

Human papillomavirus as a potential risk factor for gastric cancer: a meta-analysis of 1,917 cases

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Background: Human papillomaviruses (HPVs) are causally associated with the tumorigenesis of several classes of cancers. However, the prevalence of HPV in gastric cancer (GC) has not yet been systematically reviewed. Hence, a meta-analysis was conducted to estimate the HPV prevalence in patients with GC, and its potential etiologic significance was assessed.

Methods: The pooled HPV prevalence and 95% confidence intervals (CIs) were estimated among all GC patients. Heterogeneity was described by using the I^2 statistic. Sources of heterogeneity were explored by meta-regression and stratified analyses. The meta-influence was applied to evaluate the influence of a single study on the pooled estimates. Odds ratios (ORs) and 95% CIs were computed for case-control studies. For research providing clinicopathological parameters of age, sex, pathological, differentiated, and clinical stages, and HPV subtypes, the corresponding pooled ORs and 95% CIs were also calculated.

Results: Thirty studies were included in the current meta-analysis, involving 1,917 patients with GC and 576 controls. The pooled HPV prevalence was 28.0% (95% CI: 23.2%, 32.7%) among all the patients with GC, and the I^2 was 96.9% ($P < 0.001$). A pooled OR of 7.388 (95% CI: 3.876, 14.082) was achieved based on 15 case-control studies ($I^2 = 56.7%$, $P = 0.004$). Moreover, the HPV prevalence was significantly higher in patients from China than in those from non-Chinese regions (31% vs 9%, $I^2 = 95.0%$, $P < 0.001$). The pooled prevalence of HPV16 was 21% in GC tissues, and the pooled prevalence of HPV18 was 7% with an OR of 3.314 (95% CI = 1.617, 6.792). HPV16 was 3 times more frequently detected than HPV18.

Conclusion: HPV could play a potential role in the pathogenesis of GC. A causal relationship can be confirmed only by detecting HPV in the cells of GC precursor lesions (gastric dysplasia or adenoma). In addition, this study might be beneficial for expounding the potential etiologic significance of molecular mechanism of gastric tumorigenesis and providing opinions regarding precautionary measures.

Keywords: gastric dysplasia, gastric adenoma, gastric tumorigenesis, odds ratios, prevalence, subtypes

Introduction

A growing amount of evidence has shown that virus infection, directly or indirectly, can result in numerous malignant tumors.¹ Worldwide, annually, >550,000 new patients suffering from malignant tumors are associated with human papillomaviruses (HPVs) infection.^{2,3} Currently, >150 HPV subtypes with 15 species of high-risk types of HPV (HR-HPV) have been found. The HR-HPV family contains HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV66, and HPV68. HPV16 and HPV18 are the most common cancer-causing HPV subtypes

on a global scale.^{2,3} Simultaneously, HPV16, HPV18, and HPV33 have been confirmed to be correlated with tumors in digestive system, such as oral cancer, esophageal cancer, and colorectal cancer.^{1,4,5} In 2012, 1 million new cases of gastric cancer (GC) occurred (952,000 cases, 6.8% of the total), leading to its rank as the fifth most common malignant tumor worldwide, following lung, breast, colorectum, and prostate cancers. More than 70% of cases (677,000 cases) occurred in the developing countries (456,000 in males and 221,000 in females), and worldwide, half of all the GCs occurred in Eastern Asia (mostly in China). The fatality rate of GC was ranked third, following only lung and liver cancers.⁶ In 2015, cancer statistics estimated that new cancer cases and deaths from GC numbered 24,590 and 10,720 (1.48% and 1.82% of the total, respectively) in the USA.⁷

Several meta-analyses have shown that HPV infection is a high-risk factor for carcinogenesis at some anatomic sites, including the skin, genital tract, respiratory tract, and disparate anatomic sites of the digestive tract.^{8–11} With the assumption that repeatedly persistent infection with HPV can cause dysplasia or adenocarcinoma in situ, as precursor lesions, it will eventually result in malignant transformation.¹² Some studies have investigated HPV infection in gastrointestinal cancer.^{4,5,8,12–14} However, only sporadic research has reported the HPV prevalence in GC. Currently, whether there is a link between HPV infection and GC occurrence has not been systematically analyzed publicly.

In order to obtain insight into the HPV prevalence in GC tissues, the present meta-analysis was conducted, and this study facilitates and improves the understanding of the carcinogenicity of the virus in GC and provides new clues to GC etiology and prevention.

Materials and methods

Search strategy

The PubMed, EMBASE, Web of Science, Science Direct, Ovid, Wiley Online Library, and Cochrane Library databases, as well as the China National Knowledge Infrastructure, Chinese Chongqing VIP, Chinese Wan Fang, and China Biology Medicine databases, were searched to identify all the appropriate studies published on or before June 3, 2016, with the following search strategy: (HPV OR human papillomavirus) AND (gastric OR stomach OR cardia OR gastrointestinal) AND (adenocarcinoma OR carcinoma OR cancer OR neoplasm OR tumour OR tumor OR neoplasm* OR malignan*).

Study selection and inclusion criteria

The inclusion criteria for this meta-analysis are as follows: 1) studies had to estimate the prevalence of HPV in GC cases

where the classification was unspecified or provide sufficient information; 2) data from case reports, review articles, meeting abstracts, unpublished reports, and letters were not eligible for this study; 3) studies had to investigate HPV DNA in human GC tissue; two cohort studies detecting HPV serum antibodies in patients with GC were excluded;^{13,15} 4) only English- or Chinese-language studies could be included; and 5) the HPV detection methods used were polymerase chain reaction (PCR) and in situ hybridization (ISH).

In addition, if two or more articles were published by the same group with the same case series, the one with larger sample size was selected. The research was conducted independently by two investigators, and disagreements were resolved by discussion or consulting with a third reviewer (Figure 1).

Data extraction

The following data were extracted from the eligible studies: name of first author, published year, country, anatomic site, language, sample size (n), HPV DNA test method, materials, number of cases and controls; HPV subtype-specific, mean age, sex, pathological differentiation, and clinical stage (TNM) of GC.

