

## CAPSAICIN CONSUMPTION, *HELICOBACTER PYLORI* POSITIVITY AND GASTRIC CANCER IN MEXICO

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**Gastric cancer (GC) incidence has not declined in Mexico. We assessed whether the intake of capsaicin (CAP), the pungent compound of chili peppers, increases the risk of GC independently of *H. pylori* positivity (Hp). From 1994 to 1996, a hospital-based case-control study was performed in 3 areas of Mexico; 234 cases of GC and 468 matched controls were enrolled and their diet and other characteristics were inquired. Chili pepper intake was queried by interview and CAP content of chilies was determined in a separate analysis by gas chromatography to estimate CAP intake; IgG Hp serum antibodies were determined by ELISA. The risk of GC was increased (OR = 1.71; 95% CI = 0.76–3.88) among high-level consumers of CAP (90–250 mg of capsaicin per day, approximately 9–25 jalapeño peppers per day) as compared to low-level consumers (0–29.9 mg of capsaicin per day, approximately 0 to less than 3 jalapeño peppers per day; *p* for trend *p* = 0.026); this effect was independent of Hp status and other potential GC determinants and was higher among diffuse GC cases (OR = 3.64; 95% CI = 1.09–12.2; *p* for trend = 0.002) compared to intestinal GC cases (OR = 1.36; 95% CI = 0.31–5.89; *p* for trend = 0.493). No significant interaction was found between CAP intake and Hp on GC risk. Chili pepper consumption might be an independent determinant of GC in Mexico.**

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**Key words:** capsaicin; chili pepper; gastric cancer; *Helicobacter pylori*; histological types; Mexico

Capsaicin (trans-8-metil-vanillyl-6-nonenamida) (CAP) is the main natural pungent compound of chili peppers.<sup>1</sup> There is some evidence indicating that chili pepper consumption may increase the risk for gastric cancer (GC) in humans. This association was first reported by López-Carrillo *et al.*<sup>2</sup> in Mexico and latter supported by 2 subsequent studies from India<sup>3</sup> and Korea,<sup>4</sup> which identified an excess risk for GC due to the consumption of chilies and foods prepared with chili peppers, such as Chutney (Indian sausage) and hot pepper-soybean paste stew. A limitation of all these studies is the lack of a direct measurement of the magnitude of capsaicin intake, which varies according to the type of chili pepper.<sup>5</sup>

Experimental studies yielded conflicting results in regard to the potential of capsaicin to act as a human carcinogen,<sup>1</sup> and the way of action of capsaicin is still unclear. One possible mechanism is an interaction with *Helicobacter pylori*. *H. pylori* is considered a human carcinogen,<sup>6</sup> in view of the results reported by several prospective studies from the early 1990s.<sup>7–10</sup> Only a few studies focused on the simultaneous assessment of dietary factors and *H. pylori* infection and yielded inconclusive results,<sup>11,12</sup> but no one evaluated capsaicin intake as dietary factor. In this article, we report the results of a case-control study spanning 3 regions in Mexico designed to evaluate whether CAP intake increases the risk of GC independently of *H. pylori* positivity.

### MATERIAL AND METHODS

From 1994 to 1996, we collected data for a hospital-based case-control study in 3 geographical areas of Mexico (Mexico City

and the entire states of Puebla and Yucatán). These locations were chosen because of differences in the kind and amount of chili peppers consumed with the aim of reflecting a wider gradient of capsaicin intake. In Mexico City, the jalapeño and serrano green fresh are the most frequently consumed peppers; while the habanero fresh pepper is highly consumed in Yucatán, and in Puebla the most popular are the poblano green fresh pepper and the moles that are hot chocolate sauces prepared with guajillo and ancho peppers (the latter being the dried version of the poblano pepper).<sup>5</sup>

### Cases

All the cases were histologically confirmed as adenocarcinomas of the stomach (with no other history of cancer), aged at least 20 years, and who had at least 6 months of residency in the study area. Cases were identified from social security and government hospitals. The former are owned by the federal government but only accept formal workers or employees, whereas the latter could potentially be used by any citizen (even those who have access to the social security), but more often care for the poorest population groups. In total, there were 13 participating hospitals: 3 social security (Hospital de Oncología, Clínica 8 and Hospital de Especialidades) and 4 government hospitals (Instituto Nacional de Nutrición Salvador Zubirán, Instituto Nacional de Cancerología, Hospital GEA Gonzalez and Hospital General) located in Mexico City, 1 social security (Hospital San José) and 2 government hospitals (Hospital General and Hospital Universitario) located in Puebla City, and 2 social security (Hospital Juárez and Hospital Fenix) and 1 government hospital in Merida City (Hospital O'Horan).

