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

Hui Wang, MD[1], Xiao-Long Chen, MD, PhD[1], Kai Liu, MD, PhD[1], Dan Bai, MD[1], Wei-Han Zhang, MD, PhD[1], Xin-Zu Chen, MD, PhD[1,2,3] and Jian-Kun Hu, MD, PhD, FRCS[1] on behalf of the SIGES research group

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

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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

[1]Department of Gastrointestinal Surgery & Laboratory of Gastric Cancer, West China Hospital, Sichuan University, Chengdu, China; [2]Department of Gastrointestinal and Hernia Surgery, West China Yibin Hospital, Sichuan University, Yibin, China; [3]Department of General Surgery, West China Longquan Hospital, Sichuan University, Chengdu, China. **Correspondence:** Xin-Zu Chen, MD, PhD. E-mail: chenxinzu@scu.edu.cn. Jian-Kun Hu, MD, PhD, FRCS. E-mail: hujkwch@126.com.
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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,

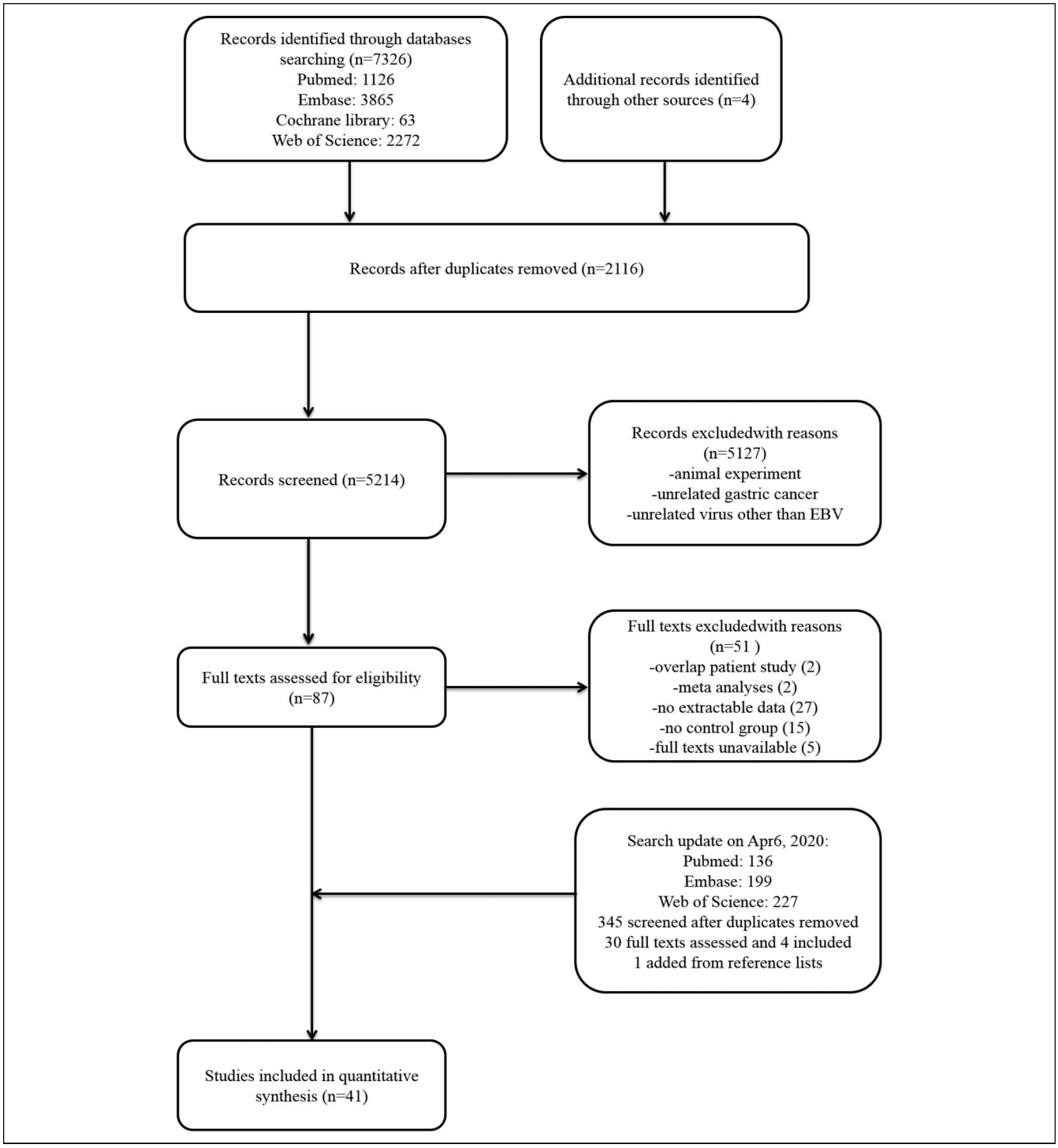

Figure 1. The flowchart of the literature search.

