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Case-case comparison of smoking and alcohol risk associations with Epstein-Barr virus-positive gastric cancer

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Abstract

Helicobacter pylori is the primary cause of gastric cancer. However, monoclonal Epstein-Barr virus (EBV) nucleic acid is also present in up to 10% of these tumors worldwide. EBV prevalence is increased with male sex, non-antral localization and surgically disrupted anatomy. To further examine associations between EBV and gastric cancer, we organized an international consortium

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DISCLOSURES
The authors disclose no conflicts.

of 11 studies with tumor EBV status assessed by *in situ* hybridization. We pooled individual-level data on 2,648 gastric cancer patients, including 184 (7%) with EBV-positive cancers; all studies had information on cigarette use (64% smokers) and 9 had data on alcohol (57% drinkers). We compared patients with EBV-positive and EBV-negative tumors to evaluate smoking and alcohol interactions with EBV status. To account for within-population clustering, multi-level logistic regression models were used to estimate interaction odds ratios (OR) adjusted for distributions of sex (72% male), age (mean 59 years), tumor histology (56% Lauren intestinal-type), anatomic subsite (61% noncardia) and year of diagnosis (1983–2012). In unadjusted analyses, the OR of EBV positivity with smoking was 2.2 (95% confidence interval [CI], 1.6–3.2). The OR was attenuated to 1.5 (95% CI, 1.01–2.3) by adjustment for the possible confounders. There was no significant interaction of EBV status with alcohol drinking (crude OR, 1.4; adjusted OR, 1.0). Our data indicate the smoking association with gastric cancer is stronger for EBV-positive than EBV-negative tumors. Conversely, the null association with alcohol does not vary by EBV status. Distinct epidemiologic characteristics of EBV-positive cancer further implicate the virus as a co-factor in gastric carcinogenesis.

Keywords

Alcohol; EBV; gastric cancer; smoking; pooled-analysis

INTRODUCTION

Although chronic *Helicobacter pylori* infection is the primary cause of gastric cancer,[1] up to 10% of these tumors contain nucleic acid of the Epstein-Barr virus (EBV),[2] a carcinogenic agent implicated in the etiology of Burkitt lymphoma and nasopharyngeal carcinoma (NPC).[3] Tumor cells of EBV-positive gastric cancer uniformly have monoclonal viral episomes,[4] indicating the virus was present at the time of initial transformation and is required for maintenance of the transformed phenotype. These molecular features suggest that EBV coinfection may play a role in gastric carcinogenesis. To examine epidemiologic associations between EBV and gastric cancer with sufficient statistical power, we have organized an international consortium of multiple case series and case-control studies with assessment of tumor EBV status by *in situ* hybridization.

Etiologic heterogeneity of tumor subtypes (e.g., classified by histology, anatomical location or molecular characteristics) is frequently evaluated in case-control comparisons of potential risk factors in which each subtype is compared with a common control group. However, Begg and Zhang[5] have demonstrated that the most efficient way to identify etiologic heterogeneity is by directly comparing risk profiles of the subtypes in a case-only study design. Following this analytical approach, we compared smoking and alcohol behaviors between patients with EBV-positive and EBV-negative gastric cancers to identify potential differences in risk associations.

METHODS

Data sources

We pooled individual-level data of 11 gastric cancer case series and case-control studies from Asia (n=5),[6–10] Europe (n=2),[11, 12] and Latin America (n=4; the Mexican study at IMSS is ongoing),[13–15] including three that have previously published data on associations of tumor EBV positivity with smoking and alcohol.[6, 9, 13] On a total of 2,648 patients diagnosed between 1983 and 2012, of whom 184 (7%) had EBV-positive tumors, we included data on cigarette smoking, alcohol consumption, and potential confounders. For all cases, the presence of EBV in cancer cells was assessed by *in situ* hybridization for EBV-encoded RNA (EBER), the gold standard assay for detecting latent infection.[16] For the cases from Mexico City at IMSS, EBER expression in formalin-fixed paraffin-embedded tumors (as tissue microarrays, with inclusion of known EBER-positive and -negative tumors as controls) was detected with an automated method, as previously described.[15] For the remaining case series, EBV results were previously reported based on the same automated method or a manual staining method that has shown excellent agreement in validation work.[15] Each contributing study received local institutional review board approval, and written informed consent was obtained for all study participants.