The study protocol established a fixed sample size of 100 cases from each geographical area. Over the enrolment period, we were able to recruit 79 of the 89 (89%) gastric cancer patients who were reported to the Mexico National Cancer Registry<sup>13</sup> by the participating hospitals in Yucatán during the study period, 91 of 108 patients in Puebla City (84%) and 111 of 205 patients in Mexico City (54%). These percentages correspond to the proportions of cases recruited in regard to the total number of cases reported to the registry in the year of reference. Overall, a total of 281 eligible

Grant sponsor: the American Institute of Cancer Research; Grant number: 96A137; Grant sponsor: the Pan-American Health Organization; Grant number: AMR941086975-01; Grant sponsor: the U.S. National Cancer Institute; Grant sponsor: the Mexico Ministry of Health.

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Received 7 November 2002; Revised 25 February 2003; Accepted 28 February 2003

DOI 10.1002/ijc.11195

patients were identified and 261 agreed to participate in the study, giving a response rate of 92.9%.

All cases were classified by 1 single expert cancer pathologist according to the criteria of Laurén.<sup>14</sup> Information about the anatomic subsite of the tumor was not available for all cases.

### Controls

For each case, we selected 2 hospital controls individually matched by age ( $\pm 5$  years), sex and city of residence. Inclusion criteria were no antecedents or current cancer, absence of current diet-related illnesses (mainly gastritis, peptic ulcer, cirrhosis of the liver and diabetes mellitus) or immunosuppressive disorders, and having resided in the same city as the index case for at least a period of 6 months before the date of interview. The most frequent diagnoses among controls were circulatory system disorders excepting hypertension (19.02%); diseases of the nervous system and sensory organs, excepting psychiatric syndromes (15.6%); osteo-muscular and connective tissue disorders (15.0%); injuries and poisoning (10.9%); diseases of the respiratory tract (9.8%); diseases of the genitourinary system (8.12%) and the skin (5.98%); other subjects were healthy individuals attending the hospitals for preventive purposes such as vaccination or papsmear (8.97%), and 6.62% had smaller proportions of other illnesses that included infectious or parasitic diseases, endocrine and metabolic disorders, complications of delivery and puerperium, or congenital anomalies. The response rate for the controls was 94.6% (523 out of 553 eligible subjects).

### Interviews

Sociodemographic, clinical and dietary information was obtained by in-person structured interviews. Interviews were performed by nurses working at the participating hospitals who were locally trained by a member of our staff. Interviewers were blind about the study hypothesis. All cases and controls were interviewed at the hospitals, and most subjects answered the questionnaire during the month before the date of the histopathologic confirmation of their diagnosis and before their eventual hospitalization. Cases and controls were inquired about their dietary habits 3 years before the onset of the symptoms that they ascribed to their current illness. Each subject received a general explanation about the study purposes but were kept blind about the study hypothesis and signed a written consent before entering the study.

### Dietary information

A validated semiquantitative questionnaire used in a previous study<sup>2</sup> was adapted to estimate daily or weekly frequencies for the consumption of the foods most frequently consumed in each city and 10 frequencies of consumption for standard portions sizes, ranging from never to 6 times or more per day, were included. The frequency of intake of fruits and vegetables was adjusted for seasonality of the food items. In Mexico City, the questionnaire had 133 items, including 20 types of chili peppers and 6 dishes prepared with chilies; in Puebla, there were 134 items (including 14 types of chili peppers and 7 dishes prepared with chili); and in Yucatán, 147 items were considered (including 14 types of chili peppers and 3 dishes prepared with chili). The types of chilies and dishes prepared with chili in Mexico City, Puebla and Yucatán that were included in this instrument are also those most frequently consumed, which are well known in each study area but are not necessarily the same in the 3 study areas.

The food consumption reported by each subject was further grouped into dairy products, fruits, vegetables, meats, legumes, cereals, local dishes, oils, sweets or desserts, nonalcoholic and alcoholic beverages. Individuals for whom the total estimated daily caloric intake was below 700 kcal ( $n = 9$ ) or above 4,500 kcal ( $n = 73$ ) were excluded because the dietary information was considered not precise, leaving 234 cases (130 diffuse, 80 intestinal and 24 indeterminate) and 468 controls available for analysis.