Table 1. Characteristics of studies on virus other than Epstein-Barr virus and risk of GC

Study	Year	Country	Design	Participants	Virus type	Age (median or mean ± SD, yr)		Sex (female/male)	
						Cases	Controls	Cases	Controls
Ghasemi et al. (27)	2012	Iran	CCS	100 cases with GC and 100 normal controls	HBV	67.14 ± 10.98	NA	31/69	NA
Wei et al. (47)	2017	China	CCS	2,318 cases with GC and 5,715 noncancer controls	HBV	NA	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	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	NA
An et al. (56)	2018	Korea	CCS	16,350 cases with GC and 118,891 healthy controls	HBV	NA	NA	55,020/63,871	NA
Song (55)	2019	China	CCS	118 cases with GC and 472 healthy controls	HBV	NA	NA	NA	NA
Baghbanian et al. (52)	2019	Iran	CSS	35 cases with GC and 259 normal controls	HBV	NA	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	NA
Jin et al. (30)	2014	China	CCS	60 cases with GC and 60 PCNT as controls	HCMV	NA	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	32/48
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	60/46
Fattahi et al. (26)	2018	Iran	CCS	63 cases with GC and 21 normal controls	HCMV	68	NA	12/51	NA
Mahmood et al. (36)	2018	Iraq	CCS	30 cases with GC and 100 normal controls	HCV	NA	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	574/376
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	49/45
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	4/8
					HPV-18				
					HPV-33				
Strickler et al. (43)	1998	USA	CCS	49 cases with GC and 48 noncancer controls	HPV-16	63	51	5/44	25/23
Xu et al. (14)	2003	China	CCS	74 cases with AEG, 102 cases with GC, and 50 normal controls	HPV-16	NA	NA	NA	NA
Van Doornum 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	50/50

Table 1. (*continued*)

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	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	3/16	NA
Roesch-Dietlen et al. (39)	2018	Mexico	CCS	10 cases with GC and 55 normal controls	HPV-18	NA	NA	NA	NA
Bozdayi 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	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	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	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	NA	11/19	NA

Table 1. (*continued*)

Study	Year	Country	Design	Participants	Virus type	Age (median or mean ± SD, yr)		Sex (female/male)	
						Cases	Controls	Cases	Controls
Ksiaa et al. (33)	2010	Tunisia	CCS	61 cases with GC and 23 noncancer controls	JCV	62	NA	26/35	8/15
Choi et al. (24)	2011	Korean	CCS	285 cases with GC with pT3 and 285 PCNT as controls	JCV	54.1 ± 12.40	54.1 ± 12.40	104/181	104/181
Izi et al. (28)	2018	Iran	CCS	31 cases with GC and 31 PCNT as controls	JCV	64.90 ± 8.87	64.90 ± 8.87	13/18	13/18
Cherati et al. (23)	2018	Iran	CSS	81 cases with GC and 51 gastritis, 20 gastric ulcer, 53 gastric congested mucosa from healthy subjects as controls	JCV	NA	NA	NA	NA
Li et al. (34)	2011	China	CCS	16 cases with GC and 800 normal controls	Parvovirus B19	NA	NA	NA	NA
Li et al. (34)	2011	China	CCS	16 GC serum samples as cases and 941 aspirate samples from children with respiratory tract infections as controls	HBoV	NA	NA	NA	NA

AEG, adenocarcinoma of the esophagogastric junction; CCS, case–control study; CSS, cross-sectional study; GC, gastric cancer; HBoV, human bocavirus; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HPV, human papillomavirus; HTLV-1, human T-cell lymphotropic virus type 1; JCV, John Cunningham virus; NA, not available; PCS, prospective cohort study; PCNT, paired corresponding normal tissues; RCS, retrospective cohort study.

