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REVIEW

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# COMPREHENSIVE META-ANALYTICAL SUMMARY ON HUMAN PAPILLOMAVIRUS ASSOCIATION WITH HEAD AND NECK CANCER

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**An etiological role of high risk human papillomavirus (HPV) in the development of cervical cancer has been well established. Hence, attention of researchers has been focused on the role of HPV in pathogenesis of other malignancies, such as head and neck cancers. An analysis of epidemiological data on the prevalence of HPV infection among healthy people and patients with precancerous lesions and/or cancer is an important step in understanding the role of HPV in head and neck carcinogenesis. More and more data demonstrate the impact of HPV infection on disease outcome. HPV-positive patients have been shown to have better responses to radiotherapy and better overall and disease-free survival than HPV-negative patients. This review presents data of the meta-analysis based on a large number of original studies on HPV prevalence in patients with precancerous lesions and in patients with oral, oropharyngeal and laryngeal cancers as well as findings on the impact of HPV infection on survival of these patients.**

*Key Words:* **meta-analysis, human papillomavirus, head and neck cancer, survival.**

Members of the *Papillomaviridae* family play an important role in the development of certain types of human malignancies, such as oropharyngeal and anogenital cancers [1, 2]. Head and neck cancer (HNC) is the fifth most common type of cancer and the sixth most common cause of cancer death worldwide. About 550,000 new cases are reported worldwide annually [3].

The HPV involvement in oral and oropharyngeal carcinogenesis was suggested based on viral tropism to the epithelial cells and oncogenic potential of high risk HPV genotypes in the pathogenesis of anogenital neoplasia, particularly in cervical squamous cell carcinoma and the morphological similarities between oropharyngeal and genital epithelia [4–9].

Almost 90% of HNC cases are of squamous epithelial cell origin that could be characterized by a multistep and multifactorial pathogenesis [10–12]. It has been shown that besides smoking and alcohol use, some infectious pathogens, such as human papillomavirus (HPV) may act as a carcinogenic factor for HNC of certain locations, particularly the oropharynx [13, 14].

To evaluate the etiological role of HPV, it is important to understand whether the prevalence of HPV DNA become higher during malignant transformation of normal epithelium to dysplasia, then to carcinoma *in situ* and finally to invasive cancer. A large amount of the data giving evidence of HPV DNA in head and neck squamous cell carcinoma (HNSCC) has been accumulated and a systematic review and meta-analyses of these data should be performed. Since most of the original studies were conducted using small number of samples, the meta-analysis is an effective statistical tool, which depends less on specific initial data than on each study individually, thus solving the problem of low statistical power of each individual study.

It should be noted that each meta-analysis determines its own inclusion criteria; therefore, the following results of evaluation are rather complementary than contradictory and allow the studied problem to be described more adequately. The meta-analyses, described in the present article are mainly focused on the following points:

- prevalence of HPV in HNSCC tissues, which is expressed as a percentage, usually with 95% confidence interval (CI);
- the odds ratio (OR) — the ratio of the probability of presence the studied risk factors in the HPV-positive patients compared with HPV-negative ones;
- survival of HPV-positive patients. Typically, the survival rate is estimated, using the Kaplan — Meier analysis and it is quantitatively assessed as a percentage survival of each group or calculated risk ratio of adverse outcome (hazard ratio — HR) in the presence of HPV-infection. The lower HR value, the difference in survival between HPV-positive and HPV-negative patients is higher.

The main aim of this review was to summarize all certain segments of available information with the focus on infection prevalence, risk of HPV-associated HNC, and also progression and survival of virus-positive and virus-negative individuals.

***The prevalence of HPV in head and neck precancerous lesions.*** There are two types of precancerous lesions in the oral cavity mucosa: leukoplakia and erythroplakia [15]. Based on published data [2], the incidence of HPV DNA in leukoplakia was 31.1% (300/964 cases). The predominant HPV types were HPV-6 and HPV-11 (HPV-6/-11, 55.8%) followed by HPV-16/-18 (28.2%). Only a few cases of erythroplakia have been described in the literature. The authors reported on 32 cases of erythroplakia, 9 of them had HPV-16 DNA. In addition, Nielsen et al. [16] de-

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*Abbreviation used:* DFS – disease-free survival; HNC – head and neck cancer; HNSCC – head and neck squamous cell carcinoma; HPV – human papillomavirus; HR – hazard ratio; OOPD – oral cavity and oropharyngeal dysplasia; OR – odds ratio; OS – overall survival.

scribed 10 cases with erythroplakia, 50% of them being HPV-positive. The prevalence of HPV-16/-18 in oral cavity and oropharyngeal dysplasia (OOPD) has been recently shown [17].

