Associations Between Gastric Cancer Risk and Virus Infection Other Than Epstein-Barr Virus: A Systematic Review and Meta-analysis Based on Epidemiological Studies

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INTRODUCTION: Besides Helicobacter pylori and Epstein-Barr virus, other viruses might play potential roles in gastric carcinogenesis. This systematic review and meta-analysis was conducted to compare the prevalence of the viruses between gastric cancer (GC) and any controls.

METHODS: Comprehensive literature was searched up to January 25, 2019, and search was updated on April 6, 2020. The studies that compared the prevalence of viruses other than Epstein-Barr virus between GC and healthy or nonmalignant controls were eligible. Stata 12.0 software was used for heterogeneity tests and meta-analyses. Meanwhile, subgroup analysis, sensitivity analysis, and publication bias evaluation were performed where applicable. The power (1–β) was estimated by the PASS 11 software for each individual study.

RESULTS: A total of 41 eligible studies were included, concerning 11 kinds of viruses. Prevalence were significantly higher in GC for hepatitis B virus (odds ratio [OR] = 1.39, 95% confidence interval [CI] 1.11–1.75), human cytomegalovirus (OR = 2.25, 95% CI 1.14–4.43), human papillomavirus (HPV) (OR = 1.63, 95% CI 1.05–2.54), and John Cunningham virus (OR = 2.52, 95% CI 1.26–5.04). In subgroup analyses, HPV-16 infection was significantly associated with GC (OR = 2.42, 95% CI 1.00–5.83).

DISCUSSION: This study demonstrated that hepatitis B virus, human cytomegalovirus, HPV, and John Cunningham virus were more prevalent in GC. However, the causal relationship between their infection and risk of GC remains inconclusive, and further investigations are required.

SUPPLEMENTARY MATERIAL accompanies this paper at https://links.lww.com/CTG/A299, links.lww.com/CTG/A294, links.lww.com/CTG/A295, links.lww.com/CTG/A296, links.lww.com/CTG/A297, http://links.lww.com/CTG/A298, links.lww.com/CTG/A333

INTRODUCTION

It is estimated that up to 50% of human cancers are caused by infectious agents. Viruses are responsible for 10%–15% particularly (1). As one of the most common cancers worldwide, the pathogenesis of gastric cancer (GC) remains unclear (2). Helicobacter pylori and Epstein-Barr virus (EBV) have been recognized as infectious agents, and the potential mechanisms inducing gastric carcinogenesis are well established (3–7). Almost 50% of the global population is infected with H. pylori, and 1% of them develop GC (7). Similarly, EBV is estimated to be responsible for 5.6%–19.5% of cases with GC globally (8).

In addition to H. pylori and EBV, other viruses might play potential roles in gastric carcinogenesis. A potential association between hepatitis B virus (HBV) and the risk of GC was found in a case–control study (9). Del Moral-Hernández et al. (10) considered human cytomegalovirus (HCMV) infection might contribute to gastritis and GC etiology. The role of HPV in GC is also indicated in several studies (11–14). Several sporadic studies sought to attach viruses other than EBV to the risk of GC; however, there is no comprehensive review to identify any potentially causative virus until now. Therefore, we performed this systematic review and meta-analysis to clarify the associations between the prevalence of...
viruses other than EBV and the risk of GC based on epidemiological studies.

**METHODS**

**Reporting**

This meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) 2000 statements, and a flow diagram was plotted (15,16). Details of study design have been reported elsewhere (17).

