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GASTRIC CANCER

Risk factors of gastric cancer specific for tumor location and histology in Cali, Colombia

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Abstract

AIM: To examine histology- and tumor-location specific risk factors of gastric cancer (GC).

METHODS: This was a case-control study. The study subjects were 216 GC patients newly diagnosed during the period 2000-2002 and 431 controls selected from non-cancer patients matching in age, gender, and hospital. We obtained information on lifestyles, dietary habits, and others by a questionnaire.

RESULTS: The subjects who were not eldest among his/her siblings were at a slightly elevated GC risk (OR 1.3; 95% CI 0.8-2.0). Salting meals before tasting was related to an increased GC risk (OR 3.5; 95% CI 1.6-7.3). Frequent consumptions of fruits (OR 0.3; 95% CI 0.1-1.0) and vegetables (OR 0.3; 95% CI 0.1-1.0) were related to decreased GC risks. On the other hand, frying foods (OR 1.9; 95% CI 1.0-3.6) and cooking with coal (OR 1.8; 95% CI 1.3-2.6) were related to increased GC risks. Neither Lauren's histological classification (intestinal and diffuse types) nor tumor location significantly affected those associations except birth order. The subjects who were not eldest among his/her siblings had an increased risk of GCs in the distal and middle thirds, and their ORs were 1.7 (95% CI 1.0-2.8) and 1.9 (95% CI 0.8-4.3), respectively. The corresponding OR in the upper third stomach was 0.3 (95% CI 0.1-0.9). The differences of those three ORs were statistically significant (P = 0.010).

CONCLUSION: The present study shows that birth order, salt intake, consumption of fruits and vegetables, the type of cooking, and cigarette smoking are related to GC risk. In histology and tumor-location specific analyses, non-eldest person among their siblings is related to an increased GC risk in the distal and middle thirds of the stomach, and is related to a decreased GC risk in the cardia.

Key words: Gastric cancer; Risk factor; Tumor location; Histological type; Colombia

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INTRODUCTION

Gastric cancer (GC) is still one of the most common cancers worldwide[1,2] although its mortality has been decreasing over the years in many countries, including Colombia[3], due to the changing dietary habits and lifestyles[1]. Lauren classified GCs into two histological types, i.e., intestinal and diffuse types[4], and pointed out that intestinal-type GC is more frequent in populations with a high GC incidence while the diffuse-type GC is more frequent in populations with a low incidence[5]. Lauren suggested the importance of environmental, dietary and socioeconomic factors in development of intestinal-type GCs while he suspected the involvement of genetic factors in diffuse-type GCs.

Correa postulated a multifactorial model for gastric carcinogenesis, in which *H pylori* infection is considered to play important roles in development of preneoplastic and precursor conditions[6-8]. Relationships between *H pylori*

and those gastric lesions have been documented in many countries[9-12]. Early childhood infection with *H pylori* is considered an important risk factor for GC[10,13]. A larger sibling size and higher birth order is related to earlier *H pylori* infection in childhood, a condition that is considered an important risk factor for GC[10,13]. In Colombia, 50% of rural populations are reported to have *H pylori* infection by age 2, and nearly 90% are infected by age 9[9].

Some studies reported that *H pylori* infection is related to both intestinal- and diffuse-type GCs[14-16]. Interestingly, microscopic studies suggest that *H pylori* infection seems to be more strongly related to intestinal-type rather than diffuse-type GCs whereas serological studies do not[16].

Regarding other risk factors, a case-control study in the US, has shown that a high intake of dietary calories increases only intestinal-type GCs[17]. A population-based prospective study in Japan, reported that the frequent intake of vegetables and fruits, even in low amounts, is associated with reduction of GC risk, and it was observed only in differentiated (intestinal) type[18]. Another study in Mexico showed that intake of dietary fiber and vitamin E tends to reduce risk of both intestinal- and diffuse-type GCs[19]. They also reported that the association between high saturated fat consumption and the increase of GC risk is statistically significant among the intestinal type but not in the diffuse type; on the other hand, polyunsaturated fatty acids reduce the GC risk in both intestinal and diffuse types[19]. The associations of tobacco smoking with different histological types of GCs have been examined by three studies, two conducted in Japan[20,21] and one in Sweden[22], to our knowledge. However, none of them showed any evident difference between intestinal and diffuse types with respect to GC risk associated with smoking.

Proximally-located GCs are known to have etiological backgrounds and clinico-pathological features different from more distally located stomach carcinomas[1]. However, only a small number of studies have examined risk factors of GC by tumor locations. Inoue *et al*[23] reported that habitual smoking was more strongly associated with the risk of GCs in the upper third of the stomach than that in more-distal parts. However, subsequent studies showed that GCs in the cardia and non-cardia have no evident differences in their associations with smoking[21,22].

In the present study, we selected factors known, or strongly suspected, to be related to GC risk, and examined whether their associations were affected by Lauren's histological types and tumor location, or not.