The meta-analysis was performed using the results of 22 studies that reported prevalence of HPV-16 and/or -18 in 458 OOPD cases. The overall prevalence of HPV-16/-18 in OOPD lesions was 24.5% (95% CI 16.4–36.7). The individual prevalence for HPV-16 alone was 24.4%. The prevalence of HPV-16/-18 in oral cavity lesions was 25.3% (95% CI 14.2–45.2). The odds of HPV-16/-18 detection in dysplastic lesions in males were twice that of females (OR 2.44). HPV-16/-18 were 3-fold more frequent in dysplastic lesions (OR 3.29; 95% CI 1.95–5.53) and invasive cancers (OR 3.43; 95% CI 2.07–5.69), than in normal tissue samples. There were no significant differences in the incidence of HPV-16/-18 between patients with mild, moderate and severe dysplastic changes.

Results of the presented meta-analysis support an assumption that the HPV-16/-18 accumulation occurs in the early stage of oral and oropharyngeal carcinogenesis.

***The prevalence of HPV in HNSCC.*** The high HPV prevalence in HNSCC explains the abundance of the reviews with the scope on a particular problem. Most of the studies took into account the specific anatomic sites and just very few of them has described HPV prevalence in HNSCC. The average of HPV prevalence in HNSCC was 21.9% [20], 25.9% [18], 34.5% [19], which is described in 3 meta-analyses performed on a cohort of about 5000 patients (Table 1).

Interestingly, the difference in HPV DNA prevalence is observed between the cohorts with similar percentage of patients. It is likely to be caused by different inclusion criteria used in studies described above. Furthermore, the following points can also have a considerable effect: variety of methods used for HPV detection, different origin of patients, varying percentage of cases with particular cancer sites. Thus, there is a definite requisite for stratification of HNC patient groups depending on the anatomical site of squamous cell carcinoma.

It was shown that HPV-16 is the most prevalent genotype among all HNSCCs (73.3% [18], 86.7% [20], 82.5% [21]), followed by HPV-18 and -33 [18, 20]. Hobbs et al. [22] in a meta-analysis based on 17 studies with the total of 2012 patients, showed that HPV is most strongly associated with tonsillar cancer (OR 15.1; 95% CI 6.8–33.7), is intermediate for oropharyngeal cancer (OR 4.3; 95% CI 2.1–8.9), and is the weakest for oral cancer (OR 2.0; 95% CI 1.0–4.2).

It was also shown that HPV status was associated with p16 expression (adjusted OR 3.00; 95% CI 0.90–9.70; p = 0.18), and HPV-positive tumors were less likely to harbor p53 mutations (adjusted OR 0.21; 95% CI 0.04–0.38; p = 0.015) [20].

Survival rate of patients with HPV-positive and HPV-negative HNSCC cases was studied in three meta-analyses, and it was shown that HPV-positive patients had better prognosis: HR for overall survival (OS) was 0.42 [20], 0.46 [23], and 0.85 [24], and HR for disease-free survival (DFS) was 0.41 [23] and 0.62 [24] (Table 2).

