

Cytomegalovirus Infection Is a Risk Factor in Gastrointestinal Cancer: A Cross-Sectional and Meta-Analysis Study

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Keywords

Cytomegalovirus · Infection · Gastrointestinal cancer · Colorectal cancer · Gastric cancer · Meta-analysis

Abstract

Background: This study was planned to investigate the association between human cytomegalovirus (HCMV) infection and gastrointestinal cancer (GIC) risk, by undertaking a meta-analysis and case-control cross-sectional study. **Summary:** A cross-sectional study analysis of 160 GIC patients and 100 control subjects indicated significantly higher HCMV prevalence in GIC patients based on the HCMV IgM test. However, a similar analysis based on an IgG test revealed no significant relationship. Further meta-analysis of 11 studies, including 1,044 patients and 991 healthy subjects, displayed HCMV infection as an important risk factor for not only colorectal cancer occurrence and development based on a HCMV DNA test, but also for GIC based on a HCMV IgM test. However, the IgG test again displayed no significant relationship between HCMV infection and GIC occurrence. **Key Message:** Overall, our study revealed that HCMV infection is associated with an increased GIC risk. However, additional studies are warranted to elucidate the molecular mechanism underlying this association.

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Introduction

Gastric cancer (GC) and colorectal cancer (CRC) are the most common gastrointestinal cancers (GIC), and, according to World Health Organization (WHO) statistics, approximately 875,000 and 1,000,000 new cases are diagnosed annually, worldwide [1, 2]. Despite little information about their pathogenesis, it is clear that both are multifactorial diseases, and various factors including infectious agents have been observed to be involved in their genesis. More specifically, infectious agents like human papillomavirus, *Helicobacter pylori*, Epstein-Barr virus, and cytomegalovirus have commonly been implicated as causative agents for CRC and GC [3–5].

Among the various infectious microorganisms, human cytomegalovirus (HCMV) prevalence is wide in human populations. HCMV has been observed to survive in the host, after initial infection for long periods [6]. Based on one study, it appears that about 70–100% of the adults are infected with HCMV in the overall population worldwide [7]. Its infection is typically asymptomatic in healthy individuals [8] but immunologically immature and immunocompromised patients display severe symptoms [9]. HCMV belongs to the betaherpesvirinae subfamily, and its virion structure, viral gene expression kinetics,

Table 1. Study participant characteristics

Characteristic	Patients with GIC (n = 160)	Controls (n = 100)	p value
Age (mean ± SD), years	62.15±11.71	62.82±10.41	0.717
Male sex, n (%)	90 (56.25)	57 (57)	0.683
Ethnicity, n (%)			
Han	158 (98.75)	99 (99)	0.859
Manchu	2 (1.25)	1 (1)	ns
BMI (mean ± SD)	24.55±3.51	27.14±3.06	0.119
Smoking, n (%)	37 (23.13)	15 (15)	0.174
Drinking, n (%)	28 (17.5)	11 (11)	0.160
HCMV detection, n (%)			
Serum HCMV IgG+	53 (33.13)	25 (25)	0.176
Serum HCMV IgM+	53 (33.13)	18 (18)	0.008

and lifetime persistence in its host are very similar to other herpesvirus family members [9]. More recent studies have focused on HCMV associations with various cancers, including glioblastoma, breast cancer, CRC, and GC [10–12]. Additionally, HCMV has also been observed to induce gastrointestinal track disorders, like inflammatory bowel disease, ulceration, cell wall erosion, and mucosal hemorrhage [13, 14].

There have been conflicting reports about HCMV associations with GIC, and, thus, herein we have investigated HCMV prevalence in GIC patients in comparison to healthy subjects by undertaking a cross-sectional analysis, along with a comprehensive meta-analysis. The study was undertaken with the intent to explore the possible role of HCMV in GIC tumorigenesis and identify new strategies for prevention and treatment.

Materials and Methods

Patient Recruitment for Cross-Sectional Study Analysis

A total of 160 serum samples were collected from GIC patients for serological analysis between January 2016 and December 2017. In addition, 100 age- and sex-matched control serum samples were also collected from healthy individuals to be used as controls (Table 1). All serum samples were stored at -80°C until analysis. This study was approved by the Ethics Committee of the Beijing Chaoyang Hospital, Capital Medical University, China (2015-research-161).