### Capsaicin intake

CAP contents for 9 different types of fresh and 8 types of dried chilies were analytically determined. For each type of chili pepper, a randomly selected sample of 15 to 20 chilies was obtained at the central market and pooled. CAP levels were determined by high-pressure liquid chromatography (HPLC), adapting methods proposed elsewhere,<sup>15</sup> and the CAP values were reported in mg/g of chili (Table I). Bell pepper was used as a internal negative control, since it does not contain capsaicin.

Due to logistic reasons in 3 types of chilies, the CAP content could not be determined by HPLC; instead, the CAP values of chili pepper with a similar pungency<sup>16</sup> were imputed as follows: chile loco was given the same capsaicin content value (0.14 mg/g) as chilaca; chile de agua was considered equal to chile poblano (0.08 mg/g); and chile cascabel received the same CAP value as chile catarino (0.98 mg/g). Also, the capsaicin content of 16 dishes prepared with chili was estimated on the basis of local known recipes.<sup>17</sup> The total individual amount of capsaicin intake was estimated by adding up the capsaicin content for the daily reported consumption of each chili and chili dish.

### Socioeconomic level

The change in the socioeconomic level was estimated for each subject by comparing their current situation with what they had during childhood on the basis of the types of water supply and sewage at his or her household. Also, current socioeconomic level was estimated by years of education.

### H. pylori positivity

We collected 10 ml of venous blood from each subject using sterile Vacutainers. Serum was extracted by centrifugation and stored at  $-70^{\circ}\text{C}$ . The presence of *H. pylori* IgG antibodies was determined by ELISA tests using a commercial kit. An individual was considered *H. pylori*-positive when the corresponding adjusted absorbance value was  $> 0.99$ ; otherwise the result was classified as negative. The sensitivity and the specificity for this method are 98.5% and 98.1%, respectively.<sup>18</sup>

### Statistical analysis

On the basis of the left-skewed distribution of capsaicin consumption, 3 categories were created. The first category included

TABLE I—CAPSAICIN CONTENT ACCORDING TO THE TYPE OF CHILI PEPPER

Chili	Genus <i>capsicum</i> specie	Capsaicin content (mg/g) <sup>1</sup>
Fresh		
Habanero	<i>Chinense</i>	8.55
De arbol	<i>Annuum L.</i>	2.35
Jalapeño	<i>Annuum L.</i>	2.08
Serrano	<i>Annuum L.</i>	0.32
Güero	<i>Acuminatum</i>	0.28
Manzano	<i>Annuum L.</i>	0.20
Chilaca	<i>Baccatum L.</i>	0.14
Poblano	<i>Annuum L. longum</i>	0.08
Bell pepper	<i>Annuum L. grossum</i>	0.00
	<i>Annuum L.</i>	
Dry		
Piquín		1.44
Catarino	<i>Aviculare</i>	0.98
Pasilla	<i>Annuum</i>	0.65
Morita	<i>L. cerasiforme</i>	0.56
Chipotle	<i>Annuum L. longum</i>	0.52
Ancho	<i>Annuum</i>	0.20
Guajillo	<i>L. abbreviatum</i>	0.11
Mulato	<i>Annuum L. dulce</i>	0.11
	<i>Annuum L. grossum</i>	
	<i>Annuum L. longum</i>	
	<i>Annuum L. grossum</i>	

<sup>1</sup>Mean values based on a sample of 15 to 20 chilies.

50% of the study population and ranged from no consumption (1% of individuals) to 29.03 mg/day (rounding the category to 29.9 is the equivalent of the capsaicin content of less than 3 jalapeño peppers per day). The second category began at 30 mg/day (exactly 3 jalapeño peppers/day) and went up to the 95th percentile (88.6 mg/day of capsaicin intake); it was rounded up to less than 9 jalapeño peppers/day (89.9 mg/day), to leave the upper exposure category for about 5% of the subjects who consume the equivalent of 9 or more of these peppers every day. Thus, these 3 categories correspond to the following mg/day of capsaicin intake: 0–29.9, 30–89.9 and 90–250, and the mean intake of capsaicin for each of these 3 categories was 12.5, 50.3 and 113.6 mg/day, respectively.