**Table 1.** HPV prevalence by different sites of HNC

| State | HPV prevalence (95% CI), % | Study type | N | Source |
|---|---|---|---|---|
| Leukoplakia | HPV-6/-11 – 55.8%<br>HPV-16/-18 – 28.2% | Review | 364 | [2] |
| Erythroplakia | HPV-16 – 28.1%<br>HPV – 50.0% | <br>Original study | 32<br>10 | <br>[16] |
| Dysplasia | HPV-16/-18 – 24.5% (16.4–36.7) | Meta-analysis of 22 studies | 458 | [17] |
| HNC | Pooled HPV – 25.9% (24.7–27.2) | Meta-analysis of 60 studies | 5046 | [18] |
| | Pooled HPV – 34.5% (28.4–40.6) | Meta-analysis of 62 studies | 4852 | [19] |
| | Pooled HPV – 21.9% (21.0–23.0) | Meta-analysis of 34 studies | 5681 | [20] |
| | HPV-16 – 86.7% (85.0–89.0) | Meta-analysis of 34 studies | 5681 | [20] |
| | HPV-16 – 82.4% | Meta-analysis of 269 studies | 13972 | [21] |
| | HPV-16 – 73.3% | Meta-analysis of 60 studies | 5046 | [18] |
| Oral cancer | Pooled HPV – 23.5% (21.9–25.1) | Meta-analysis of 35 studies | 2642 | [18] |
| | Pooled HPV – 38.1% (30.0–46.2) | Meta-analysis of 47 studies | 3238 | [19] |
| | HPV-16 – 68.2% | Meta-analysis of 35 studies | 2642 | [18] |
| Oropharyngeal cancer | Pooled HPV – 35.6% (32.6–38.7) | Meta-analysis of 27 studies | 969 | [18] |
| | Pooled HPV – 47.7% (42.9–52.3) | Meta-analysis of 269 studies | 5396 | [21] |
| | Pooled HPV – 63.8% | Original study | 323 | [28] |
| | HPV-16 – 86.7% | Meta-analysis of 27 studies | 969 | [18] |
| | HPV-16 – 96.1% | Original study | 323 | [28] |
| Laryngeal cancer | Pooled HPV – 24.0% (21.8–26.3) | Meta-analysis of 35 studies | 1435 | [18] |
| | Pooled HPV – 28.0% (23.5–32.9) | Meta-analysis of 55 studies | 2559 | [34] |
| | HPV-16 – 69.2% | Meta-analysis of 35 studies | 1435 | [18] |
| | HPV-16 – 19.8% (15.7–24.6) | Meta-analysis of 55 studies | 2559 | [34] |

***The prevalence of HPV in oral cancer.*** Several meta-analyzes demonstrated the prevalence of HPV in the oral cancer [18, 19, 23]. According to these data, the HPV prevalence in oral cancer was approximately the same as in other HNC sites (23.5%). Other data demonstrate much higher prevalence (38.1% of cases). HPV-16 was detected in 68.2% and HPV-18 in 34.1% (see Table 1).

The pooled HR for oral cancer was 0.32 (95% CI 0.16–0.68), that is mean, the OS rate in HPV-positive patients was 3 times higher than in HPV-negative ones (see Table 2).

***The prevalence of HPV in oropharyngeal cancer.*** An independent population-based study in the United States (n = 271) showed that the population-level incidence of HPV-positive oropharyngeal cancers increased by 225% from 1984 to 2004 (from 0.8 per 100,000 to 2.6 per 100,000), and incidence for HPV-negative cancers declined by 50% [25]. It is estimated that by 2020, the annual number of HPV-positive oropharyngeal cancers will exceed the annual number of cervical cancers.

In the meta-analysis of Kreimer et al. [18], the frequency of HPV detection was significantly higher in oropharyngeal cancer (35.6% of 969 cases) compared to oral cancer (23.5% of 2642 cases) and laryngeal cancer (24.0% of 1435 cases). HPV-16 was detected in 86.7% of patients with oropharyngeal cancer and HPV-18 in 2.8% of patients (see Table 1).

**Table 2.** Impact of HPV-infection on survival rate of HNC patients

| State | Survival type | Rate | Study type | N | Source |
|---|---|---|---|---|---|
| HNC | OS | HR 0.42 | Meta-analysis of 34 studies | 5682 | [20] |
| | OS | HR 0.46 (0.37–0.57) | Meta-analysis of 32 studies | 3575 | [23] |
| | DFS | HR 0.41 (0.27–0.64) | Meta-analysis of 16 studies | 1422 | [23] |
| | OS | HR 0.85 (0.7–1.0) | Meta-analysis of 19 studies | 1990 | [24] |
| | DFS | HR 0.62 (0.5–0.8) | Meta-analysis of 9 studies | 626 | [24] |
| Oral cancer | OS | HR 0.32 (0.16–0.68) | Meta-analysis of 2 studies | n/a | [23] |
| | DFS | HR 0.62 (0.13–2.98) | Meta-analysis of 3 studies | n/a | [23] |
| Oropharyngeal cancer | OS | HR 0.72 (0.5–1.0) | Meta-analysis of 4 studies | 224 | [24] |
| | DFS | HR 0.51 (0.4–0.7) | Meta-analysis of 5 studies | 293 | [24] |
| | OS | HR 0.47 (0.35–0.62) | Meta-analysis of 17 studies | n/a | [23] |
| | DFS | HR 0.37 (0.22–0.63) | Meta-analysis of 8 studies | n/a | [23] |
| | 3-year OS (HPV-positive *vs* HPV-negative), % | 82.4 (77.2–87.6) *vs* 57.1 (48.1–66.1) | Original study | 323 | [28] |
| | 3-year progression-free survival (HPV-positive *vs* HPV-negative), % | 73.7 (67.7–79.8) *vs* 43.4 (34.4–52.4) | Original study | 323 | [28] |

n/a – not available.

