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Risk and protective factors for gastric metaplasia and cancer: a hospital-based case-control study in Ecuador

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Abstract

Introduction: **worldwide, stomach cancer is the fifth most frequent cancer, with 952 000 new cases diagnosed in 2012. Ecuador currently holds the 15th place of countries with the highest incidence of stomach cancer for both sexes.**

Objectives: **the objective of this study was to evaluate risk and protective factors for gastric cancer/metaplasia.**

Methods: **a hospital-based case-control study was conducted in Quito, Ecuador. Cases were defined as patients with histological confirmation of gastric cancer (N=60) or incomplete gastric metaplasia (N=53). Controls were defined as patients free of gastric cancer or premalignant lesions (N=144). All participants were personally interviewed using a structured questionnaire to collect data about dietary habits, lifestyle and medical history.**

Results: **risk factors significantly associated to the presence of gastric cancer/metaplasia were the consumption of reheated foods at least 3 times per week (AOR: 4.57; CI: 2.2–9.5) and adding salt to more than 50% of foods (AOR: 1.32; CI: 1.04–1.67). Protective factors for gastric cancer/metaplasia were the use of non-steroidal anti-inflammatory drugs (AOR: 0.39; CI 0.19–0.83), age less than 58 years old (AOR: 0.38; CI: 0.18–0.79) and have received treatment for *H. Pylori* infection (AOR: 0.33; CI: 0.16–0.71).**

Conclusions: **this study reports for the first time, the risk and protective factors associated with gastric cancer and metaplasia in Ecuador.**

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Key words: *Gastric cancer. Metaplasia. Risk factors. Protective factors. Reheated foods. H. Pylori, salt. Non-steroidal anti-inflammatories.*

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FACTORES DE RIESGO Y PROTECCIÓN PARA METAPLASIA Y CÁNCER GÁSTRICO: ESTUDIO DE CASOS Y CONTROLES HOSPITALARIOS EN QUITO-ECUADOR

Resumen

Introducción: **el cáncer de estómago ocupa la quinta posición entre los cánceres más frecuentes en el mundo, con 952.000 casos diagnosticados en el 2012. El Ecuador ocupa el 15º lugar entre los países con la incidencia más alta de cáncer gástrico en ambos sexos.**

Objetivo: **el objetivo del presente estudio fue evaluar los factores de protección y de riesgo para cáncer/metaplasia gástrico.**

Métodos: **se realizó un estudio hospitalario de casos y controles en la ciudad de Quito, Ecuador. Se definieron como casos a los pacientes con diagnóstico histológico confirmado de cáncer gástrico (N=60) o con metaplasia gástrica incompleta (N=53). Se definieron como controles a los pacientes sin cáncer gástrico o lesiones premalignas (N=144). A todos los pacientes se les realizó una entrevista personalizada utilizando un cuestionario estructurado para recoger datos sobre hábitos dietéticos, estilo de vida e historia clínica.**

Resultados: **los factores de riesgo asociados significativamente con el diagnóstico de cáncer gástrico/metaplasia fueron el consumo de alimentos recalentados al menos tres veces a la semana, (AOR: 4,57; CI: 2,2–9,5) y añadir sal a más del 50% de las comidas (AOR: 1,32; CI: 1,04–1,67). Los factores de protección asociados significativamente para no desarrollar cáncer/metaplasia gástrico fueron el uso de antiinflamatorios no esteroideos (AOR: 0,39; CI 0,19–0,83), edad menor a 58 años (AOR: 0,38; CI: 0,18–0,79) y haber recibido tratamiento para la infección por *H. Pylori* (AOR: 0,33; CI: 0,16–0,71).**

Conclusiones: **este estudio reporta por primera vez los factores de riesgo y de protección asociados con el cáncer/metaplasia gástrico en Ecuador.**

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Palabras clave: *Cáncer gástrico. Metaplasia. Factores de riesgo. Factores de protección. Comida recalentada. H. Pylori, sal. Antiinflamatorios no esteroideos.*

Introduction

Stomach cancer is the fifth most common malignancy, and is the third leading cause of mortality for both sexes worldwide. Although the incidence of gastric cancer has decreased substantially in developed countries, more than 70% of actual cases occur in developing countries[1]. Ecuador currently holds the 15th place of countries with the highest incidence of stomach cancer for both sexes[1].

