ORIGINAL ARTICLE

Risk factors associated with the development of gastric cancer — case-control study

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INTRODUCTION

It is estimated that about 1 million (952,000) new cases of gastric cancer occurred worldwide in 2012.[1] Except for non-melanoma skin cancer, stomach cancer is currently the fifth most common cancer in the world. The National Cancer Institute (Inca)[2] estimated for Brazil 12,920 new cases of stomach cancer in men and 7,600 in women in the biennium 2016-2017. Adenocarcinoma is the histological type most commonly found in gastric tumours. It accounts for more than 95% of gastric neoplasms, and is practically a synonym of gastric cancer. Other neoplasms found in the stomach include gastrointestinal stromal tumours, leiomyomas, lymphomas, and neuroendocrine tumours.

Risk factors commonly associated with the development of gastric cancer include chronic infection with *Helicobacter pylori (H. pylori)*, low fruit and vegetable intake, high salt intake, smoking, and alcohol consumption[3]. The World Health Organization (WHO) classifies *H. pylori* as a group 1 carcinogen in humans. It is one of the most common infections in the world, with an estimated prevalence of 50%, reaching 90% in developing countries. However, only a small proportion of individuals infected with *H. pylori* develop gastric cancer, indicating the need for interaction of environmental factors, such as smoking and alcohol consumption, in individuals with genetic susceptibility in addition to the variation of the bacterial strain[4]. Since the 1960s, several cohort and case-control studies have been published with the purpose of assessing the association of smoking with the increased risk of developing stomach cancer. The analysis of these publications led the International Agency for Research on Cancer (IARC) to conclude in 2002 that there is sufficient evidence of causality between smoking and gastric cancer[5] (Figure 1).

Although moderate alcohol consumption may bring some health benefits, especially in relation to cardiovascular disease, it is considered one of the ten major risk factors contributing to disease develop-

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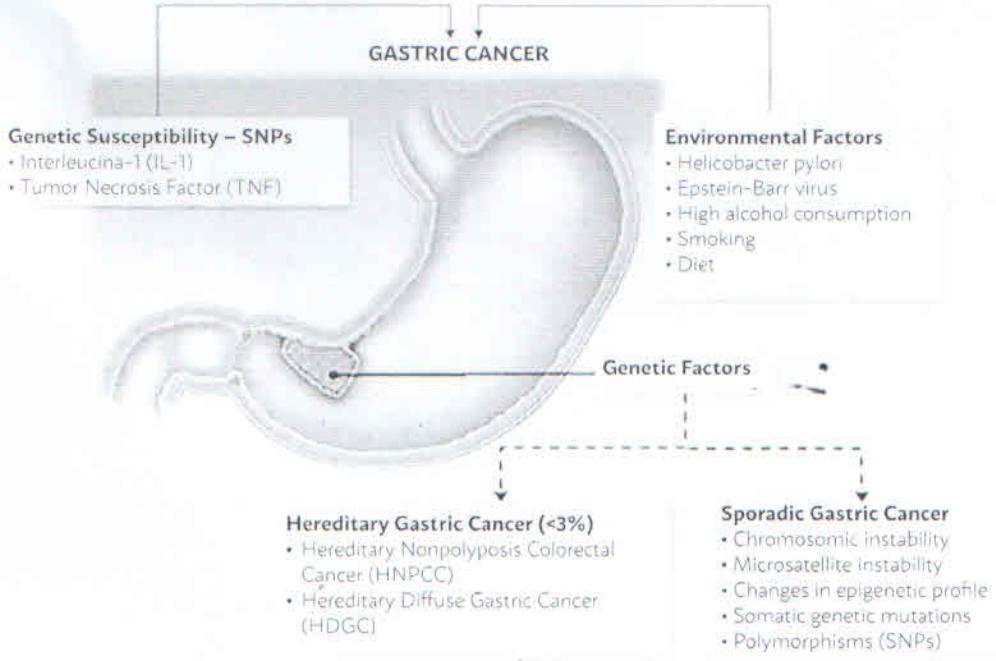
FIGURE 1. RISK FACTORS FOR GASTRIC CANCER



ment globally. Causal association with alcohol consumption was evidenced for some neoplasms, such as the oropharynx, oesophagus, liver, colorectal and breast, confirming alcohol as a group 1 carcinogen. However, the association of alcoholic beverages with gastric cancer was not consistent[6]. The lack of epidemiological evidence may be due to the association of chronic alcohol intake with nutritional deficiencies, unfavourable lifestyle and different patterns of consumption in the populations studied.