**Literature search**

PubMed, Embase, Cochrane Library, and Web of Science databases were searched up to January 25, 2019, and search was updated on April 6, 2020. The PubMed was searched with the following search terms,
| Study                     | Year | Country | Design | Participants                                                                 | Virus type | Age (median or mean ± SD, yr) | Sex (female/male) |
|--------------------------|------|---------|--------|------------------------------------------------------------------------------|------------|------------------------------|------------------|
| Ghasemi et al. (27)      | 2012 | Iran    | CCS    | 100 cases with GC and 100 normal controls                                     | HBV        | 67.14 ± 10.98 NA             | 31/69            |
| Wei et al. (47)          | 2017 | China   | CCS    | 2,318 cases with GC and 5,715 noncancer controls                             | HBV        | NA NA                        | 3,821/1,894      |
| Mahale et al. (35)       | 2019 | USA     | CCS    | 34,412 cases with GC and 200,000 cancer-free controls frequency-matched on age, calendar year of selection, sex, and race | HBV        | NA NA                        | 96,319/103,681   |
| Fattahi et al. (26)      | 2018 | Iran    | CCS    | 63 cases with GC and 21 normal controls                                      | HBV        | 68 NA                        | 12/51            |
| An et al. (56)           | 2018 | Korea   | CCS    | 16,350 cases with GC and 118,891 healthy controls                            | HBV        | NA NA                        | 55,020/63,871    |
| Song (55)                | 2019 | China   | CCS    | 118 cases with GC and 472 healthy controls                                   | HBV        | NA NA                        | NA               |
| Baghbanian et al. (52)   | 2019 | Iran    | CSS    | 35 cases with GC and 259 normal controls                                     | HBV        | NA NA                        | NA               |
| Matveeva et al. (37)     | 2013 | Russian | CCS    | 30 cases with GC, 60 cases with chronic gastritis, 60 cases with ulcer, and 30 normal controls | HCMV       | NA NA                        | NA               |
| Jin et al. (30)          | 2014 | China   | CCS    | 60 cases with GC and 60 PCNT as controls                                     | HCMV       | NA NA                        | NA               |
| Zhang et al. (51)        | 2017 | China   | PCS    | 80 cases with GC and 80 age- and sex-matched healthy controls                | HCMV       | 64.32 ± 9.70 62.82 ± 8.99    | 27/53            |
| Del Moral-Hernández et al. (10) | 2019 | Mexico | CSS    | 32 cases with GC and 106 chronic gastritis controls                          | HCMV       | 63.00 ± 13.00 50.00 ± 17.00  | 17/15            |
| Fattahi et al. (26)      | 2018 | Iran    | CCS    | 63 cases with GC and 21 normal controls                                      | HCMV       | 68 NA                        | 12/51            |
| Mahmood et al. (36)      | 2018 | Iraq    | CCS    | 30 cases with GC and 100 normal controls                                     | HCV        | NA NA                        | NA               |
| Bai et al. (21)          | 2018 | China   | CCS    | 53 cases with GC and 950 sex-, age-, and area of residence-matched healthy controls | HEV        | NA NA                        | NA               |
| Kayamba et al. (32)      | 2013 | Zambia  | CCS    | 52 cases with GC and 94 controls with symptoms of dyspepsia but no mucosal abnormality seen at endoscopy | HIV        | 60.60 54.10                 | 21/31            |
| Anwar et al. (12)        | 1995 | Japan   | CCS    | 51 cases with GC and 12 specimens of normal stomach from patients who had died of causes other than malignancy and immunocompromised diseases as controls | HPV-16     | 66.90 63.60                 | 20/31            |
| Strickler et al. (43)    | 1998 | USA     | CCS    | 49 cases with GC and 48 noncancer controls                                   | HPV-16     | 63 51                        | 5/44             |
| Xu et al. (14)           | 2003 | China   | CCS    | 74 cases with AEG, 102 cases with GC, and 50 normal controls                | HPV-16     | NA NA                        | NA               |
| Van Dommun et al. (46)   | 2003 | Sweden  | CCS    | 54 cases with GC and 100 age- and sex-matched noncancer controls             | HPV-16     | 61.50 61.80                 | 17/37            |
| Study                  | Year  | Country | Design | Participants                                                                 | Virus type       | Age (median or mean ± SD, yr) | Sex (female/male) |
|-----------------------|-------|---------|--------|-----------------------------------------------------------------------------|------------------|------------------------------|-------------------|
|                       |       |         |        |                                                                             |                  | Cases Controls               | Cases Controls    |
| Kamangar et al. (31)  | 2006  | China   | CCS    | 100 cases with AEG, 70 cases with GC, and 381 sex- and age frequency-matched noncancer controls | HPV-16, HPV-18, HPV-73 | 57.0 ± 2.87, 55.0 ± 9.00 | 68/102, 194/187   |
| Ma et al. (13)        | 2007  | China   | CCS    | 40 cases with GC and 40 PCNT as controls                                      | HPV-16           | 55                           | 14/26, 14/26      |
| Erol et al. (25)      | 2009  | Turkey  | CCS    | 38 cases with GC and 106 adjacent normal tissues of gastrointestinal cancers as controls | HPV-16, HPV-18, HPV-33 | NA, NA                      | NA, NA           |
| Zhang et al. (50)     | 2010  | China   | CCS    | 106 cases with AEG, 60 cases with GC, and 166 PCNT as controls               | HPV-16, HPV-94   | NA, NA                       | NA, NA           |
| Cândido et al. (22)   | 2013  | Brazil  | CSS    | 40 cases with GC and 40 normal controls                                      | HPV              | 60.73 ± 12.33, 53.35 ± 15.25 | 13/27, 30/10     |
| Yuan et al. (49)      | 2013  | China   | CCS    | 24 cases with GC and 44 patients with chronic gastritis and 30 patients with peptic ulcer as controls | HPV              | 57.20, 48.86                 | 14/10, 33/41     |
| Turkay et al. (11)    | 2015  | Turkey  | CCS    | 19 cases with AEG and 8 normal esophageal mucosa samples with nontumoral diseases as controls | HPV-16, HPV-39   | 65.95 ± 7.50, NA, NA         | 3/16, NA         |
| Roesch-Dietlen et al. | 2018  | Mexico  | CCS    | 10 cases with GC and 55 normal controls                                      | HPV-18           | NA, NA                       | NA, NA           |
| Bozdai et al. (53)    | 2019  | Turkey  | CCS    | 53 cases with GC and 43 patients with *H. pylori*-positive gastritis, 26 normal controls | HPV              | NA, NA                       | NA, NA           |
| Leon et al. (54)      | 2019  | Ethiopia| CCS    | 11 cases with AEG and 56 healthy controls                                    | HPV              | NA, NA                       | NA, NA           |
| Sabin et al. (40)     | 1973  | USA     | CCS    | 5 cases with GC and 57 noncancer controls                                    | HSV-1, HSV-2     | NA, NA                       | NA, NA           |
| Matveeva et al. (37)  | 2013  | Russian | CCS    | 30 cases with GC and 60 patients with chronic gastritis, 60 patients with ulcer, and 30 normal controls | HSV-1, HSV-2     | NA, NA                       | NA, NA           |
| Tahaei et al. (44)    | 2011  | Iran    | CCS    | 201 cases with GC and 219 normal controls                                    | HTLV-1           | 59.0 ± 12.80, 57.67 ± 11.29 | 56/155, 127/92   |
| Tanaka et al. (45)    | 2016  | Japan   | RCS    | 262 cases with GC born before 1990 and 3,612 normal controls born before 1990 without cancer or a history of cancer | HTLV-1           | NA                           | 51.4 ± 17.90, NA | 51/46, 1,556/2,056 |
| Shin et al. (42)      | 2006  | USA     | CCS    | 37 cases with sporadic GC and 37 PCNT as controls                            | JCV              | NA                           | NA, NA           |
| Murai et al. (38)     | 2006  | Japan   | CCS    | 22 cases with GC and 10 normal controls                                      | JCV              | 71.30, 69.40                 | 5/17, 5/5        |
| Selgrad et al. (41)   | 2008  | NA      | CCS    | 55 cases with GC and 14 *H. pylori*-positive and 10 *H. pylori*-negative subjects without malignancy as controls | JCV              | NA                           | NA, NA           |
| Yamaoka et al. (48)   | 2009  | Japan   | CCS    | 90 cases with GC and 90 PCNT as controls                                      | JCV              | 69 ± 10.00, 69 ± 10.00       | 31/59, 31/59     |
| Jang et al. (29)      | 2010  | Korean  | CCS    | 30 cases with GC and 20 patients with adenoma and 20 patients with nonneoplastic gastric mucosa as controls | JCV              | 65                           | 11/19, NA        |
Table 1. (continued)

| Study          | Year | Country | Design | Participants | Virus type | Cases | Controls | Cases | Controls |
|----------------|------|---------|--------|--------------|------------|-------|----------|-------|----------|
| Ksiaa et al. (33) | 2010 | Tunisia | CCS    | 61 cases with GC and 23 noncancer controls | JCV | 62    | NA       | 26/35 | 104/81   |
| Choi et al. (24) | 2011 | Korean   | CCS    | 285 cases with GC and 285 PCNT as controls | JCV | 54.1 ± 12.40 | 64.90 ± 8.87 | 12.40 | 104/181  |
| Izi et al. (28) | 2018 | Iran     | CCS    | 31 cases with GC and 31 PCNT as controls | JCV | 64.90 ± 8.87 | 13/18   |
| Cherati et al. (23) | 2018 | Iran     | CSS    | 81 cases with GC and 51 controls | JCV | 64.90 ± 8.87 | 13/18   |
| Li et al. (34) | 2011 | China    | CCS    | 16 cases with GC and 800 normal controls | Parovirus B19 | NA    | NA       |
| Li et al. (34) | 2011 | China    | CSS    | 16 GC serum samples as cases and 941 control samples from children with respiratory tract infections as controls | Parovirus B19 | NA    | NA       |

