RESEARCH ARTICLE

Prevalence of Human Papillomavirus 16 in Esophageal Cancer Among the Chinese Population: a Systematic Review and Meta-analysis

Shao-Kai Zhang, Lan-Wei Guo, Qiong Chen, Meng Zhang, Shu-Zheng Liu, Pei-Liang Quan, Jian-Bang Lu, Xi-Bin Sun*

Abstract

Background and Aim: No firm evidence of HPV infection in esophageal cancer has been established to date. The aim of this meta-analysis was to investigate the prevalence of HPV 16 in esophageal cancer in China, which had a high burden of the disease. Materials and Methods: Studies on HPV infection and esophageal cancer were identified and a random-effects model was used to pool the summary prevalence and corresponding 95% confidence intervals (CIs). Results: A total of 3,429 esophageal cancer cases were evaluated from 26 eligible studies in this meta-analysis. The summary estimate for HPV16 prevalence was 0.381 (95% CI: 0.283, 0.479). The prevalence varied by geographical areas of the study, publication year, HPV detection method and types of specimen. In sensitivity analysis, HPV 16 prevalence ranged from 0.368 (95% CI: 0.276, 0.460) to 0.397 (95% CI: 0.286, 0.508). Conclusions: The results indicate a relatively high level of HPV 16 prevalence in esophageal cancer among Chinese population, although there was variation between different variables. Further studies are needed to elucidate the role of HPV in esophageal carcinogenesis with careful consideration of study design and laboratory detection method, providing more accurate assessment of the HPV status in esophageal cancer.

Keywords: Human papillomavirus - genotype - esophageal cancer - meta-analysis - China

Asian Pac J Cancer Prev, **15 (23)**, 10143-10149

Introduction

Esophageal cancer is the eighth most common cancer worldwide, with an estimated 456,000 new cases in 2012, and the sixth most common cause of death from cancer with an estimated 400,000 deaths (IARC, 2014). Esophageal cancer is an aggressive malignancy and the overall ratio of mortality to incidence is 0.88 (IARC, 2014). Globally, around 80% of the cases worldwide occur in less developed regions. The China Cancer Registration Report in 2010 showed that the incidence and mortality of esophageal cancer were 21.88/100000 and 15.85/100000 (Chen et al., 2014), respectively, which indicated that China has a high burden of esophageal cancer.

However, the etiology of esophageal cancer is still unclear at present. Some studies reported that smoking, excessive drinking, obesity, deficiency of vitamins and genetic changes were the potential cause of esophageal cancer (Freedman et al., 2007; Qiao et al., 2009; Yu et al., 2010; Wu et al., 2012; Turati et al., 2013). In China, infectious agents contributed more than one quarter of the overall cancer number among population (Xiang et al., 2011). The role of infectious agents in esophageal carcinogenesis has also been suggested as either direct carcinogens or promoters.

HPV is a possible cause of esophageal cancer and HPV infection in the esophagus may activate specific antiapoptotic, proliferative, and malignant cellular responses that also may be intensified in combination with the effects of other risk factors (Zandberg et al., 2013). HPVs are small, nonenveloped double-stranded DNA viruses. So far, more than 100 types of HPV have been characterized and over 40 of them have been found to infect mucosal surfaces (zur Hausen, 2000; de Villiers et al., 2004). Based on their oncogenicity, HPV are classified into high-risk and low-risk types. High-risk HPV 16 infection has been shown to be more prevalent than any other high-risk HPV type in most regions of the world (Trottier et al., 2006).

Since Syrjanen first reported the association between HPV and malignant esophageal tumors in 1982 (Syrjanen, 1982), many studies have investigated the HPV prevalence of esophageal cancer. However, no firm evidence of HPV infection in esophageal cancer has been established to date and the International Agency for Cancer Research (IARC) has concluded that there is inadequate evidence in humans for HPV carcinogenicity in association with esophageal cancer. But the published studies made it

*Department of Cancer Epidemiology, Henan Cancer Hospital, Affiliated Cancer Hospital of Zhengzhou University, Henan Office for Cancer Control and Research, Zhengzhou, China *For correspondence: xbsun21@sina.com*

possible to assess the relation between the esophageal cancer and HPV genotypes by means of meta-analysis. Besides, the successful implication of HPV vaccine on cervical cancer has induced greater interest in preventable high risk HPV-related cancers, including esophageal cancer. Investigating the high risk HPV prevalence may give some clues of immune efficacy of HPV vaccine on esophageal cancer. Therefore, to address these issues, our present study aimed to investigate the prevalence of HPV 16 infection in esophageal cancer in China through collecting published information on HPV16 prevalence in esophageal cancer tissues that described defined materials and methods, providing useful information on this unclear issue in Chinese population.

