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Risk factors associated to diffuse gastric cancer and intestinal histological patterns in an adult population from Western Mexico

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Abstract

Introduction: *Gastric cancer (GC) is the third leading cause of cancer death worldwide, and is divided histologically in diffuse gastric cancer (DGC) and intestinal gastric cancer (IGC). Multiple risk factors have been associated with GC in different populations. The objective was to analyze the risk factors associated to DGC and IGC in a population from the western region of Mexico.* **Material and methods:** *The DGC (n = 27) and IGC (n = 26) cases, each matched by age and sex with a control group, were analyzed. Diet and lifestyle data were obtained by a questionnaire. Statistical analysis was performed with the software SPSSv18. The association of risk was calculated in odds ratio (OR); a value of p < 0.05 was considered significant.* **Results:** *In the DGC group, the factors with significant OR values were: consumption of pork OR: 3.4 (1.11-10.4; p = 0.032), smoking OR: 4.7 (1.5-15.0; p =0.007), green vegetables OR: 0.16 (0.03-0.83; p =0.029) and fruit OR: 0.28 (0.08-0.88; p = 0.029). In the IGC group, the consumption of canned sardines was a significant risk factor OR: 4.07 (1.25-13.24; p = 0.019).* **Conclusions.** *This work is the first to analyze the risk factors associated with GC in a population from western Mexico.*

KEY WORDS: *Gastric cancer. Smoking. Diet and cancer. Risk factors for cancer.*

Introduction

Gastric cancer (GC) is the fifth most common malignancy in the entire world, with around 951,600 cases reported in 2012 and, in addition, it is the most lethal type of cancer in the world, with 723,000 annual deaths[1]; in Mexico, it has an incidence of 6.8 cases per 100,000 population[1]. GC is generally diagnosed at very advanced stages, hence its low survival rate: only 4.7% of cases reaches 5 years after diagnosis[1]. GC diagnosis requires tissue histopathological assessment (gastric biopsy).

Up to 95% of GC cases correspond to adenocarcinomas, while 5% are lymphomas, carcinoid tumors or leiomyosarcomas, among others. Multiple classifications have been proposed to describe GC, either macroscopically (Borman's classification) or microscopically. One of the most popular is Lauren's classification, which divides gastric adenocarcinoma in two major histological types: intestinal and diffuse. This system describes tumors by microscopic appearance and growth patterns[2].

Diffuse-type gastric adenocarcinoma has non-cohesive cancer cells that diffusely invade the stomach

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stroma, and rather frequently shows stomach wall deep infiltration with little or no gland formation. Diffuse tumors tend to exhibit desmoplasia and associated inflammation and underlying mucosa relative preservation; they can even be described with presence of signet ring cells[3]; they possess an increased incidence among relatives and tend to affect young populations, in addition to being associated with poor prognosis[4]. In comparison, intestinal-type gastric adenocarcinoma is more related to environmental-type influences for its development, it is characterized by the formation of glands resembling those of the intestinal mucosa; gland formation varies in well-differentiated tumors and even in those poorly differentiated, and growth tends to be more expansive than infiltrating[3,4].

Although the exact causes of GC development are unknown, multiple associated risk factors have been reported, including age older than 60 years, male gender, A blood type, smoking, *Helicobacter pylori* or Epstein-Barr virus infection and diets with high content of red and smoked meat, processed foods or foods with preservatives, salt, nitrates and nitrosamines high content, as well as fruit and green vegetables low ingestion[5-10]. With regard to the diet, it has been estimated to participate in the development of cancer in up to 30% of cases in industrialized countries, and in up to 20% in developing countries[11]. Risk factors for GC can vary according to the study population. For example, several works have been reported in the Mexican population, especially conducted in central[5,12-25], eastern[16] and southeastern[17] areas of the country, and some of them have highlighted the diversity in the consumption of different groups of foods according to the studied geographic region[17].