Low socioeconomic status is associated with higher incidence and mortality of numerous diseases. Association with the risk of developing gastric cancer may also occur[7]. Although there is no clear justification for the occurrence of this association, a better social condition leads to better working conditions and financial income, favouring the adoption of a healthier lifestyle and broad access to the healthcare system. Populations with low social status also have a higher prevalence of *H. pylori* infection, smoking and diet with nutritional deficiencies, factors commonly related to the development of gastric cancer.

PURPOSES

To assess the risk of gastric cancer associated with smoking, alcohol consumption and level of education. Verify the association of the same factors according to the histological subtype and location of the lesion.

METHODS

This is a hospital-based case-control study that is part of the project "The relationship between the differences in gene expression and the clinical pathological features of human câncer", (Cancer Clinical Genome)[8] conducted between 2001 and 2007. Cases and controls were interviewed in person, using a standardized questionnaire applied by trained healthcare professionals. Patients residing in the metropolitan region of São Paulo (RMSP) for six months or more were included. The cases of gastric adenocarcinoma were diagnosed through anatomopathological examination. They had no previous treatment for the neoplasia and were admitted to the Stomach Surgery Unit of the Hospital das Clínicas - University of São Paulo Medical School

Subjects in the control group were selected from patients admitted to the same hospital with no history or suspected stomach cancer. They were matched to cases by gender and age group, by the expected distribution of cases (frequency matching). The diseases of the patients in the control group should be distributed among several diagnostic categories, so that no illness was represented in excessive num-

bers. Inclusion of cancer patients was restricted, and they should not exceed 15% of the total number of controls. The exclusion criteria adopted was individuals without physical or mental conditions to answer the questionnaire, patients with advanced and terminal stage neoplasms without a therapeutic proposal, gastric neoplasms of histological type other than adenocarcinoma and gastric stump lesions.

The gender variable entered the model dichotomously, and age was divided into six categories (20-39, 40-49, 50-59, 60-69, 70-79 and 80 years or older). The individuals were classified into four categories, according to the level of education: did not attend school and primary education incomplete; completed primary education; secondary education completed and incomplete; university education.

Individuals who smoked at least one cigarette, cigar, or pipe daily for a year were considered smokers. Those who stopped smoking 12 months or more before the interview were classified as former smokers. In order to build a variable that contemplated the total amount of tobacco consumed by each individual and that would allow the comparison among all individuals, it was considered that each cigarette contains one gram (g) of tobacco, 4g for cigars and 3g for pipes. After this transformation, the average daily consumption of tobacco was calculated in grams, which was divided by 20 (amount of tobacco, in grams, of a pack of cigarettes) and multiplied by the number of years of smoking of each individual, therefore finding the pack-year value[9].

The individual who reported drinking at least once a month was considered a current alcohol consumer. Those who stopped drinking alcohol 12 months or more before the interview were classified as former consumers. To calculate the consumption of alcohol, it was considered that beer contains 5% alcohol, wine 12%, cachaça, whiskey, vodka and rum 41%, and liquor 30%. The quantities, in litres of alcohol, found from these percentages were transformed into grams of alcohol, considering that each litre of alcohol contains 798 g. The average daily intake of alcohol was then calculated in grams, which was multiplied by the number of years of consumption of each individual, thus reaching the variable expressed in grams-year of alcohol.

For the analysis of the continuous variable that represents smoking in pack-years and alcohol consumption in grams-year, cases and controls were divided into four categories from cut-off points referring to the quartiles of the variable observed in the control group.