Materials and Methods

Literature search

Systematic literature search was conducted using MEDLINE (via PubMed), Excerpta Medica database (EMBASE) for English language, and using Chinese National Knowledge Infrastructure and Wanfang Data Knowledge Service Platform for Chinese language. Date of the literature was specified between 1 Jan 2005 and 15 July 2014. The search strategy was verified by a medical reference librarian and research articles were selected using the following keywords: human papillomavirus, papillomavirus infections, (o)esophageal neoplasms, (o) esophageal cancer, (o)esophageal carcinoma. In addition, cross-referencing from the articles found was used to complete the search.

Eligible criteria

Two authors independently evaluated all the studies and the discrepancies between the two reviewers were solved by discussion. The criteria for inclusion in this meta-analysis were as follows: *(1)* studies detected HPV DNA in the tissues of esophageal cancer; *(2)* explicitly provided the information on HPV DNA detection method. HPV DNA must be tested either by polymerase chain reaction (PCR)-based methods, including broad-spectrum PCR primers, type-specific PCR primers, or a combination of both kinds of primers; *(3)* necessary data could be directly extracted or calculated from the original article; *(4)* peer-reviewed publications with HPV prevalence data from a minimum of 30 cases of esophageal cancer; *(5)* studies conducted in the Chinese population. If the study was reported in duplication, the one published earlier or provided more detailed information was included. Review articles and editorials were included if they contained original data. Abstracts were excluded.

Data extraction

Two of the investigators performed the data extraction from each article using a standardized data extraction form, and discrepancies were resolved by consensus. If there is a question unable to determine, the study authors were contacted to obtain specific needed information. For studies meeting our inclusion criteria, the following data were extracted: General information, including name of first author, year of publication, geographical areas of the study origin; numbers of cases and HPV positive cases; HPV detection method; Types of specimen (paraffin-embedded fixed biopsies (PE), fresh or frozen biopsies (FF)).

Statistical analyses

In this study, meta-analyses were performed using STATA version 12 for Windows (StataCorp LP, College Station, TX, USA). We calculated the variance of each prevalence estimate as pq/n, where p is the prevalence, q is 1-p, and n is the number of esophageal cancer cases (Barendregt et al., 2013). Overall pooled point estimate and 95% confidence interval for HPV 16 prevalence were calculated through the method of DerSimonian and Laird using the assumptions of a random-effects model (DerSimonian et al., 1986), which incorporates between-study variability. For studies with multiple HPV types infection (including HPV 16), the multiple HPV types were separated into different types and the HPV 16 type-specific prevalence represents types for cases with either single HPV 16 infection and multiple HPV 16 infection. With respect to studies reporting HPV prevalence equal to zero, we used an empirical continuity correction method described by Sweeting to smooth the zero values (Sweeting et al., 2004). Specifically, we estimated the pooled prevalence for studies with non-zero prevalence estimates. Then the estimate divided by 100 was used as the number of HPV-positive esophageal cancer cases, and 1 minus the value added to the HPV-positive esophageal cancer cases was defined as the number of HPV-negative esophageal cancer cases.

We used I^2 (values of 25%, 50% and 75% corresponding to low, moderate and high degrees of heterogeneity, respectively)and Cochrane Q test (p<0.10 indicated a high level of statistical heterogeneity) to assess the heterogeneity between eligible studies (Higgins et al., 2002). Stratified pooled analyses were subsequently carried out according to the geographical areas of the study origin, publication years, HPV detection method and types of specimen. In the eligible studies, two studies contained different types of specimen and two studies contained different geographical areas of the study origin. For these studies, we treated them as the separate studies and pooled them into appropriated groups when performing stratified analysis. Sensitivity analysis was also conducted to assess the influence of each individual study on the strength and stability of the meta-analytic results. Each time, one study in the meta-analysis was excluded to show that study's impact on the combined effect size. Funnel plots and statistical tests of Begg adjusted rank correlation test and Egger regression asymmetry test were performed to test evidence of publication bias (Begg et al., 1994; Egger et al. 1997). In this study, a two-tailed p<0.05 was considered statistically significant.

