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Original Article

Prognostic role of human papillomavirus in esophageal cancer: a meta-analysis

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Abstract: Objective: Previous studies have assessed the relationship between human papillomavirus (HPV) infection and the prognosis of esophageal cancer, but the conclusion remains controversial. The objective of this meta-analysis was to systemically review the literature and to comprehensively evaluate the relationship between HPV and esophageal cancer. Materials and Methods: Literature searches were performed in Embase, Medline and PubMed databases to identify studies focusing on the relationship between HPV infection and overall survival (OS) of esophageal cancer before September 30, 2015. Overall hazard ratio (HR) with 95% confidence interval (95% CI) was pooled to evaluate this relationship. Subgroup analyses were performed by study region, HPV type, and therapy strategy. Results: Eight studies involving 1034 patients with esophageal cancer were included for meta-analysis. The pooled analysis showed that HPV infection caused a significantly worse OS in esophageal cancer patients (HR, 1.32; 95% CI, 1.06-1.65). Subgroup analyses showed a significant correlation between HPV infection and OS in multiple types of HPV infection subgroup (HR, 1.32; 95% CI, 1.00-1.73) and in multiple therapies subgroup (HR, 1.33; 95% CI, 1.03-1.73). Conclusion: HPV infection predicted a significantly worse prognosis in patients with esophageal cancer, and HPV might act as a promising prognostic factor for esophageal cancer.

Keywords: Esophageal cancer, human papillomavirus, prognosis, meta-analysis

Introduction

Esophageal cancer is the seventh most common cancer and the sixth leading cause of cancer mortality worldwide [1]. Due to the late stage of diagnosis and the rapid progression of tumors, the prognosis of esophageal cancer is dismal. The 5-year survival rate from 2002 to 2008 was 16.9% and ranged between 10.4% and 18.1% among individuals of different races and countries [2]. The tumor-node-metastasis (TNM) staging system has made great contributions to the selection of therapy strategy and prediction of prognosis. However, the great differences in survival within the same pathological TNM stage indicate that TNM system can not satisfy the clinical requirement. Some risk factors, such as smoking [3], inflammation [4], and elevation of tumor biomarkers [5], have been shown to be associated with poor overall survival (OS). Determining the influence of these risk factors on prognosis is helpful in the evaluation of patient outcomes and selection of therapy modalities.

The human papillomavirus (HPV) was first described as an important risk factor for cervical cancer in the mid-1970s. Epidemiologic studies have shown that HPV DNA may be detected in over 90% of patients with cervical cancer regardless of geographical location [6]. Moreover, HPV has been shown to be a risk factor for different types of squamous cell cancers, such as cancers of the oral mucosa, bronchus, upper respiratory tract, oropharynx, and eyes [7]. However, the influence of HPV infection on the prognosis of different cancers varies greatly. Some studies indicate that HPV infection causes a better prognosis [8], while other studies indicate that HPV infection causes a worse

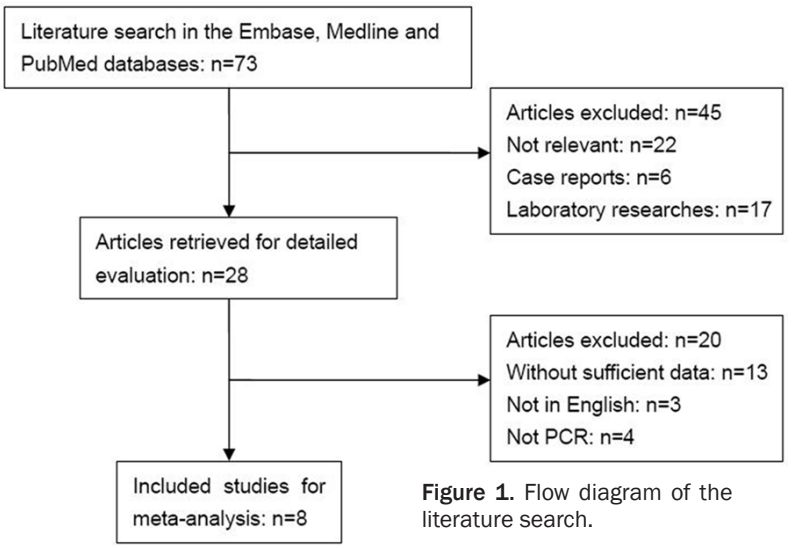

Figure 1. Flow diagram of the literature search.

