Original Article

Human papillomavirus related anal squamous cell carcinoma survival: a systematic review and meta-analysis

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: JN Yao, XX Zhang, HN Zhou; (IV) Collection and assembly of data: JN Yao, XX Zhang, HN Zhou; (V) Data analysis and interpretation: JN Yao, LF Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Human papillomavirus (HPV) has been identified to be related to progression of anal squamous cell carcinoma (ASCC). However, the results remain controversial. A meta-analysis of epidemiologic studies was therefore conducted to address this issue.

Methods: Data were collected from studies comparing overall survival (OS) and disease-free survival (DFS)/disease-specific survival (DSS)/relapse-free survival (RFS)/progression-free survival (PFS) in patients with HPV infection. The electronic databases of MEDLINE and EMBASE were searched from their inception till 30 Apr. 2017. Study-specific risk estimates were pooled using a fixed-effects model for OS and DFS/DSS/RFS/PFS.

Results: Seven studies involving a total of 488 ASCC cases were included in this meta-analysis. The pooled results showed that HPV infection was significantly associated with improved OS (HR =0.36; 95% CI, 0.22–0.58) and DFS/DSS/RFS/PFS (HR =0.29; 95% CI, 0.18–0.47). The findings from most subgroup analyses were consistent with those from the overall analysis.

Conclusions: The meta-analysis indicated that HPV infection may be of prognostic or therapeutic utility in the evaluation of factors contributing to ASCC. Testing tumor specimens for HPV might indirectly affect the treatment decisions.

Keywords: Human papillomavirus (HPV); anus carcinoma; prognosis; meta-analysis

Submitted Feb 08, 2017. Accepted for publication May 23, 2017.

doi: 10.21037/tcr.2017.06.13

View this article at: http://dx.doi.org/10.21037/tcr.2017.06.13

Introduction

Anal squamous cell carcinoma (ASCC) is an uncommon malignancy of the anal canal and perianal skin area, with annual incidences ranging from 1.0 to 2.5 per 100,000 population in many western countries (1). Its incidence is increasing by approximately 2% yearly, particularly in females (2,3).

Although many risk factors for ASCC development have been identified, such as the inherited genetic predisposition, the molecular mechanisms related to the ASCC carcinogenesis remain under investigation (4). The effect of infectious agents in anal carcinogenesis has also been suggested as direct carcinogens or promoters. Infection with oncogenic human papillomavirus (HPV) types has been identified as a causal agent in a variety of human carcinomas, including those of the cervix, anogenital region and head and neck (5-7). As reported previously, the high-risk HPVs prevalence were 89.7% in cervical cancer (8), 29.5% in head and neck cancer (9), 22.2% in esophageal

cancer (10) and 31.9% in colorectal cancer (11).

In a study of patients with cervical cancer receiving radiation therapy, HPV-positive patients have a significantly better survival (12). Some retrospective clinical studies have consistently proved that patients with HPV-positive head and neck squamous cell carcinoma (HNSCC) had a better prognosis than patients with HPV-negative tumors (13-16). Anus can be infected with these viruses in the same way as the oral cavity, tonsils, and pharynx; it is supposed that the histological similarities between the head and neck squamous epithelia and anus would suggest a similar association and clinical characteristics. The prognostic value of the HPV status has previously been investigated in patients with ASCC. However, the results are much controversial.

Therefore, this systematic review and meta-analysis is conducted to assess the effects of HPV infection on overall survival (OS) and disease-free survival (DFS)/disease-specific survival (DSS)/relapse-free survival (RFS)/progression-free survival (PFS) in ASCC patients.

Methods

Literature search strategy

A systematic search up to 30 Apr. 2017 was conducted in MEDLINE (via PubMed) and Excerpta Medica database (EMBASE) to identify relevant articles. Search terms included "human papillomavirus or HPV", "anal cancer or anal neoplasms or anal carcinoma" combined with "prognosis or prognostic or survival or outcome". Additional relevant references cited in retrieved articles were also evaluated. This meta-analysis was performed in accordance with PRISMA guidelines (see *Table S1*).