Tumours were classified histologically, according to Laurén's classification for adenocarcinomas, in intestinal and diffuse type[10]. The location of the tumour in the stomach was considered to be distal in cases where the lesion was in the antrum and pylorus, and tumours located in the region of the cardia and fundus were classified as proximal. Diffuse tumours involving the entire stomach and tumours that did not fit into the two major categories were labelled as others.

To estimate the risk of stomach cancer associated with the variables of interest, odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated through non-conditional logistic regression[11] with the Stata® program, version 10 (StataCorp LLC, Texas, United States). Statistical significance was assessed using the likelihood ratio test. The significance level for rejecting the null hypothesis was lower than 0.05. For ordered categorical variables, linear trend tests were performed in the ORs, considering the values of the categories as continuous. Interaction between two variables was analysed by the multiplicative model with the addition of product values. ORs were always adjusted by gender, age, smoking, and alcohol consumption. The study project was approved by the Ethics Committee of HC-FMUSP and the Research Ethics Committee (Protocol no. 222/01), being registered in the Brazil Platform (CAAE: 33009014.0.0000.0065). Only individuals who signed the Informed Consent Term (TCLE – *Termo de Consentimento Livre e Esclarecido*) were included.

RESULTS

The present study included 240 cases of gastric adenocarcinoma confirmed through anatomopathological examination and without previous treatment for neoplasia. Individuals in the control group were selected among patients admitted to HC-FMUSP, totalling 499 individuals. Regarding the diagnosis, the controls were distributed according to several categories of ICD10. It was observed a higher frequency of controls with diseases of the digestive system (21.6%), followed by the category of injuries and external cause poisonings (16.4%). Neoplasms represented less than 10% of controls.

In the case group, 147 individuals were male

(61.2%) and the age ranged from 30 to 93 years, with an average of 63 years old. In the control group, 304 individuals were male (60.9%) and the age ranged from 23 to 96 years, with an average of 58.3 years old. In all age groups, the number of controls was greater than that of cases.

Regarding the level of education, 94 individuals in the case-group did not attend school or did not complete primary education (39.8%) and 187 (37.7%) in the control group. University education was completed by 12 individuals (5.1%) in the case group and 45 in the control group (9.1%). There was no association of education level with an increased risk of stomach cancer (Table 1).

Most cases (63.8%) reported being current or past smokers. On the other hand, in the control group, the majority (54.9%) reported never having smoked (Table 2). An increased risk of gastric cancer was found to be more than double for both current and former smokers. All quartiles of consumption analysed were at high risk.

Regarding alcohol consumption, in the control group, less than 30% reported consuming or having consumed, whereas in the case-group, more than half were consumers or former consumers (Table 2). This difference in consumption between the two groups leads to an increased and statistically significant risk for former consumers (OR = 3.81, 95% CI: 2.45-5.91) and current consumers (OR = 2.06, 95% CI: 1.31-3.26). Among the former consumers, 22 cases (68.1%) and 16 controls (74.1%) had stopped drinking more than five years ago. Similarly to smoking, alcohol consumption was associated with increased risk in all quartiles of consumption analysed.

For analysis of the interaction between smoking and alcohol consumption, both current and former consumers were grouped in the same category (Table 2). The risk of gastric cancer in smokers who were only smokers was OR = 1.66; 95% CI: 1.06-2.60) and only alcohol consumers was OR = 1.70; 95% CI: 0.87-3.32). Simultaneous consumption of tobacco and alcohol was associated with high risk of gastric cancer (OR = 12.74, 95% CI: 7.95-20.42).