Statistical analysis

Pooled HPV prevalence and pooled odds ratios (ORs) with their 95% confidence intervals (CIs) were used to evaluate the relation of HPV infection with the occurrence and development of GC. The STATA software, Version 12.0, was applied to analyze the eligible literature using the meta-module “meta” or “metan” command. Estimates, standard errors, and 95% CIs were used to calculate the HPV prevalence percentages in all the studies. ORs and 95% CIs were measured among 15 case–control studies, and pooled HPV prevalence and 95% CIs were computed among all the 30 studies. All the prevalence estimates were transformed logarithmically, which necessitated adding a correction factor of 0.5 to both the numerator and denominator for reported prevalence of 0. In these situations, inverse variance, Mantel–Haenszel (M-H) method, and DerSimonian and Laird (D+L) method required the addition of a small quantity (usually 0.5) to the cell counts in order to avoid division by zero errors. The pooled estimates were computed by using the Mantel–Haenszel method, assuming a fixed effects model or the random effects model of the D+L method. When significant heterogeneity occurred in the pooled estimates across studies, a random effects model was considered. In addition, heterogeneity was described by using the I^2 statistic. Meta-regression models were estimated by the “metareg” command to analyze the heterogeneity of

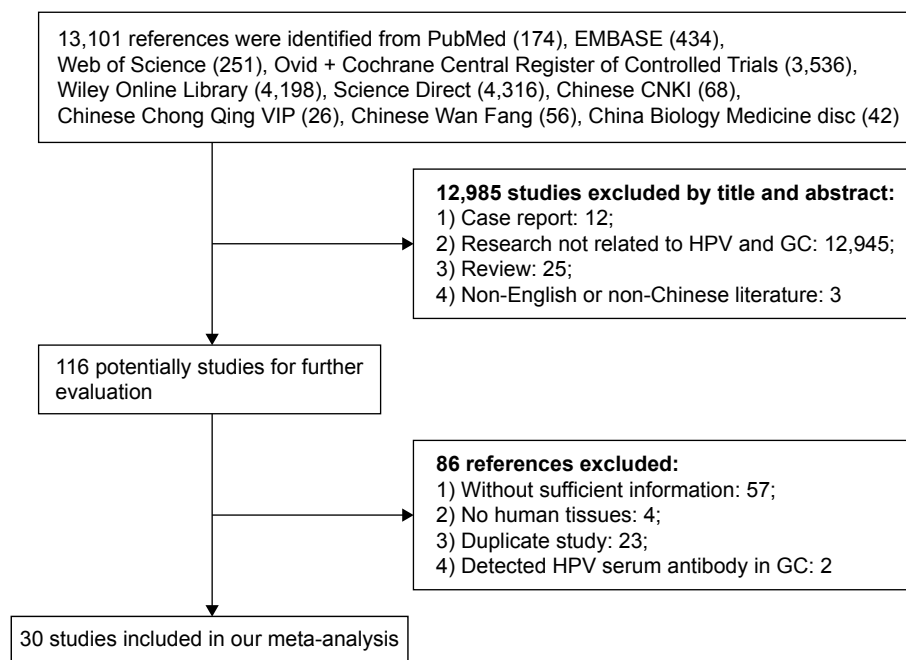


Figure 1 The flow diagram of searching and screening process as well as the number of screened, excluded, and included publications.
Abbreviations: GC, gastric cancer; HPV, human papillomavirus.

the pooled HPV prevalence in GC. Begg's test ("metabias") was accepted to draw funnel plots and describe the publication bias of funnel plot asymmetry (publication bias). The "metainf" command was selected to assess the influence of individual studies on the effect estimate. $P < 0.05$ was considered to be statistically significant. The source of heterogeneity was explored by using the following approaches: sensitivity analysis, subgroup analysis, meta-regression, and the random effects model.

Results

Eligible studies

The flowchart shows a diagram of all the studies included in this meta-analysis (Figure 1). On the basis of the primary search strategy, a total of 13,101 related publications were identified. After browsing through the titles and abstracts, 116 references were deemed as eligible based on the selection and inclusion criteria. Through a strict review of the complete articles, 86 studies were excluded, including 57 studies without sufficient information, 4 studies conducted in mouse models, 23 reduplicated studies, and 2 studies detecting HPV serum antibody in GC. As a result, 30 eligible studies were included in this meta-analysis; of them, 10 were in English and 20 in Chinese, and they involved a total of 1,917 GC cases and 576 controls. Half of the 30 studies were case-control studies, and the remaining were case-only studies; the 15 case-control studies included 944 cases and corresponding 576 controls (Table 1).

Study characteristics

Among the 30 studies, 25 were conducted in China. The materials included fresh-frozen (FF) and formalin-fixed paraffin-embedded (FFPE) tissue. Moreover, a PCR-based technique was adopted to detect HPV DNA in 26 studies, whereas only 4 studies used ISH to detect HPV *E6/E7* genes (Table 1). In addition, 15 studies provided the prevalence of HPV in different histological differentiations of patients with GC, which were divided into well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated grades.¹⁶⁻³⁰ Some studies provided concrete information about HPV prevalence in different clinical stages (TNM: I, II, III, and IV),^{16,19,27,31,32} the age and sex^{15,16,18,19,25,27,32} of the patients, and specific HPV types (HPV16 and HPV18).^{15,16,20-24,29-31,33-39} Table 1 provides the information about the studies. The sample sizes of the 30 eligible studies ranged from 30 (cases/controls: 15/15) to 236 (cases/controls: 132/104).

The overall HPV prevalence in GC

The HPV prevalence percentage was represented by decimals over forest plots. Figure 1 shows the HPV prevalence rates and 95% CI estimates from all the 1,917 GC cases, based on the D+L methods with a random effects model. The pooled HPV prevalence was 0.280 (95% CI: 0.232, 0.327), which equals a proportion of 28.0% (95% CI: 23.2%, 32.7%; $z=11.63$; $P < 0.01$). The heterogeneity between the studies was obvious ($I^2=96.9\%$, $P < 0.01$; Figure 2). The 15 case-control studies were generalized to a pooled OR of 7.388 (95% CI = 3.876,