Given the significant differences in geographic, socioeconomic and cultural distributions of stomach cancer, several studies have explored the relationship between lifestyle and primary gastric cancer[2]. Substantial evidence for the development of gastric adenocarcinoma comes from case-control and cohort studies that have found an interaction between host factors such as blood group A[3], familial predisposition[4], genetic polymorphisms[5], gastric ulcers[6] and pernicious anemia[7] with environmental factors including consumption of salt and salt-preserved foods[8], exposure to N-nitroso compounds[9], excess body weight[10], smoking[11], alcohol[12], history of gastric surgery[13], occupational exposures and infections with *Helicobacter Pylori*[14] and Epstein-Barr virus[15].

A recent National Health and Nutrition Survey (ENSANUT-ECU)[16] revealed that many of the identified risk factors for the development of gastric adenocarcinoma are present in the Ecuadorian population. Data indicate that 62.8% of Ecuadorian adults are either overweight or obese, 31.5% of adults smoke and the average consumption of fruits and vegetables is 183g/day, well below the 400g/day recommended by the World Health Organization (WHO)[17]. Moreover, studies in children in Ecuador have reported a prevalence of infection with *H. Pylori* ranging from 63 to 77%[18]. A combination of these risk factors, in addition to the fact that the average salt consumption in the Americas is between 9-12 grams/day, place the Ecuadorian population at a high risk for developing stomach cancer.

To our knowledge, no studies have explored risk or protective factors for gastric cancer in the Ecuadorian population. Consequently, the objective of this study was to compare exposure to known risks factors for gastric cancer, as well as explore risk factors with insufficient evidence through a case-control study of patients from one of the largest medical centers in Quito, Ecuador.

Materials and Methods

Subject Population

A hospital-based, case-control study was conducted in Ecuador from 2006 to 2008. Cases and Controls were recruited and enrolled consecutively from the Gastroenterology service at one the largest government teaching hospitals in Quito, Ecuador.

Cases were defined as patients with histological confirmation of primary gastric cancer (N = 60) or pre-malignant advanced lesions such as incomplete intestinal metaplasia (N = 53). Consecutive Control subjects (N = 144) were identified as patients free of gastric cancer or premalignant lesions such as atrophy, intestinal metaplasia or severe gastric dysplasia. The same team of hospital pathologists confirmed all Cases and Controls.

Based on preliminary data from patients at the hospital, we estimated a prevalence of consumption of reheated meals of 52% among Controls and 70% among Cases. The significance level was set at 95% ($P < 0.05$) with 80% power and 1:1.2 case-control ratio. The calculations produced a sample size of 116 cases and 139 controls, for a total of 255 subjects. Sample size was calculated using the Fleiss method (OpenEpi Software).

Interview

A trained physician, blinded to the subject's group allocation, personally interviewed all 257 subjects. A 33-item questionnaire was developed considering cultural diversity and consisted of four sections. Section A collected socio-demographic characteristics; Section B collected information on dietary habits, including the average consumption of salt, dairy products, red meat, eggs, fruits, vegetables, oils, fava beans, carbonated drinks, meats that were smoked, grilled, curated or canned, the source of water to prepare meals and consumption of reheated foods; Section C asked about lifestyle including smoking history, use of illegal substances, alcohol consumption, if a refrigerator was available in the house, dental hygiene and hand washing habits; and Section D collected information on medical history such as previous treatment for *H. Pylori* infection, multi-vitamin use, antiparasitic treatment, non-steroidal anti-inflammatory drug (NSAID) use, previous surgeries and family history of gastric cancer. An initial pilot study of 8 patients was conducted to validate the questionnaire for clarity and understanding of the language. These patients were not included in the final analysis of the study.

The protocol was reviewed and approved by the Hospital's Institutional Review Board and written informed consent was obtained from all participants.

Statistical Analysis

Data were analyzed using the SPSS software (version 18.0, SPSS Inc. Chicago, IL). Odd ratios (OR) and 95% confidence intervals (CI) were calculated for all variables. ANOVA was used to compare the

difference between groups for continuous variables. The estimated ORs were adjusted for confounding variables using binary logistic regression.

