Medical History and Lifestyle Factors Contributing to Epstein-Barr Virus-Associated Gastric Carcinoma and Conventional Gastric Carcinoma in Korea

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Abstract. *Background: Epstein-Barr virus-associated gastric carcinoma (EBV-GC) has been characterized as a special gastric cancer subset. Lifestyle and other major factors that may contribute to EBV-GC and non-EBV-GC were investigated here. Materials and Methods: A total of 247 patients with gastric cancer were interviewed, clinicopathological information was retrieved, and in situ hybridization was performed for EBV-encoded small RNAs. Results: There were 18 EBV-GC (male:female=17:1) and 229 non-EBV-GC patients (male:female=161:68). A history of previous gastric ulcer was associated with EBV-GC, whereas frequent and heavy alcohol drinking was related to non-EBV-GC. Additionally, skipping breakfast was correlated with EBV-GC in male patients. Other factors, such as body mass index, history of gastritis, Helicobacter pylori infection, ABO blood type, family history of gastric cancer, education level, marital status, occupation, family status, and dietary factors, showed no significant differences between EBV-GC and non-EBV-GC. Conclusion: A history of gastric ulcer, reflecting chemical injury to the stomach mucosa, appears to contribute to development of EBV-GC. Alcohol drinking was more related to non-EBV-GC than EBV-GC.*

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Gastric cancer is the second most common cause of cancer-related mortality and a major public health burden worldwide (1). Interestingly, there is a 15- to 20-fold difference in the risk of gastric cancer between populations at highest and lowest risk. Furthermore, the incidence observed among immigrants follows regional patterns (1), which suggests that risk of gastric cancer is influenced by environmental factors (2).

The Epstein-Barr virus (EBV) is a ubiquitous herpes virus which infects more than 90% of the worldwide adult population, and infection persists throughout life. Furthermore, EBV is considered an oncogenic virus, since it was discovered in Burkitt lymphoma cells in 1964 (3). Today, EBV is known to be etiologically linked to a diverse range of malignancies, and in 1997 was classified as a group 1 carcinogen by the International Agency for Research on Cancer (IARC) (3).

EBV-associated gastric carcinoma (EBV-GC) was first reported in 1990 (4). Recently, the worldwide occurrence of EBV-GC has been estimated to be more than 75,000 cases/year (5), which accounts for 2-18% of gastric carcinoma cases (2, 6). Previously, we reported that 5.6% of Korean gastric carcinoma cases are associated with EBV. Furthermore, we found that the clinicopathological characteristics of EBV-GC were male gender, a poorly differentiated (according to the WHO classification) or a diffuse type (according to the Lauren classification), a proximal stomach tumor location, and rich lymphoid stroma within or surrounding cancer cells (7). In addition, we also revealed that high rates of EBV-GC exist among some specific categories of gastric cancer types, such as gastric carcinoma with lymphoid stroma (8), gastric remnant cancer, and synchronous carcinoma without adenoma (9).

Few comprehensive studies have been conducted on the environmental risk factors that contribute to EBV-GC. A literature search revealed two original papers from Japan (10) and Columbia (11), and a review article that mainly focused on these two papers (2). Furthermore, no study has examined the

Table I. *Clinicopathological characteristics of EBV-GC and non EBV-GC patients.*