Statistical analyses

In this case-only analysis, logistic regression models including a study-specific random intercept were used to separately estimate summary odds ratios (OR) with 95% confidence intervals (CI) of tumor EBV positivity with cigarette smoking (available for all 11 studies) and with alcohol consumption (available for 9 studies which included 134 of the EBV-positive cases). These exposures were categorized as current and former or ever *vs*. never since quantitative data were not consistently available. The interaction OR derived from this case-only analytic approach is the same parameter as the ratio of the subtype-specific ORs from case-control comparisons.[5] ORs were adjusted in multivariable models including age at diagnosis (categorized as quartiles), sex (male *vs.* female), year of diagnosis (categorized as quartiles), anatomic subsite (cardia, noncardia, overlapping subsites, unspecified or surgical stump), and Lauren histologic type (intestinal, diffuse, mixed or unspecified). For studies using the Japanese histological classifications, tubular, papillary and mucinous adenocarcinomas were considered intestinal-type, and poorly differentiated adenocarcinoma, signet-ring cell carcinoma and lymphoepithelioma-like carcinoma were considered diffuse-type.[17] Fifty-seven percent of cases (n=1515; six studies) also had information on level of education, which was used for a sensitivity analysis. All p-values were two-sided, and a value less than 0.05 was considered statistically significant. Statistical analyses were performed in Stata (version 10; Stata Corp, College Station, Texas, U.S.).

RESULTS

For the patients with EBV-positive and EBV-negative tumors combined, mean age at diagnosis was 59 years and 72% were males (Table 1). Sixty-four percent of patients ever smoked cigarettes and 57% ever drank alcohol. Most of the tumors were localized to noncardia subsites (61%), and classified histologically as Lauren intestinal-type (56%).

In unadjusted analysis, the interaction OR of EBV status with ever smoking was 2.2 (95% CI, 1.6–3.2), and did not substantially differ between current and former use (ORs, 2.4 and 2.0, respectively). The OR was attenuated to 1.5 (95% CI, 1.01–2.3; p=0.04) by adjustment for the potential confounders. Restricting to the six studies with data on level of education, adjusted ORs were 1.7 (95% CI, 0.8–3.6) with, and 1.6 (95% CI, 0.8–3.5) without, further adjustment for this variable.

The crude interaction OR of EBV status with alcohol consumption was 1.4 (95% CI, 0.9–2.0) and remained non-significant in multivariable models with (adjusted OR, 1.1, 95% CI, 0.7–1.7) and without (adjusted OR, 1.0, 95% CI, 0.7–1.6) inclusion of smoking.

Regarding additional covariables, sex, histologic subtype, and anatomic subsite were statistically significant determinants of tumor EBV positivity (Figure). Specifically, tumors in males and with diffuse- or mixed-type histology were more likely to be EBV-positive. As compared to tumors localized to the cardia, tumors arising in noncardia sites had similar prevalence of EBV, whereas tumors of overlapping subsites or post-gastrectomy remnants had increased EBV prevalence. EBV positivity did not significantly differ by age or year of diagnosis. In general, these unadjusted association patterns remained in all multivariable models.

DISCUSSION

Cigarette smoking is a recognized risk factor for gastric cancer overall.[18–20] In our case-only analysis, we found variation of the smoking association by tumor EBV status, implying their interaction in gastric carcinogenesis. Three previous studies addressing this etiologic heterogeneity, and encompassed in the present aggregated analysis, found non-significant variations based on small numbers of EBV-positive tumors.[6, 9, 13]

A meta-analysis of 18 international prospective studies of gastric cancer found significant summary relative risks of 1.6 for current smokers and 1.3 for former smokers, both compared with never smokers.[19] Given this difference in risk for gastric cancer overall, our finding of a 1.5-fold interaction with EBV status indicates that EBV-positive gastric cancer is 2.4 times more frequent in current smokers and 2.0 times more frequent in former smokers.