MATERIALS AND METHODS

Patients and controls

Cases were GC patients newly diagnosed during the period between Sep 2000 and Aug 2002, in the following three major reference hospitals in Cali, Colombia: Instituto de los Seguros Sociales "Rafael Uribe Uribe", Hospital Universitario del Valle, and Hospital San Juan de Dios. These are reference hospitals not only for cancer but also for non-cancer diseases, including cardiovascular diseases (CVD), metabolic syndromes, trauma, *etc.*

We reviewed medical records, pathological reports and hospital registration records of those hospitals and affiliated medical institutions, including endoscopy clinics and oncology outpatient clinics to obtain information on clinical and pathological diagnosis, disease history, socioeconomic status, and contact address of the GC patients.

We identified 395 GC patients during the study period, and the following 81 cases were excluded: 16 recurrent cases of GCs; 65 patients who lived in Valle del Cauca less than five years. There were 91 patients we could not contact, and 7 patients refused to participate in the study. Among 216 patients in the present study, 30 had died before interview but their relatives accepted to answer the questionnaire and provide the necessary information.

Information on tumor location was obtained from pathological reports and clinical records. The location of a tumor, defined as the predominant location of the tumor, was divided into the following three categories: the upper-third, middle-third and lower-third parts according to the guidelines of the Japanese Research Society for Gastric Cancer[24]. We could not obtain information on tumor location for 23 cases, and those cases were excluded from the tumor location specific analysis.

We could retrieve formalin-fixed paraffin-embedded blocks of 173 GCs, mainly surgically resected tumors. We examined those specimens, and histological diagnosis was made based on the Japanese classification[25].

Controls were selected from hospitalized patients diagnosed as neither malignant diseases nor gastric illnesses. Two controls were selected from non-cancer patients for each case, matching in gender, age (5-year category), and hospitals. Controls were selected after their case was interviewed. The mean period of time between the interviews of a case and its controls was 25 wk (range 1-109). Among 528 patients as potential controls, 67 patients were excluded because they had lived in Valle del Cauca less than 5 years. Twenty-nine patients refused to participate in the study, including 19 patients in severe clinical conditions. After all procedures for selection and matching, one patient turned out to be inappropriate as a control because he had been diagnosed as GC 15 years before. Thus, the total number of controls was 431. Four major causes of hospitalization of control patients were cardiovascular diseases (n = 208), trauma (n = 117), infectious diseases (n = 38), and urological disorders (n = 21). The Institutional Review Board of the Faculty of Health, Universidad del Valle, Cali, Colombia, approved this study and all subjects gave informed consent.

Interview procedures

The interview was conducted during the period from Sept 2000 to Dec 2002. All subjects were interviewed during hospitalization, except 30 deceased patients. The interviewer visited at houses of those patients' relatives for interview. We used a validated questionnaire to obtain the personal and family information of all subjects as well as lifestyles, dietary intakes, culinary uses, and occupational exposure.

Answers to the questions of fruit and vegetable intakes, the way of cooking and so on were dichotomized

Table 1 Gender specific distribution of age and hospitals *n* (%)

	Male				Female			
	Case		Control		Case		Control	
Total	136		271		80		160	
Age (yr)								
-49	25	(19)	50	(19)	13	(16)	26	(16)
50-54	18	(13)	36	(13)	7	(9)	14	(9)
55-59	13	(10)	26	(10)	6	(7)	12	(7)
60-64	19	(14)	38	(14)	12	(15)	24	(15)
65-69	16	(12)	32	(12)	14	(18)	28	(18)
70-74	24	(17)	48	(17)	15	(19)	30	(19)
75+	21	(15)	41	(15)	13	(16)	26	(16)
Hospital								
ISS	43	(31)	85	(31)	24	(30)	48	(30)
HUV	66	(49)	132	(49)	38	(48)	76	(48)
HSJD	27	(20)	54	(20)	18	(22)	36	(22)

ISS: Instituto de los Seguros Sociales "Rafael Uribe Uribe"; HUV: Hospital Universitario del Valle; HSJD: Hospital San Juan de Dios.

Table 2 Clinicopathological features of GC cases (mean ± SD), *n* (%)

	Male		Age	Female		Age
Total	136			80		
Tumor location						
Upper third	16	(12)	65 ± 12	8	(10)	59.0 ± 14.8
Middle third	33	(24)	60 ± 12.8	19	(24)	62.4 ± 13.7
Lower third	74	(54)	61.3 ± 13.9	43	(54)	64.0 ± 13.1
Unknown	13	(10)	60.3 ± 15.5	10	(12)	62.1 ± 13.7
Histological type[1]						
Intestinal	62	(46)	61.4 ± 13.7	24	(30)	66.6 ± 10.1
Diffuse	51	(37)	60.7 ± 14.1	36	(45)	60.3 ± 16.1
Unknown	23	(17)	61.6 ± 13.1	20	(25)	62.5 ± 12.0
Tumor depth						
Mucosa/Submucosa	13	(10)	55.8 ± 15.4	3	(4)	80.3 ± 5.7
Muscular	4	(3)	64.8 ± 8.3	0	-	-
Serosa	68	(50)	60.6 ± 12.7	31	(39)	61.1 ± 13.5
Unknown	51	(37)	63.5 ± 14.3	46	(57)	63.0 ± 13.0