Variable	EBV-GC (n=18)	Non-EBV-GC (n=229)	OR (95% CI)[b]
Age (mean±SE, years)[a]	58.2±2.79	56.8±0.78	1.01 (0.97-1.06)
Gender (n, %)			
Men	17 (94.4)	161 (70.3)	1.0*
Women	1 (5.6)	68 (29.7)	0.15 (0.02-1.15)
Histological type (n, %, by WHO)			
Papillary adenocarcinoma	0	2 (1.0)	1.0
Tubular adenocarcinoma	12 (85.7)	173 (87.4)	
Well differentiated	0	23 (13.3)	
Moderately differentiated	7 (58.3)	76 (43.9)	
Poorly differentiated	5 (41.7)	74 (42.8)	
Mucinous carcinoma	0	5 (2.5)	
Signet ring cell carcinoma	2 (14.3)	15 (7.6)	
Mixed	0	3 (1.5)	
Tumor depth (n, %)			
Early	9 (52.9)	126 (56.0)	1.0
Advanced	8 (47.1)	99 (44.0)	1.22 (0.45-3.30)
Tumor location (n, %)			
Antrum	3 (17.6)	56 (29.8)	1.0
Body	4 (23.5)	43 (22.9)	2.18 (0.44-10.8)
Cardia	5 (29.4)	7 (3.7)	19.3 (3.31-112.2)**
Mixed	5 (29.4)	82 (43.6)	1.10 (0.25-4.86)
Lymph node stage (n, %)			
pN0	9 (64.3)	112 (58.3)	1.0
pN1	2 (14.3)	46 (24.0)	0.53 (0.11-2.59)
pN2	0 (0.0)	22 (11.5)	-
pN3	3 (21.4)	12 (6.3)	6.31 (1.23-32.3)
TNM stage (n, %), by AJCC			
Stage I (IA, IB)	10 (55.5)	148 (65.2)	1.0
Stage II	3 (16.7)	29 (12.8)	1.57 (0.40-6.16)
Stage III (IIIA, III3B)	2 (11.1)	37 (16.3)	0.87 (0.18-4.23)
Stage IV	3 (16.7)	13 (5.7)	6.63 (1.38-31.8)

OR, Odds ratio; CI, confidence interval; *$p<0.05$, **$p<0.01$. [a]Sex-adjusted mean value; [b]by multivariate logistic regression analysis adjusted for age and gender.

influence of a medical or family history in EBV-GC patients. In the present study, we compared the medical histories and lifestyle factors of patients with EBV-GC and non-EBV-GC, and identified factors that differentiated these two groups.

Materials and Methods

Study participants and EBV detection. The study protocol was approved by the Institutional Review Board of Hanyang University Hospital. A total of 247 gastric cancer patients that were newly diagnosed from March 2002 to June 2006 at Chungnam University Hospital in South Korea were enrolled.

To detect EBV infection within cancer cells, *in situ* hybridization was performed for EBV-encoded small RNAs on cancer tissues retained as formalin-fixed paraffin-embedded tissue blocks. Briefly, 3 μm-thick sections were cut from each paraffin block, and placed on glass slides. Tissue sections were then deparaffinized, dehydrated, digested with proteinase K, and hybridized for 2 h at 37˚C with a fluorescein-conjugated EBV oligonucleotide probe for EBV-encoded small RNAs (Novocastra, Newcastle upon Tyne, UK). Hybridization products were detected using an alkaline phosphatase-conjugated antibody to FITC [affinity-isolated rabbit F(ab')], and 5-bromo-4-chloro-3-indolylphosphate-nitroblue tetrazolium was used as an enzyme substrate to demonstrate alkaline phosphatase activity. Glass slides were counterstained with Mayer's hematoxylin. Under light microscopy, dark blue granules at the site of hybridization were interpreted as a positive signal. Only those cases with signals within cancer cell nuclei were considered to have EBV-GC.

Data extraction. A face-to-face interview was conducted by trained interviewers at the time of diagnosis or prior to surgery for gastric cancer. The questionnaire addressed demographics (age and sex), medical history (gastritis and gastric ulcer), family history of gastric cancer, socioeconomic factors (education level, marital status, occupation, and number of family members in the present and past) and lifestyle factors (smoking, alcohol drinking, and dietary information), which were assessed using the Likert scale (12, 13).

