

Detection of HPV infection in head and neck cancers: Promise and pitfalls in the last ten years: A meta-analysis

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Abstract. The current controversial discussion on the disease-specific survival of patients with human papillomavirus (HPV)-positive (+) and -negative (-) squamous cell carcinoma (SCC) of the head neck region was the motivation for the present meta-analysis. Different detection methods for HPV are available, though these often lack sensitivity. As a consequence, there may be false interpretation of HPV positivity. A bias concerning HPV status and therefore also survival rates is serving a non-durable relevance in the discussion of tailored therapies. A literature search was performed via the online database PubMed/NCBI, and data extraction and statistical analysis were conducted. A total of 139 studies published between 2004 and 2014 were evaluated in the present meta-analysis. The HPV detection methods, patient characteristics, tumor localizations and stages, as well as (neo-) adjuvant therapies and survival times were analyzed. The average incidence rates of HPV⁺ patients with oropharyngeal tumors were higher than those of patients with cancers of other regions of the head and neck. Upon evaluating the results of different detection methods no significant differences were identified. We have compared the HPV incidence rates of each detection method, when studies have used more than one. Regarding overall survival, the pooled adjusted hazard ratio (HR) for oropharyngeal SCC was 0.31 [95% confidence interval (CI)=0.27-0.36]. Unfortunately, only 3 equivalent studies were available on nonoropharyngeal tumors, for which the pooled adjusted HR was 1 (95% CI=0.73-1.36). Overall, the evaluation demonstrated that the survival rates reported in numerous studies were not evaluated multifactorially and important confounders were excluded from the statistics. The HPV detection methods used were often not sufficient in representing HPV positivity. In addition,

oropharyngeal and oral SCCs were assessed together in the localization. The widely differing number of HPV⁺ patients in each of the various studies may be explained by insufficient detection methods and by a lack of localization distinction. The considerations of a tailored therapy according to HPV status should be rejected based on the present information. The previously published studies should be read critically and do not represent a basis for therapeutic decisions.

Introduction

Head and neck cancer (HNC) is reportedly the sixth most common cancer diagnosed worldwide; in 2008, ~633,000 new cases were diagnosed, and ~355,000 cases resulted in mortality (1). HNC encompasses all malignant tumors of the upper aerodigestive tract, which begins at the vermilion border of the lips and extends to the beginning of the esophagus. Approximately 90% of malignant neoplasms of the head and neck are squamous cell carcinomas (SCCs), while only just >5% are adenocarcinomas (2). The incidence rate varies according to geographic region and associated risk factors of differing severity. In recent decades, a declining incidence rate, particularly for the cancers of the oral cavity, hypopharynx and larynx, has been observed as an effect of reduced tobacco consumption in industrialized countries. However, in contrast, there has been a rapid increase in the incidence rate of oropharyngeal cancers, particularly of those of the tonsils and base of the tongue, which have been associated with human papilloma virus (HPV) (3,4). In 1983, HPV was first reported in association with head and neck SCC (HNSCC) (5). The International Agency for Research on Cancer officially recognized HPV-16 infection as a risk factor for oropharyngeal SCC (OPSCC) in 2007 (6). In recent decades, the number of oropharyngeal cancers caused by HPV has risen sharply: From 1988 to 2004, it increased in the US by ≤225% (7). But not only in North America, also in Europe this observation was found (8,9). Of the 100 cancers of the pharynx, 40 are assumed to be associated with HPV (2). HPV-associated HNSCCs occur in different populations from those with cancers induced by noxious agents, and different pathogenic processes underlie their oncogenesis. In the literature, a notable discordance exists among individual studies of HPV-associated HNSCC. Estimates of the incidence rate of HPV-associated tumors also differ greatly. Furthermore, the majority of studies conclude

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that patients with HPV-associated HNSCC have a survival advantage. An important question regarding the selection of a therapeutic approach in the future is whether treatment that is less intense will be sufficient for HPV-associated tumors.

The objectives of the present study were to improve current understanding concerning: The incidence rate of HPV-associated tumors; the most reliable detection methods; and the survival probability of HPV⁺ patients.