Conditional logistic regression models were used for matched analyses to estimate the effect of capsaicin intake and *H. pylori* infection adjusted by each other as well as by the following known and suspected GC risk factors: age (continuous), sex (0 = female; 1 = male), energy (continuous kcal), schooling (years of education as continuous), fruit intake (0 = 0–1.5 portions per day; 1 = 1.6–2.5 portions per day; 2 = 2.6–4.5 portions per day; 3 > 4.5 portions per day), vegetable intake (0 = 0–2 portions per day; 1 = 2.1–3 portions per day; 2 = 3.1–4.0 portions per day; 3 > 4.0 portions per day), processed meat consumption (0 = no; 1 = 0.02–1.5 portions per week; 2 > 1.5 portions per week), smoking (pack-years continuous) and alcohol consumption (0 = no; 1 = 0.15–1.5 portions per day, 2 > 1.5 portions per day). In subsequent steps, this model was independently fitted for each histological type of GC. To test for trend, the above-mentioned categories of capsaicin intake were entered as ordinal in each 1 of the models.

To assess our data for an interaction between *H. pylori* infection and capsaicin intake, we used a multiplicative approach incorporating the product of the dichotomous values of *H. pylori* (> 0.99, and ≤0.99 absorbance units) and CAP intake (> 29.9 and ≤ 29.9 mg/day) in the models and looking at the change in the likelihood ratio statistic ( $\Delta G^2$ ). All the analyses were performed using the statistical software Stata 5.0 (Stata, College Station, TX).

## RESULTS

The levels of CAP in the fresh and the dry chilies that were analyzed are shown in Table I. As expected, the habanero pepper had the highest level of CAP (8.55 mg/g), followed by chili de arbol and the jalapeño pepper.

By design, the study population was matched by age, sex and place of residence; thus these variables were similar between cases and controls. Besides, they were also similar regarding other general characteristics. A slightly higher and nonsignificant means for education (years of schooling) and length of residence were found among cases while a slightly nonsignificant higher proportion of controls reported an improved socioeconomic level in comparison to what they had during childhood (Table II).

The potential related factors for GC risk in the study population are depicted in Table III. Cases reported significantly higher consumption of processed meats and ethanol. A borderline higher proportion of cases tested seropositive to *H. pylori* (80.69% vs. 74.67%) and had a higher daily age-sex-years of education adjusted mean intake of CAP (39.40 vs. 35.27 mg/day). The highest mean consumption of CAP in the total population was observed in Puebla (31.99 mg/day), following by Mexico City (29.84 mg/day) and Yucatán (24.54 mg/day); the mean CAP consumption between Puebla and Yucatán was statistically significant (data not included in the tables). Vegetable and fruit consumptions were very similar in this population and a higher but nonsignificant proportion of smokers was found among the cases.

Daily mean intake of CAP and *H. pylori* status are compared according to the diagnosis of cases and controls in Table IV. Diffuse GC cases had a slightly higher intake of capsaicin (32.52 vs. 31.60 mg/g) and proportion of *H. pylori*-seropositive subjects (81.40 vs. 77.50) than intestinal GC cases. Daily mean CAP intake was not significantly different throughout the clinical controls and

TABLE II – GENERAL CHARACTERISTICS OF THE STUDY POPULATION

Characteristic	Cases (234)	Controls (468)
Age (years)		
$\bar{X}^1$	58.07	57.55
Minimum-maximum	28–86	28–82
Sex (%)		
Male	56.84	56.84
Female	43.16	43.16
Schooling (years)		
$\bar{X}^1$	4.96	4.47
Minimum-maximum	0–20	0–18
Length of residence (years)		
$\bar{X}^1$	48.75	47.90
Minimum-maximum	0.5–78	1–81
Change in socioeconomic level <sup>2</sup> (%)		
Same or less	52.19	49.03
Improvement	47.81	50.97
Place		
Mexico City	39.74	39.74
Puebla	32.05	32.05
Yucatán	28.21	28.21

<sup>1</sup>.,<sup>2</sup>Current level minus socioeconomic level in childhood.