To determine body mass indices (BMIs), medical records were reviewed for information on weight and height, and BMI calculated by dividing weight (kg) by height (meters) squared. Based on the revised WHO criteria for obesity in the Asia Pacific region, patients were categorized into three groups: those with a BMI of <23 kg/m^2 were considered 'underweight or normal', those with a BMI between

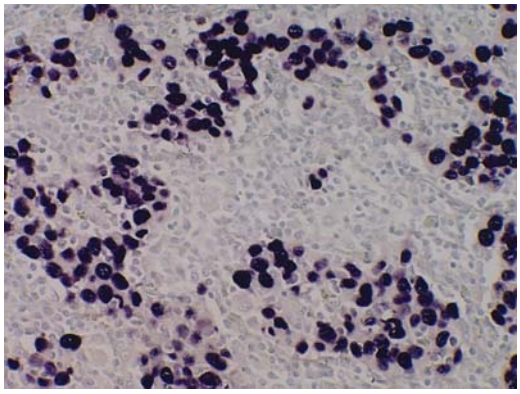

Figure 1. *In situ hybridization for Epstein-Barr virus-encoded small RNAs. Almost all cancer cell nuclei reveal positive signals in dark blue color, whereas stroma cells show no signal.*

23 and 24.9 kg/m^2 were considered 'overweight', and those with a BMI of >25 kg/m^2 or more were considered 'obese' (12). In addition, information on *Helicobacter pylori* infection and ABO blood type was retrieved from pathological reports and medical records.

To evaluate alcohol consumption, the three-tiered classification devised by the U.S. Government and issued as Recommended 'Safe' Levels for Alcohol Consumption was used: never and ex-drinkers; those that consumed ≤24 g/day for men and ≤12 g/day for women; and those that consumed >24 g/day for men and >12 g/day for women (13).

Statistical analysis. All analyses were conducted using SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA). Significant differences between EBV-GC and non-EBV-GC patients were determined using the χ^2-test for categorical variables and the *t*-test for continuous variables. Differences between the sex-adjusted mean ages of two groups were determined using the general linear model test. *P*-values of <0.05 were considered statistically significant. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated by multivariate logistic regression analysis. Age and sex were included in the logistic regression model as covariates.

Results

EBV-GC was identified in 18 patients (7.3%), and non-EBV-GC in 229 patients (Table I and Figure 1). The clinicopathological characteristics of EBV-GC and non-EBV-GC patients are summarized in Table I. In brief, EBV-GC revealed a male predominance, and cardia tumor location predisposition ($p<0.05$ and $p<0.01$, respectively). Cases with pN3 and stage IV GC were more frequently associated with, but without statistical difference.

Regarding medical and family histories, a past medical history of gastric ulcer was found to be more related to EBV-GC than to non-EBV-GC ($p<0.05$) (Table II). Obesity and a family history of gastric cancer tended to contribute to EBV-GC, but not significantly so. Unexpectedly, *H. pylori* infection seemed to be more likely in EBV-GC, but this was also not significantly so.

Socioeconomic factors, namely education, occupation, and family status, were not statistically different in the EBV-GC and non-EBV-GC groups (Table III). Furthermore, a high education level (12 years or more of formal schooling), and many family members (9 or more) during attendance at elementary school were not significantly different.

Cigarette smoking and alcohol drinking in the two groups are compared in Tables IV and V. At first glance, current smoking showed a higher OR (OR=5.4; CI=0.43-69.5) for an association with EBV-GC, and this relation was found to be significant by unadjusted analysis ($p=0.036$) (data not shown); however, this significance did not survive multivariate analysis after adjusting for age and sex. Frequent and heavy alcohol drinking were found to be significantly correlated with non-EBV-GC ($p<0.05$) (Table IV). However, when we analyzed these factors in only male patients, heavy drinking lost its significance (Table V).

In terms of dietary factors in male patients, skipping breakfast was found to be significantly associated with EBV-GC ($p<0.05$) (Table VI). Finally, a preference for Kimchi (a Korean traditional food of pickled, fermented cabbage) tended to be more related to EBV-GC than non-EBV-GC, but this was without significance.