ELISA Assay for Serum Analysis

The serum IgG and IgM antibodies against HCMV were assessed in serum samples using an ELISA kit, according to the manufacturer's instructions (Sigma-Aldrich, St. Louis, MO, USA). The blank negative and positive controls were included in the kit. The results were statistically analyzed using SPSS software version 22 (SPSS, Chicago, IL, USA). The categorical variables were com-

pared by using χ^2 and Fisher's exact tests, while continuous variables were assessed using a *t* test for data with a normal distribution and a Mann-Whitney U test for data without a normal distribution. The *p* value of less than 0.05 indicated a significant difference.

Identification of Relevant Studies for Meta-Analysis

All eligible studies were identified from PubMed and Embase databases until February 2019, using the following key terms: "human cytomegalovirus" and "gastric cancer" or "colorectal cancer." The articles published in both the English and Chinese literature were considered. After initial identification of the relevant studies, their cross-references were further scanned to identify additional studies to be included in our meta-analysis.

Inclusion Criteria and Meta-Analysis

The identified studies were included in the meta-analysis, if they met the following selection criteria: (1) studies evaluating the association between HCMV infection and GC; (2) studies evaluating the association of HCMV infection with CRC; (3) case-control or self-control studies; (4) studies having information about the HCMV infection rate (numbers or percentage) for both patients and controls. All the conference abstracts, case reports, editorials, review articles, and letters were excluded.

The data extraction was primarily performed by two authors (Ya-li Lv and Yang-jie Jia). The study was included in our analysis only when both the authors reached consensus on its eligibility. When two authors disagreed, the two authors would rematch the original data with a third person overseeing until a consensus was reached. The following information was extracted from each study: first author's surname, publication year, source of all patient cases, HCMV detection method, total numbers of cases and controls, and HCMV infection positivity rate both in cases and controls. The articles reporting the HCMV prevalence rate based on both enzyme-linked immunosorbent (ELISA) and polymerase chain reaction detection-based methods were included in the analysis.

The statistical analyses of the extracted data were performed using Review Manager (Review Manager 5.0 software) and Stata/MP 11.0 software. The heterogeneity across the included studies was assessed using Cochran's w^2 and inconsistency index (I^2) tests. All the analyses were performed using a random-effects model and

Table 2. Main characteristics of the studies included in the meta-analysis

First author	Source of cases	Study design type	Disease type	Definition of disease	Detection of HCMV	Cases		Controls	
						HCMV+	total	HCMV+	total
Zhang [16], 2017	China	Case-control Self-control	Gastric cancer	Histopathology	IgG IgM	76 5	80	78 3	80
Mehrabani-Khasraghi [21], 2016	Iran	Case-control	Colorectal cancer	Histopathology	DNA	8	15	13	35
Wang [17], 2000	China	Case-control	Colorectal cancer	Histopathology	DNA	6	8	0	3
Ye [20], 2016	China	Case-control	Colorectal cancer	Colonoscopy Histopathology	IgG IgM	57 3	60	58 1	60
Tang [18], 2007	China	Case-control	Colorectal cancer	Histopathology	IgG IgM	96 18	102	83 7	94
Chen [23], 2016	China	Self-control	Colorectal cancer	Histopathology	DNA	31	89	7	89
Tafvizi [19], 2014	Iran	Self-control	Colorectal cancer	Histopathology	DNA	15	50	5	50
Dimberg [22], 2013	Sweden Vietnam	Self-control Self-control	Colorectal cancer	Histopathology Histopathology	DNA DNA	18 33	119 83	2 10	119 83
Chen [11], 2012	China	Self-control	Colorectal cancer	Histopathology	DNA	69	163	14	163
Chen [4], 2015	China	Self-control	Colorectal cancer	Histopathology	DNA	49	115	13	115
Lv [14], 2018 (current study)	China	Self-control	Gastric and colorectal cancer	Histopathology	IgG IgM	53 53	160 160	25 18	100 100

OR (odds ratio), and their corresponding 95% confidence intervals (CI) were estimated. The statistical significance of pooled ORs was determined using a z test, and a p value of less than 0.05 was considered significant. The statistical heterogeneity was compared using χ^2 square and I^2 statistics, where a I^2 value of more than 50% reflected substantial heterogeneity [15].