TABLE III – POTENTIAL RELATED FACTORS FOR GASTRIC CANCER RISK

Factor	Cases (234)	Controls (468)	p-value
Energy (kcal)			
$\bar{X}^1$	2,198.09	2,104.16	0.186
SE	246.82	175.78	
Vegetables (portion/day)			
$\bar{X}^1$	2.88	2.75	0.324
SE	0.31	0.44	
Fruits (portion/day)			
$\bar{X}^1$	2.03	2.10	0.683
SE	0.63	0.45	
Processed meats (portion/week)			
$\bar{X}^1$	3.04	2.99	0.032
SE	0.58	0.42	
Ethanol (g/week)			
$\bar{X}^1$	34.28	25.06	0.030
SE	14.7	10.5	
% drinkers <sup>2</sup>	65.81	69.02	
$\bar{X}^1$ (among drinkers)	51.21	35.02	0.007
SE	8.06	14.8	
Tobacco (pack-years)			
$\bar{X}^1$	8.16	7.42	0.603
SE	4.92	3.5	
% smokers <sup>2</sup>	41.7	43.91	
$\bar{X}^1$ (among smokers)	12.09	10.03	0.512
SE	11.52	8.39	
Capsaicin (mg/day)			
$\bar{X}^1$	39.40	35.27	0.079
SE	8.18	5.83	
<i>Helicobacter pylori</i> (%)			
Positive	80.69	74.67	0.077

<sup>1</sup>Adjusted mean by age, sex and years of education.–<sup>2</sup>Ever/never.

ranged from 24.82 among subjects with diseases of respiratory track to 37.32 mg/g among those with diseases of the nervous system and/or sensory organs. Also, the proportion of *H. pylori*-positive did not differ significantly among controls and ranged from 67.86% for individuals with skin diseases to 83.33% for those with osteomuscular and connective tissue impairments.

In the total study population, the probability of developing GC was increased (OR = 1.71; 95% CI = 0.76–3.88) among high-level consumers of capsaicin (90–250 mg of capsaicin per day, approximately 9–25 jalapeño peppers per day) as compared to low-level consumers (0–29.9 mg of capsaicin per day, approximately 0 to less than 3 jalapeño peppers per day), with a significant test for linear trend ( $p = 0.026$ ); this effect was independent of that

TABLE IV – CAPSAICIN INTAKE (MG/DAY) AND *HELICOBACTER PYLORI* STATUS ACCORDING TO THE DIAGNOSIS OF THE STUDY POPULATION

	Capsaicin			<i>Helicobacter pylori</i> -positive		
	%	$\bar{X}$	10–90 percentile	<i>p</i> -value <sup>1</sup>	%	<i>p</i> -value <sup>2</sup>
Cases (n = 234)						
Diffuse	61.9	32.52	4.31–78.48	0.8542	81.40	0.495
Intestinal	38.1	31.60	1.43–73.67		77.50	
Controls (n = 468)						
Circulatory system	19.02	26.20	3.16–81.68	0.8916	68.54	0.605
Nervous system and sensory organs	15.60	37.32	6.90–49.32		72.60	
Osteomuscular and connective tissue	14.96	28.59	4.20–90.63		83.33	
Injuries and poisoning	10.90	24.97	3.47–43.82		77.08	
Diseases of respiratory tract	9.83	24.82	7.59–51.56		80.43	
Genitourinary system	8.12	31.51	1.24–61.30		76.32	
Skin	5.98	31.56	0–87.14		67.86	
Healthy <sup>3</sup>	8.97	30.91	8.63–79.69		73.17	
Other <sup>4</sup>	6.62	27.25	2.81–53.81		72.41	

<sup>1</sup>ANOVA.–<sup>2</sup>Chi-square.–<sup>3</sup>Healthy controls attending the hospital for preventive purposes: vaccination, pap smear, *etc.*–<sup>4</sup>Other includes infectious or parasitic diseases, endocrine and metabolic disorders, complication of delivery and puerperium or congenital anomalies.

TABLE V – ADJUSTED ODDS RATIOS FOR THE SIMULTANEOUS EFFECT OF CAPSAICIN INTAKE AND *HELICOBACTER PYLORI* SEROPOSITIVITY

	All <sup>1</sup>				Intestinal			Diffuse		
	Cases	Controls	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Capsaicin intake (mg/day)										
0–29.9 ( $\bar{X}$ = 12.5)	137	315	1.0		48	1.0		74	1.0	
30–89.9 ( $\bar{X}$ = 50.3)	83	133	1.60	1.06–2.41	28	1.30	0.61–2.75	47	2.64	1.42–4.9
90–250 ( $\bar{X}$ = 113.6)	14	20	1.71	0.76–3.88	4	1.36	0.31–5.89	9	3.64	1.09–12.2
<i>p</i> for trend			0.026				0.493			0.002
<i>p</i> for interaction			0.863				0.836			0.569
<i>Helicobacter pylori</i> <sup>2</sup>										
Negative	45	116	1.0		18	1.0		24	1.0	
Positive	188	342	1.58	1.02–2.44	62	1.03	0.49–2.15	105	2.11	1.10–4.03