Regarding the location of the lesion in the stomach, it was considered distal in 168 cases (70%), proximal in 41 cases (17.1%) and the remaining 31 cases (12.9%) were classified as others. Both locations showed an

TABLE 1. ODDS RATIOS OF STOMACH CANCER ACCORDING TO LEVEL OF EDUCATION

EDUCATION1	CASES		CONTROLS		OR (95% CI)2
	n= 236	%	n= 496	%	
Did not attend or did not complete primary education	94	39.8	187	37.7	Reference group
Primary education completed	72	30.5	134	27	1.05 (0.71 – 1.54)
Secondary education completed or incomplete	58	24.6	130	26	1.06 (0.70 – 1.61)
University	12	5.1	45	9	0.62 (0.31 – 1.25)
					Plinear trend=0.54

1 Data ignored in four cases and three controls. 2 Adjusted by gender, age, smoking habits and alcohol consumption

TABLE 2. ODDS RATIOS OF STOMACH CANCER ACCORDING TO SMOKING HABITS AND ALCOHOL CONSUMPTION – INTERACTION ANALYSIS

SMOKING HABITS	CASES		CONTROLS		OR (95% CI)1
	n= 240	%	n= 499	%	
Never	87	36.2	274	54.9	Reference group
Former smoker	93	38.8	141	28.2	2.25 (1.53 – 3.31)
Smoker	60	25	84	16.8	2.67 (1.72 – 4.13)
Pack-years					
Up to 10	43	17.9	63	12.6	2.53 (1.57 – 4.06)
>10 to 21.5	27	11.2	51	10.2	1.88 (1.08 – 3.25)
>21,5 to 38	35	14.6	55	11	2.33 (1.38 – 3.92)
>38	47	19.6	56	11.2	2.81 (1.71 – 4.60)
					Plinear trend<0.001
ALCOHOL CONSUMPTION					
Never	121	50.4	350	70.1	Reference group
Former consumer	69	28.8	62	12.4	3.81 (2.45 – 5.91)
Consumer	50	20.8	87	17.4	2.06 (1.31 – 3.26)
Grams-year3					
Up to 127.6	40	16.7	37	7.4	3.74 (2.21 – 6.33)
>127.6 to 520.75	20	8.3	36	7.2	1.99 (1.06 – 3.73)
>520.75 to 1,540.5	30	12.5	37	7.4	2.74 (1.56 – 4.82)
>1,540.5	25	10.4	36	7.2	2.41 (1.33 – 4.34)
					Plinear trend<0.001
INTERACTION					
None	70	29.2	231	46.3	Reference group
Tobacco only	51	21.2	119	23.8	1.66 (1.06 – 2.60)
Alcohol only	17	7.1	43	8.6	1.70 (0.87 – 3.32)
Tobacco and alcohol	102	42.5	106	21.2	12.74 (7.95 – 20.42)
					χ²=1.51 (1.05 – 1.96)

1 Adjusted by gender, age, smoking habits and alcohol consumption. 2 There is no dose information for one case. 3 There is no dose information for four cases and three controls