Inclusion and exclusion criteria

All papers were reviewed by two authors (Jian-Ning Yao and Hai-Ning Zhou) independently. Uncertainties and discrepancies were resolved by consensus after discussing with a senior researcher (Yan-Le Li). All studies included in the final meta-analysis satisfied the following criteria: (I) patients were pathologically diagnosed as ASCC; (II) OS or DFS/DSS/RFS/PFS as the outcome of interest; (III) reported HR estimates with their corresponding 95% CI (or sufficient data to calculate of these effect measure), and (IV) English articles. 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.

Quality assessment

The quality of each study was evaluated in accordance with the revised ELCWP scoring scale described by Steels (17). Each item was assessed using an ordinal scale (possible values: 2, 1, 0). The overall score evaluated several dimensions of the methodology, grouped into four main categories: (I) scientific design: 0–10; (II) laboratory methodology: 0–14; (III) generalizability: 0–12; (IV) results analysis: 0–8. The total scores ranged from 0 to 44. The final scores were expressed as percentages, ranging from 0% to 100%, higher values indicated a better methodological quality.

Data extraction

Two of the authors (Jian-Ning Yao and Hai-Ning Zhou) performed the data extraction from each article and discrepancies were resolved by consensus. For studies meeting our inclusion criteria, a standardized data extraction form was used to extract the following data: the first author's name, year of publication, country of origin, study design, period of enrollment, the length of follow-up, characteristics of the studied population (sample size, age, stage of disease and treatment method), HPV detection methods, and HR estimates for OS or DFS/DSS/RFS/PFS with corresponding 95% CIs. When data for HR was not available, we extracted the total numbers of observed deaths and the numbers of patients in each group to calculate HR (18). Data were extracted by Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/) from the graphical survival plots when data were only available as Kaplan-Meier curves (19), then the estimation of the *HR* was performed by the described method (18).

Statistical analysis

The HR with 95% CI was used to compute the pooled HPV infections and the OS or DFS/DSS/RFS/PFS in ASCC patients. A fix-effect or random-effect model was used to pool the data, based on the Mantel-Haenszel method (20) and the DerSimonian and Laird method (21), respectively. These two models provide similar results when between-studies heterogeneity is absent; otherwise, random-effect model is more appropriate.

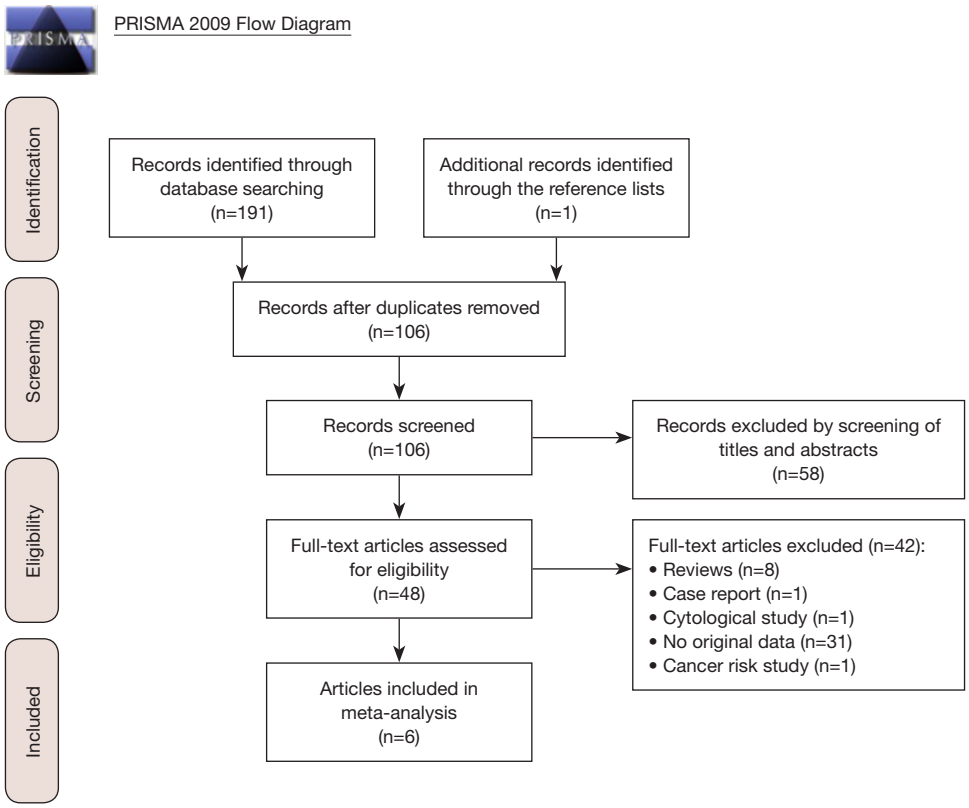

Figure 1 The PRISMA flow diagram of systematic literature search.