Results

Socio-demographic characteristics

Histologically confirmed cases were significantly older (62.0 years ± 13.4) than patients in the control group (55.5 years ± 13.1). The proportion of males to females was significantly lower in the control group (1:2.7) than in the cases (1:1). Moreover, it was found that controls (67.6%) had a lower socioeconomic status than cases (54.6%), and there was a significantly higher percentage of mestizo ethnicity among the cases (77.7%) than the control group (62.9%). There were no differences in the level of education between the two groups (Table I).

Risk Factors for the development of gastric cancer/metaplasia in the studied population

Table II shows in descending order the list of identified risk factors associated with gastric cancer/metaplasia. Thus, a bivariate analysis showed that the strongest risk factor for the development of gastric cancer or metaplasia was consumption of reheated foods that were at least 3 days old (OR: 7.7; 95% CI 1.0–172.8). Other risk factor were the addition of salt to more than half of the meals (OR: 3.5; 95% CI: 2.0–6.3); consumption of reheated meals more than 3 times per week (OR: 2.7; 95% CI: 1.6–4.5); re-using of cooking oil to prepare meals (OR: 2.7; 95% CI: 1.6–4.7); consumption of grilled meats at least once per week (OR: 2.4; 95% CI: 1.0–5.8); and consuming less than one portion of fruits and vegetables a day (OR: 2.0; 95% CI: 1.2–3.3) (Table II). In order to adjust for confounders, the factors that were significantly associated with gastric cancer or metaplasia were evaluated with

Table I
Section A: Socio-demographic characteristics

	Cases	*Controls*	*p-value*
Number of subjects	113	144	
Age (years ± S.D.)	62.0 ± 13.4	55.5 ± 13.1	< 0.001
Gender (M/F)	56/57	39/105	< 0.001
Income < 400 USD/month (%)	54.6	67.6	0.036
Mestizo Ethnicity (%)	77.7	62.9	0.038
Education (years)	11.1 ± 4.4	11.8 ± 4.5	0.240

Table II
Section B: Dietary Habits

Consumption of	*Cases (%)*	*Controls (%)*	*OR (95% CI)*
Reheated food > 3 days old	5.8	0.0	7.7 (1.03-172.8)
Add salt to more than half meals	40.0	16.0	3.5 (2.0-6.3)
Reheated meals > 3 times per week	62.0	38.0	2.7 (1.6-4.5)
Re-used cooking oil	43.9	22.5	2.7 (1.6-4.7)
Grilled meat at least once a week	20.0	9.4	2.4 (1.04-5.8)
Fruits and vegetables < once a day	54.1	36.8	2.0 (1.2-3.3)
Canned food > once per week	18.7	13.5	1.5 (0.7-3.1)
Dairy products at least every other day	85.7	82.4	1.3 (1.06-2.7)
Non-potable water	13.4	12.1	1.1 (0.5-2.4)
Fava beans	4.8	4.3	1.1 (0.3-3.7)
Red meat at least every other day	17.2	23.8	0.7 (0.3-1.3)
Eggs at least every other day	48.5	56.0	0.7 (0.4-1.3)
Colas	24.1	30.8	0.7 (0.3-1.6)
Mineral water	25.7	44.7	0.4 (0.17-1.1)