Adjusted by age (continuous), sex (0 = female; 1 = male), energy (continuous kcal), schooling (years of education, continuous), fruit intake (0 = 0–1.5 portions per day; 1 = 1.6–2.5 portions per day; 2 = 2.6–4.5 portions per day; 3 > 4.5 portions per day), vegetable intake (0 = 0–2 portions per day; 1 = 2.1–3 portions per day; 2 = 3.1–4.0 portions per day; 3 > 4.0 portions per day), processed meat consumption (0 = no; 1 = 0.02–1.5 portions per week; 2 > 1.5 portions per week), 1 = tobacco smoking (pack-years continuous) and alcohol consumption (0 = no; 1 = 0.15–1.5 portions per day; 2 > 1.5 portions per day) and the other variable in the table.–<sup>1</sup>Indeterminate adenocarcinomas of stomach are included.–<sup>2</sup>Numbers that add less than the total number of cases are due to missing values for the *H. pylori*, variable of interest.

produced by *H. pylori* status and other potential GC determinants, with results being higher among diffuse GC cases (OR = 3.64; 95% CI = 1.09–12.2; *p* for trend = 0.002) compared to intestinal GC cancer cases (OR = 1.36; 95% CI = 0.31–5.89; *p* for trend = 0.493). It was also found that *H. pylori* positivity had an odds ratio of 1.56 (95% CI = 1.02–2.44); the null value was excluded only for diffuse gastric cancer cases (OR = 2.11; 95% CI = 1.10–4.03) and had a nonsignificant test for trend (*p* = 0.624) as presented in Table V. All these results remained very similar when the variable for having changed their diet during the past 5 years was added to the model (data not shown). The model that included the interaction term for capsaicin intake and *H. pylori* positivity suggested the possibility of a synergistic effect in regard to GC risk, but we had little precision around this estimate (Table VI).

## DISCUSSION

To the best of our knowledge, this is the first joint account of human capsaicin intake and *H. pylori* infection in relation to GC risk. With regard to the results of an excess risk for GC due to CAP exposure through chili pepper consumption, the present results are consistent with our previous finding<sup>2</sup> and confirm that *H. pylori* infection is a risk factor for GC. Also, these results suggest that the effect of CAP intake on GC risk is independent from *H. pylori* infection and tends to concentrate in cases of the diffuse histological type.

Previous studies focused on the consumption of foods prepared with chili<sup>3,4</sup> and a group of condiments<sup>19</sup> that include chili powder, but made no attempt to quantify their capsaicin content. Therefore,

it is difficult to compare the results of those studies with the ones that we are reporting, since capsaicin content varies depending on the type of chili pepper and the frequency of consumption. In our previous population-based study, we were not able to detect a positive trend for GC and chili pepper exposure as measured by frequency of consumption per day. One possible explanation was a nondifferential measurement error among chili pepper consumers, which reduced the statistical power to detect such a trend, but other conditions, such as the presence of confounding, might have also contributed to that result.

To improve the understanding of our results, a few aspects of the study design need to be further discussed. Our referent group was mostly made up with ill people. If chili pepper consumption and/or *H. pylori* infection were related to any of the diseases suffered by the controls, our results could have been biased in any direction. However, we did not find a significant difference in daily capsaicin intake or the prevalence of *H. pylori* seropositivity according to the different diagnoses received by the members of such group. Thus, it is possible that the association between capsaicin intake, *H. pylori* and GC herein reported was not determined by the prevalence of any of those 2 factors from a specific disease of the controls.