Statistical analysis

The STATA 12.0 and the PASS 11 software were used for statistical analysis (19,20). All analysis was based on individual virus. The pooled prevalence of any virus infection in patients with GC was combined for rate, with 95% confidence intervals (CIs). The pooled odds ratios (ORs) and their 95% CIs for virus prevalence were calculated between patients with GC and any controls by fixed or random effect model where suitable, and reanalysis was conducted after excluding subjects with known H. pylori and EBV positive. Two-sided P values for the pooled ORs < 0.05 were considered as statistical significance. I² was estimated to evaluate the heterogeneity. Any P value < 0.05 of Begg or Egger test was considered as significance of publication bias. The leave-one-out method was applied for sensitivity analysis. In addition, L’Abbé plot and Galbraith plot were used.
Table 2. Comparison of the prevalence of virus other than Epstein-Barr virus between GC and any controls

| Study                        | Test material | Test method | Virus type | Cases  | Controls |
|------------------------------|---------------|-------------|------------|--------|----------|
|                             |               |             |            | No.    | Total    |
|                              |               |             |            | Positive | Total    |
|                              |               |             |            | No.    | Positive | Total    | Power (1–β) |
| Ghasemi et al. (27)          | FFPE          | PCR         | HBV        | 0      | 100      | 0        | 100        | 0.000       |
| Wei et al. (47)              | Serum         | ELISA       | HBV        | 333    | 2,318    | 333      | 2,318      | 0.226       |
| Mahale et al. (35)           | NA            | ICD-9       | HBV        | 288    | 34,412   | 966      | 200,000    | 1.000       |
| Fattahi et al. (26)          | FF            | RT-PCR      | HBV        | 1      | 63       | 0        | 21         | 0.000       |
| An et al. (56)               | Serum         | Immunoradiometric assay kit | HBV | 703 | 16,350 | 4,401 | 118,891 | 1.000 |
| Song et al. (55)             | Serum         | ELISA       | HBV        | 24     | 118      | 60       | 472        | 0.555       |
| Baghbanian et al. (52)       | Serum         | ELISA       | HBV        | 9      | 35       | 5        | 259        | 0.986       |
| Matveeva et al. (37)         | Serum         | ELISA       | HCMV       | 30     | 30       | 109      | 150        | 0.998       |
| Jin et al. (30)              | FF            | Nested-PCR  | HCMV       | UL133: 41 | 60      | UL133: 27 | 60      | UL133: 0.736 |
|                             |               |             |            | UL135: 6 | UL135: 0   |
|                             |               |             |            | UL136: 7 | UL136: 0   |
|                             |               |             |            | UL138: 56 | UL138: 54  | UL138: 0.089 |
| Zhang et al. (51)            | Serum         | CLIA        | HCMV       | IgG: 76 | 80       | IgG: 78  | 80         | IgG: 0.113   |
|                             |               |             |            | IgM: 5  | IgM: 3    | IgM: 0.093 |
| Del Moral-Hernández et al. (10) | FFPE         | PCR         | HCMV       | 17     | 32       | 56       | 106        | 0.050       |
| Fattahi et al. (26)          | FF            | RT-PCR      | HCMV       | 16     | 63       | 0        | 21         | 0.949       |
| Mahmood et al. (36)          | Serum         | ELISA       | HCV        | 23     | 30       | 0        | 100        | 1.000       |
| Bai et al. (21)              | Serum         | ELISA       | HEV        | 10     | 53       | 123      | 950        | 0.267       |
| Kayamba et al. (32)          | Serum         | ELISA       | HIV        | 4      | 52       | 7        | 94         | 0.056       |
| Anwar et al. (12)            | FFPE          | PCR         | HPV-16     | HPV-16: 7 | 51       | HPV-16: 0 | 12      | HPV-16: 0.018 |
|                             |               |             | HPV-18     | HPV-18: 6 | HPV-18: 0 | HPV-18: 0.005 |
|                             |               |             | HPV-33     | HPV-33: 17 | HPV-33: 2 | HPV-33: 0.168 |
|                             |               |             | HPV-33     | Total: 23 | Total: 2   | Total: 0.449 |
|                             |               |             | HPV-16     | 0       | 49       | 2        | 48         | 0.139       |
| Xu et al. (14)               | FFPE          | ISH         | HPV-16     | AEG: 50 | 176      | 10       | 50         | AEG: 1.000  |
|                             |               |             | GC: 41     | GC: 0.714 |
|                             |               |             | Total: 91  | Total: 0.991 |
| Van Doornum et al. (46)      | Serum         | ELISA       | HPV-16     | 10     | 54       | 18       | 100        | 0.052       |
| Kamangar et al. (31)         | Serum         | ELISA       | HPV-16     | 10     | 54       | 18       | 100        | 0.052       |
|                             |               |             | HPV-18     | HPV-18: 16 | HPV-18: 35 | HPV-18: 0.052 |
|                             |               |             | HPV-73     | HPV-73: 21 | HPV-73: 42 | HPV-73: 0.079 |
| Study                  | Test material | Test method   | Virus type | Cases  | Controls | Power (1–β) |
|------------------------|---------------|---------------|------------|--------|----------|-------------|
|                        |               |               |            | No.    | Positive | Total       | No.    | Positive | Total |            |
| Ma et al. (13)         | FFPE          | ISPCR, LPCR   | HPV-16     | ISPCR: 11 | 40       | ISPCR: 0.998 |
|                        |               |               |            | LPCR: 15 | 2        | LPCR: 0.974 |
| Erol et al. (25)       | FFPE          | PCR           | HPV-16     | 17     | 38       | 106         | 33     | 106       | 0.331 |
| Zhang et al. (50)      | FF            | PCR           | HPV-16     | AEG: 5  | 166      | AEG: 0.061  |
|                        |               |               | HPV-94     | GC: 5   | 2         | GC: 0.201   |
|                        |               |               | AEG: 10    | 8       | 40       | 0.077       |
| Cândido et al. (22)    | FFPE          | PCR           | HPV        | 4      | 40       | 0.436       |
| Yuan et al. (49)       | Tissue        | GenoArray test kit | HPV     | 0      | 24       | 0.000       |
| Turkay et al. (11)     | FFPE          | RT-PCR        | HPV-16     | HPV-16: 1 | 19       | HPV-16: 0.000 |
|                        |               |               | HPV-39     | HPV-39: 1 | 8        | HPV-39: 0.000 |
| Roesch-Dietlen et al. (39) | Tissue        | Nested-PCR    | HPV-16     | 0      | 10       | 0.000       |
| Bozdayi et al. (53)    | Tissue        | RT-PCR        | HPV        | 20     | 53       | 0.082       |
| Leon et al. (54)       | FF            | PCR           | HPV        | 0      | 11       | 0.000       |
| Sabin et al. (40)      | Serum         | CFT           | HSV-1      | 0      | 5        | 0.000       |
| Matveeva et al. (37)   | Serum         | ELISA         | HSV-1      | 30     | 30       | HSV-2       |
| Tahaei et al. (44)     | Serum         | ELISA         | HTLV-1     | 1      | 201      | 0.235       |
| Tanaka et al. (45)     | Serum         | PA            | HTLV-1     | 32     | 262      | 0.058       |
| Shin et al. (42)       | FFPE, FF      | PCR           | JCV        | T-Ag: 21 | 37       | T-Ag: 0.650 |
|                        |               |               |            | VP-1: 9 | 11       | VP-1: 0.085 |
|                        |               |               |            | TCR: 16 | 13       | TCR: 0.104  |
|                        |               |               |            | T-Ag: 19 | 10       | T-Ag: 0.023 |
| Murai et al. (38)      | FF            | SB, IHC       | JCV        | VP: 12  | 22       | VP: 0.121   |
|                        |               |               |            | IHC: 1  | 1        | IHC: 0.056  |
| Selgrad et al. (41)    | Tissue        | PCR           | JCV        | 37     | 55       | 0.051       |
| Yamaoka et al. (48)    | Tissue        | IHC           | JCV        | 44     | 90       | 1.000       |
to observe the heterogeneity. For an individual study, the power \((1-\beta)\) was estimated by the PASS 11 software (20). Two-sided Z test (pooled) was provided with \(\alpha = 0.05\).