((“stomach neoplasms”[MeSH Terms] OR (“stomach”[All Fields] AND “neoplasms”[All Fields]) OR “stomach neoplasms”[All Fields] OR (“gastric”[All Fields] AND “cancer”[All Fields]) OR “GC”[All Fields]) AND (“viruses”[MeSH Terms] OR “viruses”[All Fields] OR “virus”[All Fields])) NOT (“animal”[Filter] OR “review”[Publication Type] OR “case reports”[Publication Type] OR “letter”[Publication Type] OR “comment”[Publication Type]) (17). A similar search strategy was applied in searching published literature in Embase, Cochrane Library, and Web of Science databases.

Eligibility

The studies that compared the positivity of any virus between cases with histologically proven GC with healthy or nonmalignant controls were eligible. The patients with gastric lymphoma, gastrointestinal stromal tumor, and squamous cell carcinoma were ineligible. Any type of cohort study, cross-sectional study, or case–control study was considered. The detection of viruses was performed in cases and controls based on either blood/serum or tissue specimens. Any targeted virus other than EBV was eligible in this systematic review. There was no limitation on the race, sex, age, cancer stage, and treatment strategy. Only those studies with extractable data were considered for analysis (17). For overlap study, only the most recent study or the study with the larger number of participants was included.

Selection and quality assessment

Two reviewers separately browsed the titles/abstracts and assessed the potentially eligible full-texts according to the predefined inclusion and exclusion criteria. Discrepancies were resolved by consensus with a third reviewer. Risk of bias assessment of all included studies was independently performed by 2 reviewers, according to the Newcastle-Ottawa Scale (18).

Data extraction

Data were extracted independently by 2 reviewers. Extracted items included general study characteristics (publication year, country, and study design), characteristics of the study population (sample size, sex, and age), and types of measurements (specimen types and viruses detection methods). Numbers of cases and controls were extracted from publications. Included study where different test methods were applied or various types of viruses were investigated was treated as more than 1 study. For study that had taken paired corresponding normal tissues (PCNTs) from the same patients with GC and noncancer gastric mucosa samples from patients without cancer as controls simultaneously, only data about patients without cancer were extracted. Potential discrepancies in extracted items if any were resolved by further review and discussion (17).

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. I^2 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		Power (1–β)
				No. Positive	Total	No. Positive	Total	
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		UL135: 0.863
				UL136: 7		UL136: 0		UL136: 0.931
				UL138: 56		UL138: 54		UL138: 0.089
				IEI: 15		IEI: 11		IEI: 0.156
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
				Total: 23		Total: 2		Total: 0.449
Strickler et al. (43)	Serum	ELISA	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	HPV-16: 13	170	HPV-16: 29	381	HPV-16: 0.050
			HPV-18	HPV-18: 16		HPV-18: 35		HPV-18: 0.052
			HPV-73	HPV-73: 21		HPV-73: 42		HPV-73: 0.079

Table 2. (*continued*)

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	40	ISPCR: 0.998
				LPCR: 15		LPCR: 2		LPCR: 0.974
Erol et al. (25)	FFPE	PCR	HPV-16	17	38	33	106	0.331
			HPV-18					
			HPV-33					
Zhang et al. (50)	FF	PCR	HPV-16	AEG: 5	166	AEG: 6	166	AEG: 0.061
			HPV-94	GC: 5		GC: 2		GC: 0.201
				Total: 10		Total: 8		Total: 0.077
Cândido et al. (22)	FFPE	PCR	HPV	4	40	10	40	0.436
Yuan et al. (49)	Tissue	GenoArray test kit	HPV	0	24	0	74	0.000
Turkay et al. (11)	FFPE	RT-PCR	HPV-16	HPV-16: 1	19	HPV-16: 0	8	HPV-16: 0.000
			HPV-39	HPV-39: 1		HPV-39: 0		HPV-39: 0.000
				Total: 2		Total: 0		Total: 0.002
Roesch-Dietlen et al. (39)	Tissue	Nested-PCR	HPV-16	0	10	0	55	0.000
			HPV-18					
Bozdayi et al. (53)	Tissue	RT-PCR	HPV	20	53	23	69	0.082
Leon et al. (54)	FF	PCR	HPV	0	11	0	56	0.000
Sabin et al. (40)	Serum	CFT	HSV-1	0	5	0	57	0.000
			HSV-2					
Matveeva et al. (37)	Serum	ELISA	HSV-1	30	30	107	150	0.999
			HSV-2					
Tahaei et al. (44)	Serum	ELISA	HTLV-1	1	201	4	219	0.235
Tanaka et al. (45)	Serum	PA	HTLV-1	32	262	467	3,612	0.058
Shin et al. (42)	FFPE, FF	PCR	JCV	T-Ag: 21	37	T-Ag: 11	37	T-Ag: 0.650
				VP-1: 9		VP-1: 7		VP-1: 0.085
				TCR: 16		TCR: 13		TCR: 0.104
				T-Ag: 19		T-Ag: 10		T-Ag: 0.023
Murai et al. (38)	FF	SB, IHC	JCV	VP: 12	22	VP: 7	10	VP: 0.121
				Agnoprotein: 2		Agnoprotein: 1		Agnoprotein: 0.056
				IHC: 1		IHC: 0		IHC: 0.000
Selgrad et al. (41)	Tissue	PCR	JCV	37	55	16	24	0.051
Yamaoka et al. (48)	Tissue	IHC	JCV	44	90	0	90	1.000