Table 1 The characteristics of all 30 eligible studies

Author's name	Year	Country	Anatomic site	Language	Sample size (N)	Method	Materials	Case (n)		Control (N)		HPV types
								HPV(+)	Total	HPV(+)	Total	
Saegusa et al ³⁴	1997	Japan	GC	English	>50	PCR	FFPE	0	99	NA	NA	HPV16 and HPV18
Cândido et al ^{48a}	2013	Brazil	GC	English	>50	PCR	FFPE	4	40	10	40	HPV16
Anwar et al ^{16a}	1995	Japan	GC	English	>50	PCR	FFPE	23	51	2	12	HPV16, HPV18, and HPV33
Smietura et al ³⁵	2014	Poland	GC	English	>50	PCR	FFPE	0	84	NA	NA	14 HPV subtypes
Sobti et al ⁴⁹	2001	India	GC	English	<50	PCR	FFPE	4	9	NA	NA	NA
Ding et al ¹⁸	2010	China	GCC	English	<50	PCR	FFPE	5	17	NA	NA	HPV16
Yuan et al ³¹	2013	China	GC	English	<50	ISH	NA	0	24	NA	NA	13 HR-HPV, 5 LR-HPV
Koshiol et al ³³	2010	China	GCC	English	>50	PCR	FFPE	0	144	NA	NA	HPV16 and HPV18
Ma et al ^{19a}	2007	China	GC	English	>50	PCR	FFPE	15	40	2	40	HPV16
Cai et al ¹⁷	2006	China	GC	English	<50	PCR	FFPE	19	46	NA	NA	HPV16
Guo et al ³⁶	2000	China	GC	Chinese	<50	PCR	FF	6	41	NA	NA	HPV16 and HPV18
Sun et al ²⁴	2002	China	GC	Chinese	>50	PCR	NA	28	64	NA	NA	HPV16 and HPV18
Huang et al ³⁷	2000	China	GC	Chinese	>50	ISH	FFPE	39	96	NA	NA	HPV16 and HPV18
Dong et al ^{20a}	1999	China	GC	Chinese	>50	PCR	NA	10	37	0	20	HPV16 and HPV18
Du et al ²¹	2000	China	GC	Chinese	<50	PCR	NA	9	29	NA	NA	HPV16 and HPV18
Zhu et al ^{30a}	2000	China	GC	Chinese	>50	PCR	FF	11	42	0	42	HPV16 and HPV18
Wang et al ^{25a}	2013	China	GC	Chinese	>50	PCR	FFPE	20	92	4	86	HPV16
Xu et al ^{27a}	2003	China	GCC	Chinese	>50	ISH	FFPE	91	176	10	50	HPV16
Zhang et al ³⁹	2011	China	GC	Chinese	>50	PCR	FF	45	62	NA	NA	HPV16 and HPV18
Liao et al ^{40a}	2001	China	GC	Chinese	>50	ISH	NA	26	50	2	30	HPV16 and HPV18(E6)
Wei et al ²⁶	2006	China	GC	Chinese	<50	PCR	FFPE	19	46	NA	NA	HPV16
Zhang et al ^{29a}	2001	China	GC	Chinese	>50	PCR	FF	15	40	0	10	HPV16 and HPV18
Cao et al ⁵¹	2005	China	GC	Chinese	<50	PCR	FF	0	47	NA	NA	NA
Ma et al ^{22a}	2007	China	GCC	Chinese	>50	PCR	FFPE	32	93	0	21	HPV16 and HPV18
Zhang et al ⁵²	2010	China	GCC	Chinese	>50	PCR	FF	17	165	NA	NA	NA
Zhou et al ^{32a}	1999	China	GC	Chinese	>50	PCR	FFPE	19	50	0	20	HPV16
Rong et al ^{23a}	2007	China	GCC	Chinese	<50	PCR	FFPE	16	21	2	21	HPV16
Yu et al ^{28a}	1999	China	GC	Chinese	>50	PCR	FFPE	30	132	3	104	HPV16 and HPV18
Sha et al ^{38a}	1998	China	GC	Chinese	>50	PCR	FFPE	27	65	4	65	HPV16
Su and He ^{53a}	2015	China	GC	Chinese	<50	PCR	NA	1	15	0	15	HPV16 and HPV18

Note: ^aCase-control study.

Abbreviations: FF, fresh-frozen; FFPE, formalin-fixed paraffin-embedded tissue; GC, gastric cancer; GCC, gastric cardia cancer; HPV, human papillomavirus; HR-HPV, high-risk types of HPV; ISH, in situ hybridization; LR-HPV, low-risk types of HPV; NA, not available; PCR, polymerase chain reaction.