This work analyzes which the risk factors associated with intestinal and diffuse histological type patterns gastric adenocarcinoma are in an adult population of Mexico's western region.

Methods

Using a case-control design, two groups of cases were studied: diffuse gastric cancer (DGC, n = 27 patients) and intestinal-type gastric cancer (IGC, n = 26). Each group was matched 1:1 by age and gender with subjects without GC (control group). Both the cases and the controls were recruited in the department of endoscopy and general surgery of the Medical Specialty Hospital of the National Medical Center of the West, IMSS, in the city of Guadalajara, Jal., Mexico, over the years 2011 through 2014. Eligibility criteria to participate in the project were being an adult (> 18 years of age) and of Mexican nationality. Assignation of cases (DGC and IGC) and controls was based on the result provided by the pathology department. Subjects with atrophic gastritis or intestinal metaplasia, with personal history of GC or other solid or hematologic neoplasms, seropositive for hepatitis B and C viruses, seropositive for human immunodeficiency virus or with evidence of diseases known to be highly associated with the risk for cancer were not included as controls. All patients were informed on the study, and those agreeing to participate signed a consent letter and answered a questionnaire on personal data (age, gender, blood type, family and hereditary history, weight and height), alimentary habits and lifestyle.

Data on alimentary habits included the frequency of red meat (beef and pork), processed meat (smoked, marinated and salted meat, pork rind and *chorizo*), canned fish, tuna and sardines, sausages and ham, bacon, dairy products, seafood, hypercaloric foods (soft drinks, candy, chocolate), potato chips, chili pepper, coffee, citrus fruits (lime, lemon, orange, tangerine) other fruits, green vegetables (broccoli, watercress, spinach, purslane, etc.), and other vegetables consumption. Consumption frequencies were obtained with the following answer options: 1, never; 2, once monthly (x m); 3, two to three times x m; 4, once weekly (x w); 5, two to four times x w; 6, five to six times x w; 7, once daily (x d); 8, two to four times x d; and 9, four to six times x d.

In addition, other data, such as the habit of adding extra salt to food, tobacco consumption (> 90 cigarettes smoked in life), regular consumption of alcohol (equivalent to 12-14 g of ethanol), exposure to toxic substances or radiation (industrial solvents, fertilizers, pesticides, coal, tar, gasoline, rubber), and use of drugs classified by pharmacological categories regularly used for at least 1 year.

The statistical analysis was performed using the SPSSv18 software. Observed continuous and independent variables were analyzed with Student's t-test, and binary or categorical variables of the independent type were analyzed with the chi-square test and Fisher's exact test. The results were expressed as means and standard deviations (SD), and the association analysis was expressed as odds ratios (OR) with 95% confidence intervals (CI).

Results

Mean age in the DGC cases was 61.3 years (± 9.4 SD) and in their healthy controls, it was 62.4 years (± 10.08 SD)

Table 1. Frequencies of analyzed variables in western Mexico subjects with DGC and IGC and their respective controls

	DGC (n = 27) %	Controls %	IGC (n = 26) %	Controls %
Beef (≥ 2 x wk)	70.4	51.9	61.5	57.7
Pork meat (≥ 1 x wk)	66.7*	37.0*	52.0	46.2
Processed meat (≥ 1 x mo)	29.6	29.6	42.3	38.4
Fish (≥ 2 x wk)	22.2	29.6	15.4	38.5
Canned tuna (≥ 1 x wk)	22.2	25.9	19.2	30.8
Canned sardines (≥ 1 x mo)	33.3	14.8	60.0*	26.9*
Sausages and ham (≥ 1 x wk)	29.6	51.9	34.6	57.7
Bacon (≥ 1 x wk)	48.1	40.7	52.0	38.5
Dairy products (≥ 2 x wk)	69.2	76.0	75.0	66.7
Shellfish (≥ 2 x mo)	40.7	25.9	80.8	88.5
Hypercaloric products (≥ 1 x wk)	66.6	70.4	69.2	80.8
Potato chips (≥ 1 x wk)	25.9	22.2	30.8	30.8
Chili pepper (yes/no)	88.9	74.1	84.6	80.8
Coffee (yes/no)	85.2	70.4	76.9	76.9
Citrus fruits (≥ 1 x d)	38.4	37.0	23.1	38.5
Other fruits (≥ 1 x d)	25.9*	55.6*	38.5	46.1
Green vegetables (≥ 1 x d)	7.4*	33.3*	8.0	26.9
Add salt to food (yes/no)	36.0	38.5	40.0	36.0
Smoking (yes/no)	70.4*	33.3*	44.0	50.0
Alcoholism (yes/no)	59.3	40.7	46.2	50.0
Exposure to toxic substances (yes/no)	37.0	18.5	36.0	19.2
Drugs, omeprazole (yes/no)	46.7*	78.3*	41.7	73.7