[1]Histological patterns were classified on the basis of Japanese classification as follows: well differentiated tubular adenocarcinoma (tub1), moderately differentiated tubular adenocarcinoma (tub2), solid poorly differentiated adenocarcinoma (por1), non-solid poorly differentiated adenocarcinoma (por2), signet ring cell carcinoma (sig), and mucinous carcinoma (muc). Intestinal type consists of tub1, tub2, and muc, and diffuse type consists of por1, por2, and sig.

as follows: "yes" (more than 3 d/wk) and "no" (equal to or less than 3 d/wk). Salt intake was assessed by asking the habit of seasoning a dish with salt before tasting, and the answers were coded as "yes" (usually or some times) and "no" (never). To the question about salting, 4.2% of the cases and 0.9% of the controls answered "sometimes". The simplified dietary habit questionnaire used in the present study was developed on the basis of the validated semi-quantitative food-frequency questionnaire (FFQ) used in a Colombian study in 1998[26]. The FFQ has been originally developed as Colombian version of the FFQ used in the Nurses Health Study by Willet *et al*[27]. The validity of our simplified dietary habit questionnaire was confirmed in a study reported by Garcia *et al*[28].

Statistical analysis

The association between GC risk and each factor was analyzed using conditional logistic regression models. Maximum likelihood estimates of odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were calculated. All *P* values presented are two-sided. $P < 0.05$ was taken as significant.

RESULTS

We successfully interviewed 216 GC cases and 431 control patients (Table 1). Table 2 summarizes the gender specific distributions of tumor location and histological classification of GCs. We observed no difference in the distribution of tumor location between male and female cases. Male GCs were more frequently found to be intestinal-type tumors when compared to female cases. Among males, the mean age of cases was highest in the GCs located in the upper-third stomach among the three tumor locations. On the other hand, female cases with tumors in the lower-third stomach showed a relatively higher mean age than those with tumors in other locations. Regarding histological type, female cases with intestinal-type tumors showed a higher mean age than other subgroups including males.

We examined the association of GC risk with well-known or strongly suspected factors related to GC risk (Table 3). GC risk was related to the habit of seasoning a dish with salt before tasting ($P = 0.001$), the lower frequency of eating fruits ($P = 0.046$) and vegetables ($P = 0.041$), and the higher frequency of frying food consumption ($P = 0.039$), and cooking with coal ($P < 0.001$). The associations were not significantly changed after excluding patients with cardiovascular diseases or trauma from the control series. All those variables that were found to be significantly related to GC risk were independently associated with GC risk in the multivariate analysis involving all those factors (data not shown). The associations of GC risk with occupations and occupational exposures were examined as well. None of them was significantly related to GC risk (data not shown).

We estimated histology specific ORs of GC risk (Table 4). Among those who were not eldest among their siblings, diffuse-type GCs showed a significantly increased risk whereas intestinal-type GCs did not. The observations that non-eldest person among their siblings was related to diffuse-type GC risk but not to intestinal-type GC risk do not necessarily mean that those two histological types have significantly different associations with birth orders. A statistical test addressing this question gave a *P* value larger than 0.05, indicating that observed difference of ORs between intestinal and diffuse types was not statistically significant. When examining potential GC risk factors as shown in Table 3, we found that their ORs did not show any significant differences between the two histological types. On the other hand, smoking was found to be related to diffuse-type GC risk but not to intestinal-type. Here again, however, the difference in the ORs between two

Table 3 Factors related to GC risk- results of conditional logistic analysis

	Case	Control	OR	(95% CI)	*P*
Birth order [1]					0.123[2]
1	49	125	1	(referent)	
2-3	80	152	1.3	(0.8-2.0)	
4+	85	151	1.4	(0.9-2.2)	
Salting meals before tasting					0.001
No	197	420	1	(referent)	
Yes	19	11	3.5	(1.6-7.3)	
Frequent fruits intake					0.046
No	7	4	1	(referent)	
Yes	209	127	0.3	(0.1-1.0)	
Frequent vegetable intake					0.041
No	8	5	1	(referent)	
Yes	208	426	0.3	(0.1-1.0)	
Steaming foods					0.782
No	172	347	1	(referent)	
Yes	44	84	1.1	(0.7-1.6)	
Frying foods					0.039
No	13	49	1	(referent)	
Yes	203	382	1.9	(1.0-3.6)	
Smoking foods					0.161
No	160	341	1	(referent)	
Yes	56	90	1.3	(0.9-1.9)	
Cooking with oven					0.105
No	158	289	1	(referent)	
Yes	58	142	0.7	(0.5-1.1)	
Cooking with coal					< 0.001
No	100	264	1	(referent)	
Yes	116	167	1.8	(1.3-2.6)	
Roasting foods					0.243
No	74	166	1	(referent)	
Yes	142	265	1.2	(0.9-1.8)	
Cigarette smoking					0.231[2]
			P for heterogeneity = 0.098		
Never	78	188	1	(referent)	
Ex-smoker	89	145	1.5	(1.0-2.3)	
Current smoker	49	98	1.2	(0.8-1.9)	
Cigarettes smoked per day					0.323[2]
(ex-smoker and current smokers combined)			*P* for heterogeneity = 0.079		
Never	78	188		(referent)	
1-14	93	145	1.6	(1.1-2.3)	
15-24	33	79	1	(0.6-1.7)	
25+	12	19	1.6	(0.7-3.6)	
Cigarette smoking (men only)					0.731[2]
			P for heterogeneity = 0.160		
Never	36	88	1	(referent)	
Ex-smoker	65	104	1.6	(1.0-2.6)	
Current smoker	35	79	1.1	(0.6-1.9)	