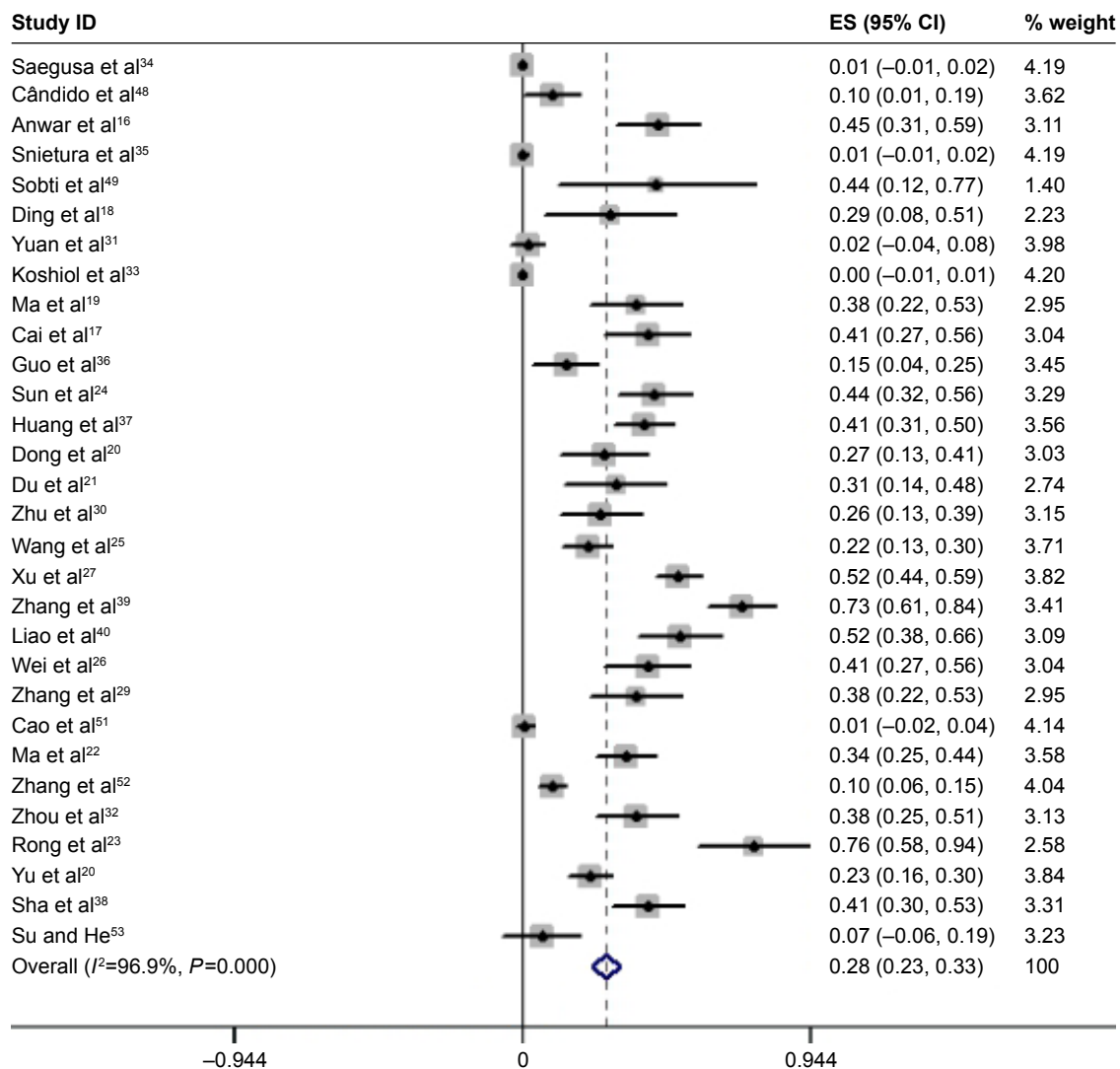


Figure 2 Overall association between HPV infection and GC risk.

Note: Forest plot (weights are from random effects analysis) of the pooled prevalence of HPV positivity in GC.

Abbreviations: GC, gastric cancer; HPV, human papillomavirus; ES, effect size.

14.082), based on the D+L methods with random effects model, which was statistically significant ($z=6.08$, $P<0.01$; Figure 3). This result indicated that the HPV prevalence in GC cases was 7-fold more than that in the corresponding normal gastric tissues, but the heterogeneity between these studies could not be ignored ($I^2=56.7%$, $P=0.004$).

The HPV prevalence in subgroups stratified by country, sample size, HPV test method, and materials All research could be stratified by country, sample size, HPV test method, and materials (Table 1; Figure 4). The HPV prevalence was higher in cases from China than in those from non-Chinese regions (31% vs 9%). The HPV prevalence in the gastric cardia (36%) was more common than that in overall GC (28%), and the HPV prevalence was similar in

cases from FFPE and FF tumor specimens (29% vs 26%). Oddly, the ISH method yielded a higher rate of HPV infection than did the PCR method (36% vs 26%), which was in contrast to the findings of many other studies.^{5,9-11} There was no distinct difference between large samples (≥ 50 cases) and small samples (< 50 cases), with HPV prevalence rates of 29% and 27%, respectively.

The HPV prevalence and its clinicopathological parameters in patients with GC

Age and sex

Information on age and sex was collected from 6 studies.^{16,18,19,25,27,32} HPV was positive in 75 of the 223 patients with GC aged > 50 years, whereas it was positive in 45 of the 106 patients with GC aged < 50 years. Then, a pooled OR

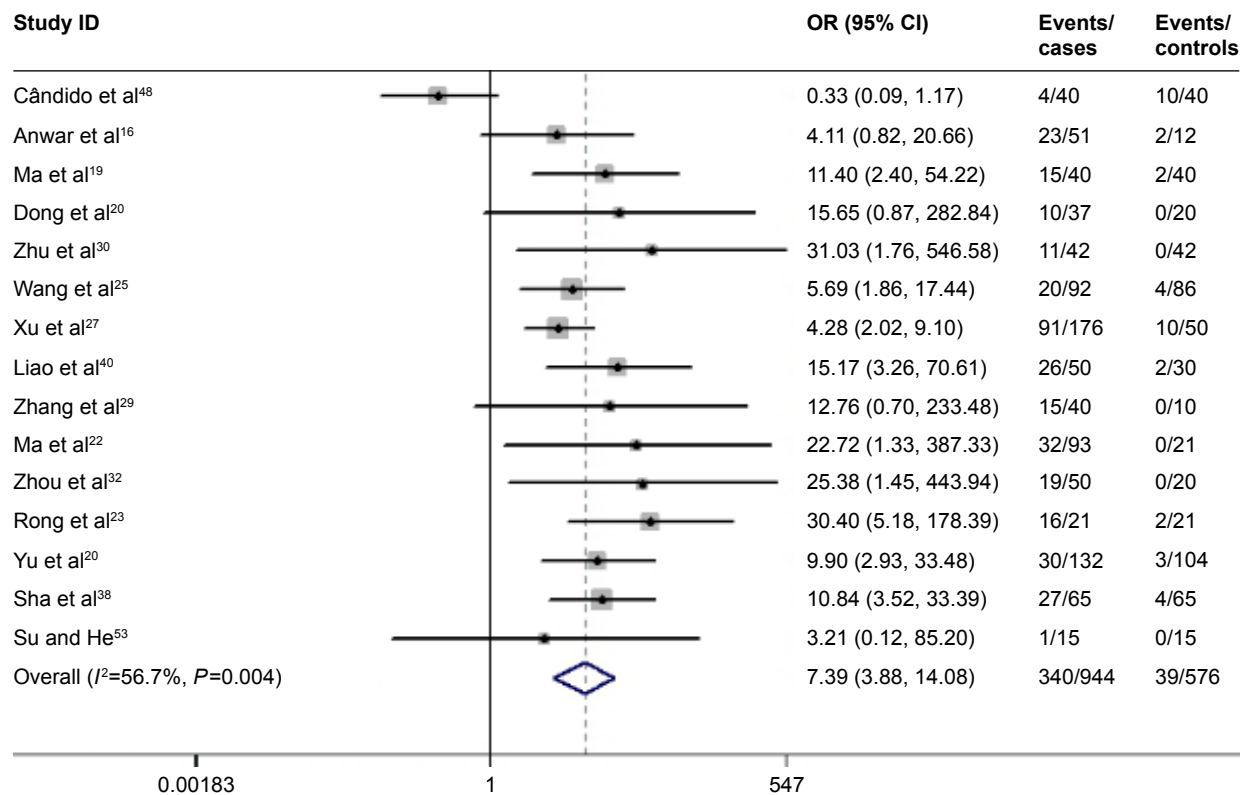


Figure 3 For 15 case-control studies, the estimates of ORs and their 95% CIs were plotted in a forest plot.

Note: Weights are from random effects analysis.

