RESEARCH COMMUNICATION

Environmental Factors Related to Gastric Cancer Associated with Epstein-Barr Virus in Colombia

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Abstract

Epstein-Barr virus (EBV)-encoded small RNA can be detected in about 1-17 % of gastric carcinomas. To elucidate lifestyles and other factors related to such an EBV-associated gastric carcinoma (EBV-GC), we conducted a case-control study in Cali, Colombia. The study subjects were 368 patients with gastric carcinoma newly diagnosed during the period between September 2000 and June 2003, including 42 EBV-GC cases. We obtained information on lifestyles, dietary habits, and occupational exposure by a questionnaire. The frequency of EBV-GC was related to birth order of patients (P for trend =0.025). More precisely, EBV-GC was much less frequent among the patients who were the eldest child in a family (P=0.007). Those findings were contrary to what was reported by the study conducted in Japan, where EBV-GC was more frequently observed among eldest brothers/sisters. A possible explanation for the apparently conflicting results is that EBV-GC risk is related to the age at first EBV infection but its relationship is not monotonic. In addition to the relationship with birth order, the present study showed that high salt intake and metal dust exposure may be related to EBV-GC as reported by the Japanese study although these associations observed in the present study were not statistically significant. No significant association was observed in other factors, including dietary habits. Further studies seem warranted to elucidate the difference between Japan and Colombia with respect to the environmental factors related to EBV-GC cases.

Key Words: Epstein-Barr virus - gastric carcinoma - only child

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Introduction

In situ hybridization (ISH) of Epstein-Barr virus (EBV)-encoded small RNA (EBER), which became available in the early 1990s, elucidated that EBER can be detected in about 1-17 % of gastric carcinomas (Shibata and Weiss, 1992; Tokunaga et al., 1993; Corvalan et al., 2001; Morewaya et al., 2004; Burgess et al., 2002). Most of the studies reported so far showed that the proportion of EBV-associated gastric carcinoma (EBV-GC) in male patients with gastric carcinoma was higher than that in female patients. Among the highest gender ratios were 7.0 observed in Caucasians living in Los Angeles (Shibata and Weiss, 1992), and 6.2 in Russians (Galetsky et al.,1997). On the other hand, studies in Mexico (Herrera-Goepfert et al., 2005) and an area near Shanghai (Qiu et al., 1997) reported the gender ratio of a mere 1.2 and 1.9, respectively. Japanese Brazilians did not show such a male predominance (Koriyama et al., 2001), either. The male predominance of EBV-GCs suggests the involvement of environmental factors in EBV-GC. The notion seems also be supported by the fact that the magnitude of male predominance is different from area to area. It is also known that the proportion of EBV-GC in remnant gastric cancers, occurring in the remaining part of the stomach after partial gastrectomy, is quite high (as high as 25%) (Yamamoto et al., 1994; Chang et al., 2000). The high frequency of EBV-GC in remnant stomach cancer suggests a possibility that mechanical injuries of stomach membrane are involved in the development of EBV-GC.

Recently, a Japanese study conducted by our group showed a significant difference in the frequency of salty foods intake between EBV-GC and non EBV-GC cases. In addition, EBV-GC cases tended to be exposed to wood dust and/or iron filings and tar although these associations were not

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statistically significant. Those findings, together with a high frequency of EBV-GC among remnant cancers after partial gastrectomy, suggest an association between mechanical injuries to stomach membrane and the risk of EBV-GC (Koriyama et al., 2005).

In the present study, we interviewed patients with gastric carcinomas in Colombia, and made comparison between EBV-GC and non EBV-GC cases with respect to environmental factors, including life-styles and other factors.

Subjects and Methods

The study subjects were gastric carcinoma patients newly diagnosed during the period between September, 2000 and, June 2003 in the following four reference hospitals in Colombia: Instituto de los Seguros Sociales "Rafael Uribe Uribe", Hospital Universitario del Valle, Hospital San Juan de Dios in Cali, and Instituto Nacional de Cancerologia in Bogota. 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.

We examined formalin-fixed paraffin-embedded blocks of 368 cases with gastric carcinomas, mainly surgically resected tumors. Histological diagnosis was made on the basis of Japanese classification (Japanese Research Society for Gastric Cancer, 1995). Briefly, histological patterns were classified 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. In data analysis, intestinal (tub1, tub2, muc) and diffuse type (por1, por2, sig) of Lauren was used (Lauren, 1965). 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 (Japanese Research Society for Gastric Cancer, 1995). We could not obtain the information on tumor location for 24 cases.