prognosis [9]. Moreover, some studies indicate that HPV infection is not correlated with the prognosis [10, 11].

HPV was first found in patients with esophageal cancer in 1982 [12]. Since then, studies have continued to investigate the relationship between HPV infection and esophageal cancer. Studies have shown that the prevalence of esophageal cancer in HPV-positive individuals is much higher than that in HPV-negative individuals [13, 14]. This suggests a close correlation between HPV infection and the carcinogenesis of esophageal cancer. However, there has been no definitive conclusion on the correlation between HPV and the prognosis of esophageal cancer. Some clinical studies have reported the relation between HPV and the OS of esophageal cancer patients, but the sample sizes were small, and the conclusions were controversial.

The aim of this meta-analysis was to combine and quantify the results from studies that address the association between HPV infection and the prognosis of esophageal cancer.

Methods

Search strategy

We searched the Embase, Medline, and PubMed databases for published studies that referred to the prognostic value of HPV in primary esophageal cancer before September 30, 2015. The following search terms were used as MeSH terms or keywords: “esophageal cancer”, “human papillomavirus”, and “prognosis”. The references of the retrieved studies were also identified.

Inclusion and exclusion criteria

Studies were considered eligible for the meta-analysis if they satisfied all of the following criteria: (1) Patients were pathologically diagnosed with primary esophageal cancer; (2) HPV infection status was assessed by polymerase chain reaction assay (PCR) before therapy; (3) Sufficient information can be acquired to estimate the hazard ratios (HRs) and their 95% confidence intervals (CIs); (4) The manuscript was written in English. Studies were excluded if they met one of the following criteria: (1) Repeated reports or duplicate data; (2) Case reports, reviews, letters, animal models, or cell line researches; (3) Studies with a sample size less than 30; (4) Insufficient information to extract HRs. However, studies could be included if the Kaplan-Meier curves were provided and the HRs could be calculated from the curves.

Assessment of the study quality

The quality assessment was performed by three independent reviewers (Liu, Li, and Zhang) according to the Newcastle-Ottawa Quality Assessment Scale [15]. This scale is an eight-item instrument that allows for the quality assessment of the studies included for meta-analysis. The assessment was performed by awarding scores for high-quality studies. The scores were summed and were used to quantitatively compare the quality of the studies.

Data extraction

Two reviewers (Liu and Li) reviewed the included studies and extracted the data independently. If disagreements arose, a third reviewer (Guo) reviewed the studies and extracted the data independently. The three groups of data were compared, and the best one was selected. The extracted data elements included the author’s name, year of publication, country, sample size, therapy strategy, and HPV type.

Table 1. Characteristics of the studies included in this meta-analysis

Study	Year	Country	Sample size	Therapy strategy	HPV type	Study quality point
He D [19]	1997	China	67	Multiple therapies	16	7
Dreilich M [20]	2006	Sweden	100	Multiple therapies	16	8
Antonsson A [21]	2010	Australia	222	Multiple therapies	mixed	7
Liu WK [22]	2010	China	69	Surgical therapy	16	8
Herbster S [23]	2012	Brazil	264	Multiple therapies	mixed	8
Wang YF [24]	2013	China	92	NA	mixed	7
Zhang DH [25]	2014	China	70	Surgical therapy	mixed	8
Wang WL [26]	2015	China	150	Multiple therapies	mixed	8

Abbreviation: NA, not reported.