Abbreviations: CI, confidence interval; OR, odds ratio.

of 0.993 (95% CI: 0.579, 1.700) was estimated by using the M-H method. There was no significant difference between HPV incidence and ages of patients with GC. Similarly, information on sex was available for 5 of the 30 studies. HPV was detected in 99 (44.4%) of the 223 male patients and in 33 (29.7%) of the 111 female patients with GC. Based on these findings, a significantly pooled OR of 1.698 (95% CI: 1.007, 2.862) was computed ($z=1.99$, $P=0.047$), which indicated that males were slightly more likely to have HPV-positive GC.

HPV subtypes

Sixteen studies provided data on specific HPV types (including HPV16 and HPV18).^{15,16,20-24,29-31,33-39} HPV16 was found in 210 (21%) of the 992 GC cases, whereas HPV18 was found in 90 (7%) of the 992 GC cases, with a significant OR of 3.314 (95% CI: 1.617, 6.792). It was found that HPV16 was 3 times more frequently detected than HPV18 (Figure 4).

Histological differentiation of GC

Fifteen studies provided the prevalence of HPV in GC of different histological differentiations, which were divided into well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated GC.¹⁶⁻³⁰ The HPV prevalence

was 30.3% (142 of 468 patients) in well-differentiated/moderately differentiated GC, whereas the HPV prevalence was 43.0% (150 of 349 patients) in poorly differentiated/undifferentiated GC, with an OR of 1.569 (95% CI: 1.148, 2.143). Therefore, there were significant associations between HPV prevalence and histological grades of GC, and poorly differentiated/undifferentiated GC patients were more likely to be HPV-positive than well-differentiated/moderately differentiated cases (Figure 4).

Clinical stages (TNM)

Five studies provided concrete information about HPV prevalence in different clinical stages (TNM: I, II, III, IV).^{16,19,27,31,32} The HPV prevalence was 51.0% (49 of 96 patients) in TNM I/TNM II GC patients and 40.6% (58 of 143 patients) in TNM III/TNM IV GC patients. The statistically significant pooled OR was 0.414 (95% CI: 0.223, 0.770); therefore, it was uncertain whether HPV played a prognostic role in GC.

HPV prevalence and p53 gene mutation

Five studies in this meta-analysis^{16,22,24,37,40} with 354 cases provided information about the relationship between HPV prevalence and the p53 gene. However, the pooled OR of 1.534 (95% CI = 0.752, 3.127) was insignificant.

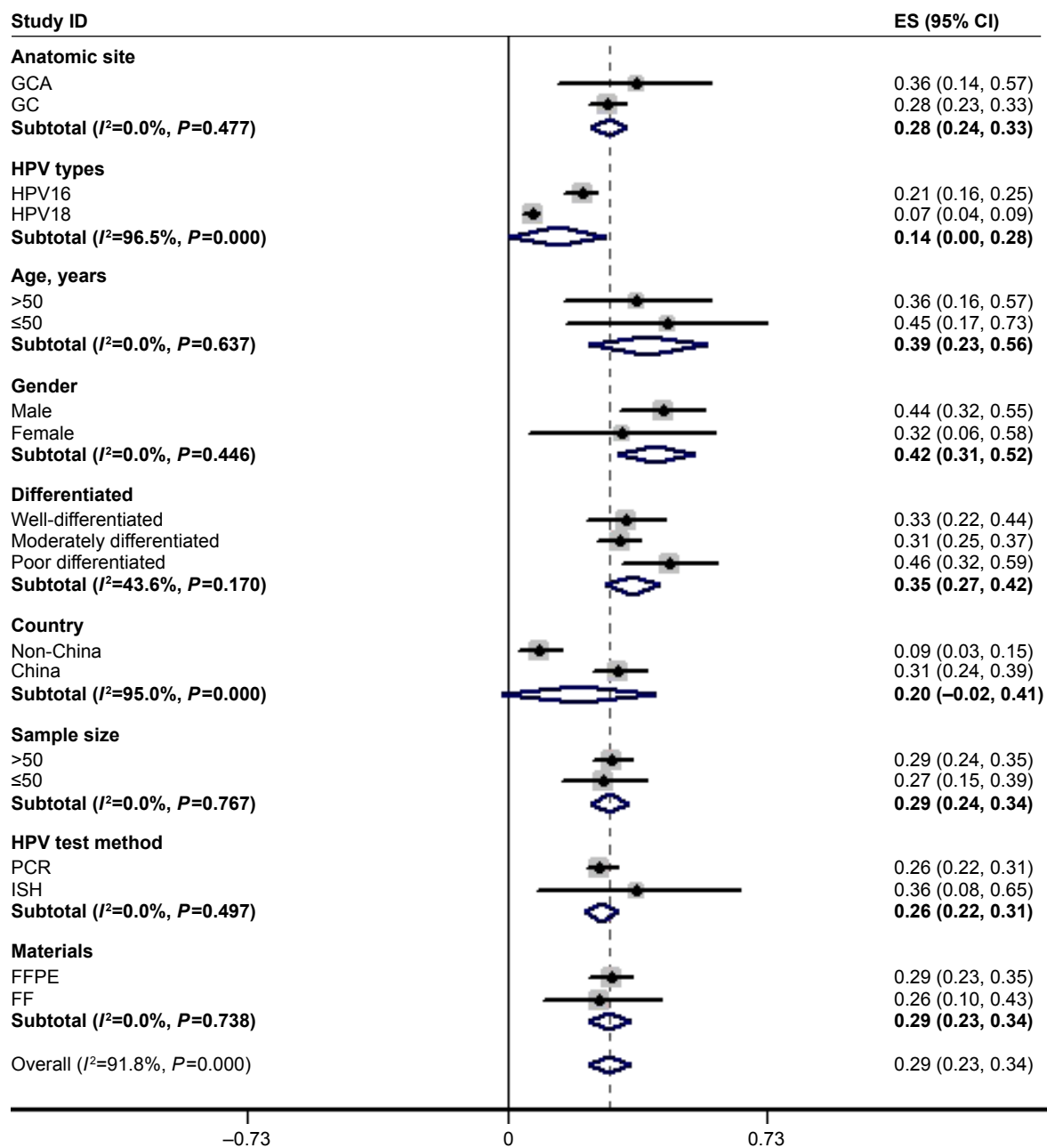


Figure 4 The estimates of HPV prevalence and their 95% CIs showed in decimals instead of percentages, plotted in a forest plot.

Notes: Weights are from random effects analysis. All searches were stratified by country, sample size, HPV test method, and materials. Five studies provided age and sex data, and 15 studies provided pathological differentiation; the 5 studies also provided clinical TNM stage information.

