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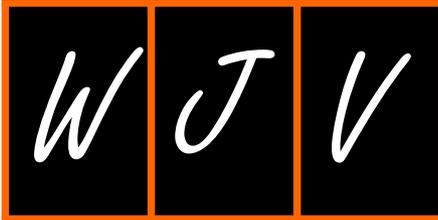
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Human papillomavirus infection and gastric cancer risk: A meta-epidemiological review

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Abstract

Gastric cancer (GC) is a multifactorial disease, and several modifiable risk factors have been reported. This review summarizes and interprets two previous quantitative systematic reviews evaluating the association between human papillomavirus (HPV) infection and GC risk. The results of two systematic reviews evaluating the same hypothesis showed a statistically significant difference in summary odds ratios and their 95% confidence intervals. Thus, it is necessary to conduct a subgroup analysis of Chinese and non-Chinese studies. Additional meta-analyses that control for heterogeneity are required. Reanalysis showed that all the Chinese studies had statistical significance, whereas the non-national studies did not. The funnel plot asymmetry and Egger's test confirmed publication bias in the Chinese studies. In addition, the proportion of HPV-positive cases in Chinese studies was 1.43 times higher than that in non-Chinese studies and 2.81 times lower in controls. Therefore, the deduced evidence is currently insufficient to conclude that HPV infection is associated with GC risk.

Key Words: Papillomavirus; Stomach neoplasm; Case-control studies; Meta-analysis; Systematic review; Risk factors

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Core Tip: Chinese studies showed that human papillomavirus infections increased the risk of gastric cancer; however, non-Chinese studies showed no statistical significance. Therefore, the deduced evidence is currently inadequate to conclude that human papillomavirus infection is associated with gastric cancer risk.

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INTRODUCTION

Gastric cancer (GC) is the fifth most common incident cancer according to Global Cancer Statistics 2018[1] and ranks third in absolute years of life lost[2]. GC is a multifactorial disease, and several modifiable risk factors have been reported[3,4].

Infection with *Helicobacter pylori* or oncogenic viruses has important implications for preventing and managing GC[5]. *Helicobacter pylori* eradication is one of the reasons behind the steady decline in global GC incidence[6]. Therefore, human papillomavirus (HPV), which is among potential oncoviruses posing GC risk reviewed by Niedźwiedzka-Rystwej *et al*[7], should be considered to control GC occurrence because HPV vaccines have been used to prevent uterine cervix cancer[8,9].

However, the International Agency for Research on Cancer did not suggest an association between HPV infection and GC risk in a monograph published in 2007 [10]. This review summarizes and interprets previous quantitative systematic reviews evaluating the association between HPV infection and GC risk.

PREVIOUS SYSTEMATIC REVIEWS

A PubMed (<https://pubmed.ncbi.nlm.nih.gov>) search, using "papillomavirus infection" and "stomach neoplasms" as the keywords of the hypothesis, identified two systematic reviews as of December 31, 2020[5,11]. Both selected case-control studies and their results are summarized in Table 1.

Zeng *et al*[11] reported that in 2016, a total of 15 case-control studies, including 12 studies on Chinese patients, and a meta-analysis showed that HPV infection increased the risk of GC by 7.39 times [95% confidence interval (CI) of summary odds ratio (sOR): 3.88–14.1]. Further, a study by Wang *et al*[5] published in 2020 selected a total of 14 case-control studies, including five studies on Chinese patients, and the sOR was 1.53 (95% CI: 1.00–2.33).