**RESULTS**

Systematic literature search and general information

Forty-one studies were included in this meta-analysis finally (Figure 1) (10,14,21–56). Eleven kinds of viruses were involved including HBV, hepatitis C virus (HCV), hepatitis E virus (HEV), HCMV, HIV, human papillomavirus (HPV), herpes simplex virus, human T-cell lymphotrophic virus type 1 (HTLV-1), John Cunningham virus (JCV), and human parvovirus (B19 and human bocavirus) (Table 1). The comparison of prevalence viruses between patients with GC and any controls with corresponding estimated power is summarized in Table 2. Quality assessment scoring of studies is tabulated in Table 3 with Newcastle-Ottawa Scale scores ranging from 6 to 9. Meta-analysis was conducted in studies involving HBV, HCMV, HPV, HTLV-1, and JCV.

**HBV and GC**

The 7 studies that investigated the relationship between HBV and GC involved 53,396 patients with GC and 325,458 any controls (26,27,34,55,56). The pooled HBV prevalence in GC was 7.6% (95% CI 4.6%–10.6%, random model, heterogeneity \(P < 0.001\)). Association between HBV infection and the risk of GC was observed (\(OR = 1.56, 95\% CI 1.18–2.07\), random model, heterogeneity \(P < 0.001\)) (see Figure 1a, Supplementary Digital Content 1, http://links.lww.com/CTG/A299). Two studies investigated the coinfection of \(H.\) pylori (26,52), and data could be extracted completely for cases and controls from only 1 study (52). We reanalyzed after excluding subjects with known \(H.\) pylori positive, and association between HBV infection and the risk of GC was observed (\(OR = 1.39, 95\% CI 1.11–1.75\), random model, heterogeneity \(P < 0.001\)) (Figure 2a).

According to the different study regions and sample size, subgroup analysis was conducted before and after excluding subjects with known \(H.\) pylori positive (Tables 4 and 5). The result showed that HBV infection was still related to the risk of GC after 1 study from United States was dropped along with a decrease of heterogeneity, which indicated that study location might be responsible for the heterogeneity (\(OR = 1.18, 95\% CI 1.08–1.29\), random model, heterogeneity \(P = 0.344\)) (Table 5).

**HCMV and GC**

Five studies sought to detect HCMV in GC with 682 samples (265 for cases with GC, 417 for noncancer controls) (10,26,30,37,51). The pooled HCMV prevalence in GC was 43.1% (95% CI 14.2%–72.0%, random model, heterogeneity \(P < 0.001\)). The pooled OR showed that HCMV infection was highly related to the risk of GC (\(OR = 2.09, 95\% CI 1.14–3.84\), random model, heterogeneity \(P = 0.058\)) (see Figure 1b, Supplementary Digital Content 1, http://links.lww.com/CTG/A299). Two studies investigated the coinfection of \(H.\) pylori and EBV (10,26), and data could be extracted completely for cases and controls from only 1 study (10). We reanalyzed after excluding subjects with known \(H.\) pylori and EBV positive, and association between HCMV infection and the risk of GC was observed (\(OR = 2.25, 95\% CI 1.14–4.43\), random model, heterogeneity \(P = 0.079\)) (Figure 2b).

According to the different study regions, control type, and test material, subgroup analysis was conducted before and after excluding subjects with known \(H.\) pylori and EBV positive (Tables 4 and 5). Compared with noncancer healthy and benign gastric
HPV and GC

Fourteen studies investigated the prevalence of HPV including 901 patients with GC and 1,205 any controls (11–14,22,25,31,39,43,46,49,50,53,54). The pooled HPV prevalence in GC was 23.6% (95% CI 15.5%–31.6%, random model, heterogeneity $P < 0.001$). Association between HPV infection and the risk of GC was observed (OR = 1.53, 95% CI 1.00–2.33, random model, heterogeneity $P = 0.002$) (see Figure 1c, Supplementary Digital Content 1, http://links.lww.com/CTG/A299). Five studies investigated the coinfection of $H. pylori$ or EBV without extractable data for cases and controls (12,13,49,53,54). We reanalyzed after excluding controls with $H. pylori$-positive gastritis in the study by Bozdayi et al., and association still existed (OR = 1.63, 95% CI 1.05–2.54, random model, heterogeneity $P = 0.002$) (Figure 2c) (53).