[1]Information on birth order was missing in 2 cases and 3 controls; [2]*P* for trend.

histological types was not statistically significant.

Table 5 summarizes the results of tumor-location specific analyses. The ORs of GCs in the lower and middle third parts of the stomach were increased among those who were not eldest among their siblings. The ORs were 1.7 and 1.9, respectively. On the other hand, the corresponding OR for GCs in the upper-third stomach was lower than the unity (OR = 0.3). The differences of ORs among those three tumor locations were statistically significant ($P = 0.010$). When cases with tumors in the lower and middle thirds of the stomach were combined, the OR of non-eldest person was 1.7 (95% CI = 1.1- 2.7, $P = 0.017$). When this OR was compared with that in the upper third of the stomach (OR = 0.3), *P* value for the difference became smaller and was 0.003. When examining the habit of seasoning a dish with salt before tasting, the low frequency of fruit and vegetable intakes, the frequent consumption of frying foods, and the use of coal for cooking, we found that their ORs were not significantly affected by tumor location.

Smoking was related to the risk of GCs in the upper third of the stomach but not in other locations. A statistical test examining the difference of the ORs in three tumor locations gave a *P* value larger than 0.05, indicating that the difference was not statistically significant.

DISCUSSION

In the present study, subjects who were not eldest among their siblings were at an elevated risk of GCs in the distal and the middle thirds, indicating a possibility that birth order may be related to age at first *H pylori* infection as suggested by Blaser *et al*[10]. On the other hand, a decreased OR of GC in the proximal third of the stomach was observed among those who were not eldest among their siblings. Those findings are of interest since *H pylori* infection is suspected to be associated with a decreased risk of GCs in the cardia or proximally located GCs, and with an increased risk of GCs in the non-cardia or distally located GCs[16]. Studies in the US and Europe showed an inverse relationship between seroprevalence of *H pylori* and GC risk in the cardia[29,30], suggesting that proximal and distal parts of the stomach may have differences in the interaction between *H pylori* and the host defense system.

We had information about *H pylori* infection for 96 patients. *H pylori* was reported positive in 24% of GCs in the lower third of the stomach ($n = 71$) and 36% of GCs located in the middle part ($n = 17$) whereas none in the tumors located in the upper third of the stomach ($n = 8$). Those findings, albeit small in number, support the notion that *H pylori* is not related to GC risk in the proximally located GCs.

High salt intake produces atrophic gastritis and decreases the acidity of the stomach, creating a condition favoring *H pylori* infection. It is also suspected that *H pylori* infection and high salt intake may act synergistically to promote GC development[11,12]. If that is the case, it may be expected that salt intake is strongly related to non-cardia cancer but not to the cancer of the cardia (since *H pylori* infection is suspected to increase non-cardia GC risk but decrease cardia GC risk). In the present study, however, the habit of seasoning a dish with salt before tasting was related to an elevated GC risk regardless of histological type or tumor location. It may be because the upper third of the stomach includes not only the cardia but also the non-cardia part of the stomach. We did not have information to identify the cases occurring in the cardia. It is of note that Mayne *et al* examined the effect of sodium intake on tumor-location-specific GC risk and