The results of two systematic reviews evaluating the same hypothesis showed a statistically significant difference in sORs and their 95% CI. These findings can be inferred from the following three reasons. First, there was a difference in selection criteria. Wang *et al*[5] included three serological studies, in addition to tissue tests. Therefore, it is necessary to limit future research to tissue studies and conduct a meta-analysis again. Second, there was a difference in search databases between the two systematic reviews. Zeng *et al*[11] and Wang *et al*[5] selected 12 and five Chinese studies, respectively. Whereas Zeng *et al*[11] did not report a subgroup analysis, Wang *et al*[5] showed different subgroup analysis results between Chinese and non-Chinese studies. Therefore, it is necessary to conduct subgroup analyses of Chinese and non-Chinese studies in all selected articles. Finally, potential bias is possible due to heterogeneity. Wang *et al*[5] found no statistical significance in subgroups with less than 50% of the I-squared value, such as non-Chinese studies, serum studies, and HPV-18 studies (Table 1). Therefore, additional meta-analyses that control for heterogeneity are required.

RE-ANALYSIS OF META-ANALYSIS

Both systematic reviews selected a total of 25 articles. After excluding three serological studies[12-14], three studies had no information on the control group[15-17], and one showed zero HPV positivity in both the case and control groups[18]; hence, 18 articles were selected for reanalysis[19-35].

Table 2 illustrates the information extracted for the reanalysis of each study. Xu *et al* [25] extracted the results for cardia as well as those for the entire region for use in subgroup analysis by GC site.

Figure 1 displays a forest plot showing the results of the reanalysis. The sOR for 18 studies was 5.80 (95% CI: 3.27–10.31), showing statistical significance. While the I-squared value was reduced from 60% in all studies to 0% in 12 Chinese studies, their sOR remained statistically significant at 7.86 (95% CI: 5.19–11.89). However, the sOR

Table 1 The summary odds ratio with its 95%CI from two systematic reviews

| Ref. | Search to | Subgroup | Case-control studies | sOR (95%CI) | P (%) |
|------------------------------|-----------|-------------|----------------------|------------------|-------|
| Zeng <i>et al</i> [11], 2016 | Jun 2016 | All | 15 | 7.39 (3.88-14.1) | 56.7 |
| Wang <i>et al</i> [5], 2020 | Apr 2020 | All | 14 | 1.53 (1.00-2.33) | 59.8 |
| | | Chinese | 5 | 1.98 (1.04-3.75) | 73.7 |
| | | Non-Chinese | 9 | 1.17 (0.68-2.02) | 33.4 |
| | | Tissue | 11 | 2.24 (1.13-4.43) | 66.5 |
| | | Serum | 3 | 1.04 (0.75-1.44) | 0.0 |
| | | HPV-16 | 8 | 2.42 (1.00-5.83) | 67.5 |
| | | HPV-18 | 3 | 1.08 (0.59-1.99) | 0.0 |

HPV: Human papillomavirus; sOR: Summary odds ratio.