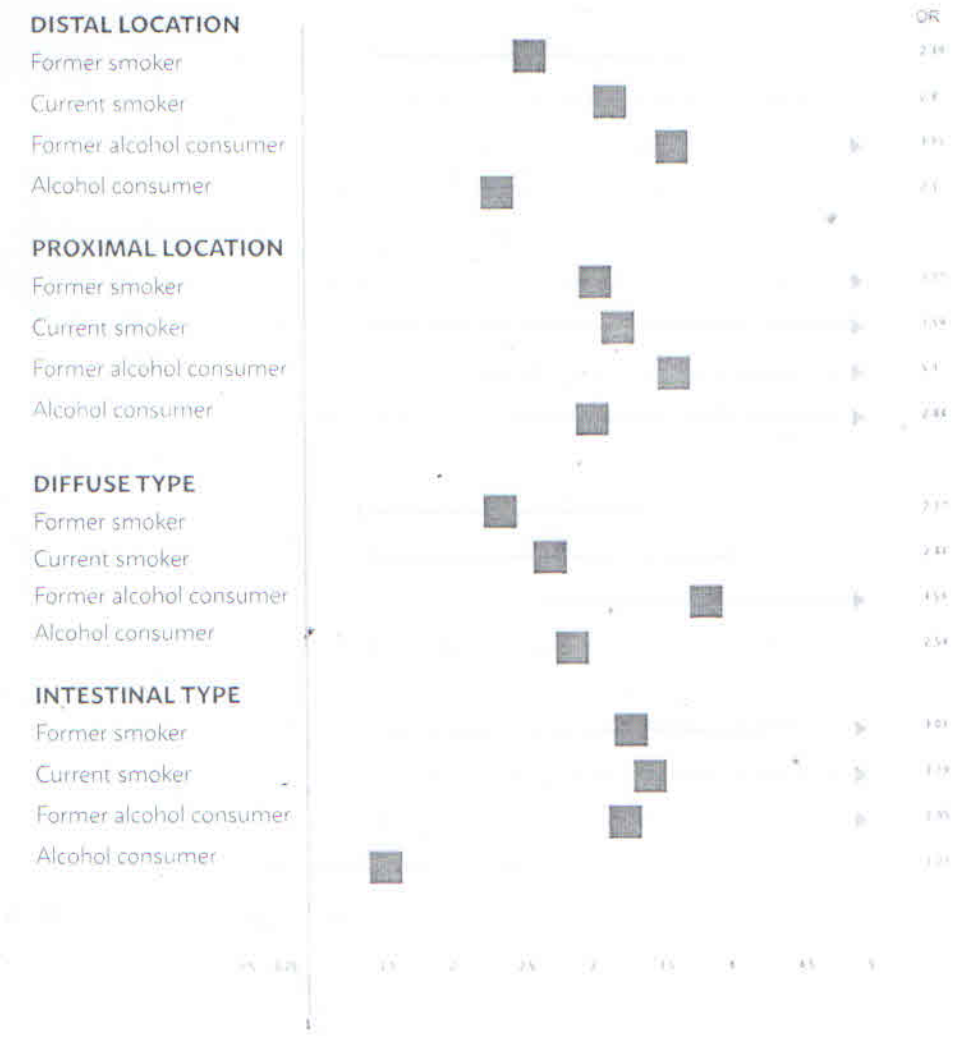
association of smoking and alcohol consumption, both current and previous, with an increased risk of gastric cancer (Figure 2). The association was more evident in proximal tumours in former alcohol consumers (OR = 5.40, 95% CI: 2.29-12.71) and current smokers (OR = 3.59, 95% CI: 1.49-8.67).

The most common histological type of Laurén was diffuse, which occurred in 152 cases (63.3%), while the intestinal type occurred in 83 cases (34.6%). Five cases did not fit into either of the two main histological types. The diffuse type was associated with current and previous smoking (Figure 2). Alcohol consumption was also associated in diffuse tumours, mainly in previous consumers (OR = 4.54, 95% CI: 2.73-7.55). The analysis of intestinal tumours also showed an association with smoking, especially in current smokers (OR = 3.79, 95% CI: 1.91-7.52), but only with former alcohol consumers (OR = 2.94; 95% CI: 1.55-5.57).

DISCUSSION

Several genetic, epigenetic and environmental factors interact in the gastric carcinogenesis. The vast majority appears sporadically, with no evidence of hereditary components. Less than 15% of the cases present clustering in families, but no whitout association with germ mutations, and less than 3% of the cases are part of hereditary cancer syndromes[12]. Tobacco smoke is probably the most important known carcinogen, being associated with the development of tumours in more than 20 different locations. There are more than 5,300 components in tobacco smoke, and more than 60 have already been shown to have a carcinogenic effect on rodents. In addition, for at least a dozen of them there is already sufficient evidence of their ability to carcinogenesis in humans. In the present study, smoking was associated with the risk of gastric cancer for both former smokers and current smok-

FIGURE 2. FOREST PLOT FOR SUBGROUP ANALYSIS ACCORDING TO LOCATION AND HISTOLOGICAL TYPE



ers. In all analyses, current smokers presented a higher risk than former smokers. A recent systematic review[13], which included 32 studies in the analysis, also showed a 60% increase in risk in smokers compared to people who had never smoked.