Abbreviations: CI, confidence interval; FF, fresh-frozen; FFPE, formalin-fixed paraffin-embedded tissue; GC, gastric cancer; GCA, gastric cardiac cancer; HPV, human papillomavirus; PCR, polymerase chain reaction; ISH, in situ hybridization.

Sensitivity analysis, meta-regression, and publication bias in case–control studies

Sensitivity analysis indicated that no individual study could influence the pooled effect estimate significantly. A meta-regression analysis was performed, and it was observed that the source of heterogeneity between the studies was from the item of country (China vs non-China, $P=0.004$). Begg's test was implemented to screen for publication bias. As a result, with continuity correction

($z=0.30$, $P>0.767$), there was no evident publication bias (Figure 5).

Discussion

GC is one of the most frequent cancers worldwide. Almost two-thirds of the GC cases occurred in undeveloped regions. Moreover, in 2005, 0.3 million deaths and 0.4 million new cases of GC caused it to become the third most common cancer among Chinese people.⁴¹ Research conducted between 2005

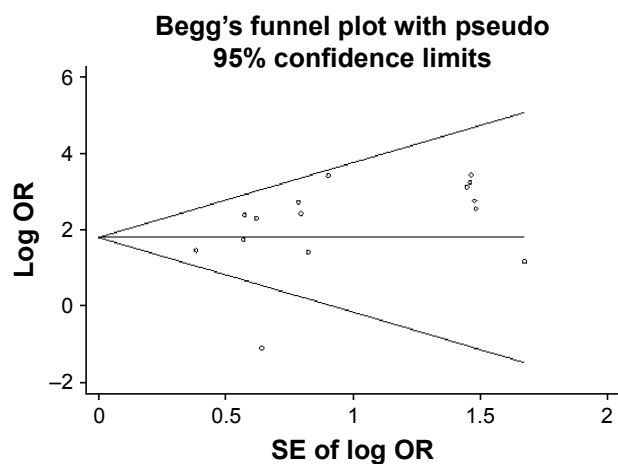


Figure 5 Begg's test for publication bias (continuity-corrected: $z=0.30$, $P>0.767$) showing no evident publication bias.

Abbreviations: OR, odds ratio; SE, standard error.

and 2010 reported that the incidence and mortality of GC were 21.04% and 19.13% of all cancer-related cases and deaths, respectively, in Zhuanghe, China.⁴² It is generally believed that gastric tumorigenesis is correlated with *Helicobacter pylori* infection.^{43,44} However, in recent years, several studies have verified that gastric carcinogenesis is also associated with Epstein–Barr virus infection.^{43,44} In the present study, it was found that HPV prevalence increased GC risk.

To date, the present study was the first meta-analysis to systematically evaluate the association between HPV prevalence and GC as well as their clinicopathological features. In this meta-analysis, a pooled HPV prevalence of 28.0% (95% CI: 23.2%, 32.7%) in 1,917 GC cases among 30 included studies was estimated, and a pooled OR of 7.388 (95% CI =3.876, 14.082) was estimated among 15 case–control studies, which demonstrated that HPV prevalence was a high-risk factor in gastric carcinogenesis.

In addition, it was found that the pooled prevalence of HPV16 was 3-fold higher than that of HPV18 (21% vs 7%) in GC. Other HPV subtypes were infrequent in GC tissues. In addition, the prevalence of HPV in gastric cardia cancer was greater than that in overall GC (36% vs 28%). If HPV could enter the pathway via an oral route from the esophagus to the stomach, a higher HPV prevalence can be expected in oral cancers than in GC. Furthermore, 15 studies, with 817 cases in total, provided data on pathological grade of differentiation, and the HPV incidence in poorly differentiated/undifferentiated GC patients was greater than that in well-differentiated/moderately differentiated GC, with an OR of 1.569. In contrast, the HPV prevalence in clinically advanced stages (TNM III/TNM IV) was slightly less than that in early stages (TNM I/TNM II; OR =0.414; 95% CI: 0.223,

0.770). Therefore, the role of HPV in the prognosis of GC remains unclear.

However, the pathogenesis of GC is multifactorial, and HPV infection might be one of the infectious risk factors. With the assumption that repeatedly persistent infection with HPV can cause dysplasia or adenocarcinoma in situ, as precursor lesions, it will eventually result in malignant transformation. Therefore, it could be hypothesized that HPV might enter the anus and colorectum, causing infection from anogenital sites. Otherwise, HPV enters orally, with downward infection from the mouth to the esophagus and finally to the stomach. It has been systematically found in reviews that HPV prevalence was related to anal, colorectal, oral, pharyngeal, and esophageal carcinogenesis.^{1,4,5,8,14,45,46} The HPV prevalence was reported to be much more common in oral and anal cancers (58.0% and 80%) than in GC in the present study.^{45,46}

Moreover, given insight into the molecular mechanism of gastric oncogenesis, the *p53* gene is suppressor gene. It had been demonstrated that overexpression of *p53* resulted in poor prognosis of GC patients.⁴⁷ In the present study, it was found that the role of the *p53* gene was unrelated with HPV prevalence in GC. Five studies included in the present meta-analysis,^{16,22,24,37,40} with 354 cases, provided information about the relationship between HPV prevalence and the *p53* gene. The wild-type *p53* gene is a tumor suppressor gene, and mutation of the *p53* gene promoted malignant transformation of human epithelium cells. However, the pooled OR of 1.534 (95% CI =0.752, 3.127) was insignificant.^{16,22,24,37,40} Nevertheless, the result was restricted to sample sizes, which could be a source of instability.

The same relationship with the *p53*, *p21*,^{17,24,26,40} and *p16*^{18,35,37} genes was reported to found with HPV prevalence. Some studies have found that HPV could coinfect with *H. pylori*, leading to canceration,²⁵ whereas others have found that HPV prevalence was unrelated to *H. pylori*.^{19,48} One study reported the prevalence of HPV in GC and also tested the telomerase activity.⁴⁹ All of the aforementioned molecular mechanisms suggest that more studies should be conducted.

Finally, the quality of all the 15 case–control studies was assessed based on Newcastle–Ottawa Scale standard conditions. As a result, 13 studies were qualified, and 2 were of good quality.^{24,26} Another 15 case-only studies were not assessed yet. Generally, the research included in the present study was appraised as being up to the standard.