Results

GIC Patients' Characteristics

In our cross-sectional study, we analyzed 160 GIC patients along with 100 age-, sex-, and ethnicity-matched control subjects for HCMV prevalence between the years 2016 and 2017. The mean age of GIC patients was 62.15 \pm 11.71 years, and 90 were male. In control subjects, the age and gender were comparable. In addition, the ethnicity and socioeconomic status of the two groups were also similar. The complete information about control and patient characteristics has been summarized in Table 1.

Analysis of HCMV Prevalence among GIC Patients

ELISA assay-based analysis revealed that HCMV prevalence was significantly higher among GIC patients in comparison to control subjects (OR 2.26 [95% CI: 1.23–

4.14]), based on an IgM antibody test. Similarly, an IgG test also showed the same trend of a slightly higher HCMV prevalence in GIC patients (33.13%) in comparison to the control subjects (25%). However, the IgG test of HCMV prevalence between GIC patients (33.13%) and the control subjects (25%) showed no significance (OR 1.49 [95% CI: 0.85–2.60]), as shown in Table 1.

Meta-Analysis of HCMV Prevalence

Based on the study selection criteria, we initially identified 296 potentially relevant studies from the electronic databases. Among these, 229 were excluded after reviewing the abstracts. The detailed evaluation of the 67 remaining studies resulted in the further exclusion of 57 due to duplicated publications, lack of adequate data, or no original date for the meta-analysis. Finally, 10 publications were included in our meta-analysis [11, 16–24]. The study selection process has been depicted as a flow chart in online supplementary Figure 1 (for all online supplementary material, see www.karger.com/doi/10.1159/000506683). In addition, we also included our cross-sectional analysis data about HCMV prevalence in 160 GIC patients and 100 control subjects as a separate study. Thus, overall, 11 studies including 1,044 patients and 991 control subjects were part of the final meta-analysis. Two different meth-

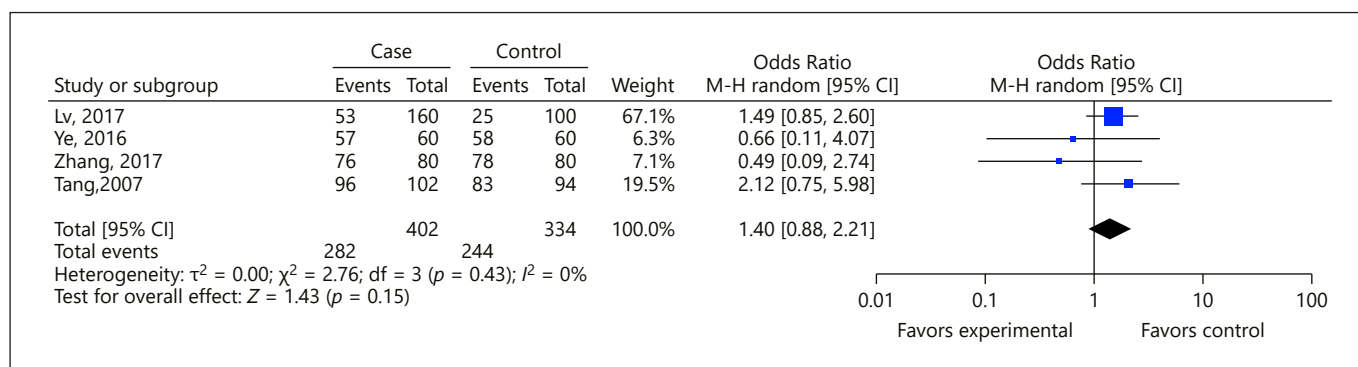


Fig. 1. Forest plot (using a random-effect model) analysis showing the association between GIC and HCMV infection, stratified using the HCMV IgG test.