Table 4 Factors related to GC risk- results of histology specific analysis

	Histological type					
	Intestinal			Diffuse		
	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)
Birth order[1]						
1	21	43	1.0 (referent)	16	58	1.0 (referent)
2+	65	125	1.1 (0.6-2.0)	70	116	2.0 (1.1-3.8)
			P = 0.876			*P* = 0.026
Salting meals before tasting						
No	79	165	1.0 (referent)	79	172	1.0 (referent)
Yes	7	6	2.3 (0.8-6.9)	8	2	8.0 (1.7-37.7)
			P = 0.128			*P* = 0.009
Frequent fruit intake						
No	4	1	1.0 (referent)	2	3	1.0 (referent)
Yes	82	170	0.1 (0.01-1.1)	85	171	0.8 (0.1-4.5)
			P = 0.063			*P* = 0.753
Frequent vegetable intake						
No	4	2	1.0 (referent)	3	2	1.0 (referent)
Yes	82	169	0.2 (0.05 -1.4)	84	172	0.3 (0.1-2.0)
			P = 0.109			*P* = 0.229
Steaming foods						
No	77	138	1.0 (referent)	64	139	1.0 (referent)
Yes	9	33	0.5 (0.2-1.1)	23	35	1.3 (0.8-2.5)
			P = 0.070			*P* = 0.263
Frying foods						
No	4	14	1.0 (referent)	3	21	1.0 (referent)
Yes	82	157	1.8 (0.6-5.3)	84	153	3.7 (1.1-12.5)
			P = 0.324			*P* = 0.038
Smoking foods						
No	65	132	1.0 (referent)	63	135	1.0 (referent)
Yes	21	39	1.1 (0.6-2.0)	24	39	1.3 (0.7-2.3)
			P = 0.792			*P* = 0.374
Cooking with oven						
No	64	110	1.0 (referent)	61	117	1.0 (referent)
Yes	22	61	0.6 (0.3-1.1)	26	57	0.9 (0.5-1.6)
			P = 0.101			*P* = 0.617
Cooking with coal						
No	37	108	1.0 (referent)	43	101	1.0 (referent)
Yes	49	63	2.2 (1.3-3.8)	44	73	1.4 (0.8-2.4)
			P = 0.003			*P* = 0.190
Roasting foods						
No	30	70	1.0 (referent)	31	64	1.0 (referent)
Yes	56	101	1.4 (0.8-2.5)	56	110	1.1 (0.6-1.9)
			P = 0.282			*P* = 0.841
Cigarette smoking						
Never	32	72	1.0 (referent)	30	88	1.0 (referent)
Ex-smoker	37	58	1.5 (0.8-2.6)	35	52	2.1 (1.1-4.0)
Current smoker	17	41	0.9 (0.4-1.9)	22	34	2.0 (1.0-4.2)
	P for trend = 0.931			*P* for trend = 0.027		
	P for heterogeneity = 0.340			*P* for heterogeneity = 0.032		

[1] Information on birth order was missing in a patient with diffuse-type GC and in 3 controls.

showed that the OR of GCs was 1.31 (95% CI = 0.86-2.00) in the cardia and was 1.46 (95% CI = 1.00-2.15) in the non-cardia[31].

The tumor-location specific analyses showed that smoking appeared to be more strongly related to tumors in the upper third of the stomach. However, the difference in the magnitude of associations was not statistically significant as was the case with histological type. A recent Japanese study showed that the association of smoking with GC in the upper third of the stomach was only slightly weaker than that with GC in the middle and lower thirds of the stomach[21]. A Swedish study by Ye *et*

Table 5 Factors related to GC risk -- results of tumor-location specific analysis

	Tumor location								
	Lower third			Middle third			Upper third		
	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)
Birth order[1]									
1	26	77	1.0 (referent)	8	27	1.0 (referent)	10	8	1.0 (referent)
2+	90	155	1.7 (1.0-2.8)	44	75	1.9 (0.8-4.3)	14	40	0.3 (0.1-0.9)
			P = 0.054			P = 0.154			P = 0.028
Salting meals before tasting									
No	106	228	1.0 (referent)	47	101	1.0 (referent)	22	47	1.0 (referent)
Yes	11	6	3.7 (1.4-9.9)	5	2	5.0 (1.0-25.8)	2	1	4.0 (0.4-44.1)
			P = 0.010			P = 0.054			P = 0.258
Frequent fruits intake									
No	5	3	1.0 (referent)	2	1	1.0 (referent)	0	0	-
Yes	112	231	0.3 (0.1-1.3)	50	102	0.3 (0.02-2.7)	24	48	-
			P = 0.099			P = 0.258			-
Frequent vegetable intake									
No	6	2	1.0 (referent)	1	1	1.0 (referent)	0	1	-
Yes	111	232	0.2 (0.03-0.8)	51	102	0.5 (0.03-8.0)	24	47	-
			P = 0.028			P = 0.624			-
Steaming foods									
No	92	190	1.0 (referent)	42	83	1.0 (referent)	21	40	1.0 (referent)
Yes	25	44	1.2 (0.7-2.1)	10	20	1.0 (0.4-2.3)	3	8	0.7 (0.2-3.0)
			P = 0.564			P = 1.00			P = 0.639
Frying foods									
No	6	30	1.0 (referent)	3	9	1.0 (referent)	1	2	1.0 (referent)
Yes	111	204	2.6 (1.1-6.2)	49	94	1.6 (0.4-6.0)	23	46	1.0 (0.09-11.02)
			P = 0.038			P = 0.525			P = 1.000
Smoking foods									
No	90	183	1.0 (referent)	35	80	1.0 (referent)	17	38	1.0 (referent)
Yes	27	51	1.1 (0.7-1.8)	17	23	1.7 (0.8-3.6)	7	10	1.5 (0.5-4.2)
			P = 0.791			P = 0.173			P = 0.468
Cooking with oven									
No	83	154	1.0 (referent)	37	73	1.0 (referent)	19	30	1.0 (referent)
Yes	34	80	0.8 (0.5-1.3)	15	30	1.0 (0.5-2.1)	5	18	0.4 (0.1-1.4)
			P = 0.301			P = 1.000			P = 0.153
Cooking with coal									
No	57	141	1.0 (referent)	20	63	1.0 (referent)	11	31	1.0 (referent)
Yes	60	93	1.6 (1.0-2.6)	32	40	2.2 (1.2-4.2)	13	17	2.3 (0.8-6.9)
			P = 0.037			P = 0.014			P = 0.109
Roasting foods									
No	46	89	1.0 (referent)	16	43	1.0 (referent)	6	15	1.0 (referent)
Yes	71	145	0.9 (0.6-1.5)	36	60	1.8 (0.8-3.8)	18	33	1.3 (0.5-3.9)
			P = 0.798			P = 0.131			P = 0.597
Cigarette smoking									
Never	41	107	1.0 (referent)	20	44	1.0 (referent)	5	23	1.0 (referent)
Ex-smoker	47	68	1.9 (1.1-3.4)	22	41	1.2 (0.6-2.5)	13	15	3.7 (1.1-12.5)
Current smoker	29	59	1.3 (0.7-2.3)	10	18	1.3 (0.5-3.4)	6	10	3.0 (0.6-13.9)
	P for trend = 0.257			P for trend = 0.597			P for trend = 0.083		
	P for heterogeneity = 0.059			P for heterogeneity = 0.859			P for heterogeneity = 0.070		