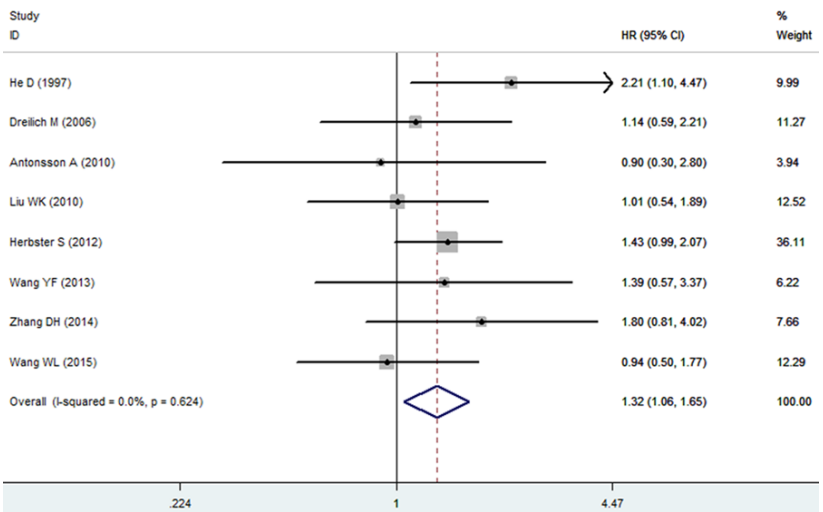

Figure 2. Forest plot for the association between HPV infection and OS of patients with esophageal cancer.

Data analysis

In this study, pooled HR and 95% CI were selected to estimate the relationship between HPV infection and OS. The HRs and 95% CIs of the included studies were extracted from the studies if the data were reported explicitly. If the information was not reported, we extracted the time-to-event data from the Kaplan-Meier curve using the software Engauge Digitizer, version 4.1, and calculated the HRs from extracted data using the formula recommended by Parmar [16]. Subgroup analyses were organized by study region, HPV type, and therapy strategy. The heterogeneity of the pooled HRs was evaluated by the inconsistency index I^2; $P<0.1$ or $I^2>50\%$ indicated significant heterogeneity [17]. A fixed-effect model was employed if heterogeneity was not significant, whereas a random-effect model was selected if heterogeneity was significant. Pooled HR>1 indicated a worse outcome in terms of OS for patients with an HPV-positive status, and the difference was statistically significant if $P<0.05$. The publication bias was evaluated by Begg's funnel plot and Egger's bias indicator test [18]. All statistical analyses were performed with the statistical software Stata version 12.0.

Results

Search results

According to the search strategy described above, 73 studies were identified. After retrieving titles and abstracts, 45 studies were eliminated. By full-text review, 13 studies were excluded due to insufficient data, three studies were excluded because they were not published in English, and four studies were excluded because the authors detected the HPV infection using a method other than PCR. Finally, eight studies were eligible for inclusion in this meta-analysis (**Figure 1**). The eight studies included a total of 1034 patients, with a range from 67 to 264 patients. Among these studies, five studies were performed in China, and the remaining three studies were performed in Sweden, Australia and Brazil, respectively. Two studies reported surgical therapy alone, and five studies reported multiple therapies, which encompassed neoadjuvant therapy, chemotherapy, radiotherapy, and surgery. One study did not report any detailed information regarding therapy. Three studies reported HPV-16 infection, and five studies reported mixed HPV types infection. The study quality points ranged from 6 to 8 (**Table 1**).