*Significant differences: $p < 0.05$.

(p = NS). Gender distribution in these groups was 61.5% of men and 38.5% of women. In the group of IGC cases, mean age was 60.2 years (± 12.68 SD) and, in their healthy controls, it was 58.8 years (± 12.86 SD) (p = NS). The distribution by gender was 51.8% men and 48.2% women. The A blood type was present in 57.1% of DGC cases, whereas in its control group it was present in 33.3% (p = NS); in turn, the IGC group had 29.2% of subjects with blood type A, whereas its control group had 34.6% (p = NS). As for tumor history, it was observed in 51.9% of DGC cases and 55.6% of their controls; in the IGC group, it was observed in 46.2% and in 61.5% of its controls. Overweight or obesity (body mass index > 25) was observed in 19% of patients with DGC and in 70% of the control group; in patients with IGC, it was observed in 39% and in 77% in the control group ($p < 0.05$).

Table 1 shows the consumption frequencies observed for each group of study subjects. The GC risk association analysis performed in the DGC group showed significant results for the risk to develop GC with pork meat consumption (OR: 3.4; 95% CI: 1.11-10.4; p = 0.032) and smoking (OR: 4.7; 95% CI: 1.50-15.00; p = 0.007), whereas protection against GC was observed with the consumption fruit (OR: 0.28; 95% CI: 0.08-0.88; p = 0.029) and the consumption of green vegetables (OR: 0.16; 95% CI: 0.03-0.83; p = 0.029) (Table 1). Risk analysis in the IGC group showed significant results for increased risk with the consumption of canned sardines (OR: 4.07; 95% CI: 1.25-13.24; p = 0.019) (Table 1).

Discussion

The results observed in this study show that diet and some environmental factors play an important role in the development of GC in our population. The risk factors for GC observed in the population of western Mexico included frequent pork meat (> 1 time per week; OR: 3.4) and canned sardines consumption (> 1 time a month: OR: 4.07), and smoking (OR: 4.7).

Pork meat consumption > 1 time a week in the population of western Mexico was higher in diffuse GC cases than in controls (66.7% vs. 37%: p > 0.05). In studies conducted in different human populations it has been established that, when meat is cooked at high temperatures, by mediation of the Maillard reaction, heterocyclic amines are produced that interact with

chromatin and can covalently or irreversibly bind to DNA and cause for mutations or errors to be generated by copying the DNA in key genes that control the cell cycle[9]. Salted pork meat consumption has been even reported to be associated with gastric mucosa pathological changes[18]. People of northeastern China who consumed this type of meat for 10 years had gastric mucosa lesions, such as necrosis and erosion; consumption for between 10 and 20 years caused hyperplasia and dysplasia, and those subjects who consumed salted pork meat for 20 to 30 years showed different degrees of dysplasia and malignancy[18]. In Mexico, in the population of the central region of the country, an increased risk for the development of GC has been reported for the consumption of red meat[5]: beef > 4 times per week (OR: 2.1; 95% CI: 0.8-5.7) or liver > 2 times per week (OR: 15; 95% CI: 0.8-2.8), which are discordant results with those observed by us, since they found no associations with pork or poultry meat (p = NS)[5].