Discussion

In the present study, a history of gastric ulcer was found to be associated with EBV-GC more than with non-EBV-GC, which suggests that chemical injury associated with peptic ulcers and prescribed medication contribute to the development of EBV-GC. Furthermore, EBV may fulfill an important role during the development of gastric remnant cancer after partial gastrectomy for a gastric ulcer, because EBV-GC is present in 27-29% of gastric remnant tumors that develop after partial gastrectomy for gastric ulcer (2, 6, 14, 15). Furthermore, it is possible that partial gastrectomy allows EBV to enter the stomach mucosa epithelium, and initiate the oncogenic process (2, 6, 14, 15). In the present study, two EBV-GC cases developed in remnant stomachs, but both had previously undergone partial gastrectomy for gastric cancer, and thus, the EBV-GCs in these cases were metachronous gastric tumors. In addition, history of a gastric ulcer was present in 33% of our EBV-GC patients and 13% of our non-EBV-GC patients. In a previous long-term follow-up study of gastric ulcer patients, refusal to undergo surgery was found to double the risk of gastric cancer, but unfortunately, no information was provided on EBV status (16).

The clinicopathological features of EBV-GC found during the present study, such as, its male predominance and a predisposition for cardia location concur with previous studies (2, 6, 7, 10, 11, 14, 17-20). As for the low proportion of women patients, the present study showed only one woman to have EBV-GC, and women comprised 30% of the total GC patients.

Table II. *Medical and family histories in the EBV-GC and non-EBV-GC groups.*

Variable	EBV-GC (n=18)	Non-EBV-GC (n=229)	OR (95% CI)[c]
History of gastric ulcer (n, %)			
No	12 (66.7)	200 (87.3)	1.0
Yes	6 (33.3)	29 (12.7)	3.36 (1.15-9.85)*
History of gastritis (n, %)			
No	15 (83.3)	161 (70.3)	1.0
Yes	3 (16.7)	68 (29.7)	0.53 (0.15-1.91)
Body mass index (n, %)[a]			
Under, Normal range (<23)	5 (33.3)	94 (46.5)	1.0
Overweight (23-24.9)	4 (26.7)	46 (22.8)	1.53 (0.38-6.06)
Obese (≥25)	6 (40.0)	62 (30.7)	1.78 (0.51-6.20)
Helicobacter pylori infection (n, %)			
No	4 (50.0)	74 (63.8)	1.0
Yes	4 (50.0)	42 (36.2)	2.06 (0.46-9.24)
Blood type (n, %)			
A	6 (40.0)	62 (35.0)	1.0
B	2 (13.3)	35 (19.8)	0.65 (0.12-3.45)
AB	1 (6.7)	22 (12.4)	0.44 (0.05-3.94)
O	6 (40.0)	58 (32.8)	0.90 (0.27-3.01)
Family history of gastric cancer (n, %)[b]			
No	12 (66.7)	186 (81.2)	1.0
Yes	6 (33.3)	43 (18.8)	1.99 (0.70-5.69)

OR, Odds ratio; CI, confidence interval; *$p<0.05$. [a]Weight divided by height squared (kg/m^2). Patients were categorized into three groups by BMI based on the re-defined WHO criteria for obesity in the Asia Pacific Region. [b]Only first-degree relatives were included. [c]By multivariate logistic regression analysis adjusted for age and gender.

Table III. *Socioeconomic variables relating to EBV-GC and non-EBV-GC patients.*

Variable	EBV-GC (n=18)	Non-EBV-GC (n=229)	OR (95% CI)[a]
Education (n, %)			
Uneducated	1 (5.6)	21 (9.4)	1.0
6-11 years	6 (33.3)	107 (48.0)	1.05 (0.11-9.93)
≥12 years	11 (61.1)	95 (42.6)	2.60 (0.27-24.7)
Marital status			
Married	18 (100.0)	201 (88.2)	1.0
Single (unmarried, divorce, bereaved)	0 (0.0)	27 (11.8)	-
Occupation (n, %)			
Non-manual	10 (55.5)	96 (41.9)	1.0
Manual	7 (38.9)	79 (34.5)	0.72 (0.26-2.01)
Other (housewife, unemployed)	1 (5.6)	54 (23.6)	0.34 (0.04-3.17)
Number of family members, at present (mean±SD)	3.28±1.23	3.21±1.40	
1-2	6 (33.3)	86 (37.6)	1.0
3-4	9 (50.0)	109 (47.6)	1.60 (0.48-5.36)
≥5	3 (16.7)	34 (14.8)	1.49 (0.33-6.72)
Number of family members, at the time of elementary school (mean±SD)	7.67±2.06	6.77±2.00	
≤5	1 (16.7)	29 (31.5)	1.0
6-8	3 (50.0)	46 (50.0)	1.73 (0.15-20.1)
≥9	2 (33.3)	17 (18.5)	3.02 (0.23-40.4)
Number of family members sharing the same bedroom, at the time of elementary school (mean±SD)	3.50±0.71	4.48±1.83	
≤3	1 (50.0)	13 (27.1)	1.0
≥3	1 (50.0)	35 (72.9)	0.33 (0.02-6.46)