Materials and methods

Search strategy. The meta-analysis was conducted according to the guidelines of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (10,11). For an online literature search, the PubMed database was used. To identify the primary studies, the following terms were combined: 'HPV' and 'HNSCC', 'oral cavity', 'OPSCC', 'oropharyngeal' or 'tonsil' and 'overall survival', 'disease-specific survival' or 'treatment modalities'.

Study eligibility and data extraction. The following conditions were defined for the incorporation of studies into the meta-analysis: The object of interest had to be a patient diagnosed with HNSCC; each study had to include at least 50 patients (two exceptions - there have been ≥ 50 patients, but only 42 respectively 49 were available for HPV testing. These two studies were included because they seemed to be very useful, due to the fact both evaluated many parameters and also considered the kind of treatment.); HPV detection had to be conducted and explained; and the survival rates had to be described and separated into HPV⁺/HPV⁻ groups. Reviews and previous meta-analyses were not eligible. The publication was not included if it was more than 10 years old (two exceptions) and if it was not written in German or English. Additionally, the publication had to be available as full text. The selected studies were analyzed with respect to the following parameters: Number of patients, HPV detection method and the number of HPV⁺/HPV⁻ test results, HPV subtypes, tumor localization, treatment, mean age of HPV⁺/HPV⁻ patients at the time of diagnosis, alcohol consumption of HPV⁺/HPV⁻ patients, tobacco use of HPV⁺/HPV⁻ patients, sex of HPV⁺/HPV⁻ patients, tumor, node and metastasis (TNM) stage, country and outcome. The extracted data were collected in an Excel spreadsheet.

Statistical analysis. In the statistical evaluation, the respective minima, maxima, means and medians were determined for all extracted data sets of the above-mentioned criteria. The statistical analysis of the data to compare the detection methods and the data on the supposed survival advantage was carried out with the support of the staff of the Institute of Medical Statistics and Epidemiology of the Technical University of Munich.

For the comparison of the different detection methods the 'Random-Effect' model was used and the Risk Difference (RD) with the 95% CI was calculated. After the heterogeneity test, also for the statistical evaluation of the supposed survival advantage, the 'Random-Effect' model was used. And by using the published hazard ratios (HR) and their 95% confidence interval (CI) the pooled HR for overall survival (OS) was calculated. For data collection, statistical analysis



Figure 1. Schematic of the methodology employed for the literature research (Bischof C: PhD Thesis, in prep). Workflow of the data acquisition via literature research: Identification by keyword queries in PubMed, followed by removal of duplicates, inclusion of two additional older but well cited papers, then data extraction and the final dataset.

and the preparation of tables and charts, Microsoft Excel 2011 (Microsoft Corporation, Redmond, WA, USA) and R packages (cran.r-project.org/) were used.

Results

Literature search results. The literature search via PubMed yielded a total of 987 hits. The flow diagram in Fig. 1 illustrates how a final of 139 publications were selected. All abstracts were read to identify useful publications, and duplicates were rejected. In total, 459 publications, which were perceived as helpful, were read as full text. Among the sources of these publications, two further studies (>10 years) were identified to be useful and included in the present meta-analysis. The relevant data were extracted and transferred to an Excel spreadsheet. In 139 publications out of the 461 studies, including a total of 21,774 patients, fulfilled the final criteria. Of these studies, 80 were concerned solely with OPSCC (7,12-90), 13 with oral SCC (OSCC) (91-103) and 31 with both OPSCC and OSCC (104-134); 15 studies provided results on HNSCC in general (135-149).

HPV prevalence. The average percentage of patients tested as HPV⁺ estimated from all included studies in the meta-analysis was 42.62% [95% CI=0.39-0.46]. The mean incidence rate of the 80 OPSCC studies (12,662 patients, 6,383 HPV⁺) was 49.85% (95% CI=0.45-0.54). By contrast, for the 13 studies on OSCC, the mean incidence rate was 27.39% (95% CI=0.18-0.36). In a further analysis, anatomic regions were divided more specifically. As the anatomical localization of the oropharynx is of special interest according to HPV positivity, this region was further divided into: Base of the tongue, tonsils and neither of these two locations [listed as other oropharyngeal SCC (OOPSCC) in Table I]. The average incidence rate of HPV⁺ patients with OPSCC was 50.47% (95% CI=0.47-0.54). Notably, cancers of the base of the tongue, with an average incidence of HPV⁺ patients of 48.61% (95% CI=0.42-0.56), and of the tonsils, with an average incidence of HPV⁺ patients of 55.32% (95% CI=0.50-0.61), exhibited a relatively high association with HPV infection in particular. By contrast, oropharyngeal cancer, classified as being outside of these two regions, tested as HPV⁺ to a much lower extent, with an average

Table I. Overview of the incidence rates.

