ESCC, particularly among patients with gastric atrophy. When the correlation between gastric atrophy and ESCC was assessed independently from the *H. pylori* serotype, gastric atrophy exhibited a strong association with increased risk for ESCC. The authors suggest that gastric mucosal atrophy represents an intermediate step in the pathway from a CagA-positive *H. pylori* infection to ESCC[9]. More recently, a meta-analysis[10] selected and analyzed seven studies that investigated this association and concluded that AG increases the risk of ESCC[3,9,11-15]. However, this meta-analysis did not address any studies that considered populations outside Northern Europe or Asia; therefore, the association has not been studied in Latin-American populations. Considering that the South American and Caribbean populations include 572 million people and represent 8.6% of the world population[16], the present study aimed to investigate the correlation between gastric mucosal atrophy and ESCC in a sample from that unexamined population.

MATERIALS AND METHODS

All of the patients with ESCC who were treated at the Cancer Hospital of Barretos between April 2011 and April 2012 were retrospectively analyzed. Exclusion criteria included the following: a diagnosis of obstructive ESCC, *i.e.*, where endoscopic access to the stomach was hindered; previous gastrointestinal (GI) tract surgery and age greater than 80 years. For each case, a gender- and age-matched control was randomly selected among patients who had been subjected to upper GI endoscopy due to dyspeptic complaints at the General Hospital of the Botucatu Medical School. The controls were chosen from patients with dyspeptic complaints, because in Brazil there is no protocol to screen asymptomatic individuals by means of upper GI endoscopy. Because the two centers that participated in the present study are referral centers for patients nationwide, demographic characteristics were not taken into account for matching.

Following routine protocols at both hospitals, all of the patients were subjected to endoscopic biopsies of the gastric antrum and body. The *H. pylori* infection was diagnosed by urease test (pink color after 30 min) and Warthin-Starry stain (Artisan-Dako, Denmark), was used for the visualization of *H. pylori* (with this method *H. pylori* is stained black while the background is stained golden yellow). The criteria for the diagnosis of ESCC were based on the endoscopy aspects and the final pathology report. The histopathologic features included true invasion of lamina propria, at least, by tumoral isolated cells or tumor clusters from the squamous esophagic epithelium. The cells were generally polygonal with pink cytoplasm and distinct cell borders and the nuclei were enlarged, hyperchromatic and pleomorphic. At high power intercellular bridges and keratinization within the cells were commonly seen, although they were absent in poorly differentiated tumors. The adjacent surface epithelium sometimes exhibited the same neoplastic cells, containing therefore, an intraepithelial ("*in situ*") component. All cases with ESCC were reviewed by a single pathologist, who applied standard criteria for the diagnosis of mucosal atrophy, intestinal metaplasia, and dysplasia. All three conditions were classified as AG in the present study.

The data on the patients' age, sex, smoking status, and alcohol consumption were collected from clinical records, and any missing information was completed by telephone interview. Alcohol consumption was calculated as grams of ethanol per day, and tobacco consumption was calculated as number of packs per year.

Statistical analysis

For statistical analysis, categorical values are given in frequencies and percentages. Means, medians, and standard deviations were calculated for numerical variables. To assess the risk factors of ESCC, univariate and multiple conditional logistic regressions were used. In addition, to assess the correlation between the use of alcohol or smoking and AG, non-conditional logistic regression was performed. The level of significance was established as 5%. Analyses were performed using software SPSS version 19 and Stata/SE. The research ethics committees of both participating centers approved the present study.

Table 1 Clinical, lifestyle, and diagnostic characteristics between cases and controls *n* (%)

Characteristic	Category	Case	Control
Gender	Female	7 (14.3)	7 (14.3)
	Male	42 (85.7)	42 (85.7)
Age group (yr)	36-45	3 (6.1)	3 (6.1)
	46-55	14 (28.6)	14 (28.6)
	56-65	21 (42.9)	21 (42.9)
	66-75	8 (16.3)	8 (16.3)
	76-85	3 (6.1)	3 (6.1)
Alcohol	Never drinker	10 (20.4)	16 (32.7)
	Current drinker	39 (79.6)	16 (32.7)
	Former drinker	0 (0.0)	17 (34.7)
Tobacco	No	8 (16.3)	24 (49.0)
	Yes	41 (83.7)	25 (51.0)
Hot drinks	No	49 (100)	49 (100)
Tylosis	No	49 (100)	49 (100)
Achalasia	No	48 (98.0)	49 (100)
	Yes	1 (2.0)	0 (0.0)
Caustic esophagitis	No	49 (100)	49 (100)
Plummer-Vinson	No	49 (100)	49 (100)
Head and neck SCC	No	49 (100)	49 (100)
Endoscopic gastric	No	10 (20.4)	42 (85.7)
atrophy	Yes	39 (79.6)	7 (14.3)
Gastric atrophy	No	37 (75.5)	45 (91.8)
	Yes	12 (24.5)	4 (8.2)
Intestinal metaplasia	No	34 (69.4)	41 (83.7)
	Yes	15 (30.6)	8 (16.3)
Helicobacter pylori	No	25 (51.0)	22 (44.9)
	Yes	24 (49.0)	27 (55.1)
Low-grade dysplasia	No	47 (95.9)	49 (100)
	Yes	2 (4.1)	0 (0.0)
High-grade dysplasia	No	48 (98.0)	49 (100)
	Yes	1 (2.0)	0 (0.0)
Total		49 (100)	49 (100)