a binary logistic regression model. This model confirmed that the consumption of reheated foods more than 3 times per week (AOR: 4.57; 95% CI: 2.2–9.5) and adding salt to more than 50% of meals (AOR: 1.32; 95% CI: 1.04–1.67) were significantly more prevalent in cases than control subjects, Table V. In relation to potential protective factors for the development of gastric cancer, data indicated that previous treatment for *H. Pylori* infection (OR: 0.2; 95% CI: 0.1–0.4) and the use of NSAIDs at least once per month (OR: 0.5; 95% CI: 0.3–0.8) were associated with decreased risk (Table IV). A binary logistic regression model also confirmed that treatment for *H. Pylori* (AOR: 0.33; 95% CI: 0.16–0.71), NSAIDs consumption (AOR: 0.39; 95% CI: 0.19–0.83) and being < 58 years of age (AOR: 0.38; 95% CI: 0.18–0.79) were protective factors, table V. Data also indicated that dietary factors not related to the risk of stomach cancer or metaplasia were consumption of canned foods, dairy products, non-potable water, fava beans, red meat, eggs, colas or mineral water (Table II). Lifestyle habits such as being a current smoker, consumption of liquor at least once a week, use of recreational drugs, having a refrigerator at home, taking vitamin supplements, dental hygiene and hand-washing were not found to be significant risk factors for having gastric cancer, in this study (Table III). Medical factors that were not associated with stomach cancer were having a family history of cancer, use of vitamin supplements, anti-parasitic treatment or previous cholecystectomy (Table IV). For the logistic regression model, gender was maintained due to previous studies that show that men have an increased risk for gastric cancer. All variables present in table V predicted 78.9% of the variability of gastric cancer in the studied population (Table V).

Discussion

The aim of this hospital-based case-control study was to identify risk and protective factors for gastric cancer in the Ecuadorian population. Our study showed that consuming reheated meals more than 3 days old, adding salt to more than half of the meals, reheating meals more than 3 times per week, re-using cooking oil, consumption of grilled meat at least once a week and low consumption of fruits and vegetables were significantly more common in cases than in controls subjects. However, in the adjusted logistic regression model only consumption of reheated meals more than 3 times per week and adding salt to more than half of the meals were significant risk factors. On the other hand, present data also showed that consumption of NSAIDs and previous treatment to *H. pylori* infection had a protective effect for gastric cancer development.

These findings are consistent with previous literature where systematic reviews of observational studies and meta-analysis of prospective studies[19] have found a direct association on dietary salt intake and risk of gastric cancer. D'Elia *et al*., found in their analysis of 7 prospective studies that the relative risk of developing gastric cancer with high intake of salt was 1.68; 95% C.I. [1.17–2.41], $p=0.005$, compared to the group who had low salt intake. This was true even after the authors corrected for potential sources of heterogeneity such as year of publication, age, gender and geographic location[19]. These findings correlate with the AOR of 1.32 for salt consumption in our study. Similarly, a meta-analysis of 11 cohort and case-control studies showed that high salt intake was positively associated with gastric cancer (OR = 2.05; 95% CI [1.60, 2.62][20].

Several mechanisms have been proposed to explain the causal role of salt intake in the development of gastric cancer. *In vivo* studies have shown that mice infected with *H. Pylori* that received a salt-rich diet presented a significantly higher number of colony-forming units (CFU) when compared to mice that received a normosodic diet[21]. The mice on the high-salt diet also presented more proliferation of the gastric epithelium in the proximal corpus and antrum, as well as a decrease in the number of parietal cells[21]. Moreover, it has also been shown that salt directly damages gastric mucosa in a dose-dependent manner, and that it can be responsible for tumor promotion by causing temporary cell proliferation as part of the repair process[22].

Similar to other studies, our results showed that NSAIDs had a protective effect for gastric cancer. Randomized controlled trials and observational stu-

Table III
Section C: Lifestyle habits

	Cases (%)	*Controls (%)*	*OR (95% CI)*
Use of recreational drugs	3.0	0.0	4.4 (0.4-11)
Current smoker	21.2	13.8	1.7 (0.8-3.5)
Liquor at least once a week	37.7	28.4	1.5 (0.9-2.6)
Refrigerator at home	92.9	94.4	0.8 (0.3-2.1)
Brush teeth > than once a day	82.7	90.9	0.5 (0.2-1.0)
Wash hands before eating	91.8	95.8	0.5 (0.2-1.4)

Table IV
Section D: Medical History

	Cases (%)	*Controls (%)*	*OR (95% CI)*
NSAID use at least once a month	41.1	60.0	0.5 (0.3-0.8)
Previous treatment for H. Pylori	21.7	56.3	0.2 (0.1-0.4)
First degree relative with any cancer	8.0	8.8	0.9 (0.1-5.8)
Anti-parasite treatment at least once a year	53.8	58.3	0.8 (0.5-1.4)
First degree relative with gastric cancer	10.0	11.9	0.8 (0.4-1.8)
Vitamin supplements > 2 bottles/year	19.2	27.5	0.6 (0.3-1.2)
Previous cholecystectomy	34.7	45.5	0.6 (0.3-1.5)