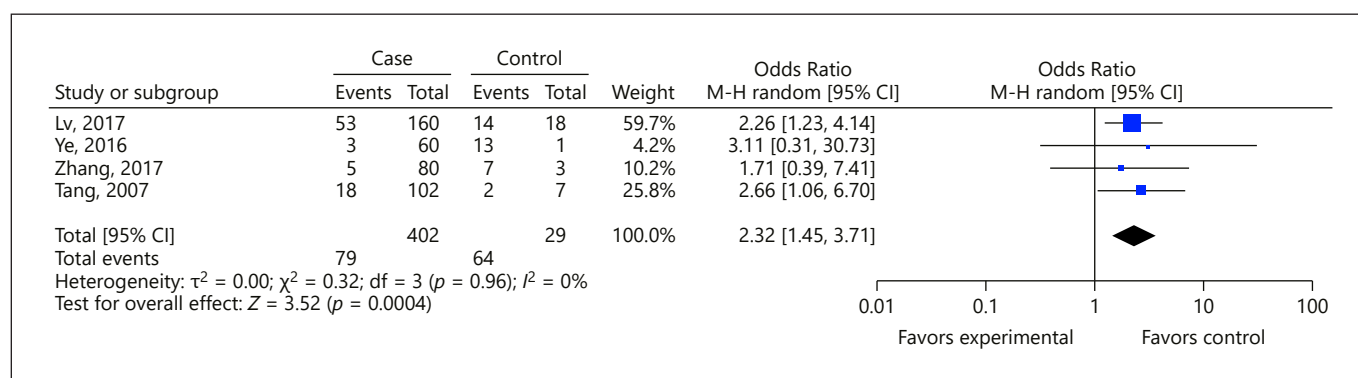


Fig. 2. Forest plot (using a random-effect model) analysis showing the association between GIC and HCMV infection, stratified based on the HCMV IgM test.

ods were used in these studies to detect the HCMV infection. A total of 4 studies used an ELISA assay to identify the HCMV infection, while another 7 studies used a more sensitive polymerase chain reaction-based assay. Also, 10 studies included an Asian population, while 1 study analyzed patients from two different regions (Sweden and Vietnam). All 11 studies were case-control studies. The complete characteristics of patients and control subjects have been summarized in Table 2.

Meta-analysis of the 11 studies revealed that an HCMV association, based on IgG tests, was evident in 70.15% of the GIC patients (282/402) and 73.05% of the control subjects (244/334), as shown in Figure 1. In parallel, IgM tests demonstrated HCMV association in 19.65% of the GIC patients (79/402) and 8.68% of the control subjects (29/334; Fig. 2). Furthermore, a DNA test revealed an HCMV association in 35.66% of the GIC patients (229/642) and 9.74% of the control subjects (64/657; Fig. 3). Therefore, 2 out of 3 tests demonstrated that exposure to an HCMV infection increased the risk for GIC, as an

IgM test revealed an OR of 2.32 (95% CI: 1.45–3.71; Fig. 2), while a DNA test showed an OR of 5.72 (95% CI: 4.14–7.91; Fig. 3).

Sensitivity Analysis

In addition, we also performed a sensitivity analysis to examine the stability of our results. After exclusion of one study at a time, our meta-analyses showed no significant changes in the overall OR values, as shown in Table 3. This indicated that no single particular study significantly affected the final OR values, and, therefore, our data appeared to be stable and reliable.

Publication Bias

Next, we also conducted a publication bias analysis of the included studies using a Begg's funnel plot and Egger's test. Our data indicated no evidence of publication bias, as seen in online supplementary Figure 2. The funnel plot showed some dissymmetry, but Egger's test provided no statistical evidence of funnel plot asymmetry.