SCC: Squamous cell carcinoma.

Table 2 Univariate and multiple logistic regression for case-control study according to gastric atrophy, alcohol intake, and tobacco consumption

Variables	Univariate		Multiple	
	OR unadjusted	*P* value	OR adjusted	*P* value
Gastric atrophy	5.332	0.008	3.76	0.063
Alcohol				
Non-drinker	1		1	
0-32 g ethanol/d	1.29	0.736	0.98	0.985
> 32 g ethanol/d	7.57	0.014	4.54	0.081
Tobacco				
No smoker	1		1	
51 pack/yr	14.55	0.011	7.85	0.058
> 51 pack/yr	21.40	0.006	11.57	0.040

OR: Odds ratio.

RESULTS

The comparison between both investigated groups is described in Table 1. Most patients were male, and the median age was 59 years (range: 37-79 years) in both the ESCC and control groups.

Only one individual in the ESCC group exhibited achalasia, and none of the patients exhibited any of the following classic risk factors: consumption of warm beverages, caustic esophagitis, squamous cell carcinoma of the head and neck, Plummer-Vinson syndrome or tylosis.

Table 2 describes the association between risk factors and ESCC. Univariate analysis showed AG to be an independent risk factor, which increased the odds of ESCC 5.332 times ($P = 0.008$). On multiple analysis, AG exhibited risk of 3.76 ($P = 0.063$), as adjusted for alcohol and smoking.

Univariate analysis showed that an intake of ethanol greater than 32 g/d was an independent risk factor that increased the odds of ESCC 7.57 times ($P = 0.014$); upon multiple analyses, alcohol intake of ethanol greater than 32 g/d exhibited a risk of 4.54 ($P = 0.081$), as adjusted for AG and smoking.

Smoking was shown to be an independent risk factor that increased the odds of ESCC 14.55 times ($P = 0.011$)

for individuals who smoked 0 to 51 packs/year and 21.40 times ($P = 0.006$) for those who smoked more than 51 packs/year. Upon multiple analyses, those who smoked up to 51 packs/year exhibited a risk of 7.85 ($P = 0.058$), and those who smoked more than 51 packs/ year had a risk 11.57 times higher ($P = 0.04$), as adjusted for AG and alcohol consumption.

Non-conditional logistic regression assuming alcohol consumption and smoking as risk factors for AG did not find evidence for an association.

In the present study, *H. pylori* infection did not exhibit association with ESCC [odds ratio (OR) = 0.81, $P = 0.578$] and behaved as a protective factor against AG (OR = 0.3, $P = 0.009$).

DISCUSSION

Recent interest in the correlation between AG and ESCC led to a meta-analysis of seven studies from Asia and northern Europe that demonstrated an association between the conditions[10].

The present case-control study also discovered significant statistical associations from a non-adjusted analysis between the following: AG and ESCC; heavy use of alcohol (more than 32 g of ethanol/d) and ESCC; and smoking and ESCC. Nevertheless, the use of adjusted models to investigate AG, alcohol, and smoking found a statistically significant association between ESCC and heavy smoking (more than 51 packs/d) alone. From the seven studies included in the aforementioned meta-analysis, three did not adjust their analysis for other risk factors besides AG[12,13,15]. The fact that the associations discovered by the present study often lost statistical significance after adjustment could be explained by the small sample sizes (*n* = 49 cases, *n* = 49 controls). The loss of significance attributable to heavy alcohol consumption, in particular, corroborates this interpretation; alcohol consumption is a classic risk factor for ESCC in Western countries. de Vries *et al*[15] suggest that the association between AG and ESCC might be explained by confounding factors, such as smoking, after demonstrating an association between AG and small cell lung car-

cinoma. However, in the present study, univariate non-conditional logistic regression did not indicate an association between alcohol consumption or smoking with AG. It is worth noting that four other studies performed logistic regression adjusted for risk factors, and each study found a statistically significant association between AG and ESCC[3,9,11,14].