Clinical controls may differ from the general population in several ways. In this study, patients seeking care at private hospitals were not included. It is possible that our referent group may not fully represent the frequency and magnitude of capsaicin intake or the prevalence of *H. pylori* infection in the overall population of non-GC subjects which also includes ill people at home and those in good health. Since this is the first report that

**TABLE VI**—ADJUSTED ODDS RATIOS FOR THE EFFECT TO CAPSAICIN INTAKE AND *HELICOBACTER PYLORI* SEROPOSITIVITY ON GASTRIC CANCER RISK

Capsaicin intake (mg/day)	<i>Helicobacter pylori</i>	
	Negative	Positive
0–29.9		
OR	1.0	1.51
95% CI		0.67–3.40
Cases, controls	31, 87	105, 220
30–250		
OR	1.15	2.51
95% CI	0.90–2.61	1.40–4.52
Cases, controls	14, 29	83, 122
<i>p</i> for interaction		0.855

Adjusted by age (continuous), sex (0 = female, 1 = male), energy (continuous kcal), schooling (years of education, continuous), fruit intake (0 = 0–1.5 portions per day; 1 = 1.6–2.5 portions per day; 2 = 2.6–4.5 portions per day; 3 > 4.5 portions per day), vegetable intake (0 = 0–2 portions per day; 1 = 2.1–3 portions per day; 2 = 3.1–4.0 portions per day; 3 > 4.0 portions per day), processed meat consumption (0 = no; 1 = 0.02–1.5 portions per week; 2 > 1.5 portions per week), 1 = tobacco smoking (pack-years continuous) and alcohol consumption (0 = no; 1 = 0.15–1.5 portions per day; 2 > 1.5 portions per day) and the other variable in the table.

focuses on human capsaicin intake, no similar information was available in the scientific literature to compare the relative magnitude of CAP intake between our controls and other groups of human subjects. The only piece of information that we have at hand is the proportion of nonconsumers of chili peppers among controls from this study (*i.e.*, 2.9%; data not shown in tables), which was much smaller than the 19.3% observed in our previous study, where healthy controls were randomly selected from a population-based sampling frame.<sup>2</sup> Hence, we had a higher proportion of chili pepper consumers in our hospital-based control group, which could have biased our results toward the null value; in other words, the effect of capsaicin on GC from this study may be a conservative estimate of the true effect. The frequency of *H. pylori* seropositivity in our control group (80.7%) was very similar to that reported by the Mexico National Seroepidemiologic Survey, where the estimated prevalence for *H. pylori* seropositivity for adults above 20 years of age was 82.6%,<sup>20</sup> suggesting a consistent estimation of *H. pylori* prevalence in this referent group.

The probability of having a differential report of chili pepper consumption and therefore a wrong estimation of CAP intake in the study population is low. In a previous study, we found that chili pepper consumption is not significantly related with any belief about health outcomes among Mexicans,<sup>21</sup> and for the current study the interviewers were blind to the study hypothesis. In contrast, the possibility of differential misclassification of *H. pylori* status should not be disregarded. It is known that there is an increase of false negative seropositivity to *H. pylori* among cases of GC near the date of the diagnosis. Some years before, a GC diagnosis is made, and many cases could have experienced a severe atrophic gastritis and intestinal metaplasia, which are conditions that promote the loss of *H. pylori* colonization and a subsequent loss of seropositivity.<sup>22</sup> In this study, blood specimens were drawn around the date of GC diagnosis, making it possible to

have a greater proportion of false negatives to the *H. pylori* test among cases than controls. This differential measurement error could have biased our estimate of the association between *H. pylori* and GC toward the null value.

Further research suggested that *H. pylori* infection may facilitate the synthesis and delivery of carcinogens to the site of exposure (particularly N-nitroso compounds), inhibit the local effect of antioxidants (l-ascorbic acid) and induce mutations.<sup>6</sup> Hence, in this study, we controlled for the intake of foods that are sources of N-nitroso compounds (processed meats, salt, alcohol, *etc.*) as well as ascorbic acid (fruit and vegetable consumption). Furthermore, it is necessary to take into account that fresh chili peppers contain ascorbic acid.<sup>23</sup> In this regard, however, additional analyses adjusting for ascorbic acid (mg/day) did not change the results about an effect of CAP intake on GC (data not shown). Our results do not show any confounding effect between CAP intake and *H. pylori* infection regarding GC risk, since odds ratios for CAP intake were similar when *H. pylori* status was either present or absent in the multivariate model shown in Table V. However, due to insufficient power and random misclassification of *H. pylori* status, the possible existence of an interaction between these 2 factors on GC risk cannot be ruled out with our results.