According to publication year, study regions, sample size, control type, test material, case type, and subtype of HPV, subgroup analysis was conducted before and after excluding subjects with known $H. pylori$ positive (Tables 4 and 5). HPV infection was associated with GC for studies from China, publication year from 2000 to 2009, and if tissue specimens were tested. Compared with noncancer healthy and benign gastric disease controls, the prevalence of HPV in patients with GC was higher than that in PCNT controls significantly. Statistically significant association between HPV-16 infection and the risk of GC was also observed (OR = 2.42, 95% CI 1.00–5.83, random model, heterogeneity $P = 0.003$) (Table 5).

HTLV-1 and GC

Serum antibodies to HTLV-1 were measured in 4,293 serum samples (463 cases with GC, 3,831 noncancer controls) in 2 studies (44,45). The pooled HTLV-1 prevalence was 6.20% (95% CI 0.61–1.30, fixed model, heterogeneity $P = 0.272$) (see Figure 1d, Supplementary Digital Content 1, http://links.lww.com/CTG/A299).

JCV and GC

Nine studies involving 1,356 tissue samples (692 for GC and 664 for any controls) investigated the association between JCV and GC (23,24,28,29,33,38,41,42,48). The pooled JCV prevalence was 35.6% (95% CI 23.2%–48.1%, random model, heterogeneity $P < 0.001$). Significant correlation between JCV infection and the risk of GC was revealed (OR = 2.28, 95% CI 1.14–4.56, random model, heterogeneity $P < 0.001$) (see Figure 1e, Supplementary Digital Content 1, http://links.lww.com/CTG/A299). Three studies investigated the coinfection of $H. pylori$ or EBV, and data could be extracted completely for cases and controls from only 1 study (23,41,48). Subjects with JCV infection were not accompanied with EBV coinfection in the study by Cherati et al. (23). We reanalyzed disease controls, the prevalence of HCMV in patients with GC was higher than that in PCNT controls significantly. By comparison with serum samples, association between HCMV infection and the risk of GC was observed in gastric tissues. Study location might be responsible for the heterogeneity among the studies from China ($I^2 = 23.2\%, P = 0.252$) and other regions ($I^2 = 66.4\%, P = 0.051$) (Table 5).

**Table 3. Methodological quality by the Newcastle-Ottawa Scale**

| Study | Selection | Comparability | Exposure | Overall |
|-------|-----------|---------------|----------|---------|
| Ghasemi et al. (27) | 3 | 1 | 3 | 7 |
| Wei et al. (47) | 3 | 1 | 3 | 7 |
| Mahale et al. (35) | 4 | 2 | 3 | 9 |
| Fattahi et al. (26) | 3 | 1 | 3 | 7 |
| An et al. (56) | 3 | 1 | 3 | 7 |
| Song et al. (55) | 3 | 2 | 3 | 8 |
| Baghbani et al. (52) | 3 | 1 | 3 | 7 |
| Matveeva et al. (37) | 3 | 1 | 3 | 7 |
| Jin et al. (30) | 3 | 2 | 3 | 8 |
| Zhang et al. (51) | 3 | 2 | 3 | 8 |
| Del Moral-Hernández et al. (10) | 3 | 1 | 3 | 7 |
| Mahmood et al. (36) | 3 | 1 | 3 | 7 |
| Bai et al. (21) | 4 | 2 | 3 | 9 |
| Kayamba et al. (32) | 3 | 2 | 3 | 8 |
| Anwar et al. (12) | 3 | 1 | 3 | 7 |
| Strickler et al. (43) | 3 | 1 | 3 | 7 |
| Xu et al. (14) | 3 | 1 | 3 | 7 |
| Van Doornum et al. (46) | 3 | 2 | 3 | 8 |
| Kamangar et al. (31) | 4 | 2 | 2 | 8 |
| Ma et al. (13) | 3 | 2 | 3 | 8 |
| Erol et al. (25) | 2 | 2 | 3 | 7 |
| Zhang et al. (50) | 3 | 2 | 2 | 7 |
| Cândido et al. (22) | 3 | 1 | 3 | 7 |
| Yuan et al. (49) | 2 | 1 | 3 | 6 |
| Turkay et al. (11) | 3 | 1 | 3 | 7 |
| Roesch-Dietlen et al. (39) | 3 | 1 | 3 | 7 |
| Bozdayi et al. (53) | 3 | 1 | 3 | 7 |
| Leon et al. (54) | 3 | 1 | 3 | 7 |
| Sabir et al. (40) | 3 | 2 | 3 | 8 |
| Hirata et al. (73) | 3 | 1 | 3 | 7 |
| Tahaei et al. (44) | 3 | 1 | 3 | 7 |
| Tanaka et al. (45) | 3 | 1 | 3 | 7 |
| Shin et al. (42) | 3 | 2 | 3 | 8 |
| Murai et al. (38) | 3 | 1 | 3 | 7 |
| Selgrad et al. (41) | 2 | 1 | 3 | 6 |
| Yamaoka et al. (48) | 2 | 2 | 3 | 7 |
| Jang et al. (29) | 3 | 1 | 3 | 7 |
| Ksiaa et al. (33) | 2 | 1 | 3 | 6 |
| Choi et al. (24) | 3 | 2 | 3 | 8 |
| Izi et al. (28) | 3 | 2 | 3 | 8 |
| Cherati et al. (23) | 3 | 1 | 3 | 7 |
| Li et al. (34) | 3 | 1 | 3 | 7 |
after excluding *H. pylori*-positive controls in the study by Selgrad et al. and subjects with EBV positive in the study by Yamaoka et al., and association still existed (OR = 2.52, 95% CI 1.26–5.04, random model, heterogeneity *P* < 0.001) (Figure 2d) (41,48).

According to the publication year, study regions, sample size, control type, and the test method, subgroup analysis was conducted before and after excluding subjects with known *H. pylori* and EBV positive (Tables 4 and 5). JCV infection was associated with GC for studies from non-Asian regions, publication year from 2010 to 2019, and using polymerase chain reaction method or immunohistochemistry method. Compared with noncancer healthy and benign gastric disease controls, the prevalence of JCV in GC was higher than PCNT controls significantly (Table 5).