Table 2 Extracted information of the 18 selected case-control studies

| Ref. | Year | Nation | Site | Test | Sample | PCa | NCa | PCo | NCo |
|---------------------------|------|----------|---------|------|--------|-----|-----|-----|-----|
| Sha <i>et al</i> [19] | 1998 | China | Gastric | PCR | FFPE | 27 | 38 | 4 | 61 |
| Dong <i>et al</i> [20] | 1999 | China | Gastric | PCR | Other | 10 | 27 | 0 | 20 |
| Yu <i>et al</i> [21] | 1999 | China | Gastric | PCR | FFPE | 30 | 102 | 3 | 101 |
| Zhou <i>et al</i> [22] | 1999 | China | Gastric | PCR | FFPE | 19 | 31 | 0 | 20 |
| Zhu <i>et al</i> [23] | 2000 | China | Gastric | PCR | FF | 11 | 31 | 0 | 42 |
| Liao <i>et al</i> [24] | 2001 | China | Gastric | ISH | Other | 26 | 24 | 2 | 28 |
| Xu <i>et al</i> [25] | 2003 | China | Cardia | ISH | FFPE | 50 | 24 | 10 | 40 |
| Xu <i>et al</i> [25] | 2003 | China | Gastric | ISH | FFPE | 111 | 125 | 10 | 40 |
| Ma <i>et al</i> [26] | 2007 | China | Gastric | PCR | FFPE | 15 | 25 | 2 | 38 |
| Ma <i>et al</i> [27] | 2007 | China | Cardia | PCR | FFPE | 32 | 61 | 0 | 21 |
| Rong <i>et al</i> [28] | 2007 | China | Cardia | PCR | FFPE | 16 | 5 | 2 | 19 |
| Wang <i>et al</i> [29] | 2013 | China | Gastric | PCR | FFPE | 20 | 72 | 4 | 82 |
| Su <i>et al</i> [15] | 2015 | China | Gastric | PCR | Other | 1 | 14 | 0 | 15 |
| Anwar <i>et al</i> [30] | 1995 | Japan | Gastric | PCR | FFPE | 23 | 28 | 2 | 10 |
| Erol <i>et al</i> [31] | 2009 | Turkey | Gastric | PCR | FFPE | 17 | 21 | 33 | 73 |
| Cândido <i>et al</i> [32] | 2013 | Brazil | Gastric | PCR | FFPE | 4 | 36 | 10 | 30 |
| Türkay <i>et al</i> [33] | 2015 | Turkey | Cardia | PCR | FFPE | 2 | 17 | 0 | 8 |
| Bozdayi <i>et al</i> [34] | 2019 | Turkey | Gastric | PCR | Other | 20 | 33 | 5 | 21 |
| Leon <i>et al</i> [35] | 2019 | Ethiopia | Cardia | PCR | FF | 11 | 51 | 0 | 56 |

FF: Fresh frozen tissue; FFPE: Formalin-fixed paraffin-embedded tissue; ISH: *In situ* hybridization; NCa: Negative in cases; NCo: Negative in controls; PCa: Positive in cases; PCo: Positive in controls; PCR: Polymerase chain reaction.

for six non-Chinese studies was 1.97 (95%CI: 0.79–4.89), which was not statistically significant. In other words, all Chinese studies showed statistical significance; however, the non-national studies did not. This finding was the same in the subgroup analysis by cardiac tissue, formalin-fixed paraffin-embedded tissue, fresh frozen tissue, and polymerase chain reaction (Table 3).

Twelve Chinese studies were examined for publication bias. The asymmetry of the funnel plot (Figure 2) and Egger's test ($P = 0.013$) confirmed publication bias. The trimming sOR from trim-and-fill analysis[36] was 6.78 (95%CI: 4.40–10.45).

Table 3 Subgroup analysis by nationality

| | All | Chinese studies | Non-Chinese studies |
|---------|-------------------------------|------------------------------|-----------------------------|
| All | 5.80 (3.27-10.31) [60.0] <18> | 7.86 (5.19-11.89) [0.0] <12> | 1.97 (0.79-4.89) [56.8] <6> |
| Area | | | |
| Gastric | 4.83 (2.64-8.83) [62.4] <14> | 7.08 (4.60-10.89) [0.0] <10> | 1.54 (0.60-3.92) [62.6] <4> |
| Cardia | 10.88 (5.42-21.8) [0.0] <5> | 11.17 (5.34-23.35) [0.0] <3> | 8.62 (0.88-84.8) [14.2] <2> |
| Sample | | | |
| FFPE | 5.13 (2.55-10.34) [68.4] <12> | 8.02 (4.74-13.6) [19.6] <8> | 1.38 (0.45-4.16) [58.5] <4> |
| FF | 27.9 (3.70-211.7) <2> | 31.0 (1.76-546.6) <1> | 25.2 (1.45-439.1) <1> |
| Methods | | | |
| PCR | 5.88 (3.00-11.52) [62.2] <16> | 10.93 (6.44-18.5) [0.0] <10> | 1.97 (0.79-4.98) [56.8] <6> |
| ISH | 6.23 (1.56-24.9) [64.0] <2> | 6.23 (1.56-24.9) [64.0] <2> | - |

Study: Summary odds ratio (95% confidence interval) [I^2 value (%)] <Number of selected studies>; FF: Fresh frozen tissue; FFPE: Formalin-fixed paraffin-embedded tissue; ISH: *In situ* hybridization; PCR: Polymerase chain reaction.