OR, Odds ratio; CI, confidence interval. [a]By multivariate logistic regression analysis adjusted for age and gender.

Table IV. *Smoking and alcohol drinking habits in the EBV-GC and non EBV-GC groups.*

Variable	EBV-GC (n=18)	Non EBV-GC (n=229)	OR (95% CI)[d]
Cigarette smoking (n, %)			
Never	1 (5.6)	75 (32.8)	1.0
Ex-smoker	7 (38.9)	79 (34.5)	3.31 (0.24-45.1)
Current smoker	10 (55.6)	75 (32.8)	5.45 (0.43-69.5)
Duration of smoking (mean±SD, years)[a]	34.7±10.9	31.7±11.4	1.04 (0.97-1.11)
Pack-years (mean±SD)[a,b]	11,645±9002	11,060±6670	1.00 (1.00-1.00)
Alcohol drinking (n, %)			
Never	3 (16.7)	69 (30.1)	1.0
Ex-drinkers	7 (38.9)	31 (13.5)	2.56 (0.57-11.6)
Current drinkers	8 (44.4)	129 (56.3)	0.77 (0.18-3.25)
Frequency of alcohol drinking			
Never and ex-drinkers	10 (55.6)	100 (43.7)	1.0
<1/week	5 (27.8)	32 (14.0)	1.16 (0.35-3.84)
≥1/week	3 (16.7)	97 (42.4)	0.21 (0.06-0.80)*
Amount of alcohol drinking[c]			
Never and ex-drinking	10 (55.6)	100 (43.7)	1.0
≤24 g/day for men, 12 g/day for women	5 (27.8)	45 (19.7)	0.85 (0.26-2.71)
>24 g/day for men, 12 g/day for women	3 (16.7)	84 (36.7)	0.23 (0.06-0.90)*

OR, Odds ratio; CI, confidence interval; *$p<0.05$. [a]including only current smokers; [b]obtained by multiplying the average number of 20-cigarette packs smoked per day by smoking days. [c]Classified by U.S. Government Recommended 'Safe' Levels for Alcohol Consumption. [d]By multivariate logistic regression analysis adjusted for age and gender.

Table V. *Smoking and alcohol drinking among men in the EBV-GC and non EBV-GC groups.*

Variable	EBV-GC (n=17)	Non EBV-GC (n=161)	OR (95% CI)[d]
Cigarette smoking (n, %)			
Never	0 (0.0)	16 (9.9)	1.0
Ex-smoker	7 (41.2)	77 (47.8)	-
Current smoker	10 (58.8)	68 (42.2)	-
Duration of smoking (mean±SD, years)[a]	34.7±10.9	32.4±11.0	1.04 (0.97-1.11)
Pack-years (mean±SD)[a,b]	11,645±9002	11,414±6619	1.00 (1.00-1.00)
Alcohol drinking (n, %)			
Never	2 (11.8)	25 (15.5)	1.0
Ex-drinkers	7 (41.2)	28 (17.4)	3.13 (0.59-16.5)
Current drinkers	8 (47.1)	108 (67.1)	0.93 (0.19-4.64)
Frequency of alcohol drinking			
Never and ex-drinkers	9 (52.9)	53 (32.9)	1.0
<1/week	5 (29.4)	26 (16.2)	1.67 (0.53-5.29)
≥1/week	3 (17.6)	59 (50.9)	0.31 (0.08-1.18)
Amount of alcohol drinkingc			
Never and ex-drinkers	9 (52.9)	53 (32.9)	1.0
≤24 g/day	5 (29.4)	34 (21.1)	0.88 (0.27-2.88)
>24 g/day	3 (17.6)	74 (46.0)	0.24 (0.06-0.93)*