Variables	No. of studies	No. of patients	Patients HPV ⁺	Average HPV ⁺ (%)	Minimum HPV ⁺ (%)	Maximum HPV ⁺ (%)	Median HPV ⁺ (%)
All studies	139	21,774	9,016	42.62	5.68	89.20	40.20
OSCC studies	13	2,044	495	27.39	5.68	64.00	25.09
OPSCC studies	80	12,662	6,383	49.85	11.54	89.20	51.14
HNSCC	20	3,433	1,049	32.93	11.56	68.63	29.68
In HNSCC studies							
OSCC	40	3,550	737	24.14	0.00	75.68	21.03
OPSCC	110	14,230	7,178	50.47	3.23	95.00	50.38
OOPSCC	33	809	205	26.39	0.00	52.94	23.08
Base of tongue	34	1,501	760	48.61	1.85	82.26	50.00
Tonsils	55	4,316	2,272	55.32	4.29	95.00	57.78
Larynx	24	1,402	232	20.61	0.00	58.33	15.59
Hypopharynx	22	629	132	22.18	0.00	81.97	16.12

OPSCC, oropharyngeal squamous cell carcinoma; OSCC, oral squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; OOPSCC, other oropharyngeal squamous cell carcinoma.

incidence of HPV positivity of 26.39% (95% CI=0.22-0.31). The average incidence rates of HPV⁺ patients with tumors of other head and neck regions excluding OPSCCs were generally below those for oropharyngeal tumors: For OSCC, 24.14% (95% CI=0.18-0.30), for laryngeal cancer, 20.61% (95% CI=0.140-0.27) and for hypopharyngeal cancer, 22.18% (95% CI=0.14-0.31). For HNSCC, the average incidence of HPV positivity was 32.93% (95% CI=0.27-0.39; Table I).

HPV detection. Of the studies, 95 involved polymerase chain reaction (PCR), 80 used p16 immunohistochemistry (IHC) and 30 studies employed *in situ* hybridization (ISH). A total of 79 studies determined HPV status with one detection method, while 60 studies used two, or all three, of the above methods. Evaluation of the different results regarding the incidence rates, if studies have used multiple detection methods, revealed no significant difference between PCR and IHC, ISH and PCR, and IHC and ISH (Fig. 2A-C).

HPV subtypes. A total of 80 studies (11,455 patients) provided information on the HPV subtypes. Among the 4,086 patients that tested HPV⁺, the two high-risk types HPV16 and 18 were the most frequently detected subtypes. In OPSCC (44 studies), HPV16 was detected on average in 90.55% (95% CI=0.87-0.94) of cases, and HPV18 was responsible for the infection on average in 8.10% (95% CI=0.05-0.11) of cases. Among the HPV-associated OSCC cases (10 studies), HPV16 and 18 were detected on average in 69.66% (95% CI=0.52-0.87) and 26% (95% CI=0.19-0.33) of the cases, respectively.

Associations with HPV profile. Data regarding other risk factors (age, TNM status, alcohol and tobacco consumption, sex) and differences between HPV^{+/−} cases are summarized in Fig. 3. The most interesting finding was, that HPV⁺ patients with OPSCC were often described to be younger than HPV[−]

patients, also the mean age was lower for HPV⁺ patients with OPSCC (56.5 vs. 60.8 years). But this fact could not be observed for HPV^{+/−} patients with OSCC. Distribution of the studies according to the various countries and the mean incidence rates for OPSCC according to country are also given in Fig. 3.