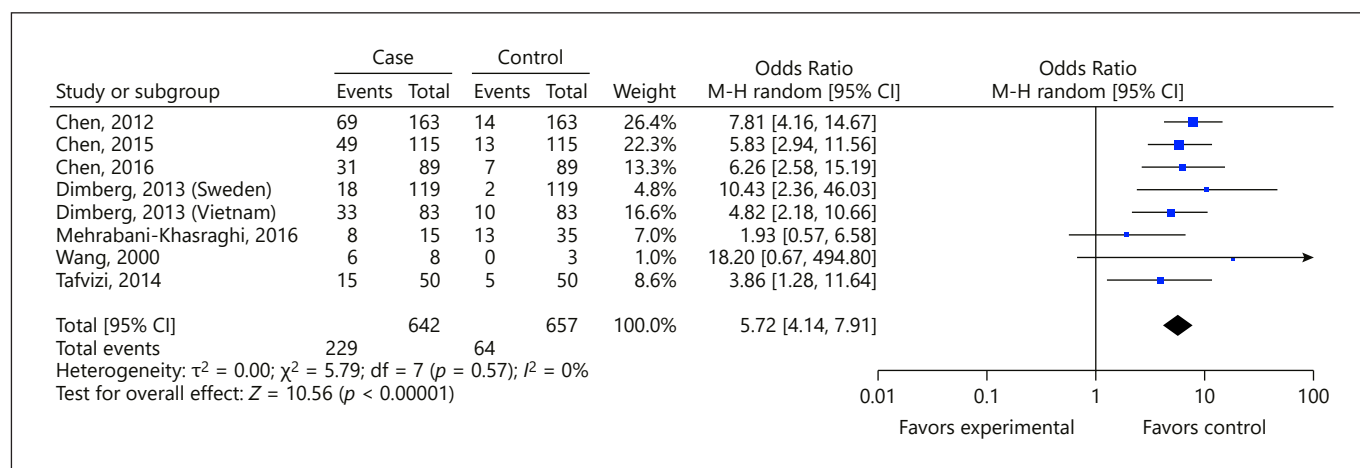


Fig. 3. Forest plot (using random-effect model) analysis showing the association between GIC and HCMV infection, stratified based on the HCMV DNA test.

Table 3. Sensitivity analysis

Study excluded	OR	95% CI	<i>p</i>
<i>IgG tests</i>			
None	1.40	0.88–2.21	0.15
Lv [14], 2017	1.12	0.43–2.93	0.82
Ye [20], 2016	1.47	0.90–2.40	0.12
Zhang [16], 2017	1.51	0.94–2.44	0.09
Tang [18], 2007	1.26	0.76–2.11	0.37
<i>IgM tests</i>			
None	2.32	1.45–3.71	0.0004
Lv [14], 2017	2.42	1.15–5.07	0.02
Ye [20], 2016	2.29	1.42–3.70	0.0007
Zhang [16], 2017	2.40	1.46–3.94	0.0005
Tang [18], 2007	2.21	1.28–3.81	0.004
<i>DNA tests</i>			
None	5.72	4.14–7.91	<0.00001
Chen [11], 2012	5.11	3.51–7.46	<0.00001
Chen [4], 2015	5.69	3.94–8.21	<0.00001
Chen [23], 2016	5.64	3.98–7.99	<0.00001
Dimberg [22], 2013 (Sweden)	5.55	3.98–7.73	<0.00001
Dimberg [22], 2013 (Vietnam)	5.92	4.15–8.44	<0.00001
Mehrabani-Khasraghi [21], 2016	6.21	4.44–8.68	<0.00001
Wang [17], 2000	5.66	4.09–7.83	<0.00001
Tafvizi [19], 2014	5.94	4.23–8.33	<0.00001

Discussion

The GIC (including GC and CRC) seems to be linked with the second and third highest mortality rates, respectively, among all cancers and, thus, pose an enormous threat to public health [25, 26]. A high mortality rate and

metastasis risk highlights that early detection of their pathogenesis is crucial for patients [27]. Historically, the relationship between HCMV and CRC was first noticed in the year 1978 [28], and, since then, this topic has attracted much attention from the scientific community, including clinicians. However, the exact role of the HCMV infection in GIC patients has still not been deciphered, despite multiple efforts. Moreover, there have been conflicting reports in the literature about an HCMV association with GIC. Therefore, we, in our current study, first performed a cross-sectional analysis to detect the association and prevalence of an HCMV infection among GIC patients and healthy control subjects, using ELISA-based IgG and IgM antibody analyses. In addition, we also undertook a comprehensive meta-analysis by identifying relevant studies from the literature, to clearly understand the association between an HCMV infection and GIC.