Cochrane *Q* test (P<0.10 indicated a high level of statistical heterogeneity) and I^2 (values of 25%, 50% and 75% corresponding to low, moderate and high degrees of heterogeneity, respectively) was used to assess the heterogeneity between eligible studies, which test total variation across studies that was attributable to heterogeneity rather than to chance (22). Subgroup analyses for HPV infections and the OS or DFS/DSS/RFS/PFS in ASCC patients were subsequently carried out according to the study type, geographical region, number of patients, clinical stage, detection method, PCR primers, HPV type, treatment method, hazard ratio and ELCWP score. 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 plot and Begg adjusted rank correlation test for funnel plot asymmetry were performed to test any existing publication bias.

All statistical analyses were performed using STATA version 12 for Windows (StataCorp LP, College Station, TX, USA). A two-tailed P<0.05 was considered statistically significant.

Results

Literature search

As shown in *Figure 1*, the search strategy generated 191 citations, of which 48 were considered of potential value after screening of titles and abstracts and the full text was retrieved for detailed evaluation. Of these 48 articles, 42 were subsequently excluded from the meta-analysis for various reasons, including 8 were reviews, 1 was case report, 1 was cytological study, 31 that did not provide HRs or CIs and 1 was cancer risk study. So, 6 studies were eligible and included in this systematic review and meta-analysis (23-28).

Characteristics of the selected studies

Individual characteristics of the included six studies are summarized in *Table 1*. They were published from 2007 to 2015 and involved a total of 488 ASCC cases. The sample sizes ranged from 47 to 137. All six studies investigated

Table 1 Characteristics of the included studies

First author	Year	Period of recruitment	Country	Study design	Location	Stage	No. of patients	Genotype (s)	HPV + ve N (%)	Age, y	Treatment	DNA method	Median follow-up period (months)	Survival analysis	Hazard ratio
Laytragoon-Lewin	2007	1987–2000	Sweden	Prospective	ASCC	NA	72	16, 18, 33	65 (90.3)	72/68 (females/males)	C, R or S	PCR	NA	OS	SC
Yhim	2011	1998–2009	Korea	Retrospective	ASCC	I–III	47	16	31 (66.0)	65 [44–90]	CRT	PCR	51.7 (5.1–136.0)	OS/PFS	Unadjusted
Ravenda	2014	2000–2012	Italy	Prospective	ASCC	I–III	50	16, 18, 31, 33, 45	42 (84.0)	62 [54–69]	CRT	PCR	48 (4.8–165.6)	OS/DFS	Adjusted
Serup-Hansen	2014	2000–2010	Denmark	Prospective	ASCC	I–III	137	16, 18, 31, 33, 45, 52, 58	120 (87.6)	63 [36–97]	CRT or R	PCR	51.2 (0.4–144.4)	OS/DSS	Unadjusted
Baricevic	2015	2004–2009	UK	Retrospective	ASCC	I–IV	110	16	100 (90.9)	62.4 [34–93]	CRT	PCR	28	OS/RFS	Unadjusted
Morris	2015	1995–2013	USA	Retrospective	ASCC	IV	72	16, 18, 31, 33, 51	68 (94.4)	52.1	NA	ISH & IHC[#]	44.5	OS	Unadjusted

[#], patients were considered to have HPV-positive tumors if HPV DNA was detected by ISH and/or p16 was detected in the tumor cells by IHC. HPV + ve, human papillomavirus positive; C, chemotherapy; R, radiotherapy; S, surgery; CRT, chemo-radiotherapy; PCR, polymerase chain reaction; ISH, *in situ* hybridization; IHC, immunohistochemistry; OS, overall survival; DFS, disease-free survival; DSS, disease-specific survival; RFS, relapse-free survival; PFS, progression-free survival; SC, survival curve; NA, not available.