HPV and patient survival. In the 135 studies providing information on patient survival, 94 reported an improved outcome for patients who tested HPV⁺, 5 documented a poorer survival rate, 25 could not detect any significant difference, and 11 reported a higher probability of survival only with HPV⁺ oropharyngeal tumors. Out of the 135 studies, 77 focused on oropharyngeal tumors with information on survival; 67 of these reported of an improved outcome in HPV⁺ patients, and 10 could not detect a significant difference. Of the 12 studies on OSCC with data on survival rates, 3 reported an improved outcome in HPV⁺ patients, 3 a poorer outcome, and 6 could not detect a significant difference. The data on the probability of survival were described in various formats, with the largest amount of comparable data being available for overall survival. The pooled adjusted hazard ratio (HR) for OPSCC was 0.31 (95% CI=0.27-0.36). Unfortunately, only 3 equivalent studies were available for nonoropharyngeal tumors, for which the pooled adjusted HR was 1 (95% CI=0.73-1.36, Fig. 4A and B).

Discussion

In the literature, the way in which prevalence rates of HPV-associated HNSCC are described varies greatly, with the main variant factors being insufficient description and fractionation of anatomical localizations, different risk factors (attributable to the time-point and the place of study), and non-uniform detection methods. In the present meta-analysis, the average incidence rate of HPV-associated

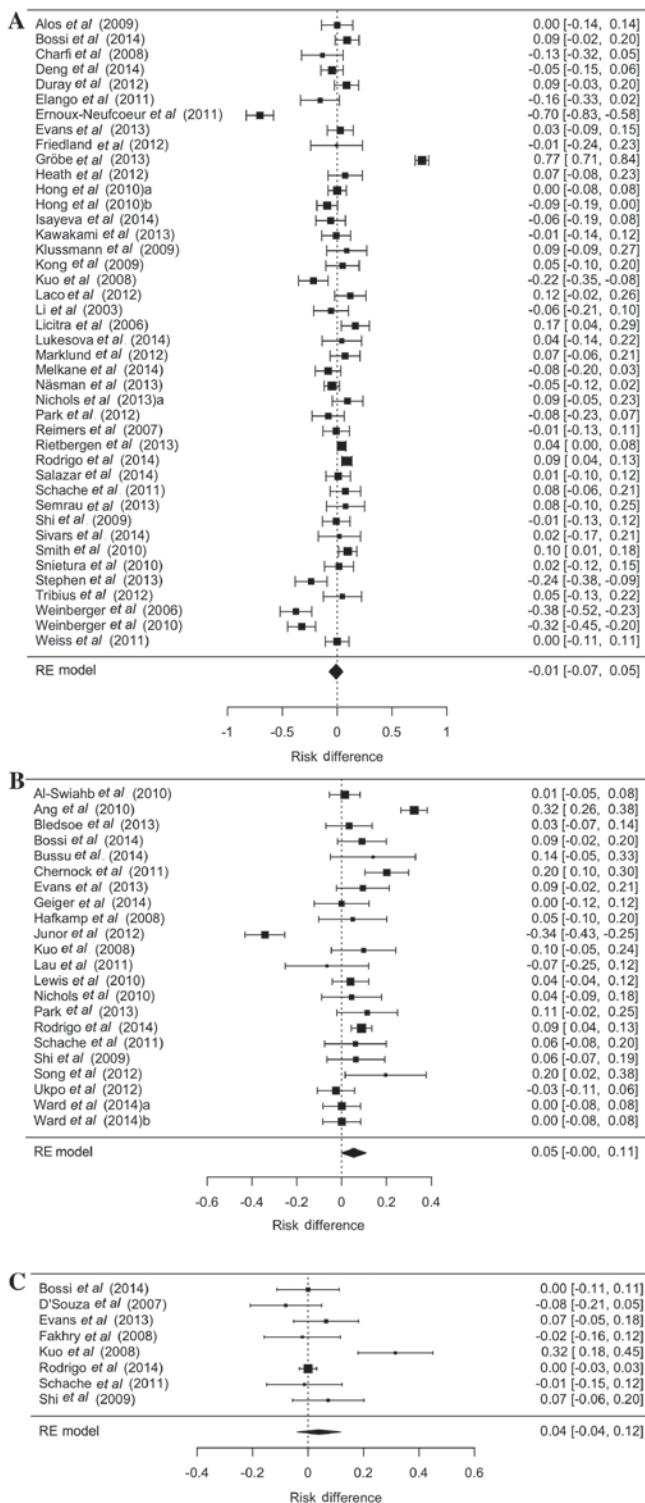


Figure 2. Risk differences due to HPV detection method in studies which used several HPV detection methods (Bischof C: PhD Thesis, in prep). (A) PCR and IHC; (B) ISH and PCR; and (C) IHC and ISH. By pooling the proportion of patients tested HPV-positive by the different methods the present study performed comparisons between them. HPV, human papillomavirus; PCR, polymerase chain reaction; IHC, immunohistochemistry; ISH, *in situ* hybridization.