Table 2. (*continued*)

Study	Test material	Test method	Virus type	Cases		Controls		Power (1–β)
				No. Positive	Total	No. Positive	Total	
Jang et al. (29)	FFPE	PCR, IHC	JCV	PCR: 9 IHC: 5	30	PCR: 10 IHC: 1	40	PCR: 0.077 IHC: 0.590
Ksiaa et al. (33)	FFPE	PCR	JCV	16	61	2	23	0.430
Choi et al. (24)	Tissue	IHC	JCV	56	285	0	285	1.000
Izi et al. (28)	FFPE	RT-PCR	JCV	17	31	10	31	0.452
Cherati et al. (23)	FFPE, FF	RT-PCR	JCV	1	81	1	124	0.072
Li et al. (34)	Serum	Nested-PCR	Parvovirus B19	9	16	36	800	0.999
Li et al. (34)	Serum, sputum	Nested-PCR	HBoV	8	16	33	941	0.998

AEG, Adenocarcinoma of the esophagogastric junction; CFT, complement fixation test; CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; FF: fresh-frozen; FFPE: formalin-fixed and paraffin-embedded tissue; GC, gastric cancer; HBoV, human bocavirus; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HPV, human papillomavirus; HSV, herpes simplex virus; HTLV-1, human T-cell lymphotropic virus type 1; ICD-9, International Classification of Diseases, version 9; IHC, immunohistochemistry; ISH, *in situ* hybridization; ISPCR, *in situ* PCR; LPCR, liquid PCR; PA, gelatin particle agglutination method; PCR, polymerase chain reaction; RT-PCR, real-time PCR; SB, Southern blot; UL133, UL135, UL136, UL138, and IE1, different sequences of HCMV genome; T-Ag, VP, TCR, and agnoprotein, different sequences of JCV genome (T-Ag, VP, and agnoprotein were tested by SB and T-Ag was tested by IHC in the study by Murai et al.).

to observe the heterogeneity. For an individual study, the power (1–β) 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 lymphotropic 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 (26,27,35,47,52,55,56). 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 been 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

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
Baghbanian 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
Sabin 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

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).

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 −5.3% to 17.7%, random model, heterogeneity $P < 0.001$). No association was observed between HTLV-1 infection and the risk of GC (OR = 0.89, 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