The interview was conducted during the period from September, 2000 to June 2003. All subjects were interviewed during hospitalization. We used a questionnaire to obtain the personal and family information of all subjects as well as lifestyles, dietary intakes, culinary uses, and occupational exposure. The Institutional Review Board of the Faculty of Health, Universidad del Valle, Cali, Colombia, approved this study and all subjects gave informed consent.

The ISH assay of paraffin-embedded tissue samples was conducted using a digoxigenin-labeled EBER-1 oligonucleotide probe as described before (Chang et al., 1992). A case was considered to be EBER positive on the basis of an intensive nuclear dark purple signal under microscopy. In every ISH assay, lymph node sections from a patient with infectious mononucleosis and a sense probe for EBER-1 were used as positive and negative controls, respectively. In the present study, the case with EBER-1-positive tumor cells but not in the surrounding normal epithelial cells was determined to be an EBV-GC, and we defined the case with EBER-1-negative tumor cells as a non EBV-GC.

In data analyses, answers to the questions of fruit and vegetable intakes, the way of cooking and so on were dichotomized as follows: “yes” (more than 3 times per week) and “no” (equal to or less than 3 times per week). 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, there were 9.5% of the cases and 7.3 % of the controls having answered “sometimes”. The association between EBV-GC risk and each factor was analyzed using 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.

Table 1. Clinicopathological Features of EBV-GCs (40) and non EBV-GCs (326)

	EBV-GC		non EBV-GC		
	N	(%)	N	(%)	P value[1]
Gender					0.001
Female	8	(19)	130	(40)	
Male	34	(81)	196	(60)	
Age			(P for trend)		0.269
- 49	11	(26)	69	(21)	
50-	6	(14)	60	(18)	
60-	16	(38)	87	(27)	
70+	9	(22)	110	(34)	
Histological type					0.002
Intestinal	15	(36)	189	(58)	
Diffuse	27	(64)	137	(42)	
Tumor depth					0.885
Early	4	(10)	36	(11)	
Advanced	20	(47)	155	(48)	
Unknown	18	(43)	135	(41)	
Tumor location					0.399
Upper third	4	(9)	43	(13)	
Middle	16	(38)	72	(22)	
Lower third	20	(48)	189	(58)	
Unknown	2	(5)	22	(7)	
Institution[2]					0.044
ISS	8	(19)	32	(10)	
HUV	5	(12)	71	(22)	
HSJD	5	(12)	26	(8)	
INC	24	(57)	197	(60)	

[1]P values were obtained by likelihood ratio test using gender, age, histology, and institution as covariates. [2]ISS: Instituto de los Seguros Sociales "Rafael Uribe Uribe", HUV: Hospital Universitario del Valle, HSJD: Hospital San Juan de Dios, INC: Instituto Nacional de Cancerologia

Results

Demographic and clinico-pathological features of EBV-GC and non EBV-GC patients are compared in Table 1. The P values presented here were obtained by logistic analysis models including gender, age (continuous), histology, and institution as covariates. As expected, the male predominance of EBV-GC was evident. There was no difference in the age distribution between EBV-GC and non EBV-GC cases. The diffuse type of Lauren classification was more frequently observed in EBV-GCs (P=0.002). On the other hand, EBV-GC was less frequently observed in the lower third of the stomach but the observed difference in the distribution of tumor location was not statistically significant. The frequency of EBV-GC in patients from Hospital Universitario del Valle (6%) was the lowest among those of 4 institutions.

Table 2 shows the results of comparison with respect to the non-dietary factors that showed differences between EBV-GCs and non EBV-GCs in Japanese study (Koriyama et al., 2005). In this logistic analysis, the effects of gender, age, histological type, and institution were adjusted. EBV-GCs were significantly related to the birth order of patients (P for trend=0.025). Apparently, the frequency of EBV-GCs among the patients born as the eldest child was lower than others (OR=0.2, 95%CI=0.1-0.8, P=0.007). This association was observed regardless of the number of siblings (data not shown). On the other hand, the number of siblings was not significantly related to the frequency of EBV-GCs. There were 11 patients who was the only child of a family and none of them was an EBV-GC patient. The frequency of the only child was not significantly different in EBV-GC and non EBV-GC cases (P =0.620, Fisher's exact test).