The mechanisms underlying higher gastric cancer risk for smokers are incompletely elucidated. Tobacco carcinogens may directly damage the gastric mucosa[21] and, indirectly, smoking may favor *H. pylori* infection persistence[22] and diminish efficacy of anti-*H. pylori* eradication treatment.[23] Alternatively, the interaction of smoking with EBV-positive gastric cancer may be mediated by EBV reactivation. Cigarette smoke extract induces EBV reactivation in the EBV-positive cell lines Akata and B95-8.[24] Smoking is also associated with risk of NPC, another EBV-associated malignancy, as well as with immunoglobulin A antibodies to the EBV viral capsid antigen in subjects without NPC.[24] In addition, smoking is associated with risk of EBV-positive, although not EBV-negative, Hodgkin lymphoma.[25]

Regarding an association with alcohol consumption, we found no heterogeneity by tumor EBV status. The potential role of alcohol in gastric carcinogenesis is still uncertain.[20] An

international meta-analysis of the association between alcohol drinking and gastric cancer found a significantly increased risk only with heavy consumption (≥4 drinks per day).[26] A meta-analysis restricted to Latin American populations[27] found an increased risk of gastric cancer in drinkers overall compared to never drinkers, which may be related to greater alcohol consumption and/or differences in the type of alcohol consumed in the Americas as compared to other parts of the world.[28] Unfortunately, we could not rule out an effect restricted to heavy drinking because data on amount and frequency of alcohol consumption was available only for a limited number of cases. Future studies of EBV-positive gastric cancer should assess possible quantitative associations with alcohol consumption.

Gastric cancer is more common in developing countries, [29] and risk in both high and low incidence areas is inversely associated with markers of socioeconomic status (SES), such as level of education.[30] In a subset of studies for which data on education were available, further adjustment for this variable did not materially change the magnitude of the association with smoking. Thus, the association that we found between tumor EBV status and smoking likely would not be explained by confounding with SES.

We found that smoking disproportionally increases the risk of EBV-positive gastric cancer. Previous reports have indicated that EBV-positive gastric tumors tend to be proximally located, account for a greater proportion of cases in males than in females, are found more commonly in surgically disrupted anatomy,[2, 31, 32] and have a better overall survival as compared to EBV-negative tumors.[33] Also, elevated titers against proteins related to EBV reactivation have been shown to precede development of premalignant[34] and malignant gastric lesions,[35] or are associated with EBV-positive gastric cancer.[36, 37] Taken together, the combined epidemiologic evidence supports an etiologic role of EBV as a co-factor in gastric carcinogenesis. Our finding also warrants lifestyle modifications to reduce smoking in post-gastrectomy patients, and other populations at high risk of EBV-positive gastric tumors.

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APPENDIX

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WHAT IS NEW?

While chronic *Helicobacter pylori* infection is the primary cause of gastric cancer, Epstein-Barr virus (EBV) nucleic acid is present in a subset of these tumors. EBV-positive gastric cancer is differentially associated with smoking, but not associated with alcohol consumption. These behavioral data add to previous studies by us and others identifying demographic, clinicopathological and genetic features that distinguish EBV-positive and EBV-negative gastric cancers. Taken together, this evidence suggests an etiologic role of EBV as a co-factor in gastric carcinogenesis. Our findings provide additional rationale for cigarette cessation in population groups at high risk of EBV-positive gastric cancer.