HNSCC was 42.62%. In a similar meta-analysis of 60 studies (5,046 patients), the average incidence rate was 25.9% (95% CI=0.25-0.27) (150). Another meta-analysis of 34 studies (5,681 patients) reported that 21.95% (95% CI=0.21-0.23) of

HNSCCs were associated with HPV (151). The significantly higher incidence rate in the present analysis may be attributable either to i) more than half of the included studies (80 studies, 12,662 patients) only investigating OPSCC, which is known to be more frequently associated with HPV (150); ii) studies older than 10 years not being included. Analysis of the 5% of studies with the highest/lowest incidence rates of HPV-associated HNSCC revealed notable similarities: In contrast to the studies with low incidence rates, most studies with high incidence rates were from North America and involved exclusively OPSCC (15,28,31,46,49,54,79,94,97,100,112,120,136,140). The average prevalence rate in the 110 studies (14,230 patients) that provided data on tumors of the oropharynx was 50.47%; in the two meta-analyses mentioned above, the average incidence rate of HPV-associated OPSCC was 35.6% (95% CI=0.33-0.39) (150) and 41% (95% CI=0.38-0.44), respectively (151). Again, the different time periods over which the studies were conducted may be responsible for the observed differences. Many studies have reported a dramatic increase in the incidence of HPV-associated OPSCC in recent decades (8,9). However, even among the HPV-associated OPSCC cases, a relatively high level of variation exists in incidence rate (minimum: 11.54%, maximum: 89.20%) (28,49). Furthermore, analysis of the 5% of OPSCC studies with the highest/lowest incidence rates of HPV-association determined some similarities: All of the 5% of studies with the highest incidence rates were conducted in North America, whereas none of the studies with the lowest incidence rates was conducted in North America (15,22,28,31,41,49,54,73). The studies with the low incidence rates of HPV-associated HNSCC mentioned the different geographic regions (41,73), the higher prevalence of 'classic' risk factors and therefore a lower HPV prevalence (22,41,73), and the data collection over many years (28,73) as possible causes of the low incidence rates of HPV-associated HNSCC.

In the present analysis, OPSCCs were further divided into groups. Notably, a significantly higher HPV association for cancers of the tonsils and base of the tongue was observed, in contrast to cancers of other oropharyngeal regions. The average incidence rate of HPV-associated tumors (3,550 patients) of the 40 studies on OSCC was 24.14%, and therefore was similar to that determined in the meta-analysis by Kreimer: 23.5% (95% CI=0.22-0.25) (150). The current meta-analysis highlights the importance of a detailed description and distinction of the relevant anatomical localizations, since different HPV infection rates are obvious (8,52,53). As another factor, the time of the study appears to influence the HPV incidence rate (8,9); this may be explained by the significant decrease in smoking populations over the past decades (152). Due to the elimination of 'classic risk factors', including smoking and alcohol abuse, the number of cancers associated with other possible triggers increases. However, an increased HPV prevalence is also likely to serve a role; this may be attributable to changes in sexual practices and potential transmission via oral sex (24).