Our data from the cross-sectional study revealed that HCMV detection was significantly higher among GIC patients compared to control subjects, based on an IgM test. However, an IgG test displayed no significant relationship between GIC patients and control subjects. The reasons may be that DNA and IgM are respectively used as indicators of virus replication, proliferation, and short-term infection, while IgG is used as indicator of long-term infection. However, as a latent virus, HCMV might not consistently express products during the whole period of infection, which would cause false-negative results on an IgG test [29, 30]. This observation was consistent with the results observed in other studies included in our meta-analysis, where multiple serological and histological stud-

ies demonstrating that an HCMV infection is a distinct risk factor for CRC occurrence and development based on HCMV DNA tests and for GIC based on IgM tests. Importantly, some studies showed no significant relationship between an HCMV infection and GIC occurrence because they typically analyzed viral proteins, like IE, US28, and pp65 [12, 31]. These studies were however small and were not included in our own meta-analysis.

Therefore, despite variable HCMV detection rates using different methods, it is clear that its prevalence is significantly higher in tumor serum and tissue samples than the paired normal controls, based on IgM and DNA tests. On average, we suspect that HCMV infections might be 2–5 times higher in GIC patients than in control subjects, thereby pointing towards a strong association between GIC and HCMV. Consistent with our data, two independent studies [12, 28] also suggested HCMV infection is an important risk factor for CRC and GC. However, 2 other studies were not able to confirm this association [32, 33]. The controversy about an HCMV association with GIC can be attributed to the methodology used to detect the virus and the analysis of variable protein markers. This warrants the use of more powerful techniques along with larger statistical populations in future studies to further resolve this issue of HCMV infection and GIC.

Typically, GIC is a multifactorial disease, and its occurrence and development are regulated by multiple factors including microbial infection, genetic predisposition, and environmental factors [34–36]. Some studies have indicated that viral modification of the host epigenome can play an important role in GIC initiation and progression [37]. However, some other studies have demonstrated that cytokine gene polymorphism can regulate HCMV reactivation in cancer patients [38]. Specifically, it has been proposed that HCMV may increase and reinforce cancerous cell malignant properties by activating the cell survival and growth signaling pathway [39]. In addition, it has also been hypothesized that the virus is carried to the neoplasm by myeloid cells and later indwelled at the malignant mucosal epithelium [11]. Another study [40] has reported that proteins displayed on HCMV prevent host immune system cells from identifying and eliminating this virus and, thereby, facilitating long-time infection, which subsequently leads to tumor progression. However, the exact molecular mechanism underlying HCMV association with GIC has still not been elucidated, and additional studies would be required to understand this complex relationship.

It is equally important to highlight the limitations of our study. First, in the cross-sectional study analysis, we only used an ELISA method to detect HCMV infection in

the serum. Second, we only focused on detecting HCMV IgG and IgM levels in our cross-sectional analysis study, and the studies included for meta-analysis also only focused on IgG and IgM, along with a DNA-based detection method. The data based on detection of other viral proteins was not considered. Third, our meta-analysis was only based on 11 studies due to strict inclusion criteria, which appears to be small, and, thus, additional large cohort studies would be helpful to analyze the association.

Conclusions

In conclusion, based on our data, an HCMV infection appeared to be significantly associated with an increased risk of GIC. However, additional studies using a larger sample size would be helpful to further establish this association and also help to understand the molecular mechanism underlying it.

Acknowledgments

Thanks are due to Zirui Wan for drafting this manuscript and critically revising it for important intellectual content.

Statement of Ethics

This study was approved by the Ethics Committee of the Beijing Chao-Yang Hospital, Capital Medical University, China (2015-research-161). Written informed consent was obtained from all individual participants included in the study.

Disclosure Statement

The authors declare that they have no conflict of interest.

Funding Sources

This study was supported by the Beijing Natural Science Foundation (grant No. 7151004) and the Natural Science Foundation of China (grant No. 81500336).

Author Contributions

Ya-li Lv, Yang-jie Jia and Fei-fei Han extracted data and reached a consensus on all of the eligibility items according to the inclusion criteria listed above. Ya-li Lv participated in the sequence alignment and drafted the manuscript. Zhuo-ling An, Ling-ling Xuan, Li-li Gong, Wen Zhang, Lu-lu Ren, and Song Yang participated in the design of the study and performed the statistical analysis. Li-hong Liu and Liu He conceived the study, participated in its design and coordination, along with helping to draft the manuscript. All authors read and approved the final paper.

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