Results

As shown in Figure 1, the search strategy generated 417 citations using different combination of key words, of which 156 were considered of potential value and the full text was retrieved for detailed evaluation. One hundred

and twenty-two of the 156 articles were subsequently excluded from the meta-analysis. The majority of the reasons for exclusion were: Studies not conducted in Chinese population, studies not report HPV 16 prevalence or studies not tested by PCR-based assay. Duplication studies and reviews without detailed information were also excluded. Furthermore, eight studies were excluded because of the limited number. In total, we included 26 eligible studies in the meta-analysis (Cao et al., 2005; Yang et al., 2005; Dai et al., 2007; He et al., 2007; Shuyama et al., 2007; Zhou et al., 2007; Chen et al., 2008; Li et al., 2008; Liu et al., 2008; Lu et al., 2008; Liu et al., 2009; Zhao et al., 2009; Liu et al., 2010; Koshiol et al., 2010; Wang et al., 2010; Ayshamgul et al., 2011; Han et al., 2011; Zhang et al., 2011; Guo et al., 2012; Hu et al., 2012; Qu et al., 2012; Wang et al., 2012; Liu et al., 2013; Zhang et al., 2013; Cui et al., 2014; Liu et al., 2014).

Individual characteristics of the included 26 studies are summarised in Table 1. The included studies were conducted during 2005-2014 and the sample size of them was ranged from 31 to 347. In total, 3429 esophageal cancer cases were evaluated in all of the 26 included studies. Of these 26 studies, 13 were conducted in Henan province which is a high risk area of esophageal cancer in China, with the remaining studies conducting in other eight provinces of China as follows: Xinjiang, Shandong, Hebei, Shaanxi, Gansu, Chongqing, Guangdong and Inner Mongolia. The type of esophageal specimens used to test HPV DNA status were either PE or FF tissue, and HPV detection region of these studies were L1 or HPV E6/E7.

In this study, the HPV 16 prevalence ranged from 0% to 69.2%. The pooled prevalence estimates for studies with non-zero prevalence (25 studies) were 0.397. The value of the prevalence estimate was used to smooth values for studies with zero HPV-positive cases.

There was high heterogeneity observed between the included studies (Q test P heterogeneity <0.001, I^2=98.9%). Based on a random-effects model, the summary estimate for HPV 16 prevalence was 0.381 (95% CI: 0.283, 0.479). However, there was indication of publication bias in the meta-analysis (Begg test p=0.002, Egger p<0.001).

Results stratified by different variables for HPV 16 prevalence according to geographical areas of the study origin, publication years, types of specimen and HPV detection method were presented in Table 2. The highest pooled HPV 16 prevalence was observed in South of China

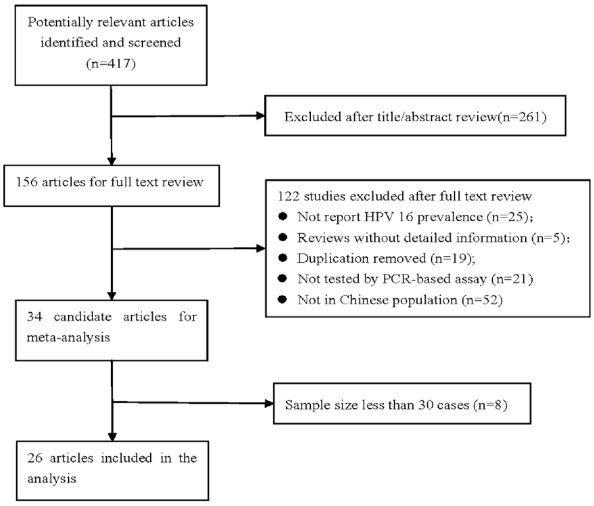

Figure 1. Flow Diagram of Systematic Literature Search on Human Papillomavirus 16 Infection in Esophageal Cancer

Table 1. Characteristics of 26 Studies included in the Meta-analysis of Overall Prevalence of Human Papillomavirus (HPV) Among Esophageal Cancer Cases