Smoking or dust exposure was not related to the frequency of EBV-GC (Table 2). Metal dust exposure was,

Table 2. Comparison of Non-dietary Factors Between EBV-GCs and non EBV-GCs

	EBV-GC	non EBV-GC	OR (95%CI)[1]	P value[2]
Birth order[3]			P for trend =0.025	
			P for heterogeneity = 0.077	
1	3	82	1.0 (referent)	
2	11	85	3.4 (0.9 – 13.0)	
3	12	68	4.9 (1.3 – 18.8)	
4-5	7	57	3.8 (0.9 – 16.1)	
6+	8	33	5.7 (1.3 – 24.3)	
Number of Siblings[3]			P for trend =0.238	
			P for heterogeneity = 0.117	
1-	5	48	1.0 (referent)	
3-	12	123	1.1 (0.4 – 3.4)	
5-	5	62	0.9 (0.2 – 3.6)	
7-	10	33	3.7 (1.1 – 13.1)	
9+	9	59	1.6 (0.4 – 5.4)	
Cigarette smoking[4]			P for trend=0.289	
			P for heterogeneity=0.565	
Never	17	175	1.0 (referent)	
Current	10	70	1.2 (0.5 – 3.0)	
Ex-	15	80	1.6 (0.7 – 3.5)	
Cigarettes smoked per day[4] (ex-smoker and current smokers combined)			P for trend=0.675	
			P for heterogeneity=0.208	
Never	17	175	1.0 (referent)	
1-14	19	115	1.3 (0.6 – 2.9)	
15-24	3	29	0.8 (0.2 – 3.4)	
25+	3	6	6.1 (1.1 – 33.1)	
Exposure to wood dust[5]				0.570
No	40	304	1.0 (referent)	
Yes	2	19	0.6 (0.1 – 3.1)	
Exposure to metal dust[5]				0.245
No	38	314	1.0 (referent)	
Yes	4	11	2.3 (0.6 – 8.8)	
Exposure to mineral dust[5]				0.642
No	38	292	1.0 (referent)	
Yes	4	32	0.8 (0.2 – 2.6)	

[1]Odds ratios and 95% confidence intervals were obtained by logistic regression model using gender, age, histology, and institution as covariates. [2]P values were obtained by likelihood ratio test using gender, age, histology, and institution as covariates. [3]Information on birth order and number of siblings were missing in one EBV-GC and one non EBV-GC cases.[4]Information on smoking was missing in one non EBV-GC case.[5]Information on exposure to wood, metal, and mineral dusts were missing in 3, 1, and 2 non EBV-GC cases, respectively.

Table 3. Comparison of Dietary Factors between EBV-GCs and non EBV-GCs

	EBV-GC	non EBV-GC	OR (95%CI)[1]	P value[2]
Salting meals before tasting				0.182
No	33	272	1.0 (referent)	
Yes	9	54	1.8 (0.8 - 4.3)	
Frequent fruit intake				0.809
No	5	42	1.0 (referent)	
Yes	37	284	0.9 (0.3 – 2.5)	
Frequent vegetable intake[3]				0.753
No	5	42	1.0 (referent)	
Yes	37	283	1.2 (0.4 - 3.4)	
Steaming foods				0.740
No	26	199	1.0 (referent)	
Yes	16	127	0.9 (0.4 - 1.8)	
Frying foods				0.976
No	12	96	1.0 (referent)	
Yes	30	230	1.0 (0.4 - 2.3)	
Smoking foods				0.499
No	38	286	1.0 (referent)	
Yes	4	40	0.7 (0.2 – 2.2)	
Cooking with oven				0.411
No	36	269	1.0 (referent)	
Yes	6	57	0.7 (0.2 - 1.8)	
Cooking with coal[4]				0.197
No	34	245	1.0 (referent)	
Yes	8	80	0.5 (0.2 - 1.4)	
Roasting foods				0.059
No	28	189	1.0 (referent)	
Yes	14	137	0.5 (0.2 - 1.0)	

[1]Odds ratios and 95% confidence intervals were obtained by logistic regression model using gender, age, histology, and institution as covariates. [2]P values were obtained by likelihood ratio test using gender, age, histology, and institution as covariates. [3]Information on vegetable intake was missing in one non EBV-GC case. [4]Information on cooking with coal was missing in one non EBV-GC case.

however, more frequently observed among EBV-GC patients although the difference was not significant.

Table 3 summarizes the results of comparison for dietary habits between EBV-GC and non EBV-GC. Salting foods before tasting was more frequently observed in EBV-GC patients but the difference was not statistically significant. Other factors related to dietary habit showed no significant difference between EBV-GC and non EBV-GC, either.

Discussion

The clinicopathological features of EBV-GC observed in the present study are similar to what has been reported in the literature (Takada, 2000). We observed an association between birth order and the frequency of EBV-GC in the present study. EBV-GC patients were evidently less frequent among eldest sons and daughters (P=0.007). However, this association was contrary to what was observed in the Japanese study, where EBV-GC patients tended to be elder brothers and sisters (Koriyama et al., 2005). Since the low EBV-GC risk in the patients who was the eldest child in a family was observed regardless of the number of siblings (OR=0.3, 95%CI=0.1-0.9, P=0.015), it is of interest to examine the EBV-GC risk among only child of a family. However, the number of only child was too few to address this question.