All quartiles of tobacco consumption analysed were at a higher risk than non-smokers. Individuals classified in the quartile of more intense consumption, greater than 38 pack-years, presented higher OR. However, the intermediate quartiles presented discordant values. The progressive increase in risk with increasing smoking, quantified in pack-years, was not clear. The presence of a dose-effect relationship indicates a biological gradient between exposure and disease, being an important criterion in establishing a cause and effect relationship. Evidence of dose-effect relationship of smoking is contradictory both in relation to intensity and duration of smoking.

Alcohol consumption was also associated with risk of developing gastric cancer. Attention was drawn to the low frequency of individuals who reported being current consumers. In the case-group, 20.8% were current consumers and, among the controls, this value was 17.4%. According to a survey published by the World Health Organization[14], data related to Brazil showed that 20.4% were former consumers and 57.7% were current alcohol consumers. Often individuals may underestimate their consumption while conducting interviews. This can occur simply because of the difficulty in remembering the consumption, remembering that the average age of the case-group was 63 years, or simply due to the belief that the consumption is not relevant. It is very common during a medical consultation the patient says that they do not consume or consume alcohol in small amount and be corrected in detail by a relative. The general knowledge of the population that alcohol is a risk factor for the development of cancer and other diseases is not as widespread as smoking, leading to a lower consumption report[15]. Many patients are also afraid to report current alcohol use during hospital stay, believing that this may disrupt or cancel their treatment. In another hospital case-control study conducted in Brazil[16], it was verified that 31% of the cases and 13% of controls were current alcohol consumers. These values are more similar to those found.

Another interesting result was the fact that former consumers present a higher risk than current consumers. It has been reported that discontinuation of alcohol consumption increases the risk of developing oesophageal cancer in the first two years after cessation of consumption, and then it decreases progressively[17]. With regard to gastric cancer, other studies have also reported an increased risk of development in former consumers compared to current consumers[18]. A possible explanation for the phenomenon of increased risk in the first two years after the suspension is the sick quitter behaviour. In this case, individuals stop drinking alcohol when they have the initial symptoms of the disease. As the diagnosis can still take some time to be done, individuals will report being former consumers at the time of diagnosis. However, in the present study, 68.1% of the cases and 74.1% of the controls classified as former consumers had stopped consumption more than five years ago. Another possible explanation is the inclusion of individuals who were heavy consumers in the former consumer group. Because they showed a significant decrease in consumption, this group ends up reporting being a former consumer even if they still consume alcohol in small quantity.

Several hypotheses have been formulated to explain the possible effects of alcoholic beverages on the genesis of gastric cancer[6]. Alcohol may act as a contributing factor causing chronic irritation of the gastric mucosa or promoting the appearance of intragastric nitrogen compounds by reducing gastric pH. Another possibility is that alcohol is not directly responsible, but other components of alcoholic beverages. Some alcoholic beverages, especially beer, contain nitrosamines, a known carcinogen[18]. Tramacere et al.[19] published in 2012 a meta-analysis encompassing 44 case-control studies and 15 cohort studies. This study found association with gastric cancer only in consumers classified as heavy. In addition, tumours located in cardia and Asian populations presented even lower relative risk.

When two or more independent variables are involved in the outcome of a study, it may be necessary to analyse not only the main effect of each variable, considering that the effect of one variable may depend on the level of exposure to the other. When the combined effect of two variables is greater or less than the simple "sum of the parts", it is possible that an interaction has occurred. The interaction of smoking and alcohol consumption has been reported mainly in cases of head and neck tumors[20].

In the present study, the analysis of the interaction between alcohol consumption and smoking was positive. The biological explanation for this interaction considers that ethanol present in alcoholic beverages may act as a solvent, facilitating the penetration and action of other carcinogens present in the beverage itself or in cigarette smoke.

It is believed that the mechanism of carcinogenesis relating smoking to esophagogastric tumours may involve the direct action of tobacco smoke on the esophagogastric epithelium or due to the ingestion of bronchial mucous secretions containing tobacco particles. Therefore, a greater risk magnitude is assumed in smokers for tumours of the distal and cardiac oesophagus in relation to the gastric distal tumors[21]. However, the overall increase in the incidence of proximal gastric lesions is occurring even with the decrease in the prevalence of smoking. This suggests the need for the interaction of other factors such as gastroesophageal reflux, alcohol consumption, *H. pylori* infection and obesity for the development of proximal gastric tumors[22]. In fact, we found the association of smoking and alcohol consumption stronger in tumours of proximal location, but distal tumours also showed association.