OR, Odds ratio; CI, confidence interval; *$p<0.05$. [a]Including only current smokers; [b]obtained by multiplying the average number of 20-cigarette packs smoked per day by smoking days. [c]Classified using the U.S. Government's Recommended 'Safe' Levels for Alcohol Consumption. [d]By multivariate logistic regression analysis adjusted for age.

Likewise, previous papers reported that there was one (7) or no woman (17, 18) with EBV-GC, and women made up 32% (7) or 30% (17, 18) of the total group. However, according to a meta-analysis (20), which included 48 studies from various regions, women comprised 20% of EBV-GC patients, and 36% of the total GC patients. Despite differences in the percentage of women among EBV-GC patients, all of the previous studies showed male predominance of EBV-GC patients.

The relationship between EBV and *H. pylori* infection has been disputed. In the present study, *H. pylori* infection appeared

Table VI. *Food preferences among men in the EBV-GC and non EBV-GC groups.*

Variable	EBV-GC (n=17)	Non EBV-GC (n=161)	OR (95% CI)[a]
Vitamin supplement intake			
No	16 (94.1)	146 (90.7)	1.0
Yes	1 (5.9)	15 (9.3)	0.60 (0.07-4.85)
Regular meal			
Like much – like	10 (58.8)	110 (68.3)	1.0
Fair	2 (11.8)	19 (11.8)	1.21 (0.24-6.01)
Dislike – dislike much	5 (29.4)	32 (19.9)	1.93 (0.57-6.57)
Regular breakfast			
Like much – like	13 (76.5)	137 (85.1)	1.0
Fair	0 (0.0)	12 (7.5)	-
Dislike – dislike much	4 (23.5)	12 (7.5)	4.24 (1.05-17.2)*
Shortage of rice, at meals			
Like much – like	9 (52.9)	59 (36.6)	1.0
Fair	3 (17.6)	31 (19.3)	0.63 (0.16-2.49)
Dislike – dislike much	5 (29.4)	71 (44.1)	0.46 (0.14-1.44)
Hot (spicy) food			
Like much – like	11 (73.4)	87 (66.9)	1.0
Fair	2 (13.3)	15 (11.5)	0.99 (0.20-4.97)
Dislike – dislike much	2 (13.3)	28 (21.5)	0.51 (0.11-2.49)
Salty food			
Like much – like	10 (66.7)	64 (49.2)	1.0
Fair	2 (13.3)	30 (23.1)	0.43 (0.09-2.08)
Dislike – dislike much	3 (20.0)	61 (27.7)	0.54 (0.14-2.11)
Soup			
Like much – like	8 (88.9)	54 (81.8)	1.0
Fair	1 (11.1)	4 (6.1)	1.52 (0.15-15.6)
Dislike – dislike much	0 (0.0)	8 (12.1)	-
Snack			
Like much – like	7 (41.2)	42 (26.1)	1.0
Fair	4 (23.5)	17 (10.6)	1.27 (0.33-4.87)
Dislike – dislike much	6 (35.3)	102 (63.4)	0.41 (0.14-1.23)
Instant food			
Like much – like	2 (18.2)	11 (11.3)	1.0
Fair	3 (27.3)	13 (13.4)	1.22 (0.17-8.72)
Dislike – dislike much	6 (54.5)	73 (75.3)	0.42 (0.07-2.43)
Consumption of green tea			
Low	13 (72.2)	156 (68.1)	1.0
Medium	3 (16.7)	46 (20.1)	0.81 (0.22-3.02)
High	2 (11.1)	27 (11.8)	0.98 (0.20-4.85)
Coffee			
Low	7 (38.9)	81 (35.4)	1.0
Medium	7 (38.9)	104 (45.4)	0.78 (0.26-2.36)
High	4 (22.2)	44 (19.2)	0.99 (0.26-3.74)
Kimchi			
Low	9 (50.0)	143 (62.4)	1.0
Medium	2 (11.1)	46 (20.1)	0.62 (0.13-3.03)
High	7 (38.9)	40 (17.5)	2.67 (0.92-7.74)