Sensitivity, publication bias, and heterogeneity
Sensitivity and publication bias were conducted for studies involving HBV, HCMV, HPV, and JCV. In the leave-one-out analysis, we found that the pooled ORs were always consistent by excluding any single study, which verified the reliability of this meta-analysis statistically (Figure 3). Because all *P* values for Begg test and Egger test were >0.05, it meant that no evidence for publication bias was indicated. The *L*’Abbé plot and the Galbraith plot demonstrated the existence of heterogeneity in this meta-analysis for HBV, HCMV, HPV, and JCV. The Begg funnel plot, Egger regression plot, *L*’Abbé plot, and Galbraith plot of the all-included meta-analysis are shown in Supplementary Figures 2–5, respectively (Supplementary Digital Content 2–5, http://links.lww.com/CTG/A294, http://links.lww.com/CTG/A295, http://links.lww.com/CTG/A296, http://links.lww.com/CTG/A297).

**DISCUSSION**

GC is one of the infection-associated malignancies, and the potential mechanisms inducing gastric carcinogenesis are well established for *H. pylori* and EBV (3–7). However, the potential carcinogenesis of viruses other than EBV associated with GC risk remains unclear until now; thus, this systematic review and meta-analysis was conducted to clarify this issue (see Figure legend Supplementary Digital Content 6, http://links.lww.com/CTG/A298). This systematic review and meta-analysis demonstrated that HBV, HCMV, HPV, and JCV are each associated with a statistically significantly increased risk of GC.

As a causative pathogen for hepatocellular carcinoma, HBV infection was shown to be associated with the risk of GC in some sporadic studies (9,57). One meta-analysis that included 3 case–control studies and 5 cohort studies also found that HBV infection is associated with a higher risk for GC (OR = 1.23, 95% CI 1.10–1.37) (58). As shown in this study, HBV DNA was investigated directly in gastric mucosa tissue by polymerase chain reaction method only in 2 studies with the low positive rate (0%–3.2% in GC), which was consistent with a previous study (59). In addition, the prevalence of HBV might be underestimated for studies that applied serologic assay due to the existence of
Table 4. Subgroup analysis of HCMV, HPV, and JCV prevalence between GC and any controls before excluding subjects with known *H. pylori* and Epstein-Barr virus positive

| Stratification | No. of studies | OR (95% CI of effect) | P value | Heterogeneity |
|----------------|----------------|-----------------------|---------|---------------|
|                |                |                       |         | I² (%)        | P value |
| **HBV**        |                |                       |         |               |         |
| Study region   |                |                       |         |               |         |
| Asia           | 6              | 1.46 (1.08–1.97)      | 0.013   | 82.6          | <0.001 |
| Others         | 1              | 1.74 (1.52–1.98)      | <0.001  | —             | —       |
| Sample size    |                |                       |         |               |         |
| ≤500           | 4              | 6.32 (0.40–99.08)     | 0.189   | 63.9          | 0.096   |
| >500           | 3              | 1.37 (1.09–1.73)      | 0.007   | 89.6          | <0.001  |
| **HCMV**       |                |                       |         |               |         |
| Study region   |                |                       |         |               |         |
| China          | 2              | 1.95 (1.10–3.45)      | 0.023   | 23.2          | 0.252   |
| Others         | 3              | 5.48 (0.39–77.18)     | 0.207   | 78.2          | 0.010   |
| Control type   |                |                       |         |               |         |
| Noncancer healthy |          | 4.63 (0.50–42.77)    | 0.177   | 77.5          | 0.004   |
| Benign gastric disease | | 2.77 (0.18–43.03) | 0.467 | 72.8 | 0.055 |
| PCNT           | 1              | 2.32 (1.25–4.32)      | 0.008   | 20.6          | 0.284   |
| Test material  |                |                       |         |               |         |
| Serum          | 2              | 2.09 (0.28–15.57)     | 0.474   | 69.5          | 0.038   |
| Tissue         | 3              | 2.13 (1.13–4.00)      | 0.019   | 41.3          | 0.116   |
| **HPV**        |                |                       |         |               |         |
| Year           |                |                       |         |               |         |
| 1990–1999      | 2              | 1.17 (0.06–23.18)     | 0.920   | 67.6          | 0.079   |
| 2000–2009      | 5              | 1.84 (1.07–3.18)      | 0.027   | 70.2          | 0.001   |
| 2010–2019      | 7              | 0.97 (0.52–1.81)      | 0.921   | 19.6          | 0.292   |
| Study region   |                |                       |         |               |         |
| China          | 5              | 1.98 (1.04–3.75)      | 0.036   | 73.7          | 0.001   |
| Others         | 9              | 1.17 (0.68–2.02)      | 0.576   | 33.4          | 0.173   |
| Sample size    |                |                       |         |               |         |
| ≤150           | 10             | 1.96 (0.81–4.74)      | 0.137   | 65.9          | 0.005   |
| >150           | 4              | 1.53 (1.00–2.33)      | 0.179   | 55.6          | 0.046   |
| Control type   |                |                       |         |               |         |
| Noncancer      | 11             | 1.25 (0.81–1.93)      | 0.315   | 53.5          | 0.022   |
| PCNT           | 3              | 3.42 (1.08–10.83)     | 0.036   | 69.4          | 0.020   |
| Test material  |                |                       |         |               |         |
| Serum          | 3              | 1.04 (0.75–1.44)      | 0.817   | 0.0          | 0.859   |
| Tissue         | 11             | 2.24 (1.13–4.43)      | 0.021   | 66.5          | 0.002   |
| Case type      |                |                       |         |               |         |
| AEG            | 5              | 1.63 (0.76–3.50)      | 0.209   | 73.7          | 0.002   |
| GC             | 12             | 1.51 (0.94–2.40)      | 0.086   | 55.8          | 0.007   |
| Subtype of HPV |                |                       |         |               |         |
| HPV-16         | 8              | 2.42 (1.00–5.83)      | 0.049   | 67.5          | 0.003   |
| HPV-18         | 3              | 1.08 (0.59–1.99)      | 0.797   | 0.0          | 0.414   |
| Others         | 3              | 1.24 (0.74–2.09)      | 0.420   | 0.0          | 0.666   |
occult HBV infection in which circulating hepatitis B surface antigen is absent (60). However, HBV serologic assay are still irreplaceable effective method to evaluate the status of HBV infection currently, and low prevalence rates of occult HBV infection has been reported in Asia, where most of the studies included in this meta-analysis were performed (61–63).