Gastric tumours of the intestinal type are associated with the presence of chronic inflammation of the gastric mucosa, which causes chronic atrophic gastritis and intestinal metaplasia. *H. pylori* is the causal factor most associated with the onset of this inflammation. However, other environmental factors may also contribute[23]. Taking this into account, the intestinal type is expected to be more related to smoking and alcohol consumption. This assumption was not confirmed in our cases, since both types had a positive association. The major prevalence of diffuse tumours, over 63%, and the role of *H. pylori* as a confounding variable may have impaired the analysis of this association.

Low socioeconomic status is associated with a higher incidence and mortality of numerous diseases, including gastric cancer[24]. Level of education is one of the ways to classify the socioeconomic conditions of a population[25]. We did not find association of low level of education with risk of gastric cancer. The study design, with the use of hospital controls that end up presenting more similar socioeconomic characteristics, may have influenced the result found. Another factor to be considered is the high prevalence of *H. pylori* infection in the entire Brazilian population. As in Brazil, and in other developing countries, the infection is not restricted only to those with the most disadvantaged socioeconomic conditions, its role as a causal agent ends up appearing in all socioeconomic strata.

In case-control studies, the selection of participants is a major challenge to minimize the occurrence of any bias. In this study, all individuals in the case-control group were recruited in the same hospital, which is an important reference center. This increases the likelihood of groups being comparable in terms of willingness to participate in the study, willingness to provide information and to answer the questionnaire, as well as their own knowledge of the history of smoking and alcohol consumption. Thus, the occurrence of classification and recall bias may have occurred in a similar way in both groups, leading to a random or non-differential bias. The applied questionnaire was developed in order to facilitate the recall of information and to standardize the quantification of consumption.

In the study of gastric adenocarcinomas, *H. pylori* infection, low fruit and vegetable intake and high salt intake are confounding factors. The prevalence of *H. pylori* infection in the Brazilian population is high, and its research in the control group and characterization of the bacterial strain would imply the performance of other diagnostic tests. The characterization of feeding patterns is difficult and complex and should be evaluated by specific questionnaires[26]. In addition, many patients with gastric tumours alter their eating habits due to the symptoms of the disease. In case-control studies, this fact leads to an important recall bias and incorrect cause associations between diet and tumour development by the participants.

The present study has the merit of having the largest sample in Brazil, with a number of participants comparable to other studies conducted in the world[16,27,28]. The data were collected prospectively as part of a large project related to the study of carcinogenesis that resulted in other studies. Our results are consistent with those found in other studies with consistent values and trends. Discordant values occurred in analyses with subgroups composed of few individuals. Smoking was associated with a higher risk of developing gastric cancer, especially in the proximal location, with current consumption and higher dose. Alcohol consump-

tion also presented higher risk, with the highlight that the risk was higher in former consumers than in current consumers.

The recent classification of gastric adenocarcinomas, based on the molecular profile[29], opened a new possibility for the evaluation of risk factors, such as smoking and alcohol consumption in gastric carcinogenesis. There are already examples of tobacco-related molecular differences that may influence tumour biology, triggering or potentiating carcinogenesis and leading to a change in prognosis[30]. Doubts as to whether this result suggests that smoking-related tumours represent distinct molecular phenotype or whether the changes resulting from smoking in the tumour environment cause such poor prognosis remain open to discussion.

CONCLUSIONS

This study confirmed smoking and alcohol consumption as risk factors for the development of gastric cancer, with no predilection for histological type and location of the lesion. The simultaneous consumption of both potentiates the risk. Level of education has not been shown to be a risk factor.

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PALAVRAS-CHAVE: *Neoplasias gástricas. Fatores de risco. Estudos de casos e controles.*

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