HPV and OS in esophageal cancer

The HR data from eight studies were combined to investigate the relationship between HPV

Table 2. Subgroup analyses of pooled HR for positive HPV and OS in esophageal cancer

Subgroup	No. of studies	No. of patients	Pooled HR (95% CI)	*P* value	Heterogeneity I^2 (%)	*P* value
Region						
Asia	5	448	1.33 (0.97, 1.83)	0.079	10.6%	0.346
Other regions	3	586	1.31 (0.96, 1.79)	0.084	0.0%	0.663
HPV type						
HPV-16	3	236	1.33 (0.91, 1.94)	0.147	32.6%	0.227
Mixed types	5	798	1.32 (1.00, 1.73)	0.047	0.0%	0.675
Therapy strategy						
Multiple therapies	5	803	1.33 (1.03, 1.73)	0.029	0.0%	0.406
Surgical therapy	2	139	1.26 (0.77, 2.06)	0.363	19.4%	0.265

Abbreviation: HR, Hazard ratio; CI, Confidence interval.

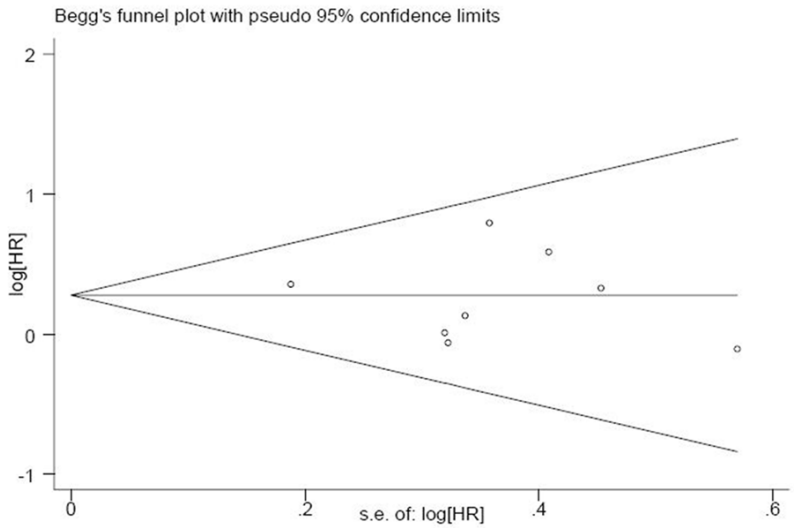

Figure 3. Begg's funnel plot for publication bias of the included studies.

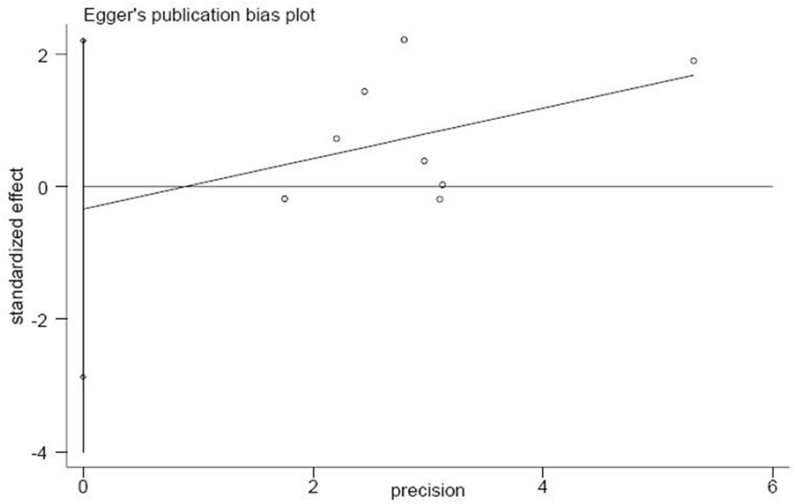

Figure 4. Egger's plot for publication bias of the included studies.

and OS. The heterogeneity test indicated that heterogeneity was not significant among the included studies (I^2=0.0%, P=0.624), and thus a fixed-effect model was employed. The pooled HR was 1.32 (95% CI, 1.06-1.65; P=0.014). The statistical results showed that HPV infection was linked to a significantly worse OS in patients with esophageal cancer (**Figure 2**).