[1]Information on birth order was missing in a patient with tumor in the lower third of the stomach and in 3 controls.

al[22] also reported that smoking was related not only to cancer of the cardia but also to cancer of the non-cardia. Both studies mentioned above also showed no evident difference of smoking-related GC risk between the two histological types.

Frequent intakes of fruits and vegetables were related to a decreased GC risk in the present study. No significant difference in magnitude of their associations with respect to histological type and tumor location was observed, confirming what was reported by other previous studies[17,32,33]. Although the mechanisms involved in the protective effects of frequent fruit and vegetable intakes on GC risk are yet to be elucidated, Yuasa *et al*[34] showed the intake of some specific vegetables may prevent hypermethylation of the CDX2 gene, which upregulates the expression of MUC2, an important mucin protein related to the intestinal phenotype of GCs.

We observed a significant association between GC risk

and frying foods. In Cali, Colombia, residents tend to fry starch-rich foods, including potatoes, green banana, corn, and mandioca. De Stefani *et al*[35] reported a relationship between starchy rich foods and the GC risk, suggesting mechanical damages to the gastric mucosa and promotion of nitrosation by low-protein diets. Mayne *et al*[31] suggested that this association may be related with micronutrient deficiencies.

We also observed an association between cooking with coal and the GC risk. It is known that barbecued foods contain high concentrations of N-benzil pyrene and nitrites, which are related to an increased GC risk[11,21]. Although some studies suggest that cooking meats at a very high temperature produces nitrosamines and mutagen substances[36,37], further studies are required to confirm this association.

Taken together, well-known and strongly-suspected risk factors of GCs did not show any statistically significant predisposition to particular histological types or tumor location. An exception was the finding that the non-eldest person was related to an increased risk of GCs in the distal and middle third of the stomach, and was associated with a decreased cancer risk in the proximal third of the stomach.

One of the explanations for the absence of difference in other risk factors was a lack of statistical power. It may be particularly so with respect to tumor location; the number of cancer cases in the upper third of the stomach in the present study may be too small to find any differences. That may also be true for the lack of difference in the risk factors for two histological-type GCs. However, another explanation may also be possible; those findings in the present study, together with the observations that *H pylori* infection is related to both intestinal- and diffuse-type GCs, may be casting a doubt on the hypothesis that intestinal- and diffuse-type GCs are distinctly different in their etiological backgrounds.

Intestinal and diffuse types of Lauren's classification correspond, in principle, to well-differentiated and poorly differentiated ones of Sugano and Nakamura[38,39], respectively. It is of note, here however, that Lauren's classification is created by studying advanced tumors while the classification of Nakamura and Sugano is obtained from analysis of early carcinomas. Nakamura[39] reported that 85% of micro carcinomas of the stomach (< 5 mm) were of well-differentiated type, and, conversely, the proportion of undifferentiated type was higher in larger tumors; thus such a proportion increased according to tumor size. On the basis of mucin phenotype expression of GCs, Tatematsu *et al*[40] have postulated that GC starts as gastric-phenotype carcinomas, expressing mucin that is only expressed in gastric membranes, and during development into large carcinomas, some tumors express mucins whose expressions are specific for intestinal membranes. They pointed out a possibility of intestinal metaplasia accompanying GCs, particularly intestinal-type GCs, unrelated to GC development.