Table 2 Methodological assessments of the studies included in the meta-analysis

First author	Global score (%)	Scientific design [/10]	Laboratory methodology [/14]	Generalizability [/12]	Results analysis [/8]
Laytragoon-Lewin	56.8	8	8	6	3
Yhim	72.7	8	6	12	6
Ravenda	70.5	9	8	9	5
Serup-Hansen	77.3	10	4	12	8
Baricevic	70.5	8	6	9	8
Morris	65.9	7	8	10	4

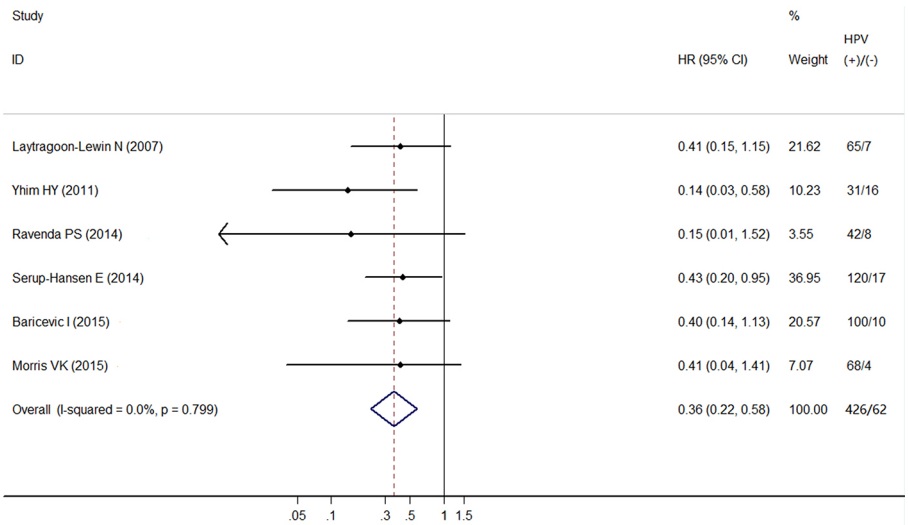

Figure 2 Forest plot comparing HPV-positive to HPV-negative ASCC patients and OS. HPV, human papillomavirus; ASCC, anal squamous cell carcinoma; OS, overall survival.

the prognostic role of HPV infection in OS, and 4 studies (23,26-28) explored the prognostic impact of HPV infection in DFS/DSS/RFS/PFS. HRs and 95% CIs were extracted directly from the survival curve from one study (24). One study (24) did not give accurate data for follow-up. The median follow-up period of all studies ranged from 28 to 51.7 months. The prevalence of HPV ranged from 66.0% to 94.4%.

Quality assessment

In methodological quality of studies, the global quality score ranged 56.8% to 77.3%, with a median of 69.0% (*Table 2*). The subscore of laboratory methodology had the lowest value, with a median quality score of 6.7 out of 14. The most poorly described items were the blinding evaluation, tissue sample conservation, and description of the revelation test procedure.

Results of the meta-analysis

OS

Among the studies included, all showed a negative association comparing HPV-positive to HPV-negative cancers, two (27,28) of which showed statistical significance. The heterogeneity test indicated there was very low degree of heterogeneity among included studies (Q test $P_{heterogeneity}$=0.799, I^2=0.0%), thus a fixed effects model was employed to obtain the pooled *HR*. The pooled *HR* from the 6 individual effect estimates comparing HPV-positive to HPV-negative cancers was 0.36 (95% CI, 0.22–0.58), which was significantly correlated with improved OS (*Figure 2*).