*$p<0.05$. [a]By multivariate logistic regression analysis adjusted for age.

to be higher in EBV-GC cases, but it was evaluated in only around one half of the 247 cases. In one study, all six EBV-GC cases were infected with *H. pylori* (17), whereas others have reported that rates of *H. pylori* infection are lower in EBV-GC than in non-EBV-GC, but no statistical association was found between EBV and *H. pylori* infection (18, 19, 21). Furthermore, in 2009, a meta-analysis review found no significant association between *H. pylori* infection and EBV-GC (20).

We supposed that smoking and EBV infection would be found to be independent risk factors of gastric cancer. However, in the present study, cigarette smoking as a risk factor did not show a statistically significant difference between EBV-GC and non-EBV-GC by multivariate analysis, although 'current' smokers appeared to have a higher risk of developing EBV-GC. These findings are consistent with the findings of two previous studies in which smoking was not found to be statistically significantly associated with EBV-GC, despite a high OR for EBV-GC (10, 11). In addition, according to a meta-analysis of cohort studies conducted in 2008, cigarette smoking is the most important behavioral risk factor for gastric cancer; however, EBV infection status was not evaluated (22).

In the present study, alcohol drinking was found to be statistically more related to non-EBV-GC rather than EBV-GC. This is not compatible with the findings of the only study conducted on the subject: in the Japanese study, no significant difference was found between alcohol drinking EBV-GC and non-EBV-GC cases (10). In the present study, we investigated the effects of alcohol consumption by using three categories, namely, 'experience, frequency, and amount' and assigned three grades to each (Tables IV and V), whereas the Japanese study evaluated alcohol drinking using the three items, 'never, occasional, and daily drinkers.'

In male patients, skipping breakfast, which reflects a poor overall diet quality (23), was found to be significantly more related to EBV-GC than non-EBV-GC after adjusting for age. Furthermore, in the present study, the salty food factor (including Kimchi consumption, an important part of the normal Korean diet) showed no statistical difference between the two study groups. This concurs with the findings of a Colombian study (11), but is at odds with the findings of a Japanese study in which it was found that the frequent intake of salty food is more related to EBV-GC than non-EBV-GC (10). Moreover, the general population of Korea also consumes a considerable amount of salt, thus salt intake comparisons between the patient and control group was probably misconceived (24). Furthermore, the association between salt intake and the risk of gastric cancer is debatable. On one hand, a high intake of salt and *N*-nitroso compounds (which are usually present at high concentrations in preserved meats) has been reported to be a risk factor of gastric cancer (25), but on the other, doubt has been expressed regarding the association between salty food and gastric cancer (26).

In the present study, no significant differences were found between the EBV-GC and non-EBV-GC groups with respect to socioeconomic factors, such as education level, marital status, occupation, and number of family members, and number of family members sharing a bedroom during elementary school

days. Unfortunately, we cannot refer to any literature regarding the associations between socioeconomic factors and EBV-GC. Although in two previous studies birth order patterns were found to be significantly different between EBV-GC and non-EBV-GC patients, their results were contradictory, that is EBV-GC was more prevalent (10) among eldest siblings, whereas EBV-GC was less frequent among eldest siblings (11).

Summarizing, a history of a gastric ulcer was found to be significantly associated with the development of EBV-GC rather than non-EBV-GC, which suggests that chemical injury to the stomach mucosa may allow EBV to invade the stomach mucosal epithelium, and initiate the oncogenic process. Furthermore, our findings suggest that alcohol drinking is a more potent risk factor of non-EBV-GC than of EBV-GC.

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