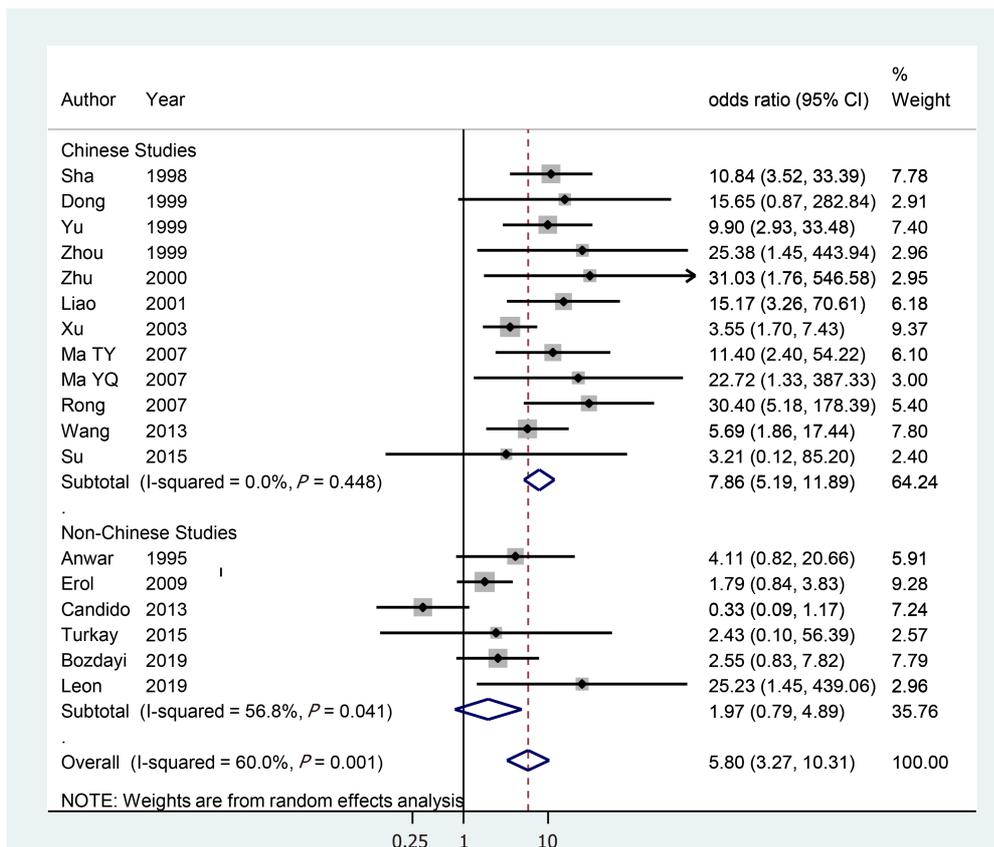


Figure 1 Forest plot for estimating summary odds ratio. CI: Confidence interval.

CONCLUSION

To summarize the above reanalysis results, Chinese studies demonstrated that HPV infections increased the risk of GC; nonetheless, non-Chinese studies showed no statistical significance. Therefore, the deduced evidence is currently insufficient to conclude that HPV infection is associated with GC risk.

The following interpretations and suggestions may be made based on the significant associations observed only in Chinese studies. First, there is a possibility that publication bias was involved in the selection of Chinese studies. After checking for

Table 4 Proportion of human papillomavirus positivity (%) by nationality

| | Chinese studies | Non-Chinese studies |
|------------------|------------------|---------------------|
| Total | | |
| Positive/Observe | 335/1225 | 127/511 |
| PP (95%CI) | 27.3 (24.9-29.9) | 24.9 (21.2-28.8) |
| Case | | |
| Positive/Observe | 298/711 | 77/263 |
| PP (95%CI) | 41.9 (38.2-45.6) | 29.3 (23.8-35.2) |
| Control | | |
| Positive/Observe | 37/514 | 50/248 |
| PP (95%CI) | 7.2 (5.1-9.8) | 20.2 (15.4-25.7) |

PP: Human papillomavirus positivity.