Reference	Region	Number of cases	Number of positive cases	Prevalence(95% CI)	Types of specimen[1]	HPV detection method
Koshiol, 2010	Henan	267	1	0.004(0.000,0.0111)	PE	L1
Shuyama, 2007	Shandong/Gansu	59	15	0.254(0.143,0.365)	PE	L1
Dai, 2007	Henan	100	10	0.100(0.041,0.159)	PE	L1
Zhou, 2007	Henan	160	97	0.606(0.531,0.682)	PE	E7
Lu, 2008	Xinjiang	67	5	0.075(0.012,0.138)	PE	L1
Liu, 2009	Shaanxi	69	35	0.507(0.389,0.625)	PE	E6
Liu, 2014	Henan	78	54	0.692(0.590,0.795)	FF	L1
Wang, 2010	Henan /Xinjiang/ Guangdong	347	96	0.277(0.230,0.324)	PE	E6/E7
Chen, 2008	Xinjiang	80	34	0.425(0.317,0.533)	PE	E6
Zhao, 2009	Hebei	42	19	0.452(0.302,0.603)	PE	E6
Liu, 2007	Chongqing	112	43	0.384(0.294,0.474)	FF	L1
Hasim, 2011	Xinjiang	50	19	0.380(0.245,0.515)	PE	E6
Zhang, 2013	Henan	99	52	0.525(0.427,0.624)	PE/FF	E6
Wang, 2012	Henan	82	17	0.207(0.120,0.295)	PE	L1
Guo, 2012	Henan	300	70	0.233(0.185,0.281)	FF	L1
Hu, 2012	Xinjiang	200	82	0.410(0.342,0.478)	PE	E6
Zhang, 2014	Guangdong	106	62	0.585(0.491,0.679)	PE	E6
Liu, 2013	Xinjiang	253	52	0.206(0.156,0.255)	PE	E6
Cao, 2005	Henan	265	182	0.687(0.631,0.743)	PE	E7
Cui,2014	Xinjiang	183	53	0.290(0.224,0.355)	PE	L1
Han,2011	Shandong	204	121	0.593(0.526,0.661)	PE	L1
Li, 2008	Henan	31	19	0.613(0.441,0.784)	FF	E6
He, 2007	Henan	110	56	0.509(0.416,0.603)	PE	E6
Liu, 2009	Henan	78	49	0.628(0.521,0.735)	FF	L1
Qu,2012	Henan	46	15	0.326(0.191,0.462)	PE/FF	L1
Yang, 2005	Inner Mongolia	41	0	0.000(---,---)	FF	L1

[1]FF, Fresh-Frozen; PE, Paraffin-Embedded

Table 2. HPV 16 Prevalence in Esophageal Cancer by Region, Publication Date, Specimen, and HPV Detection Method

Variables		Number of studies	Cases	Prevalence (95% CI)	$P_{heterogeneity}$	I^2 (%)
Total		26	3429	0.397 (0.286, 0.508)	<0.001	98.9
Region	North	16	2061	0.397 (0.249, 0.545)	<0.001	99.1
	Northwest	10	1047	0.300 (0.182, 0.418)	<0.001	96.6
	South	3	321	0.478 (0.362, 0.594)	0.01	78.3
Year	2005-2009	13	1214	0.402 (0.238, 0.565)	<0.001	98.4
	2010-2014	13	2215	0.362 (0.223, 0.501)	<0.001	99
Specimen[(1)]	PE	20	2711	0.365 (0.242, 0.489)	<0.001	99
	FF	8	718	0.433 (0.235, 0.631)	<0.001	98.2
HPV detection method	L1	13	1617	0.288 (0.180, 0.396)	<0.001	98.6
	E6/E7	13	1812	0.474 (0.373, 0.574)	<0.001	95.1