With regard to the consumption of canned sardines (> 1 time a month), it was higher in the IGC group than in controls (60% vs. 26.9%; OR: 4.07; 95% CI: 1.25-13.24; p = 0.019). To our knowledge, there are no reports in the literature on canned sardines consumption and the risk for cancer; however, a study conducted in Brazilian population reported that low consumption of canned foods confers protection against intestinal metaplasia (OR: 0.26: 95% CI: 0.118-0.575)[19]. Intestinal metaplasia is a gastric lesion associated with increased risk for GC, mainly with IGC, and the authors of this work considered the consumption of canned foods as being with the following frequencies: 1-2 times per week, < 1 time a month or never, whereas high consumption was 3-4 times per week. With these authors' data[19], we carried out an association analysis (OR), with canned food consumption higher than 3-4 times per week being regarded as a risk factor for metaplasia, and we found an OR of 3.84 (95% CI: 1.71-8.6; p = 0.001), which might be related to data observed for GC in our population with this type of canned food, and having more studies available confirming this association would therefore be highly convenient.

Smoking is another well known risk factor for the development of GC and other types of cancer (especially lung cancer), owing to the large amount of toxic substances that are produced during tobacco combustion, which can cause cellular changes. Risk increase is up to 3-fold higher in smokers than in non-smokers[9,20]; in addition, gastric and peptic ulcers are more common, as well as gastric mucosa chronic deterioration[20,21]. In our study, we observed that 70.4% of patients with DGC were smokers or former smokers (> 90 cigarettes smoked in life), as compared with 33.3% of the control group (OR: 4.75; 95% CI: 1.5-15.0; p = 0.007), which is similar to reports in the literature[9,20]. Of note, one fourth of the patients with DGC (25.9%) consumed more than one pack of cigarettes a day (approximately 20), in comparison with 14.8% in the control group (p = NS). Our results are consistent with those reported in a Colombian population (OR: 5.6; 95% CI: 1.8-17.6; p = 0.002) for the consumption of 40 cigarettes or more per year[22].

On the other hand, other factors related to protection against GC were observed; for example, regular consumption of fruit (OR: 0.28) and green vegetables (OR: 0.16). The ideal consumption of fruits and vegetables is known to be 5 daily portions[11], but our results show that only 25.9% of patients with DGC consume more than one fruit portion per day, in comparison with 55.5% of the control group (OR: 0.28; 95% CI: 0.08-0.88; p = 0.029). These data are similar to those previously reported in a meta-analysis, the authors of which found evidence in 26 studies (including those in Mexican population) that regular consumption of fruit (100 g a day) confers protection against GC (OR: 0.67; 95% CI: 0.59-0.76)[23]. Furthermore, our results are similar to others recently reported in two Mexican populations: in Mexico City[15] and in Veracruz[16]. The first reports that an alimentary pattern mainly based on fruit, vegetables and white meat regular consumption confers protection against GC, with an OR of 0.43 (95% CI: 0.24-0.77; p = 0.010)[15], and the second reports and OR of 0.45 (95% CI: 0.23-0.86; p = 0.015) for the consumption of > 7 fruit portions per week[16].

With regard to the consumption of green vegetables (> 1/day) observed in our study population, consumption was lower in DGC cases (7.4%) than in controls (33.3%) with an OR of 0.16 (95% CI: 0.03-0.83; p = 0.029). These results on green vegetables consumption protecting effect against GC are similar to those previously reported in a meta-analysis[23] (OR: 0.65; 95% CI: 0.51-0.85) for the consumption of 100 g/day of non-starchy vegetables (green or yellow), the analysis of which was based on 11 case-control-type studies, including Mexican populations.