As one of the 8 well-known herpes viruses, HCMV infection has been reported in immunocompetent patients with gastrointestinal disease such as gastritis, and its appearance was also detected in patients with carcinomas such as colon cancer (64–66). Michaelis et al. reported that HCMV might accelerate malignant process by strengthening tumor inflammation, which indicated its role in cancer (65). Our study demonstrated that the HCMV is associated with the risk of GC and the positivity of HCMV in GC tissues was higher than any controls especially. HCMV infection might explain this result (72). As a risk factor of malignant neoplasia of the digestive tract with epithelial mucosa, HPV-16 might play a role in the development of GC initiate with infecting gastric glandular epithelium cells (13).

Significant association between infection with HTLV-1 and reduced risk of GC was suggested in several studies (73–75). In our meta-analysis, no causal association between HTLV-1 infection and GC was found. However, correlation between HTLV-1 and gastric carcinogenesis was verified in another meta-analysis, which included 3 cohort studies that inferred that HTLV-1 infection reduces the risk of GC by intervening H. pylori infection and proliferation possibly (76).

In addition, there are some other viruses, such as JCV, which belong to the polyomavirus family, were included in our study. The presence of JCV has been detected in the normal gastrointestinal tract and colon cancer in humans (77,78). In our study, the prevalence of JCV was associated with increased risk of GC. The presence of JCV transforming antigen was identified in all included studies, because transforming antigen, which is encoded by all polyomaviruses, was supposed to bind and inactivate tumor suppressor genes resulting in genomic instability, an important event in the oncogenesis progression (23,24,28,29,33,38,41,42,48).

### Strengths and Limitations

To our knowledge, this study was the first meta-analysis to systematically evaluate the associations between the prevalence of viruses other than EBV and GC till now. However, because of limited published data, differences in sensitivity of test methods and test samples, sample size, and environmental or geographical factors, significant heterogeneity existed. Because of the insufficient

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**Table 4. (continued)**

| Stratification         | No. of studies | OR (95% CI of effect) | P value | Heterogeneity |
|------------------------|----------------|-----------------------|---------|---------------|
|                        |                |                       |         | I² (%) | P value |
| JCV                    |                |                       |         |        |         |
| Year                   |                |                       |         |        |         |
| 2000–2009              | 4              | 1.59 (0.69–3.63)      | 0.273   | 61.7   | 0.007  |
| 2010–2019              | 5              | 4.15 (1.16–14.83)     | 0.029   | 71.5   | 0.004  |
| Study region           |                |                       |         |        |         |
| Asia                   | 4              | 3.47 (0.59–20.53)     | 0.170   | 81.5   | 0.000  |
| Others                 | 5              | 1.85 (1.21–2.84)      | 0.005   | 0.0    | 0.654  |
| Sample size            |                |                       |         |        |         |
| ≤100                   | 6              | 1.65 (1.13–2.39)      | 0.009   | 0.0    | 0.510  |
| >100                   | 3              | 31.28 (1.34–728.34)   | 0.032   | 73.7   | 0.022  |
| Control type           |                |                       |         |        |         |
| Noncancer healthy      | 5              | 1.07 (0.61–1.88)      | 0.820   | 0.0    | 0.616  |
| Benign gastric disease | 2              | 3.30 (0.91–11.89)     | 0.068   | 0.0    | 0.508  |
| PCNT                   | 4              | 5.13 (1.35–19.41)     | 0.016   | 84.1   | 0.000  |
| Test method            |                |                       |         |        |         |
| PCR                    | 6              | 1.76 (1.19–2.62)      | 0.005   | 0.0    | 0.713  |
| SB                     | 1              | 0.53 (0.15–1.81)      | 0.309   | 0.0    | 0.831  |
| IHC                    | 4              | 22.78 (2.33–223.00)   | 0.007   | 63.9   | 0.040  |

AEG, adenocarcinoma of the esophagogastroduodenal junction; 95 % CI, 95 % confidence interval; GC, gastric cancer; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HPV, human papillomavirus; IHC, immunohistochemistry; JCV, John Cunningham virus; noncancer, included noncancer healthy and benign gastric disease controls; OR, odds ratio; PCR, polymerase chain reaction; PCNT, paired corresponding normal tissues; SB, Southern blot.
| Stratification | No. of studies | OR (95 % CI of effect) | $P$ value | $I^2$ (%) | $P$ value |
|----------------|----------------|------------------------|-----------|-----------|-----------|
| HBV            |                |                        |           |           |           |
| Study region   |                |                        |           |           |           |
| Asia           | 6              | 1.18 (1.08–1.29)       | <0.001    | 10.9      | 0.344     |
| Others         | 1              | 1.74 (1.52–1.98)       | <0.001    | —         | —         |
| Sample size    |                |                        |           |           |           |
| ≤500           | 3              | 3.56 (0.55–23.16)      | 0.184     | 0.00      | 0.330     |
| >500           | 4              | 1.37 (1.09–1.73)       | 0.007     | 89.6      | <0.001    |
| HCMV           |                |                        |           |           |           |
| Study region   |                |                        |           |           |           |
| China          | 2              | 1.95 (1.10–3.45)       | 0.023     | 23.2      | 0.252     |
| Others         | 3              | 4.66 (0.28–77.64)      | 0.284     | 66.4      | 0.051     |
| Control type   |                |                        |           |           |           |
| Noncancer healthy | 3          | 4.63 (0.50–42.77)     | 0.177     | 77.5      | 0.004     |
| Benign gastric disease | 2 | 2.03 (0.04–108.93) | 0.727 | 75.0 | 0.045 |
| PCNT           | 1              | 2.32 (1.25–4.32)       | 0.008     | 20.6      | 0.284     |
| Test material  |                |                        |           |           |           |
| Serum          | 2              | 2.09 (0.28–15.57)      | 0.474     | 69.5      | 0.038     |
| Tissue         | 3              | 2.40 (1.18–4.88)       | 0.016     | 33.2      | 0.175     |
| HPV            |                |                        |           |           |           |
| Year           |                |                        |           |           |           |
| 1990–1999      | 2              | 1.17 (0.06–23.18)      | 0.920     | 67.6      | 0.079     |
| 2000–2009      | 5              | 1.84 (1.07–3.18)       | 0.027     | 70.2      | 0.001     |
| 2010–2019      | 7              | 1.14 (0.45–2.92)       | 0.782     | 49.2      | 0.116     |
| Study region   |                |                        |           |           |           |
| China          | 5              | 1.98 (1.04–3.75)       | 0.036     | 73.7      | 0.001     |
| others         | 9              | 1.31 (0.69–2.52)       | 0.411     | 42.5      | 0.107     |
| Sample size    |                |                        |           |           |           |
| ≤150           | 10             | 2.27 (0.89–5.79)       | 0.086     | 64.5      | 0.006     |
| >150           | 4              | 1.35 (0.87–2.10)       | 0.179     | 55.6      | 0.046     |
| Control type   |                |                        |           |           |           |
| Noncancer      | 11             | 1.34 (0.84–2.15)       | 0.225     | 56.6      | 0.014     |
| PCNT           | 3              | 3.42 (1.08–10.83)      | 0.036     | 69.4      | 0.020     |
| Test material  |                |                        |           |           |           |
| Serum          | 3              | 1.04 (0.75–1.44)       | 0.817     | 0.0       | 0.859     |
| Tissue         | 11             | 2.51 (1.26–5.00)       | 0.009     | 63.0      | 0.006     |
| Case type      |                |                        |           |           |           |
| AEG            | 5              | 1.63 (0.76–3.50)       | 0.209     | 73.7      | 0.002     |
| GC             | 12             | 1.62 (0.99–2.65)       | 0.054     | 56.7      | 0.006     |
| Subtype of HPV |                |                        |           |           |           |
| HPV-16         | 8              | 2.42 (1.00–5.83)       | 0.049     | 67.5      | 0.003     |
| HPV-18         | 3              | 1.08 (0.59–1.99)       | 0.797     | 0.0       | 0.414     |
| Others         | 3              | 1.24 (0.74–2.09)       | 0.420     | 0.0       | 0.666     |
number of included studies, meta-analysis was impossible for some viruses. Moreover, because of the property of study design and almost included studies did not take H. pylori or EBV coinfection into consideration, it was hard to determine the causal relationship between infection of viruses and risk of GC.