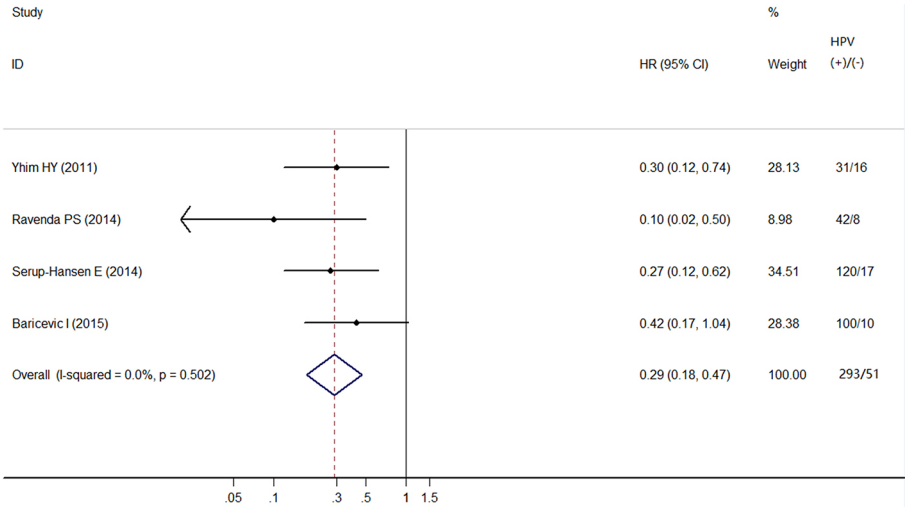

Figure 3 Forest plot comparing HPV-positive to HPV-negative ASCC patients and DFS/DSS/RFS/PFS. HPV, human papillomavirus; ASCC, anal squamous cell carcinoma; DFS, disease-free survival; DSS, disease-specific survival; RFS, relapse-free survival; PFS, progression-free survival.

DFS/DSS/RFS/PFS

Among the studies included, all showed a negative association comparing HPV-positive to HPV-negative cancers, three (26-28) of which showed statistical significance. The heterogeneity test indicated there was low degree of heterogeneity among included studies (Q test $P_{heterogeneity}$=0.502, I^2=0.0%), thus a fixed effects model was employed to obtain the pooled HR. The pooled HR from the four individual effect estimates comparing HPV-positive to HPV-negative cancers was 0.29 (95% CI, 0.18–0.47), which was significantly correlated with improved DFS/DSS/RFS/PFS (*Figure 3*).

Subgroup analyses

Table 3 presents detailed results of subgroup analyses.

The associations of HPV status and OS in ASCC patients did not differ by study type, geographical region, number of patients, clinical stage, detection method, PCR primers, HPV type, treatment method, hazard ratio and ELCWP score. When cancer cases stratified by HPV type, the pooled HR comparing HPV-16 positive to HPV-16 negative cancers was 0.28 (95% CI, 0.12–0.66).

The associations of HPV status and DFS/DSS/RFS/PFS in ASCC patients did not differ by study type, geographical region, number of patients, clinical stage, detection method, PCR primers, HPV type, treatment method, hazard ratio and ELCWP score. Exploratory subgroup analysis according to study type showed that HPV infection had more significantly prognostic value for improved DFS/DSS/RFS/PFS in prospective studies (HR =0.22, 95% CI, 0.11–0.46). In short, the estimated heterogeneity for studies included decreased to some degree but did not obliterate.

Influence analysis of individual studies

To address the potential bias due to the quality of the included studies, we performed the sensitivity analysis by calculating pooled HRs again when omitting one study at a time. *Figure 4A,B* showed the results of sensitivity analysis for OS and DFS/DSS/RFS/PFS respectively. The pooled HRs for OS comparing HPV-positive to HPV-negative cancers ranged from 0.32 (95% CI, 0.18–0.59) to 0.40 (95% CI, 0.24–0.66). The pooled HRs for DFS/DSS/RFS/PFS comparing HPV-positive to HPV-negative cancers ranged from 0.5 (95% CI, 0.14–0.44) to 0.32 (95% CI, 0.19–0.53). The meta-analysis result of the pooled HRs for OS and DFS/DSS/RFS/PFS comparing HPV-positive to HPV-negative cancers were not significantly affected by omission of any of the individual studies analysed, which indicated that each single study didn't influence the stability of pooled HR estimate.

Publication bias

There was no evidence of publication bias as demonstrated by the non-significant P values of Begg's test for OS (0.060) and DFS/DSS/RFS/PFS (0.142), and the near-symmetric