Limitations

There are some limitations of this study. First, the included studies were cross-sectional studies; therefore, it could not

be affirmed that the prevalence of HPV in GC tissue was caused by the temporal infection or by contamination of tissue samples after GC tumorigenesis. Second, the present study was restricted such that only HPV test methods and research detecting HPV in human GC tissues were included. In addition, Kirkegård et al⁵⁰ performed an observational cohort study of HPV infection and GC risk in females with cervical conization. Kamangar et al¹³ and Van Doornum et al¹⁵ searched for HPV antibodies in serum samples from GC patients. None of these three studies were included in the present study, but they had insignificant consequences. Last but not least, among the 30 included suitable searches, 25 were performed in China, which is a substantial source of between-study heterogeneity for the estimated HPV prevalence in GC (a result of meta-regression). The pooled prevalence of HPV was significantly greater in China than in non-Chinese regions (31% vs 9%), which could be partly explained by the very high frequency of GC incidence in Chinese people. However, several studies have indicated that HPV-related cancers were more inclined to occur in the developing countries or economically and sanitationally underdeveloped areas.⁵

Conclusion

In conclusion, this meta-analysis indicated a high incidence of HPV infection in 1,917 GC patients, with a pooled prevalence of 28.0% and a significantly pooled OR of 7.388 between HPV prevalence and GC risk. Hence, HPV could play a vital role in the pathogenesis of GC, which would be conducive to expounding the potential etiologic significance of gastric tumorigenesis and could provide opinions regarding precautionary measures, but causal relationship can be confirmed only by detecting HPV in the cells of GC precursor lesions (gastric dysplasia or adenoma).

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Chaturvedi AK, Anderson WF, Lortet-Tieulent J. World-wide trends in incidence rates for oral cavity and oropharyngeal cancer. *Clin Oncol*. 2013;31(36):4550–4559.
2. Tommasino M. The human papillomavirus family and its role in carcinogenesis. *Semin Cancer Biol*. 2014;26(1):13–21.

3. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189(1):12–19.
4. Hardefeldt HA, Cox MR, Eslick GD. Association between human papillomavirus (HPV) and oesophageal squamous cell carcinoma: a meta-analysis. *Epidemiol Infect*. 2014;142(6):1119–1137.
5. Baandrup L, Thomsen LT, Olesen TB, Andersen KK, Norrild B, Kjaer SK. The prevalence of human papillomavirus in colorectal adenomas and adenocarcinomas: a systematic review and meta-analysis. *Eur J Cancer*. 2014;50(8):1446–1461.
6. International Agency for Research on Cancer. Globocan 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed November 14, 2016.
7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65(1):5–29.
8. Stanley MA, Winder DM, Sterling JC, Goon PK. HPV infection, anal intra-epithelial neoplasia (AIN) and anal cancer: current issues. *BMC Cancer*. 2012;12(9):398.
9. Thomas LK, Bermejo JL, Vinokurova S, Jensen K, Bierkens M, Steenbergen R. Chromosomal gains and losses in human papillomavirus-associated neoplasia of the lower genital tract – a systematic review and meta-analysis. *Eur J Cancer*. 2014;50(1):85–98.
10. Wang J, Aldabagh B, Yu J, Arron ST. Role of human papillomavirus in cutaneous squamous cell carcinoma: a meta-analysis. *J Am Acad Dermatol*. 2014;70(4):621–629.
11. Zhai K, Ding J, Shi HZ. HPV and lung cancer risk: a meta-analysis. *J Clin Virol*. 2015;63:84–90.
12. Rietbergen MM, Leemans CR, Bloemena E, et al. Increasing prevalence rates of HPV attributable oropharyngeal squamous cell carcinomas in the Netherlands as assessed by a validated test algorithm. *Int J Cancer*. 2013;132(7):1565–1571.
13. Kamangar F, Qiao YL, Schiller JT, et al. Human papillomavirus serology and the risk of esophageal and gastric cancers: results from a cohort in a high-risk region in China. *Int J Cancer*. 2006;119(3):579–584.
14. Ali YB, Faris ME, Mohamed SA. Screening for high risk human papillomavirus (HR-HPV) subtypes, among Sudanese patients with oral lesions. *Int J Clin Exp Med*. 2013;6(4):275–281.
15. Van Doornum GJ, Korse CM, Buning-Kager JC, Bonfrer JM, Horenblas S. Reactivity to human papillomavirus type 16 L1 virus-like particles in sera from patients with genital cancer and patients with carcinomas at five different extragenital sites. *Br J Cancer*. 2003;88(7):1095–1100.
16. Anwar K, Nakakuki K, Imai H, Inuzuka M. Infection of human papillomavirus (hvp) and epstein-barr-virus (ebv) and p53 overexpression in human gastric-carcinoma. *Int J Oncol*. 1995;7(2):391–397.
17. Cai JL, Sun JZ, Yao F, Sun SG. Implication of HPV 16 infection and P21 gene mutation in the carcinogenesis and prognosis of gastric cancer. *Chinese-German J Clin Oncol*. 2006;5(2):99–100.
18. Ding GC, Ren JL, Chang FB, et al. Human papillomavirus DNA and P16INK4A expression in concurrent esophageal and gastric cardia cancers. *World J Gastroenterol*. 2010;16(46):5901–5906.
19. Ma TY, Liu WK, Chu YL, et al. Detection of human papillomavirus type 16 DNA in formalin-fixed, paraffin-embedded tissue specimens of gastric carcinoma. *Eur J Gastroenterol Hepatol*. 2007;19(12):1090–1096.
20. Dong WG, Yu JP, Luo HS. [Relationship between human papillomavirus infection and the development of gastric carcinoma]. *World Chinese J Digestol*. 1999;7(1):50–52. Chinese.
21. Du GL, Li CP, Chen GD. [The role HPV in the athenogenesis of gastric adenocarcinoma]. *Chinese J Clin Gastroenterol*. 2002;12(3):116–117. Chinese.
22. Ma YQ, Pu HW, Chen ZL. [Biopathological significance of the abnormal expression of HPV16/18, p53 in cardiac cancer tissues in Xinjiang]. *J Xinjiang Med Univ*. 2007;30(9):955–957. Chinese.
23. Rong XS, Chen J, Li M. [A study of the relationship between Human papilloma virus and gastric cardia cancer]. *Acta Uni Med Nanjing (Natural Science)*. 2007;27(9):1023–1024. Chinese.