The present study did not find an association between ESCC and *H. pylori*, which, in fact, proved to be protective against AG. Although seemingly paradoxical, this finding may be explained by the fact that *H. pylori* does not colonize atrophic mucosa nor areas with intestinal metaplasia.

This study, as well as other similar studies, encountered limitations regarding the selection of healthy controls. Although some Japanese studies, such as the one by Akiyama *et al*[3], have been able to use healthy controls undergoing screening upper GI endoscopy, these studies also report difficulty in selecting appropriate controls. As such screening programs do not exist in Brazil, the controls used in the present study were individuals subjected to endoscopy due to dyspeptic complaints; consequently, higher odds of exhibiting pathological findings in the GI tract may exist.

Although related literature shows an association between AG an ESCC, whether that relationship is causal is still unknown. A possible mechanism of this relationship is that achlorhydria in patients with gastric atrophy may generate an intragastric environment that favors bacterial overgrowth and n-nitrosation, thus resulting in increased exposure of the esophageal mucosa to carcinogenic endogenous nitrosamines[17].

Other explanations for the positive association between gastric atrophy and ESCC are worth exploring. It is possible that both conditions share genetically determined pathogenetic mechanisms that facilitate a similar destructive process (*i.e.*, inflammatory response or defective DNA repair), damaging both gastric and esophageal epithelia[15,18-20].

It is also possible that the observed association between ESCC and AG is due to the fact that patients with advanced ESCC can only ingest small amounts of food, owing to esophageal stenosis and lack of appetite, and this reduced ingestion may lead to disuse atrophy. That hypothesis, however, is contested in the study by Kamangar *et al*[13], which found that a lower serum PGI/Ⅱ ratio was linearly associated with higher risk of esophageal squamous dysplasia, a preneoplastic condition of ESCC. It is worth noting that patients with esophageal dysplasia do not exhibit dysphagia.

Despite the abovementioned limitations, the present study, as far as we know, is the first to identify a statistically significant association by univariate conditional logistic regression between AG and ESCC in the Latin-American population. In conclusion, in the present study the AG was an independent risk factor in this sample from Latin-America population, as has been demonstrated in studies of population samples from Asia and northern Europe. This fact highlights the importance of conducting pro-spective, multicenter studies enrolling larger populations that represent different ethnic groups, to investigate the causal relationship between AG and ESCC.

COMMENTS

Background
Esophageal cancer (EC) is the eighth most common cancer worldwide with 481 000 new cases (3.8% of all cancers) estimated in 2008, and is the sixth most common cause of death from cancer with 406 000 deaths (5.4%). The highest mortality rates of esophageal squamous cell carcinoma (ESCC) are found in East Asia, Southern and Eastern Africa. In Brazil, which is the largest Latin-American country, ESCC represents 96% of all EC. The main risk factors for ESCC in the Western countries are alcohol consumption and smoking. More recently, a meta-analysis concluded that AG increases the risk of ESCC. However, this meta-analysis did not address any studies that considered populations outside of Northern Europe or Asia; therefore, the association has not been studied in Latin-American populations. Considering that the South American and Caribbean populations include 572 million people and represent 8.6% of the world population, the present study aimed to investigate the correlation between gastric mucosal atrophy and ESCC in a sample from that unexamined population.

Research frontiers
The better knowledge of risk factors and pathophysiological mechanisms of EC can lead to better preventive and therapeutic options in a cancer type that presents with low survival rates.

Innovations and breakthroughs
An increased risk of ESCC was initially reported among patients with pernicious anemia and more recently, patients with atrophic gastritis (AG) were also found to be more susceptible. This hypothesis was strengthened by a Swedish study that assessed the association among *Helicobacter pylori* (*H. pylori*) infection, gastric mucosal atrophy and ESCC. These researchers discovered that an infection by cytotoxin-associated gene A (CagA)-positive *H. pylori* was associated with a higher risk of ESCC, particularly among patients with gastric atrophy. When the correlation between gastric atrophy and ESCC was assessed independently from the *H. pylori* serotype, gastric atrophy exhibited a strong association with increased risk for ESCC. The authors suggest that gastric mucosal atrophy represents an intermediate step in the pathway from a CagA-positive *H. pylori* infection to ESCC.

Applications
The study results suggest an association between AG and ESCC.

Terminology
All three conditions (mucosal atrophy, intestinal metaplasia, and dysplasia) were classified as AG in the present study.

Peer review
This is a small but well conducted study that shows that also in South America AG seems to predispose to ESCC thus showing that the association can be found despite the obvious environmental differences between Asia, Europe and North America. The study thus further generalizes the hypothesis and should encourage research into the mechanism behind this.

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