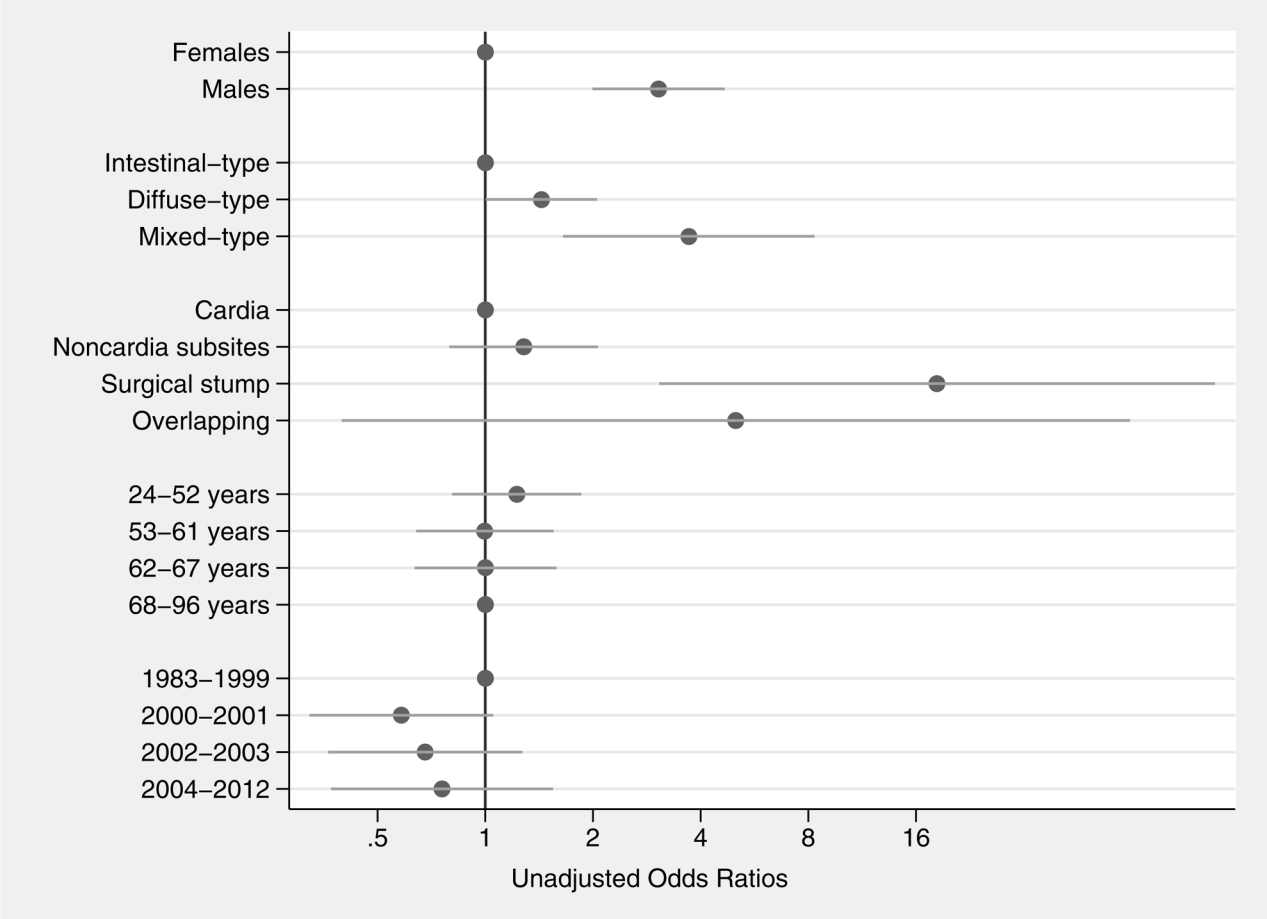

Figure 1.

Figure Unadjusted odds ratios and 95% confidence intervals for the associations of sex, subsite, histologic type, age and year of diagnosis with gastric tumor EBV-positivity

Table 1

Selected characteristics of the study populations

Continent	Country (city)	EBV-positive cases/EBV-negative cases	Period of diagnosis	Age in years, mean (range)	Males, %	Smokers, %	Drinkers, %	High school or less education, %	Tumor characteristics, %[1]	
									Noncardia[2]	Intestinal-type
ASIA	China (Hong Kong)	6/39	1999–2006	55 (26–80)	60	29	13	79	64	80
	China (Shanxi)	21/1018	1996–2004	58 (26–79)	81	71	58	-	35	54
	Japan (Kagoshima)	43/162	1996–2001	65 (31–88)	70	65	68	-	78	69
	Japan (Nagoya)	20/351	2001–2005	58 (27–79)	73	67	36	-	-	33
	Korea (Seoul)	18/229	2002–2006	57 (24–81)	72	69	71	88	94	92
EUROPE	Eurgast-EPIC[3]	4/83	1994–2002	62 (34–77)	70	70	87	88	67	50
	Poland (Warsaw)	11/76	1994–1996	60 (30–80)	68	86	76	69	80	87
AMERICAS	Colombia (Cali)	42/326	2000–2003	61 (24–96)	63	48	-	-	86	55
	Honduras (Santa Rosa de Copan)	3/32	2003	63 (40–83)	63	43	43	-	100	47
	México (México City at INCAN[4])	8/127	1983–2000	57 (26–85)	50	46	-	95	98	42
	México (México City at IMSS[5])	8/21	2009–2012	65 (29–91)	41	34	44	90	92	50
ALL	-	184/2,464	1983–2012	59 (24–96)	72	64	57	82	61	56

[1] excluding unspecified cases.

[2] including subsite localization to fundus, corpus, antrum, pylorus, lesser and greater curvatures.

[3] Eurgast-EPIC, European Prospective Investigation into Cancer and Nutrition cohort, which includes cases from Denmark, Germany, Greece, Italy, Netherlands, Spain, and United Kingdom.

[4] INCAN, Instituto Nacional de Cancerología.

[5] IMSS, Instituto Mexicano de Seguro Social; study on going.