The lack of uniform standards for HPV detection makes it difficult to compare individual studies. Each detection method has its own advantages and disadvantages: In addition to sensitivity and specificity, the type of histological specimen, financial aspects, time available, and personal and equipment resources affect the choice of detection. Due to the various

HPV subtypes								
	Number of studies	Number of patients	Patients HPV+	Patients HPV-16	Patients HPV-18	Average % HPV-16	Average % HPV-18	
All studies	80	11 455	4 086	3 583	169	87.32%	11.65%	
OPSCC	44	6 791	2 707	2 478	69	90.55%	8.10%	
OSCC	10	1 533	384	229	71	69.66%	26.00%	
Age								
	Number of studies	Number of patients	HPV+ younger	HPV+ older	n.s.			
All studies	99	17 977	43	4	52			
OPSCC	60	11 591	32	2	26			
OSCC	7	1 008	0	0	7			
	Number of studies	Number of patients	Mean age HPV+	Mean age HPV-				
All studies	66	11 633	57.4	61.1				
OPSCC	46	8 261	56.5	60.8				
OSCC	3	521	61.5	59.4				
Tumor stage								
	Number of studies	Number of patients	Patients HPV+	Patients HPV-	TNM I/II HPV+ (mean%)	TNM III/IV HPV+ (mean%)	TNM I/II HPV- (mean%)	TNM III/IV HPV- (mean%)
All studies	73	11 487	4 939	6 539	749 / 18.95%	4 190 / 81.05%	1 808 / 23.18%	4 731 / 76.82%
OPSCC	46	7 258	3 464	3 794	379 / 14.27%	3 085 / 85.73%	974 / 19.73%	2 820 / 80.27%
OSCC	5	487	176	311	98 / 54.44%	78 / 45.56%	139 / 42.52%	172 / 57.48%
Alcohol								
	Number of studies	Number of patients	Patients HPV+	Patients HPV-	Alc HPV+	Alc HPV-	Alc HPV+ (mean%)	Alc HPV- (mean%)
All studies	55	8 084	3 640	4 444	1 879	2 894	52.60%	62.70%
OPSCC	32	4 884	2 772	2 112	1 310	1 273	43.74%	59.26%
OSCC	7	671	234	437	150	238	62.34%	58.29%
Smoking								
	Number of studies	Number of patients	Patients HPV+	Patients HPV-	Tobacco HPV+	Tobacco HPV-	Tobacco HPV+ (mean%)	Tobacco HPV- (mean%)
All studies	74	11 029	5 218	5 811	3 168	4 533	61.84%	76.65%
OPSCC	45	7 445	4 205	3 240	2 469	2 538	57.87%	78.65%
OSCC	8	779	245	534	167	317	62.03%	60.88%
Gender								
	Number of studies	Number of patients	Patients HPV+	Patients HPV-	Female HPV+ (mean%)	Female HPV- (mean%)	Male HPV+ (mean%)	Male HPV- (mean%)
All studies	92	14 309	6 309	8 000	1 223 / 20.24%	1 626 / 21.40%	5 075 / 79.33%	6 233 / 76.43%
OPSCC	58	9 161	4 934	4 227	936 / 20.33%	809 / 20.62%	3 998 / 79.67%	3 342 / 77.32%
OSCC	10	1 114	343	771	75 / 21.49%	168 / 22.50%	267 / 77.60%	525 / 65.43%
Countries								
		Europe	North America	Asia	Australia	South America		
Number of studies		61	46	23	7	2		
OPSCC	Number of studies		Number of patients	Patients HPV+		Mean incidence rate		
Europe		33	5 891	2 686		48.08%		
North America		28	4 577	2 716		52.07%		
Asia		14	1 678	661		43.64%		

Figure 3. Data regarding HPV risk factors (Bischof C: PhD Thesis, in prep). Age: The upper panel summarizes data without detailed age information (only HPV+ patients are older/younger, no significant difference), the lower panel of the data summarizes detailed age information. Alcohol: The number of patients who described themselves as regular alcohol consumers. Smoking: The number of patients who described themselves as regular tobacco consumers. Data are presented as the n number of patients and/or the mean percentage. HPV, human papillomavirus; n.s., not significant; TNM, tumor-node-metastasis; OPSCC, oropharyngeal squamous cell carcinoma; OSCC, oral squamous cell carcinoma.

advantages and disadvantages, the most reliable HPV detection method may be a combined approach that establishes both an accurate result and a cost- and time-effective test method;

for instance, the high sensitivity method of p16 IHC may be combined with the high specificity method of PCR and a chip system as described previously (153). The current analysis