In conclusion, the present study showed that birth order, salt intake, consumptions of fruits and vegetables, the type of cooking, and cigarette smoking are related to GC risk. In histology and tumor-location specific analyses, non-eldest person among their siblings is related to an increased GC risk in the distal and middle thirds of the stomach, and is related to a decreased GC risk in the cardia. Those findings may help understand the mechanisms of the GC development in different locations of the stomach. Further studies seem warranted.

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REFERENCES

1 **Correa P**, Chen VW. Gastric cancer. *Cancer Surv* 1994; **19-20**: 55-76
2 **Neugut AI**, Hayek M, Howe G. Epidemiology of gastric cancer. *Semin Oncol* 1996; **23**: 281-291
3 **Piñeros M**, Hernández G, Bray F. Increasing mortality rates of common malignancies in Colombia: an emerging problem. *Cancer* 2004; **101**: 2285-2292
4 **LAUREN P.** THE TWO HISTOLOGICAL MAIN TYPES OF GASTRIC CARCINOMA: DIFFUSE AND SO-CALLED INTESTINAL-TYPE CARCINOMA. AN ATTEMPT AT A HISTO-CLINICAL CLASSIFICATION. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49
5 **Henson DE**, Dittus C, Younes M, Nguyen H, Albores-Saavedra J. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973-2000: increase in the signet ring cell type. *Arch Pathol Lab Med* 2004; **128**: 765-770
6 **Correa P**, Haenszel W, Cuello C, Tannenbaum S, Archer M. A model for gastric cancer epidemiology. *Lancet* 1975; **2**: 58-60
7 **Correa P**. A human model of gastric carcinogenesis. *Cancer Res* 1988; **48:** 3554-3560
8 **Correa P**, Cuello C, Duque E, Burbano LC, Garcia FT, Bolanos O, Brown C, Haenszel W. Gastric cancer in Colombia. III. Natural history of precursor lesions. *J Natl Cancer Inst* 1976; **57**: 1027-1035
9 **Bravo L**, Cortes A, Carrascal E, Jaramillo R. Helicobacter pylori: patologia y prevalencia en biopsias gastricas en Colombia. *Colombia Medica* 2003; **34:** 124-131 (in Spanish) Available from: URL:http//colombiamedica.univalle.edu.co/Vol34No3/helicobacter.pdf
10 **Blaser MJ**, Chyou PH, Nomura A. Age at establishment of Helicobacter pylori infection and gastric carcinoma, gastric ulcer, and duodenal ulcer risk. *Cancer Res* 1995; **55:** 562-565
11 **Hwang H**, Dwyer J, Russell RM. Diet, Helicobacter pylori infection, food preservation and gastric cancer risk: are there new roles for preventative factors? *Nutr Rev* 1994; **52**: 75-83
12 **Tsugane S**. Salt, salted food intake, and risk of gastric cancer: epidemiologic evidence. *Cancer Sci* 2005; **96**: 1-6
13 **Correa P**. Helicobacter pylori infection and gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2003; **12**: 238s-241s
14 **Parsonnet J**, Friedman GD, Orentreich N, Vogelman H. Risk for gastric cancer in people with CagA positive or CagA negative Helicobacter pylori infection. *Gut* 1997; **40**: 297-301
15 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789
16 **Kikuchi S**. Epidemiology of Helicobacter pylori and gastric cancer. *Gastric Cancer* 2002; **5**: 6-15
17 **Harrison LE**, Zhang ZF, Karpeh MS, Sun M, Kurtz RC. The

role of dietary factors in the intestinal and diffuse histologic subtypes of gastric adenocarcinoma: a case-control study in the U.S. *Cancer* 1997; **80**: 1021-1028

18 **Kobayashi M**, Tsubono Y, Sasazuki S, Sasaki S, Tsugane S. Vegetables, fruit and risk of gastric cancer in Japan: a 10-year follow-up of the JPHC Study Cohort I. *Int J Cancer* 2002; **102**: 39-44

19 **Lopez-Carrillo L**, Lopez-Cervantes M, Ward MH, Bravo-Alvarado J, Ramirez-Espitia A. Nutrient intake and gastric cancer in Mexico. *Int J Cancer* 1999; **83**: 601-605

20 **Kato I**, Tominaga S, Ito Y, Kobayashi S, Yoshii Y, Matsuura A, Kameya A, Kano T. A comparative case-control analysis of stomach cancer and atrophic gastritis. *Cancer Res* 1990; **50:** 6559-6564

21 **Inoue M**, Ito LS, Tajima K, Yamamura Y, Kodera Y, Takezaki T, Hamajima N, Hirose K, Kuroishi T, Tominaga S. Height, weight, menstrual and reproductive factors and risk of gastric cancer among Japanese postmenopausal women: analysis by subsite and histologic subtype. *Int J Cancer* 2002; **97**: 833-838