[(1)]FF, Fresh-Frozen; PE, Paraffin-Embedded

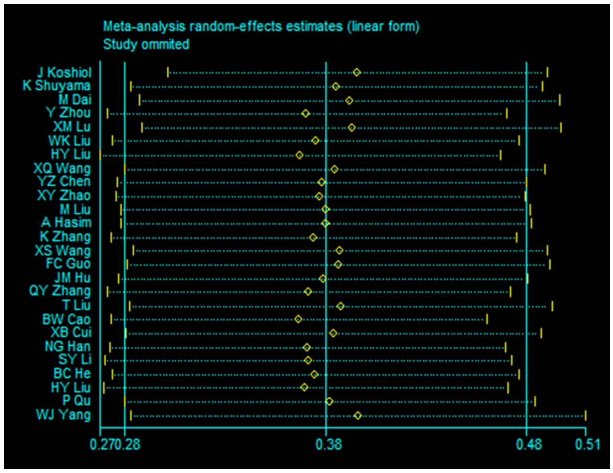

Figure 2. Sensitive Analysis for Individual Studies on the Summary Effect

(0.478; 95% CI: 0.362, 0.594), followed by that in North of China (0.397; 95% CI: 0.249, 0.545) and in Northwest of China (0.300; 95% CI: 0.182, 0.418). The prevalence of HPV 16 in the studies published before 2010 (0.402; 95% CI: 0.238, 0.565) was higher than studies published in or after 2010 (0.362; 95% CI: 0.223, 0.501). Similarly, studies which HPV DNA extracted from FF tissue had a higher HPV 16 prevalence (0.433; 95% CI: 0.235, 0.631) than which HPV DNA extracted from PE tissue (0.365; 95% CI: 0.242, 0.489). Moreover, HPV detection method can significantly affect the HPV 16 detection in esophageal cancer lesions. Detected gene from L1 region of HPV was generally revealed to be higher HPV16 detection rate in esophageal tissues (0.474; 95% CI: 0.373, 0.574) than that of gene from E6/E7 region of HPV (0.288, 95% CI: 0.180, 0.396).

To address the potential bias due to the quality of the included studies, we performed the sensitivity analysis by calculating pooled HPV 16 prevalence again when omitting one study at a time. Figure 2 showed the results of sensitivity analysis. The HPV 16 prevalence ranged from 0.368 (95% CI: 0.276, 0.460) to 0.397 (95% CI: 0.286, 0.508). Results didn't show significant difference when any study was omitted, which indicated that each single study didn't influence the stability of overall HPV 16 prevalence estimate.

Discussion

To our knowledge, this is the first meta-analysis to explore the HPV 16 prevalence in esophageal cancer tissues in China, pooling data on 3429 esophageal cancer cases from 26 studies. In this analysis, factors which could influence the prevalence of HPV 16 were also investigated, including geographic location, publication date, HPV detection method and types of specimen. Interestingly, results of this meta-analysis showed that more than 35% of esophageal cancer cases infected with HPV 16, indicating a high level of HPV 16 infection in esophageal cancer cases of China. Our results were consistent with studies conducted in other Asian countries, which also found that HPV infection rates in esophageal cancer were relatively high (Yahyapour et al., 2012; Mohiuddin et al., 2013). Findings in these studies increase the evidence that HPV is involved in esophageal carcinogenesis.

HPV 16 was the predominant type in many of HPV-related cancers, such as cervical cancer, anal cancer, oral cancer and head and neck cancer (Zandberg et al., 2013). With respect to esophageal cancer, studies also reported that HPV 16 was the main HPV type (Yong et al., 2013; Li et al., 2014; Petrick et al., 2014), although there is a controversy on this issue. Meta-analysis conducted by Petrick et al showed that HPV 16 prevalence ranged from 17.3% to 35.9% in esophageal cancer using different detecting method (Petrick et al., 2014). Yong et al also reported that the prevalence of HPV 16 in esophageal cancer was 11.7% (Yong et al., 2013). Results in this study were consistent with these recent meta-analysis and even with a higher prevalence level in our study because the included cases were testing by PCR method which can improve the HPV 16 positive rate in the case tissues. Furthermore, as Li reported (Li et al., 2014), HPV infection might be disappeared during the development of cancer and this clearance of HPV infection may lead to underestimation of the HPV 16 infection. In other words, the high prevalence of HPV 16 may suggested a relative high overall HPV prevalence in esophageal cancer cases. This indicated that HPV vaccine might benefit more populations except cervical cancer for women.

Although Kreimer et al found that the geographic differences in oral HPV prevalence are obvious (Kreimer et al., 2010), Ferlay et al reported that HPV could not be expected to fully account for the geographical variation seen in esophageal cancer incidence (Ferlay et al., 2013). Consistent with Ferlay's report, our sub-group analysis by regions of different incidence of esophageal cancer incidence were not in accordance with HPV 16 prevalence. For example, provinces of Henan, Shandong and Hebei were high-risk areas of esophageal cancer, however,

the HPV 16 prevalence were lower than provinces of Chongqing and Guangdong, which had lower incidence of esophageal cancer. The pooled result of this meta-analysis presented a relative high level of HPV prevalence, but the result varied across the publication years of the studies. The stratified analyses according to publication year showed that the HPV 16 prevalence was higher in studies published before 2010 than that in studies published in or after 2010. Since all studies were conducted based on PCR assay, there is no evidence that this variation is caused by HPV detection method.