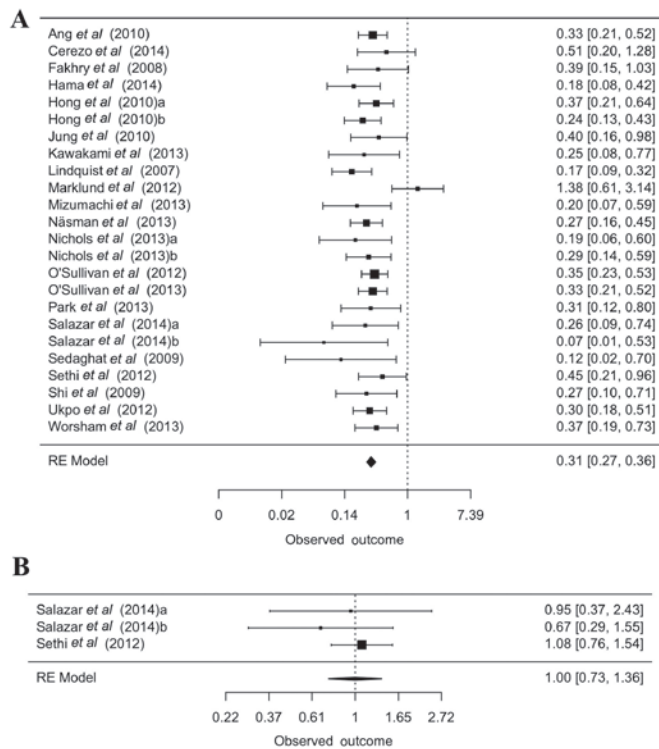


Figure 4. Overall survival regarding HPV positivity, revealed a better outcome for HPV⁺ patients. (A) oropharyngeal tumors and (B) non-oropharyngeal tumors (Bischof C: PhD Thesis, in prep). Pooled adjusted hazard ratio for the overall survival of patients with oropharyngeal squamous cell carcinoma and nonoropharyngeal tumors. The hazard ratios were given in the studies. HPV, human papillomavirus.

compared the results of the various detection methods, but no significant difference was observed. There is an urgent need for uniform standards regarding the HPV test procedure. However, the test method combination described above must first be confirmed as sufficiently accurate. Furthermore, the potential association between viral biological activity/ integration into the host genome/higher viral load and higher survival rate must be clarified.

HPV16 and 18 were the most commonly detected subtypes (11,455 patients in 80 studies on subtype), with this result being consistent with other studies (150,151). Notably, HPV16 was more common in OPSCC than in OSCC (90.55 vs. 69.66%), and HPV18 was more often detected in OSCC than in OPSCC (26.00 vs. 8.10%). These observations have previously been described in other studies (8,150).

As mentioned above, the majority of studies observed a survival advantage for HPV⁺ HNSCC patients. It needs to be clarified whether all HPV-associated HNSCCs have this prognostic advantage, or whether only certain subsets of HPV-associated HNSCC are affected. Not only the anatomical sub-localizations but also the HPV detection method, the respective HPV subtype, the biological activity and the viral load may limit the extent of potential survival benefit. To avoid insufficient treatment, it needs to be examined more closely whether the survival benefit is independent of the applied treatment. A comparison of the individual studies is difficult, because they differ in certain key points including tumor localization, HPV detection method, the applied treatment and the endpoint of study. In concordance with other studies,