Table 3 Results of subgroup analyses

Group	OS (fixed-effect model)				DFS/DSS/RFS/PFS (fixed-effect model)			
	No. of study	HR (95% CI)	P for heterogeneity test	I^2 (%)†	No. of study	HR (95% CI)	P for heterogeneity test	I^2 (%)†
All	6	0.36 (0.22–0.58)	0.799	0.0	4	0.29 (0.18–0.47)	0.502	0.0
Study type								
Prospective	4	0.34 (0.20–0.60)	0.519	0.0	2	0.22 (0.11–0.46)	0.281	13.9
Retrospective	2	0.40 (0.16–0.99)	0.981	0.0	2	0.36 (0.19–0.67)	0.607	0.0
Geographic region								
Europe	4	0.40 (0.24–0.67)	0.892	0.0	3	0.28 (0.16–0.50)	0.309	14.8
Number of patients								
<100	4	0.29 (0.14–0.60)	0.619	0.0	2	0.23 (0.10–0.51)	0.244	26.3
≥100	2	0.42 (0.22–0.78)	0.913	0.0	2	0.33 (0.18–0.61)	0.479	0.0
Clinical stage								
I–III	3	0.32 (0.16–0.62)	0.350	4.7	3	0.25 (0.14–0.44)	0.489	0.0
Detection method								
PCR	5	0.36 (0.22–0.58)	0.676	20.7	4	0.29 (0.18–0.47)	0.502	0.0
PCR primers								
Type-specific	3	0.36 (0.20–0.63)	0.407	11.3	3	0.32 (0.19–0.53)	0.767	0.0
Combination*	2	0.36 (0.14–0.91)	0.467	0.0	1	–	–	–
HPV type								
16	2	0.28 (0.12–0.66)	0.256	22.4	2	0.36 (0.19–0.67)	0.607	0.0
Treatment method								
CRT	4	0.34 (0.19–0.60)	0.526	0.0	4	0.29 (0.18–0.47)	0.502	0.0
Others/unknown	2	0.41 (0.17–0.99)	1.000	0.0	0	–	–	–
Hazard ratio								
Unadjusted	4	0.42 (0.25–0.69)	1.000	0.0	2	0.33 (0.18–0.61)	0.479	0.0
Adjusted	2	0.14 (0.04–0.51)	0.963	0.0	2	0.23 (0.10–0.51)	0.244	26.3
ELCWP score								
<70%	2	0.41 (0.17–0.99)	1.000	0.0	0	–	–	–
≥70%	4	0.34 (0.19–0.60)	0.526	0.0	4	0.29 (0.18–0.47)	0.502	0.0

†, I^2 is interpreted as the proportion of total variation across studies that are due to heterogeneity rather than chance; *, combination of primers: broad spectrum plus type-specific primers. OS, overall survival; DFS, disease-free survival; DSS, disease-specific survival; RFS, relapse-free survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence intervals; PCR, polymerase chain reaction; HR-HPV, high-risk HPV; CRT, chemo-radiotherapy.

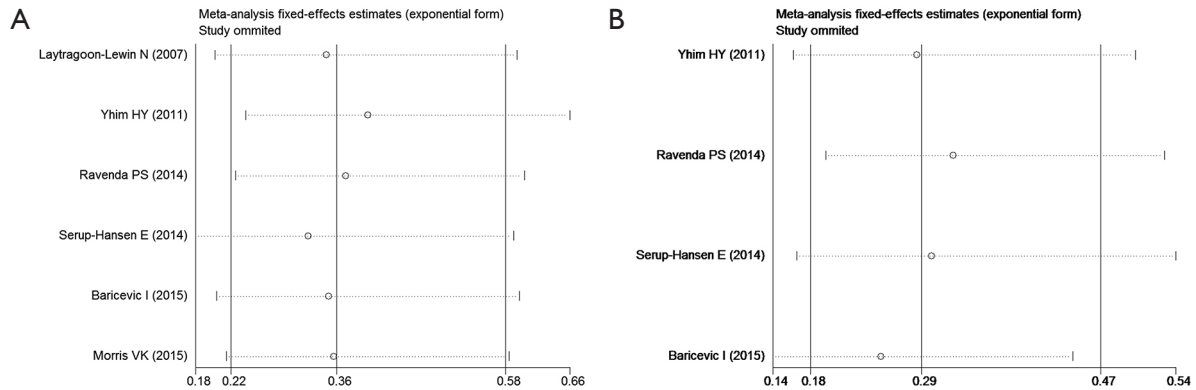

Figure 4 Influence analyses for omitting individual study on the summary HR for OS (A) and DFS/DSS/RFS/PFS (B). OS, overall survival; DFS, disease-free survival; DSS, disease-specific survival; RFS, relapse-free survival; PFS, progression-free survival.