In contrast to the comprehensive model available for *H. pylori* carcinogenesis,<sup>24</sup> a clear mechanism to explain the effect of capsaicin intake regarding GC causation has yet to be elucidated. The ingestion of large amounts of capsaicin causes erosion of the gastric mucosa and necrosis of the liver, but these effects are not found at low doses. Capsaicin induces duodenal adenocarcinomas in mice and promotes stomach and liver tumors in rats. Nevertheless, *in vitro* evidence shows that capsaicin suppressed the metabolism and covalent DNA binding of the known carcinogens aflatoxin B1, benzo-a-pyrene and 4-methylnitrosamino-1-3-pyridyl-1-butanone.<sup>1</sup>

Repeated topical applications of capsaicin induced papilloma formation of the skin in mice. However, a cream preparation containing capsaicin as topical analgesic is effective in reducing the pain caused by *Herpes zoster* infection and arthritis. Contradictory results have also been reported in regard to capsaicin mutagenicity.<sup>25,26</sup> It is possible that capsaicin exerts a dual effect depending on the dose, but available information about the mechanisms possibly involved for carcinogenicity and mutagenicity of capsaicin is far from conclusive.

Besides other points, further research, in the case of Mexico, should focus in trying to explain why the trends in morbidity and mortality are still increasing<sup>27</sup> as opposed to what happens elsewhere in the world. Information on *H. pylori* seroprevalence trends as well as smoking and dietary habits, including capsaicin consumption, needs to be developed for this purpose.

#### ACKNOWLEDGEMENTS

The authors thank Ms. Cielo Fernandez for her participation as fieldwork coordinator, Dr. Oralia Ladrón de Guevara, Dr. Patricia Padilla-Cortés and Dr. Laura García-Rubio for their assistance in the chemical analysis of capsaicin, Dr. Beatriz Vega, Dr. Leticia Rodríguez and Dr. Edith Suárez for providing access and reading the histological slides in their work places, and Ms. Reina Collado for editing the article.

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## APPENDIX

Description of chili peppers is as follows.<sup>5,16</sup> Ancho: Dried poblano pepper. Brick-red to dark mahogany, with an orange-red cordovan tint when held up against the light. Measures 5 inches long. Bell pepper (green): Bright medium green. Shaped like a cube rounded at the edges. Measures about 5 inches long. Does not have pungency. Other names include dulce, morrón and pimiento. Cascabel: Dark reddish brown, smooth and round in shape, measuring about 2 inches in diameter. Catarino: Garnet in color, tear-drop or bullet-shaped, sometimes tapering at the point. Measures about 2 inches long. Chilaca: Dark brown. Elongated and often curving in shape. Measures about 6-9 inches long. Other names are negro, para-deshebrar and prieto. Chipotle: Large dried, smoked jalapeño pepper. Dull tan to coffee-brown in color, veined and ridged, measuring about 4 inches long. Also called ahumado, meco, pocchilli and tamarindo. De agua: Medium green to red. Tapered to a point. Measures 5 inches long. De arbol: Bright, brick-red, elongated and pointed, about 3 inches long. Among other names, alfilerillo, cuauhchilli and cola de rata. Guajillo: Shiny, deep orange-red with brown tones. Elongated, tapering to a point and sometimes slightly curved. Measures about 6 inches long. Güero: Yellow, 3-5 inches long. Among other names, largo, tornachile and ixcatlic. Habanero: Dark green to orange-red. Lantern shaped, about 2 inches long. It is the hottest chili pepper in the world. Jalapeño: Bright medium, dark green to red. Tapering to a rounded end. About 3 inches long. Among other names, acorchado, candelaria and cuaresmeño. Loco: Medium green and yellow-orange to red. Triangled in shape. Manzano: Yellow-orange. Its shape is similar to the bell pepper. Measures about 3 inches long. Among other names, caballo, canario and cera. Morita: Small- to medium-size, dried, smoked jalapeño pepper. Bright orange-red to red-brown, tapered and measuring about 2 inches long. Mulato: A type of dried poblano. Deep dark, chocolate-brown. Rounded shoulders usually tapering to a point, measuring about 5 inches long. Pasilla: Dried chilaca pepper. Dark raisin-brown, wrinkled, elongated and tapering. Measures about 6 inches long. Piquín: Light orange-red. Oval shape. Measures about 3/4 inch long. Among other names, chilillo, chiltepín and de monte. Poblano: Dark green, with a purple-black tinge tapering down from its shoulders to the point, about 5 inches long. Serrano: Bright, yet dark to scarlet. Measures about 2 inches long. Cylindrical with a tapered rounded end. Other names are chile verde, balín and serranito.