In addition, the results observed for the population of western Mexico are similar to those reported by Verdalet et al.[16] in a population of the east of the country, where regular consumption of vegetables (> 7 portions per week) showed protection against GC (OR: 0.43; 95% CI: 0.22-0.88; p = 0.011)[16].

With these results, we can conclude that patients with GC ingest less vitamins and antioxidants originating in the diet (fruit and vegetables) and, in consequence, they receive less protecting effect, since these products also contain fiber, and together they help to decrease free radical noxious effects and to better intestinal transit, thus avoiding accumulation of bacteria that can cause inflammation and allowing for better nutrient absorption[9].

It is important to point out that differences were observed with regard to omeprazole regular consumption (> 1 year) between the DGC and control groups (46.7% vs. 78.2%). Risk calculation showed an OR of 0.24, but statistical significance was not sufficient (95% CI: 0.05-1.00; p = 0.0506). Some studies have suggested a protective effect of proton pump inhibitors against gastrointestinal disorders, such as a decrease in the risk for the development of dysplasia and adenocarcinoma in patients with Barret esophagus[24]. In 1920 patients treated for more than 3 years with proton pump inhibitors, no case of GC was observed (the review included 16 trials)[25], and neither was an association observed of proton pump inhibitors with gastric premalignant lesions, such as atrophy or enterochromaffin cell hyperplasia[26]. Our results suggest that omeprazole could be a protective factor against GC in the population of western Mexico; however, further studies are required to confirm this observation, since multiple variables could be intervening, e.g., the dose used on each subject and the age at which omeprazole use was started (since the participants of this study were older than 60 years), which might generate differences in the results. One limitation of this study is the analyzed sample size.

In our study, DGC cases mean age was 61.3 years, and in the group of IGC cases, mean age was 60.2 years; this is consistent with previous reports, which refer that GC diagnosis occurs in advanced-age subjects (older than 60 years), probably owing to higher accumulation of mutations in genes in charge of cell maintenance and repair[27].

With regard to gender, our results are consistent with findings reported in the literature (ratio of affected men per each woman, 2:1)[27], but only for the group of DGC cases (1.6:1 ratio) and not for IGC (1.1:1).

On the other hand, in patients with DGC and IGC, there was a lower number observed of subjects with overweight or obesity (19% and 39%, respectively) than in their control groups (70% and 77%, respectively). These results show that, in both GC groups, most patients experienced weight loss, which is attributable to disease's own manifestations, while in the control groups, most patients (> 70%) had overweight or obesity, which is similar to reports for the Mexican general population between 30 and 60 years of age (70%)[28].

Higher frequency of blood type A was observed in patients with DGC (57.1%) than in the control group (33.3%), but the difference was not statistically significant (p = NS). On the other hand, in the IGC cases, frequencies were also similar (29.2% vs. 34.6%, respectively; p = NS). Higher proportions of blood type A have been reported in patients with GC; however, the exact causes of this finding are not known, although Lewis b antigen has been reported to act as a receptor for adherence factor BabA possessed by *H. pylori*, which might activate the transference of other virulence factors of the bacterium, such as CagA and VacA, to produce direct damage to the gastric epithelium through inflammatory or autoimmune reactions[29]. In addition, *H. pylori* strains of different parts of the world have the ability to adhere to Lewis b antigens of co-carriers of both A-Lewis b (ALeb) and O-Lewis B (OLeb) blood types[30].

One of the limitations of our study was not having *H. pylori* infection determination in participants, since this biological factor might be acting together with other biological or environmental factors for the development of GC. In addition, bias sources of this study include the recording of previous exposure, which is subject to imprecision in the interrogatory, depending on the cultural and educational level of participants.

Finally, there are different risk factors involved in the development of GC, out of which some may be preventable and others not. Efforts should be joined in order to prevent inasmuch as possible the development of this disease, by promoting healthy habits and trying to avoid cancer predisposing factors. In addition, it would be highly convenient to have adequate diagnostic methods to opportunely detect the disease before it becomes clinically apparent, in order to improve the prognosis and patient survival.

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