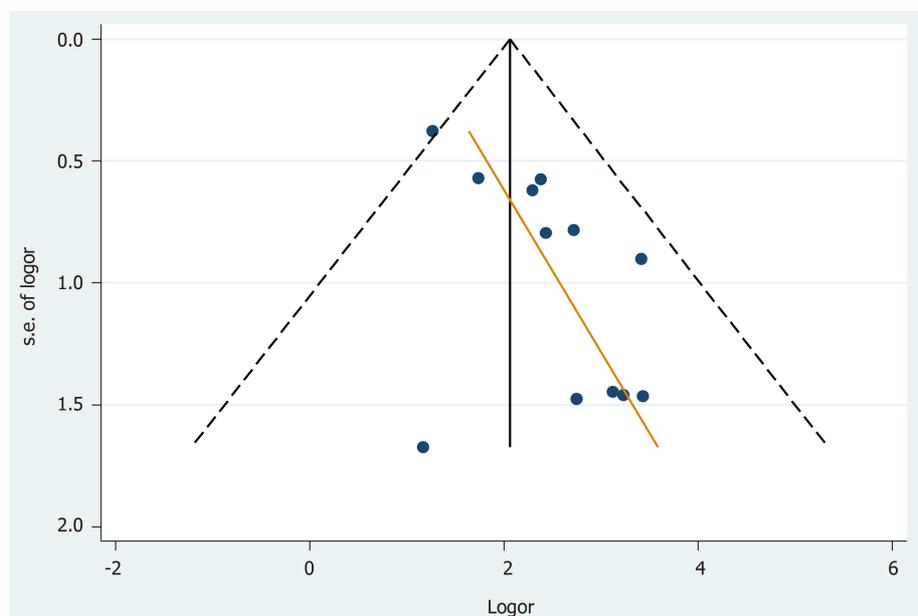


Figure 2 Funnel plot in 12 Chinese studies (P value of Egger test = 0.013).

publication bias using the funnel plot (Figure 2) and Egger's test, trim-and-fill analysis was performed. However, the trimming sOR in Chinese studies showed that HPV infections persistently increased the risk of GC. This mandated an alternative interpretation. The author attempted to infer that HPV positivity might have been different between Chinese and non-Chinese studies.

Using the information in Table 2, the proportion (%) of HPV positivity (PP) was obtained from both Chinese and non-Chinese studies (Table 4). On combining both the case and control groups, the PPs in Chinese and non-Chinese studies were 27.3% (95%CI: 24.9-29.9) and 24.9% (95%CI: 21.2-28.8), respectively. Their 95% CIs overlapped, showing no statistically significant differences. However, the case-group PP in Chinese studies was 41.9% (95%CI: 38.2-45.6), higher than that in non-Chinese studies (29.3%;95%CI: 23.8-35.2), and their 95% CIs did not overlap, showing a statistically significant difference. In contrast, the control-group PP in Chinese studies was 7.2% (95%CI: 5.1-9.8), lower than the 20.2% (95%CI: 15.4-25.7) in non-Chinese studies, and their 95% CIs did not overlap. In other words, the case PP in Chinese studies was 1.43 times ($= 41.9/29.3$) higher than that in non-Chinese studies and 2.81 times ($= 20.2/7.2$) lower in controls. This indicates a potentially significant relationship between HPV infection and GC risk in Chinese studies.

Given that the PP in the control group of the Chinese studies was significantly lower, descriptive epidemiological studies on HPV infection in the Chinese population are warranted. It is also necessary to conduct follow-up studies on whether the GC incidence rate due to HPV infection will change in the future due to the HPV vaccination project currently targeted at the Chinese population.

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