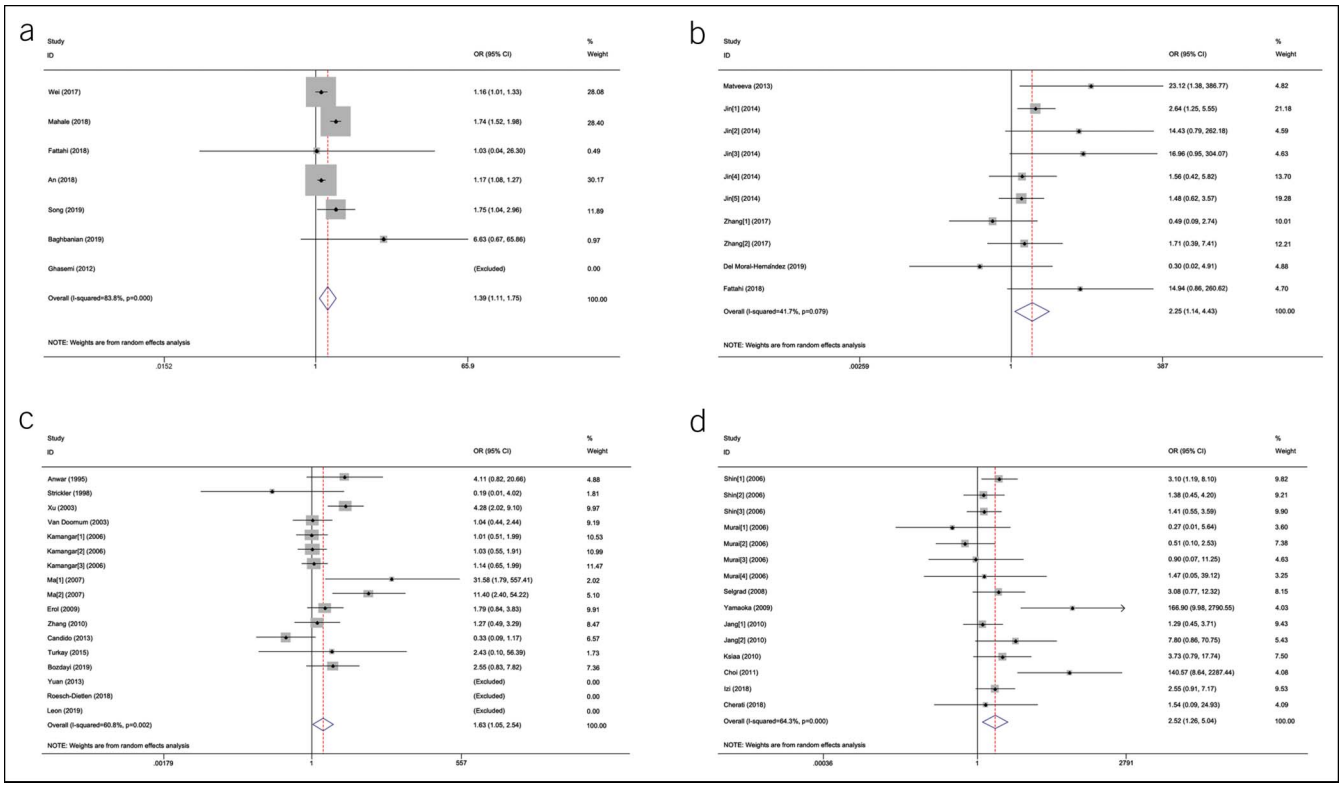

Figure 2. The forest plots of the comparison on virus prevalence between patients with gastric cancer and any controls after excluding subjects with known *H. pylori* and EBV positive: (**a**) the forest plot for HBV; (**b**) HCMV: Jin [1–5]: different sequences of HCMV genome were detected; Zhang [1–2]: IgG or IgM was detected; (**c**) the forest plot for HPV: Kamangar [1–3]:different subtypes of HPV were investigated; Ma [1–2]:different test methods were used; and (**d**) the forest plot for JCV: Jang [1–2]: different test methods were used; Murai [1–3]: different sequences of JCV genome were detected by Southern blot; Murai [4]: T-Ag were detected by immunohistochemistry; Shin [1–3]: different sequences of JCV genome were detected. CI, confidence interval; EBV, Epstein-Barr virus; HCMV, human cytomegalovirus; HPV, human papillomavirus; JCV, John Cunningham virus; OR, odds ratio; T-Ag, transforming antigen.

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	
				I^2 (%)	*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	3	4.63 (0.50–42.77)	0.177	77.5	0.004
Benign gastric disease	2	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

Table 4. (*continued*)

Stratification	No. of studies	OR (95% CI of effect)	*P* value	Heterogeneity	
				I^2 (%)	*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 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 noncancer healthy and benign gastric disease controls; OR, odds ratio; PCR, polymerase chain reaction; PCNT, paired corresponding normal tissues; SB, Southern blot.

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 contribute to gastritis and GC subsequently (10).

The role of HPV in the etiology of cervical cancer has been established, in addition to anal and colorectal cancers potentially (67–69). Our study verified the association between the prevalence of HPV (especially HPV-16, a high-risk subtype of HPV) and GC, and the pooled HPV prevalence in GC was 23.6%, no obvious difference from the previous report (70). Although HPV serologic test was considered as a good marker for HPV detection, significant association between HPV infection and the risk of GC was observed in gastric tissues by comparison with serum samples (71). Mechanisms of HPV escaping from the host immune system 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

Table 5. Subgroup analysis of HCMV, HPV, and JCV prevalence between GC and any controls after excluding subjects with known *H. pylori* and Epstein-Barr virus positive

Stratification	No. of studies	OR (95 % CI of effect)	*P* value	Heterogeneity	
				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

Table 5. (*continued*)

Stratification	No. of studies	OR (95 % CI of effect)	*P* value	Heterogeneity	
				I^2 (%)	*P* value
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.