To further investigate the relationship between HPV and OS, subgroup analyses were conducted by study region, HPV type, and therapy strategy. Subgroup analyses showed a significant relation between HPV infection and OS in multiple types of HPV infection subgroup (HR 1.32, 95% CI 1.00-1.73) and in multiple therapies subgroup (HR 1.33, 95% CI 1.03-1.73). However, in Asia subgroup and HPV-16 subgroup, the correlation between HPV infection and OS were not statistically significant (**Table 2**).

Publication bias

The Begg's and Egger's tests were adopted to assess the publication bias of the eight included studies. The *p* values indicated no significant publication bias in terms of the OS (Begg's test: P=0.805, Egger's test: P=0.757) (**Figures 3** and **4**).

Discussion

The HPV was initially discovered to be risk factor of cervical cancer. But later it was detected in other epithelial cancers, and proved to be risk factor of a serial

of cancers, such as oropharyngeal cancer [27], lung cancer [28], and skin cancer [29]. Since the presence of HPV in esophageal cancer was first demonstrated in 1982, the correlation between HPV infection and esophageal cancer has attracted considerable attention [12]. It has been shown that HPV infection is involved in the carcinogenesis of esophageal cancer [13, 14]. However, no definitive conclusion has been made regarding the relationship between HPV and the prognosis of esophageal cancer. Some studies showed that HPV infection was linked to a favorable prognosis [21, 26], while other studies linked HPV infection to a worse prognosis [24, 25]. Moreover, some studies showed no correlation between HPV infection and prognosis of esophageal cancer [22].

The controversial conclusions made it necessary to perform a systematic review to confirm this relationship. To the best of our knowledge, this is the first meta-analysis to investigate the relationship between HPV infection and the prognosis of patients with esophageal cancer. In this meta-analysis, we combined eight included studies with 1034 patients, and calculated the pooled HR. Because the heterogeneity of included studies was not statistically significant, we used a fixed-effect model to pool the extracted data. A pooled HR of 1.32 with a 95% CI of 1.06-1.65 indicated that HPV infection was associated with a significantly worse prognosis in patients with esophageal cancer. Although the heterogeneity of the included studies was not significant in our analysis, subgroup analyses were conducted to further investigate the correlation between HPV infection and OS of esophageal cancer patients. The subgroup analyses showed that the HPV infection caused a significantly worse OS in multiple therapies subgroup and mixed HPV subtypes subgroup, which included the detection of high-risk HPV subtypes and low-risk HPV subtypes. However, in other subgroups, HPV infection did not significantly affect the OS of patients.

The morbidities and prevalence of HPV in esophageal cancer vary greatly in different regions. The prevalence of HPV infection in Asia is much higher than the average rate worldwide [30]. However, our subgroup analysis showed that HPV infection did not cause a significantly worse OS in the high prevalence region. Besides, infection of high-risk HPV subtypes such as HPV-16 and HPV-18 is highly correlated with the risk of esophageal cancer. However, our subgroup analysis showed that infection of HPV-16 did not affect the OS significantly. The above results indicated that risk factors of carcinogenesis might not affect the prognosis of esophageal cancer patients.

The Begg's and Egger's tests showed that there was no obvious publication bias for this analysis, which enhanced the reliability of the conclusion.

Several limitations should not be ignored. First, the number of included studies and the total sample size were limited. Second, most of the included studies were retrospective and case-control studies. The survival analysis of cancer patients often requires a long and variable study period, thus a case-control study is a time-efficient and economical method. However, this meta-analysis would be improved if some randomized controlled trials were included. Third, the morbidities, pathological types, and therapy strategy of esophageal cancer varied greatly among different geographical regions. Although the heterogeneity was not significant in this meta-analysis, heterogeneity should not be ignored. The conclusion might be more reliable if some large-scale and multicentric studies with a unified diagnosis and therapy criteria could be conducted.

In conclusion, our meta-analysis showed that HPV infection predicted a significantly worse prognosis in patients with esophageal cancer. As a more and more popular biomarker, HPV is a promising prognostic factor for esophageal cancer.

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Disclosure of conflict of interest

None.

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