24. Sun SR, Yao F, Zhang AM. [A research on the influence of HPV16, HPV18 infection and p53, p21 gene mutation in the prognosis of gastric cancer]. *Cancer Res Clin*. 2002;12(2):84–85. Chinese.
25. Wang ZJ, Zhang YQ, Zhang YT. [Analysis of relationship of the infection of human papillomavirus 16 H. pylori cagA gene and ureA gene in gastric carcinogenesis]. *J Pract Med Tech*. 2013;20(10):1061–1064. Chinese.
26. Wei W, Sun SR, Yao F. [Correlation of HPV16 infection and P21 gene mutation in gGastric cancer]. *Med J Wuhan Univ*. 2006;27(1):42–43. Chinese.
27. Xu WG, Zhang LJ, Lu ZM. [Detection of human papillomavirus type 16 E6 mRNA in carcinomas of upper digestivetract]. *Natl Med J China*. 2003;83(21):74–78. Chinese.
28. Yu JP, Deng T, Yu HG. [Study on association of human papillomavirus type 16 with gastric carcinoma]. *Chinese J Digest Endoscopy*. 1999;16(1):29–31. Chinese.
29. Zhang WL, Li CH, Xiao B. [Significance of human papillomavirus infection in gastric carcinoma]. *J Fourth Military Med Univ*. 2001;22(17):1603–1606. Chinese.
30. Zhu GB, Zhang LF, Cheng J. [Association of human papillomavirus 16 and its serum antibody in gastric carcinoma]. *Chinese J Gen Surg*. 2000;15(12):50–52. Chinese.
31. Yuan XY, Wang MY, Wang XY, Chang AY, Li J. Non-detection of Epstein-Barr virus and human papillomavirus in a region of high gastric cancer risk indicates a lack of a role for these viruses in gastric carcinomas. *Genet Mol Biol*. 2013;36(2):183–184.
32. Zhou Y, Ye WT, Wu LD. [Research of the relationship between HPV 16 infection and gastric cancer]. *World Chinese J Digestol*. 1999;7(2):168. Chinese.
33. Koshiol J, Wei WQ, Kreimer AR, Ren JS, Gravitt P. The gastric cardia is not a target for human papillomavirus-induced carcinogenesis. *Cancer Epidemiol Biomarkers Prev*. 2010;19(4):1137–1139.
34. Saegusa M, Hashimura M, Takano Y, Ohbu M, Okayasu I. Absence of human papillomavirus genomic sequences detected by the polymerase chain reaction in oesophageal and gastric carcinomas in Japan. *Clin Pathol Mol Pathol*. 1997;50:101–104.
35. Snietura M, Waniczek D, Piglowski W, et al. Potential role of human papilloma virus in the pathogenesis of gastric cancer. *World J Gastroenterol*. 2014;20(21):6632–6637.
36. Guo L, Luo B, Mu YX. [Study of infected HPV16/18 of the 41 case stomach neoplasm state]. *China J Cancer Prev Treat*. 2000;7(2):141–142. Chinese.
37. Huang ZM, Li Q, Yan PS. [Detection of high risk human papillomavirus, p16 and p53 proteins in gastric carcinoma and precancerous lesions]. *Chinese J Diagn Pathol*. 2000;7(3):201–203. Chinese.
38. Sha Q, Cheng HZ, Xie XY. [Detection of HPV16,18 in gastric adenocarcinoma and adjacent tissues and its clinical significance]. *Chinese J Digest*. 1998;18(5):320. Chinese.
39. Zhang K, Yang YL, Ci YL. [Detection of HPV prevalence in gastric cardia cancer tissues]. *Chinese J Gerontol*. 2011;31(19):3835–3837. Chinese.
40. Liao ZL, Wei YJ, Yang YC. [Researches on HPV E6 (16, 18), p53, p21WAF1 gene protein expression in gastric cancer tissues]. *J Guangxi Med Univ*. 2001;18(4):489–490. Chinese.
41. Yang L. Incidence and mortality of gastric cancer in China. *World J Gastroenterol*. 2006;12(1):17–20.
42. Jing JJ, Liu HY, Hao JK, et al. Gastric cancer incidence and mortality in Zhuanghe, China, between 2005 and 2010. *World J Gastroenterol*. 2012;18(11):1262–1269.
43. Murphy G, Pfeiffer R, Camargo MC, Rabkin CS. Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location. *Gastroenterology*. 2009;137(3):824–833.
44. Lee JH, Kim SH, Han SH, An JS, Lee ES, Kim YS. Clinicopathological and molecular characteristics of Epstein-Barr virus-associated gastric carcinoma: a meta-analysis. *J Gastroenterol Hepatol*. 2009;24(3):354–365.
45. Zhu C, Ling Y, Dong C, Zhou X, Wang F. The relationship between oral squamous cell carcinoma and human papillomavirus: a meta-analysis of a Chinese population (1994–2011). *PLoS One*. 2012;7(5):e36294.
46. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. *Int J Cancer*. 2009;124(7):1626–1636.
47. Serrano B, de Sanjose S, Tous S, et al. Human papillomavirus genotype attribution for HPV6, 11, 16, 18, 31, 33, 45, 52 and 58 in female anogenital lesions. *Eur J Cancer*. 2015;51(3):1732–1741.
48. Cândido AC, De Lima Filho JL, Martins DB, Mendes CM, Vieira JR, Ferraz AA. Association of human papillomavirus genomic sequences by polymerase chain reaction in gastric carcinomas in Brazil. *Anal Quant Cytopathol Histopathol*. 2013;35(1):1–6.
49. Sobti RC, Kochar J, Singh K, Bhasin D, Capalash N. Telomerase activation and incidence of HPV in human gastrointestinal tumors in North Indian population. *Mol Cell Biochem*. 2001;217(1–2):51–56.
50. Kirkegård J, Farkas DK, Søgaard M, Schmidt SA, Ostfeld EB, Cronin-Fenton D. Conization as a marker of persistent cervical human papillomavirus (HPV) infection and risk of gastrointestinal cancer: a Danish 34-year nationwide cohort study. *Cancer Causes Control*. 2014;25(12):1677–1682.
51. Cao HR, Wang JX, Yue XL. [Searches on the relation between human papillomavirus (HPV) infection and gastric cancer in gastric cancer tissue]. *J Pract Oncol*. 2005;19(6):422–424. Chinese.
52. Zhang J, Tian XY, Wu XJ, Zong XL, Wu J, Ji JF. [Role of papillomavirus in adenocarcinoma of esophagogastric junction]. *Natl Med J China*. 2010;90(32):2259–2262. Chinese.
53. Su LJ, He F. [Analysis of the correlation between human papillomavirus (HPV) and Epstein-Barr virus (EBV) infection and upper gastrointestinal tumor patients]. *Int J Virol*. 2015;22:159–161. Chinese.

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