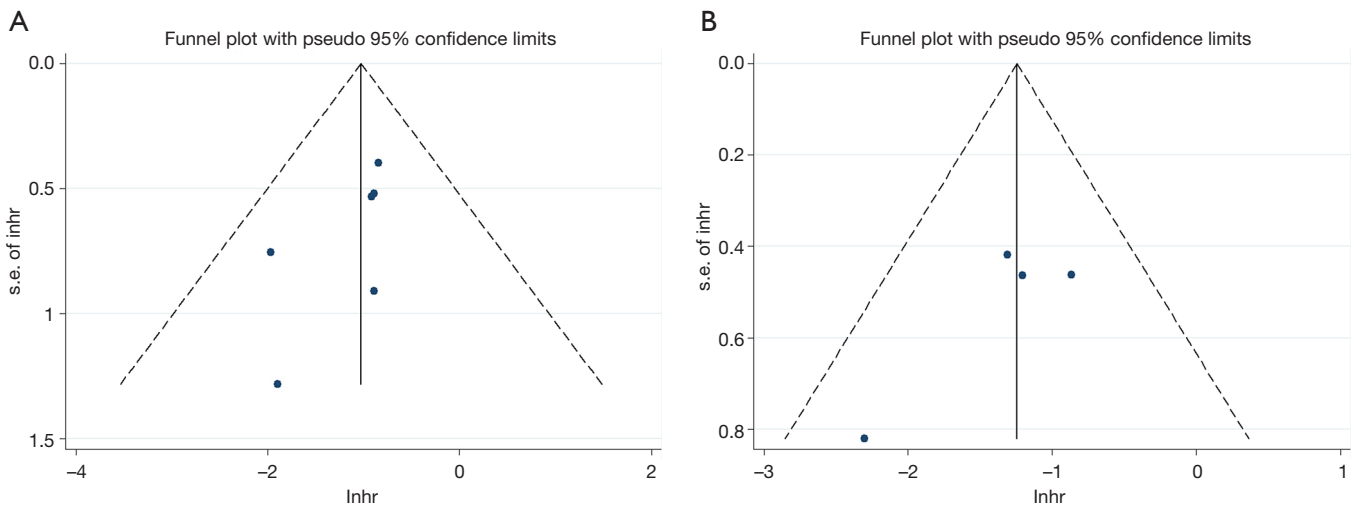

Figure 5 Funnel plots for publication bias of OS (A) and DFS/DSS/RFS/PFS (B). OS, overall survival; DFS, disease-free survival; DSS, disease-specific survival; RFS, relapse-free survival; PFS, progression-free survival.

funnel plot (*Figure 5*).

Discussion

This is the first systematic review investigating survival in HPV-related ASCCs. Pooled effect estimates from included studies demonstrated that HPV infection was significantly associated with improved survival in ASCC patients, suggesting that HPV infection may be of prognostic or therapeutic utility in the evaluation of factors contributing to ASCC.

The association between HPV infection and the occurrence of ASCC was first reported in the late 1980s (29-31). After then, an accumulating amount of studies have investigated the relationship between HPV infection and ASCC prognosis. However, the conclusions drawn were inconsistent. It was reported that HPV-positive HNSCCs was associated with a 54% reduction in overall mortality, in comparison to HPV-unrelated HNSCCs (32). Furthermore, Kim *et al.* (33) reported that the tumor HPV viral load in cervical cancer, in which more than 90% of patients had HPV infection, was a strong independent prognostic factor for DFS. In this sense, we are interested in the impact of tumor HPV status on treatment outcomes in terms of OS and DFS/DSS/RFS/PFS in ASCC. We found that HPV-positive ASCCs were associated with a 64% reduction

in OS and a 71% reduction in DFS/DSS/RFS/PFS, in comparison to HPV-unrelated ASCCs. These findings could be explained with better responsiveness of HPV-positive ASCC to chemoradiotherapy, as already showed in oropharyngeal squamous cell carcinoma (26). However, it has not been well known why HPV positive tumors have better responsiveness to radiotherapy, chemotherapy or both and warrants further study.