Age at first infection is suspected to play important roles for hepatocellular carcinomas related to Hepatitis B virus (HBV), and Hodgkin's diseases related to EBV (Pearce et al., 1988; Yeoh, 1990; Gutensohn and Cole, 1981). For example, in the case of HBV, its infection before ages around 3 is important to establish the HBV carrier state, which is related to an elevated hepatocellular carcinoma risk (Pearce et al., 1988; Yeoh, 1990). In the case of Hodgkin's disease, the delay of first EBV infection until adolescence is related to an increased risk of this disease (Gutensohn and Cole, 1981).

In all countries, most of people get infected with EBV by their adolescence (Straus et al., 1993; Rickinson and Kieff, 1996). However, eldest brothers and sisters in a family are considered to get the first EBV infection at older ages than younger brothers since the lack of elder brothers or sisters decreases the chance of EBV infection. Therefore, the decreased EBV-GC risk among eldest children, observed in the present study, suggests that first EBV infection at older ages is related to a decreased EBV-GC risk. As pointed out earlier, a Japanese study made an observation contrary to ours (Koriyama et al., 2005); the eldest and second eldest children had an increased risk of EBV-GC, suggesting that first EBV infection at older ages is related to an increased EBV-GC risk. A possible explanation for the apparently conflicting results is that EBV-GC risk is related to the age at first EBV infection but the relationship is not monotonic. Suppose that EBV-GC risk is the highest among the subjects with the first EBV infection at ages around 3, and that the risk decreases among the subjects with the first EBV infection at ages younger or older than age 3. Under this assumption, EBV-GC risk is decreased among eldest children in the population where most of children get EBV infection at ages much older than age 3 since being the eldest child delays the age at first EBV infection. On the other hand, in the population where most of children get EBV infection by age 3, EBV-GC risk is increased among eldest children since being eldest children increases the chance of EBV infection at ages closer to age 3.

In Japan, it is reported that EBV infection occurs in early childhood (until age 3) in most of people (more than 90%) in old generations (Hinuma et al., 1969; Shinkura et al., 2000; Kanegane et al., 1997), which were the subjects of the Japanese study we mentioned. Regarding the EBV seroprevalence in Colombia, Niederman et al. (1970) investigated the presence of EBV antibody among 18-20 year-old Colombian military recruits in 1966, and 89% of them (95 out of 109 subjects) were sero-positive for EBV antibody. In another study, the EBV antibody prevalence at ages 4-6 years was around 55-75% among Brazilian and Mexican populations, which is higher than in Western countries but relatively lower than in Asian and African countries (Niederman and Evans, 1997). Ferres et al. (1995) reported that around 30% and 75% of children from families in high and low/middle socioeconomic levels, respectively, got the first EBV infection by the age three in Chile. These observations suggest that most of Latin American population including Colombia may get the first EBV infection at ages older than Japanese population because of different cultural practices such as sharing a room although we do not have data of seroprevalence among Colombian children. Carrascal et al. (2003) reported an age-dependent increase of the EBV-GC frequency in Colombia and their results suggested that the incidence of EBV-GCs may reach its peak in their seventies or eighties. Interestingly, on the other hand, nasopharyngeal carcinoma (NPC) in southern China, another EBV-related malignancy, has the incidence reaching its peak in ages of 40-60 years. Thus, the peak incidence of EBV-GC is much older than that of NPC, and these results suggest that the age at first EBV infection or the age at exposure to yet-unknown cofactor(s) may be much older in Colombian EBV-GC patients than in Chinese NPC cases.

In the analysis of lifestyle-related factors, we showed that salt intake and metal dust exposure may be related to EBV-GCs as reported by a Japanese study (Koriyama et al., 2005). Although these observations suggested an association between mechanical injuries to the stomach membrane and the high frequency of EBV-GCs, this hypothesis cannot explain rare EBV-associated cancer in the esophagus. Zur Hausen et al. (2004) proposed a hypothesis that EBV infection is just a late event in gastric carcinogenesis since they observed that EBV could only infect neoplastic gastric cells. Further studies are required to clarify the aetiological role of EBV infection in the carcinogenesis of EBV-GC.

In conclusion, the present study has shown that EBV-GC is less frequently observed among patients who were the eldest child of a family. The finding appears to be at variance with what was observed in a similar study in Japan.

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