However, as one of the infection-associated malignancies, the development of GC is a multifactorial and multistep process. Several studies have shown that significant difference in H. pylori prevalence between the GC and any controls was not found, although H. pylori is a well-known carcinogenic associated with GC, and its prevalence is very common (3,4,26,32–81). We reanalyzed after excluding subjects with known H. pylori and EBV positive for studies involving HBV, HCMV, HPV, and JCV, and their relationships with the increased risk of GC had not changed. Wei et al. believed that evidence supporting the interaction between HBV and H. pylori was insufficient (9,82,83). Fattahi et al. found that HCMV viral loads were much higher in H. pylori-negative tissues compared with those in H. pylori-positive tissues, and the prevalence of H. pylori was lower in tumor tissues than that in nontumor tissues for GC (26,84). No correlation between HPV and H. pylori or EBV infection in gastric carcinogenesis was found in previous studies too (12,13,49).

CONCLUSION

In short, this study demonstrated that HBV, HCMV, HPV, or JCV were more prevalent in GC. However, the causal relationship between infection of HBV, HCMV, HPV, or JCV and risk of GC remains inconclusive, and further investigations are required (see PRISMA checklist 2009, Supplementary Digital Content 7, http://links.lww.com/CTG/A333).

CONFLICTS OF INTEREST

Guarantor of the article: Xin-Zu Chen, MD, PhD, and Jian-Kun Hu, MD, PhD, FRCS, gave final approval of the version to be published. Specific author contributions: Hui Wang and Xiao-long Chen, MD, PhD, contributed equally to this work. H.W., X.-L.C., X.-Z.C., and J.-K.H.: made substantial contributions to conception and design of the study. H.W., X.-L.C., K.L., D.B., and W.-H.Z.: participated in this systematic review for literature search, selection, quality assessment, and data extraction. H.W. and X.-L.C.: drafted this systematic review. H.W., X.-L.C., and J.-K.H.: gave critical revision for important intellectual content. K.L., D.B., and W.-H.Z., X.-Z.C., and J.K.H: participated in critical revision for important intellectual content. Financial support: (1)The 13th Five Year Project for Disciplines of Excellence, West China Hospital, Sichuan University (No. ZY2017304); (2) National Natural Science Foundation of China, (No. 81702366); (3) Sichuan Science and Technology Program (No.2019YS0255); (4) Wu Jieping Medical Foundation (No. 320.2710.1815, No.320.2710.1865). Potential competing interests: None to report. Ethics and dissemination: The meta-analysis was not submitted for any ethical approval due to the literature-based nature. Registration: The present systematic review (registration number: CRD42015029703) was registered in the PROSPERO International Table 5. (continued)

| Stratification | No. of studies | OR (95 % CI of effect) | P value | Heterogeneity |
|---------------|----------------|------------------------|---------|---------------|
| JCV           |                |                        |         |               |
| Year          |                |                        |         |               |
| 2000–2009     | 4              | 1.89 (0.81–4.40)       | 0.142   | 60.1          | 0.010         |
| 2010–2019     | 5              | 4.15 (1.16–14.83)      | 0.029   | 71.5          | 0.004         |
| Study region  |                |                        |         |               |
| Asia          | 4              | 3.53 (0.60–20.90)      | 0.164   | 81.5          | <0.001        |
| Others        | 5              | 2.19 (1.40–3.42)       | 0.001   | 0.0           | 0.826         |
| Sample size   |                |                        |         |               |
| ≤100          | 6              | 1.85 (1.26–2.72)       | 0.002   | 0.0           | 0.545         |
| >100          | 3              | 32.93 (1.37–793.59)    | 0.031   | 74.2          | 0.021         |
| Control type  |                |                        |         |               |
| Noncancer healthy | 5 | 1.33 (0.72–2.45)     | 0.360   | 0.0           | 0.434         |
| Benign gastric disease | 2 | 3.30 (0.91–11.89)  | 0.068   | 0.0           | 0.508         |
| PCNT          | 4              | 5.21 (1.38–19.69)      | 0.015   | 84.1          | <0.001        |
| Test method   |                |                        |         |               |
| PCR           | 6              | 2.02 (1.34–3.05)       | 0.001   | 0.0           | 0.815         |
| SB            | 1              | 0.53 (0.15–1.81)       | 0.309   | 0.0           | 0.831         |
| IHC           | 4              | 23.65 (2.36–237.33)    | 0.007   | 64.7          | 0.037         |

AEG, adenocarcinoma of the esophagogastric junction; 95 % CI, 95 % confidence interval; GC, gastric cancer; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HPV, human papillomavirus; IHC, immunohistochemistry; JCV, John Cunningham virus; noncancer, included nonancer healthy and benign gastric disease controls; OR, odds ratio; PCR, polymerase chain reaction; PCNT, paired corresponding normal tissues; SB, Southern blot.
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