22 **Ye W**, Ekström AM, Hansson LE, Bergström R, Nyrén O. Tobacco, alcohol and the risk of gastric cancer by sub-site and histologic type. *Int J Cancer* 1999; **83**: 223-229

23 **Inoue M**, Tajima K, Hirose K, Kuroishi T, Gao CM, Kitoh T. Life-style and subsite of gastric cancer--joint effect of smoking and drinking habits. *Int J Cancer* 1994; **56**: 494-499

24 **Japanese Research Society for Gastric Cancer**. Macroscopic Findings. In: Japanese classification of Gastric Carcinoma. First English Edition. Tokyo: Kanehara Press, 1995; 3-13

25 **Japanese Research Society for Gastric Cancer**. Japanese Classification of Gastric Carcinoma. In: Criteria for histological classifications. First English Edition. Tokyo: Kanehara Press, 1995; 39-43

26 **Gracia B**, de Plata C, Pradilla A, Leiva J. Factores de riesgo de enfermedades de mayor prevalencia en el Valle del Cauca utiles para el desarrollo de estrategias de prevencion. *Colombia Medica* 2003; **34:** 47-55 (in Spanish) Available from: URL: http://colombiamedica.univalle.edu.co/Vol34No1/PDF/factoresderiesgo.pdf

27 **Willett WC**, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985; **122**: 51-65

28 **Gracia B**, de Plata C, Méndez F, Cruz M, Leiva J, Conde L, Rueda A, Mosquera M, Pradilla A. [Evaluation of early manifestations of chronic no transmitted diseases risk in school population in Cali-Colombia]. *Arch Latinoam Nutr* 2005; **55**: 267-278 (in Spanish)

29 **Chow WH**, Blaser MJ, Blot WJ, Gammon MD, Vaughan TL, Risch HA, Perez-Perez GI, Schoenberg JB, Stanford JL, Rotterdam H, West AB, Fraumeni JF Jr. An inverse relation between cagA+ strains of Helicobacter pylori infection and risk of esophageal and gastric cardia adenocarcinoma. *Cancer Res* 1998; **58**: 588-590

30 **Hansen S**, Melby KK, Aase S, Jellum E, Vollset SE. Helicobacter pylori infection and risk of cardia cancer and non-cardia gastric cancer. A nested case-control study. *Scand J Gastroenterol* 1999; **34**: 353-360

31 **Mayne ST**, Risch HA, Dubrow R, Chow WH, Gammon MD, Vaughan TL, Farrow DC, Schoenberg JB, Stanford JL, Ahsan H, West AB, Rotterdam H, Blot WJ, Fraumeni JF Jr. Nutrient intake and risk of subtypes of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 1055-1062

32 **Ekström AM**, Serafini M, Nyrén O, Hansson LE, Ye W, Wolk A. Dietary antioxidant intake and the risk of cardia cancer and noncardia cancer of the intestinal and diffuse types: a population-based case-control study in Sweden. *Int J Cancer* 2000; **87**: 133-140

33 **Ito LS**, Inoue M, Tajima K, Yamamura Y, Kodera Y, Hirose K, Takezaki T, Hamajima N, Kuroishi T, Tominaga S. Dietary factors and the risk of gastric cancer among Japanese women: a comparison between the differentiated and non-differentiated subtypes. *Ann Epidemiol* 2003; **13**: 24-31

34 **Yuasa Y**, Nagasaki H, Akiyama Y, Sakai H, Nakajima T, Ohkura Y, Takizawa T, Koike M, Tani M, Iwai T, Sugihara K, Imai K, Nakachi K. Relationship between CDX2 gene methylation and dietary factors in gastric cancer patients. *Carcinogenesis* 2005; **26**: 193-200

35 **De Stefani E**, Correa P, Boffetta P, Deneo-Pellegrini H, Ronco AL, Mendilaharsu M. Dietary patterns and risk of gastric cancer: a case-control study in Uruguay. *Gastric Cancer* 2004; **7**: 211-220

36 **Terry PD**, Lagergren J, Wolk A, Steineck G, Nyrén O. Dietary intake of heterocyclic amines and cancers of the esophagus and gastric cardia. *Cancer Epidemiol Biomarkers Prev* 2003; **12**: 940-944

37 **Kazerouni N**, Sinha R, Hsu CH, Greenberg A, Rothman N. Analysis of 200 food items for benzo[a]pyrene and estimation of its intake in an epidemiologic study. *Food Chem Toxicol* 2001; **39**: 423-436

38 **Sugano H**, Nakamura K, Kato Y. Pathological studies of human gastric cancer. *Acta Pathol Jpn* 1982; **32** Suppl 2: 329-347

39 **Nakamura K**, Sugano H, Takagi K. Carcinoma of the stomach in incipient phase: its histogenesis and histological appearances. *Gann* 1968; **59**: 251-258

40 **Tatematsu M**, Tsukamoto T, Inada K. Stem cells and gastric cancer: role of gastric and intestinal mixed intestinal metaplasia. *Cancer Sci* 2003; **94**: 135-141

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