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 (3,4,26,32,79–81). 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., and W.-H.Z., X.-Z.C., and J.K.H: participated in critical revision for important intellectual content.
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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

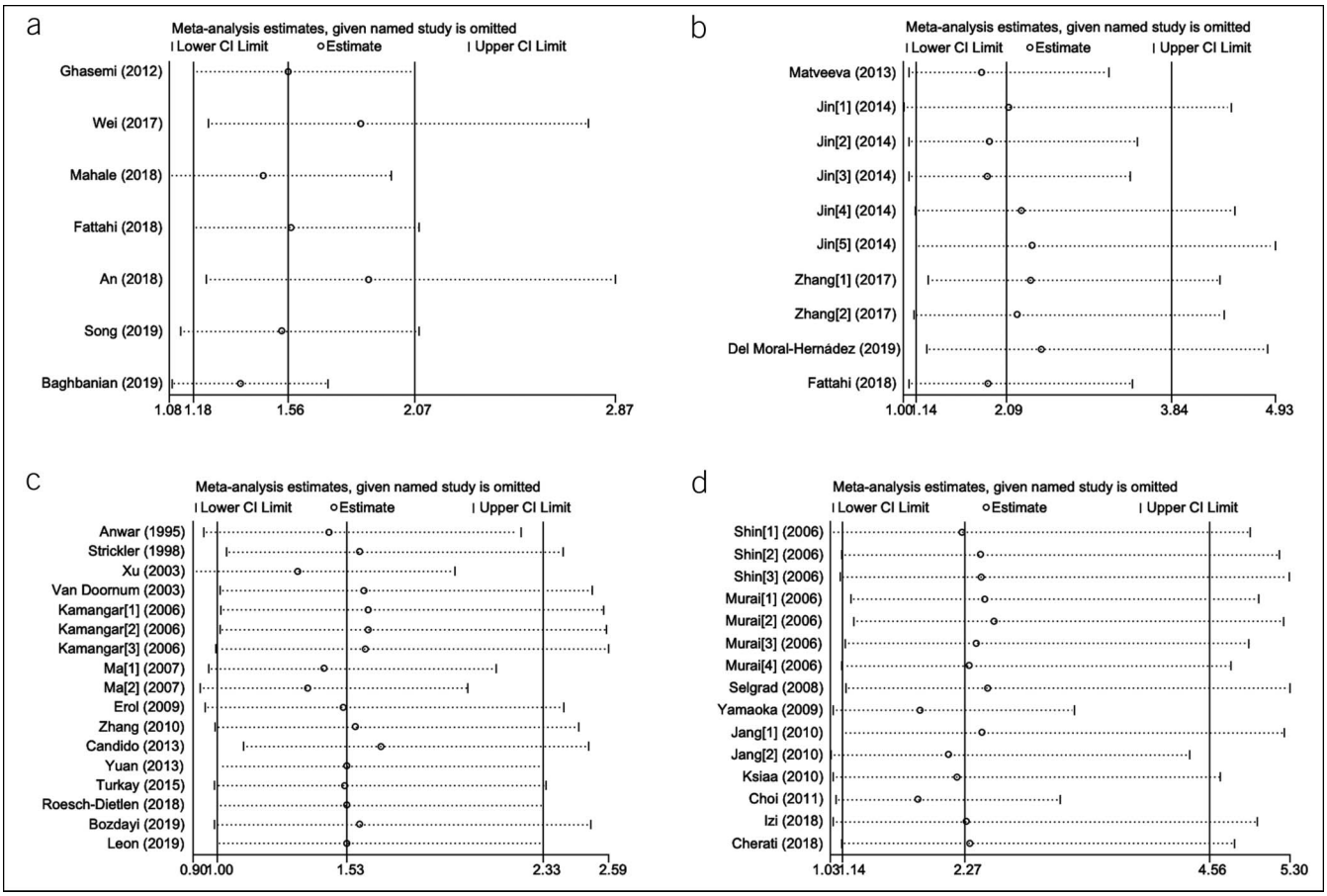

Figure 3. Sensitivity analysis of the meta-analysis: (**a**) HBV; (**b**) HCMV; (**c**) HPV; and (**d**) JCV. CI, confidence interval; HBV, hepatitis B virus; HCMV, human cytomegalovirus; JCV, John Cunningham virus.

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