Table V
Adjusted Odds ratios (AOR) from logistic regression model for predictors of gastric metaplasia

Variable	*AOR (95% CI)*
Intake of reheated meals > 3 times per week	4.57 (2.2 – 9.5)
Male	1.76 (0.83 – 3.73)
Adding salt > 50% of meals	1.32 (1.04 – 1.67)
Consumption of NSAID at least once a month	0.39 (0.19-0.83)
Age < 58	0.38 (0.18 – 0.79)
History of treatment against *H. Pylori* gastric metaplasia	0.33 (0.16 – 0.71)

dies have shown that aspirin can serve not only as a chemopreventive agent, but depending on the dose administered it can reduce cancer mortality by 20%[23]. Analyses from randomized controlled trials found the use of daily aspirin for 5 years decreased mortality in gastric cancer patients. These effects seemed to last for over 20 years[23]. A systematic review of observational trials found aspirin reduced the long-term risk of several cancers, including gastric cancer and the risk of distant metastasis[24]. The anti-neoplastic action of NSAIDs have demonstrated to work through COX-2 inhibition and COX-2 independent mechanisms such as inhibition of NF-kB, mTOR signaling inhibition, activation of AMP-activated kinase pathways and induction of apoptosis through up-regulation of bax and bak[25].

Consumption of reheated food was the strongest risk factor found among cases subjects that in control individuals for the developed of gastric cancer or metaplasia. Reheating meals repeatedly exposes food to prolonged high temperatures that can lead to the formation of acrylamide, heterocyclic amines and polycyclic aromatic hydrocarbons[26]. Acrylamide (AA) is formed when food is exposed to cooking, frying, broiling, frying and other high-temperature processes. AA formation increases with higher temperatures and prolonged heating time[27]. Although there are studies that show a relation between AA exposure and carcinogenesis, human studies are inconclusive[27]. Epidemiological studies are confounded by other factors such as the presence of AA in the environment and various dietary sources, the lack of reliable markers for different cancers and non-systematic assessments[27]. Heterocyclic amines (HCA) are mutagenic compounds formed during high temperature exposure of meats[28]. The link between cancer and HCA comes from animal studies, where HCA induced tumors in various organs[29]. Epidemiological studies have shown conflicting results as well. A Japanese study showed a positive association between grilled fish and gastric cancer[30]. Another study showed an association between barbequing/grilling meat and stomach and esophageal cancer[31]. However, subsequent studies have shown no association between HCA and stomach cancer[32]. In the case of polycyclic aromatic hydrocarbons (PAHs), which are formed by incomplete combustion of organic material, a nested case-control study found that high concentrations of a PAH metabolite were related to gastric cancer risk[26].

We acknowledge limitations to the present study, for instance it is uncommon to combine within the group of cases, patients with histological confirmation of primary gastric cancer and patients with intestinal metaplasia. Animal models have shown that intestinal metaplasia precedes gastric carcinoma[33] and human studies have found that intestinal metaplasia is involved in the development of intestinal-type gastric can-

cer[34] and is prevalent in areas with high incidence of gastric cancer[35]. It is possible that risk and protective factors could have been different if we had differentiated the cases according to their corresponding histological group. Other limitations include the retrospective nature of the data, which limits the quantification of the exposure to potential protective as well as risk factors for gastric cancer/metaplasia.

Conclusions

Our study provides an analysis of different risk and protective factors for gastric cancer and metaplasia collected from a cross-culturally adapted questionnaire. This case control study evaluated known dietary and lifestyle risk factors, but also explore additional factors such as food reheating, which are less studied in the medical literature. Although mechanisms through which salt and *H. Pylori* cause gastric cancer are well explored, clinical studies of carcinogenic compounds such as acrylamide, heterocyclic amines and polycyclic aromatic hydrocarbons that come from exposing foods to prolonged heat are still lacking. This underlines the importance of continuing to explore novel factors in the etiology of gastric cancer, especially in developing countries, where the incidence and mortality due to stomach cancer is high.

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