There are more than 100 HPV genotypes, which are categorized low and high-risk in accordance with their ability to induce malignant transformation of epithelial cells (34). The overall prevalence of HPV in anal carcinoma is around 84.3%, wherein more than 75% and less than 10% were HPV 16 and 18 positive respectively (35). HPV-associated cancers often have a viral sequence integrated into the genome of the cancer cells. Two of the HPV early structural genes, E6 and E7, are known as oncogenes promoting tumor growth and malignant transformation. The E6 and E7 proteins contribute to the genetic instability through their inactivation of p53 and the retinoblastoma protein (pRb). pRb is a negative regulator of the cyclin-dependent kinase inhibitor p16, and inactivation of pRb leads to upregulation of p16. p16 is often used as a surrogate marker of HPV infection. Studies of HNSCC have demonstrated high concordance between expression of p16 and HPV positivity (13,36). In HNSCC, HPV and p16 status have been evaluated as prognostic factors with positive HPV status or increased p16 expression being associated with improved prognosis (37,38). One study of cervical cancer found that increased p16 expression was associated with a better prognosis (39). Few studies have evaluated HPV or p16 status as prognostic factors in patients with anal carcinoma (40). Results from subgroup analyses stratified by HPV type showed that HPV-16 infection had more significantly prognostic value for improved OS and less significantly prognostic value DFS/DSS/RFS/PFS. Future studies are encouraged to investigate the difference in survival between different HPV genotypes in ASCC.

Clinical stage at diagnosis is the most important prognostic factor for ASCC (41). It's also a prerequisite for identifying ASCC patients who are candidates for chemoradiotherapy prior to surgery. However, only one study (26) reported the adjusted HRs for clinical stage. Other HRs were estimated either from univariate analysis or survival curves. So, future studies should therefore be encouraged to accurately adjust for other potential prognostic factors when comparing survival outcomes.

The present study has several strengths. First, the present analysis is the first to examine survival differences in HPV-positive and HPV-negative ASCCs, making it the most methodologically robust and comprehensive review to date. Second, we applied a rigorous inclusion/exclusion criterion, fully outcomes of interest (OS and DFS/DSS/RFS/PFS) and advanced meta-analysis of HR for survival. Moreover, subgroup analyses stratified by the study type, geographical region, number of patients, clinical stage, detection method, PCR primers, HPV type, treatment method, hazard ratio and ELCWP score. Thus, the effect of potential confounders was minimized. In addition, no publication bias was observed in our analyses, combined with the results of sensitivity analysis, indicating that our results are robust.

However, the present meta-analysis has several limitations. First, it is well known that the estimates of HPV infection might be influenced largely by the sensitivity and accuracy of HPV DNA detection method and HPV types covered by the method. Therefore, to some extent, potential bias could not be completely excluded considering that different methods have been used in the included studies. Second, the included studies were restricted to those published in English in our study, which might introduce language bias as well. Finally, only one study reported the adjusted *HR*s for clinical stage, which might cause residual confounding by other potential prognostic factors.

Conclusions

In conclusion, the findings of this meta-analysis indicated that HPV infection was significantly associated with improved survival in ASCC patients. Given its potential prognostic significance in ASCC, testing tumor specimens for HPV might indirectly affect the choice of chemotherapy and radiotherapy when considering treatment decisions. Considering the limitations of the present meta-analysis, further large prospective studies are encouraged to stratify survival analysis by pathological type and HPV type.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.

org/10.21037/tcr.2017.06.13). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Yao JN, Zhang XX, Zhou HN, Li YL, Xu HR, Wang CF, Chen LD, Gao B, Cheng P, Zhang LF. Human papillomavirus related anal squamous cell carcinoma survival: a systematic review and meta-analysis. Transl Cancer Res 2017;6(3):463-473. doi: 10.21037/tcr.2017.06.13

Supplementary

Table S1 PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	1–2
Objectives	4	Provide an explicit statement of questions being addressed with reference to PICOS	2
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	2–3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	2–3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis	3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	3
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	5–6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (I) simple summary data for each intervention group; (II) effect estimates and confidence intervals, ideally with a forest plot	5–6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	5–6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	6–7
Additional analysis	23	Give results of additional analyses, if done [e.g., sensitivity or subgroup analyses, meta-regression (see item 16)]	6–8
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)	8–9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	9
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	9

PICOS, participants, interventions, comparisons, outcomes, and study design. From: Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.