a survival advantage of a 69% lower risk of fatality associated with any cause was observed for patients with HPV-associated OPSCC. For patients with non-oropharyngeal cancers, no survival benefit was identified, although only 3 comparable studies have been conducted. Many studies suggest that not all HPV-associated HNSCC have an improved prognosis, and that the anatomical localization is of prognostic importance (128,154). Also a recent study conducted at the TU Munich found no survival benefit for patients with HPV-associated OSCC (155). Among the above-mentioned five studies (HPV and patient survival) that reported of a worse outcome of patients with HPV-associated carcinomas, mainly patients with non-OPSCC were investigated (92,96,98,110,126). An interesting study by Marklund indicated that perhaps even the localization of 'oropharynx' is too vague, as for neither p16⁺ nor HPV⁺ patients with oropharyngeal tumors outside the tonsils and base of the tongue could prognostic benefits be observed (53). Furthermore, in another study, the survival advantage of HPV-associated OPSCC was limited to tumors of the tonsils and base of the tongue (52). Therefore, in future, the description and separation of OPSCC should be more detailed. The reason for HPV-associated cancers having an improved long-term prognosis is still not wholly clear, although several theories have been proposed. The favorable prognosis may be based on the fact that HPV-associated carcinomas have markedly fewer genetic alterations compared with carcinomas induced through noxious agents (44), and thus, an increased sensitivity to DNA-damaging processes exists (156). This observation is also in accordance with the fact that, among patients with HPV-associated cancers, fewer smokers are observed; as the probability of genetic alterations rises with each additional pack year (13). Additionally, this hypothesis is supported by the finding that HPV⁺ tumors with TP53 mutations have not been associated with an improved prognosis (48,157). No conclusion can be made as to whether the improved prognosis for surgically treated patients is invalid because of the small number of cases. Just as TP53 mutations can be observed less frequently in HPV-associated carcinomas (158), other relationships with specific biomarkers have been discussed, for example, the lower expression of epidermal growth factor receptor and a rarer amplification at 11q13 (159). Furthermore, combined effects of the immune response to the virus and the tumor may be responsible; specific T-cells against HPV16 E7 protein have been detected, but their role remains unclear (160). The fact that patients with HPV-associated HNSCC rarely develop secondary tumors may contribute to improved survival rates (161), although it should be noted that patients affected by HPV-associated cancers are mostly younger (13,88,139,162-165) and are less often tobacco and alcohol consumers (87,116). Certain studies claim that tobacco consumption is of prognostic significance in HPV⁺ and HPV⁻ patients (13,32,33,54). However, some other studies refute this thesis, claiming the improved prognosis observed in HPV⁺ patients is independent of their tobacco consumption (26). Regarding comorbidities, for patients with HPV⁺ OPSCC and, in general, HNSCC with lower comorbidities, a significantly improved long-term survival has been observed (104). In contrast, for patients with HPV-associated OPSCC/HNSCC with higher comorbidities, no prognostic benefit has been recognized (104). This suggests that the

health status of the patients should be considered (104). With respect to the detection methods, as explained above, the examination of HPV status with a combined method utilizing p16 IHC, PCR and chip analysis may be advantageous (153). However, the molecular mechanisms that underlie the presumed survival advantage have not yet been sufficiently studied. Thus, no definitive recommendations can be made for HPV detection, and further studies are still needed. Additional tests, including for TP53 mutations, amplification at 11q13, and E6 and E7 PCR may be helpful (154). In addition to the previously described factors that may influence the prognostic relevance of HPV-associated HNSCC, one important question is whether the supposed improved outcome is independent of the treatment method employed. An improved response to chemotherapy and radiotherapy has been discussed, but even for this there is disagreement; p16⁺ patients often underwent a more aggressive adjuvant therapy, because of their more frequent lymph node involvement and lower rate of comorbidities (14). This raises the question as to whether the prognostic benefits are attributable to the more intense treatment and not to the less aggressive tumors (14). Baumeister *et al* (14) also indicated that the most common causes of mortality in patients with HPV-associated carcinomas were distant metastases and the relatively late tumor onset; thus a 10-year monitoring period was suggested to be advantageous.

Regarding published studies on HPV infection in HNSCC, it should be noted that the detection methods and study cohorts may provide bias. Furthermore, the role of HPV infection in OSCC is of minor relevance, and only a minority of cases are HPV⁺. In OPSCC, and particularly in cancers of the tonsils and base of the tongue, HPV infection and positivity for the surrogate marker p16 may be of high relevance for survival. Therefore, p16-positivity is included in the recent World Health organization TNM classification for OPSCC. In the next few years, the predicted rising numbers of vaccination against HPV infection may serve a notable role regarding the incidence of HPV⁺ cancers. For details see also 'Bischof C: PhD Thesis, in prep'.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CG, CB, LS, KDW and AK designed the study. CG, CB, LS, KDW and AK conducted the study. CG and CB collected the data. CG, LS and CB analyzed the data. CG and CB interpreted the data. CG, CB, LS, KDW and AK drafted the manuscript. CG, CB, LS, KDW and AK wrote the manuscript. CG, CB, LS,

KDW and AK approved the final version of the manuscript. CG, CB, LS, KDW and AK take responsibility for the integrity of the data analysis.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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