In this study, the majority of included studies applied paraffin-embedded tissue for HPV DNA detection. As we know, significant DNA degradation might occur with paraffin-embedded tissue (Srinivasan et al., 2009). Therefore, we are not surprised to find that the HPV 16 prevalence in PE tissue was lower than that in FF tissue. In the analysis stratified by HPV DNA source (L1 or E6/E7), we found that HPV 16 prevalence was lower in studies using L1 region of HPV DNA for detection than in studies using E6/E7 region. This is mainly because of the disruption of L1 region when the integration of HPV into the host genome (Hebner et al., 2006), which may be a important event that promotes and initiates esophageal carcinogenesis.

There are some limitations of this meta-analysis that should be addressed. First, the included studies were heterogeneous in this meta-analysis. We investigated the heterogeneity of the HPV 16 prevalence in esophageal cancer cases by geographic location, publication date, DNA source and types of specimen directly. It is obvious that many factors might contribute to the heterogeneity of studies. Therefore, the heterogeneity may not be fully explained in such cases and the HPV 16 prevalence estimates were still heterogeneous in some of stratified results. This is to be expected, as a full explanation of heterogeneity demanded information of all factors of HPV 16 prevalence in esophageal cancer cases and a sufficient number of studies to explore possible combinations of all such variables. In any event, we investigated several variables that consisted of substantial proportions of the heterogeneity in this study. Second, we couldn't excluded the confounders which may affect the HPV 16 prevalence in esophageal cancer cases because little of the included studies provided information on confounders such as age, gender, smoking, assumption of alcohol, consumption of hot or pickled food which were also risk factors of esophageal cancer. Further studies should focus on this issue and provide more exact information on type-specific HPV prevalence in esophageal cancer. Third, publication bias exist in this meta-analysis. This is mainly because studies with negative HPV 16 results tend not to be published. As we know, publication bias may lead to false result of the meta-analysis and overestimation of the HPV 16 prevalence. However, given the large cases available for analysis, it is unlikely that missing studies could have large affection on the main conclusions of this study. In addition, our meta-analysis included both English language and Chinese language studies which conducted in Chinese population, language bias could be ruled out. Fourth, we didn't investigate the overall HPV prevalence of esophageal cancer in Chinese population. However, understanding the overall HPV prevalence is essential for esophageal cancer prevention. It has been estimated that HPV is responsible for approximately 5.1% of the global cancer burden and contributes 20%-50% of non-anogenital cancers (Parkin, 2006; Ferlay et al., 2010). China has a high burden of esophageal cancer and clarifying the role of HPV in esophageal cancer is imperious. Thus, besides HPV 16 prevalence, we will conduct further research to acquire more information on HPV and esophageal cancer in Chinese population.

In addition, we cannot exclude the contamination of samples in this study which can directly affect the detection of HPV 16. Roden et al reported that dehydrated HPV could maintain 100% infectivity for one day (Roden et al., 1997). Ferenczy et al and Strauss et al found that HPV DNA existed on fomites and various medical surfaces (Ferenczy et al., 1989; Strauss et al., 2002), which should be responsible for contaminating samples (Roden et al., 1997). Despite our effort to control affection of contamination, this was difficult for us as many studies do not report on these issues. Future studies about HPV and esophageal should try their best to avoid contamination and record the quality control measures, which will help us to understand the real role of HPV in esophageal cancer.

In conclusion, our results indicate a relatively high level of HPV 16 prevalence in esophageal cancer among Chinese population, although there is a variation between different variables, such as geographical areas of the study origin, publication years, HPV detection method and types of specimen. Although this study cannot give information on etiology of HPV and esophageal cancer, it is an important step to fully assess the relationship between HPV and esophageal cancer in Chinese population, and it could also give some clues of the effect of HPV vaccine on esophageal cancer. Further studies are needed to elucidate the role of HPV in esophagus carcinogenesis with careful consideration of study design and laboratory detection method, providing more accurate assessment of HPV status in esophageal cancer.

Acknowledgements

We are grateful to Le-Ni Kang for her advice on meta-analytic methods.

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