A meta-analysis of Mehanna et al. [21] based on 269 studies (1970–2008) included 5396 patients with oropharyngeal cancer and 13,972 patients with non-oropharyngeal cancer. The overall pooled HPV prevalence in patients with oropharyngeal cancer was 47.7% (95% CI 42.9–52.5). Overall HPV prevalence in oropharyngeal cancer increased significantly over time in Europe ($p < 0.004$) and in North America ($p < 0.002$) from 40.5% (95% CI 35.1–46.1) in the 54 studies that recruited patients before 2000 to 64.3% (95% CI 56.7–71.3) in cohorts recruited between 2000 and 2004 (22 studies) and to 72.2% (95% CI 52.9–85.7) from 2004–2008 (4 studies) (see Table 1). These findings were consistent with the data obtained by Chaturvedi et al. [25]. Overall HPV prevalence differed by geographic region. The overall prevalence was 35.3% in Europe, 50.7% in North America and 32.2% in all other regions ($p = 0.008$). For oropharyngeal cancer, HPV-16 was positive in 1353 (95.7%) of 1414 cases.

Overall HPV prevalence in non-oropharyngeal cancer was 21.8% (95% CI 18.9–25.1), and there appeared to be statistically insignificant, declining trend over time. Thus, the pooled HPV prevalence was 22.2% before 2000 (95% CI 18.4–26.4), compared with 17.2% (95% CI 11.9–24.4) between 2000 and 2004 and 6.1% (95% CI 0.7–39) from 2004 to 2008. No statistically significant difference between the regions was found. The HPV-16 was detected in 1626 (73.9%) out of the 2199 HPV-positive patients with oropharyngeal cancer.

Gillison et al. [26] reported that the major risk factors for HPV-positive oropharyngeal cancer are: high lifetime number of both oral and vaginal sexual partners, early age of sexual debut, anogenital warts and the consumption of marijuana. HPV-negative oropharyngeal cancer is strongly associated with tobacco and alcohol consumption, older age and poor oral hygiene.

According to a meta-analysis of Ragin et al. [24], HPV-positive patients with oropharyngeal cancer had a 28% lower risk of dying compared with HPV-negative patients (HR 0.72; 95% CI 0.5–1.0) (see Table 2). Similar findings were published in a prospective analysis of data from clinical trials [27]. In order to evaluate other favorable prognostic factors associated with HPV status of the tumor, Ang et al. [28] analyzed survival rates of patients with oropharyngeal squamous cell carcinoma. A total of 63.8% of patients with oropharyngeal cancer (206 of 323) had HPV-positive tumors, and 198 (96.1%) of 206 were positive for HPV-16. Kaplan — Meier analysis revealed that HPV-positive cancer patients had better overall and DFS compared with HPV-negative patients ($p < 0.001$). 3-year OS was 82.4% (95% CI 77.2–87.6) in HPV-positive patients and 57.1% (95% CI 48.1–66.1) in HPV-negative patients. The 3-year DFS rates were 73.7% (95% CI 67.7–79.8) and 43.4% (95% CI 34.4–52.4), respectively.

In the multivariable analysis, the age, race, performance status, tumor stage, nodal stage, and number of pack-years of tobacco smoking were also significant determinants of the OS and DFS.

Tumors were evaluated for the expression of not only HPV, but also for p16, a known biomarker of HPV infection. The presence of HPV and p16 expression in tumors were in good agreement ($\kappa = 0.80$; 95% CI 0.73–0.87). Using p16 expression as a stratification factor, the differences in the OS and DFS rates, that were consistent with those based on HPV status, were shown. Thus, the 3-year survival rate was 83.6% in patients with p16-positive expression and 51.3% (95% CI 41.5–61.0) in the patients with p16-negative expression.

Recursive-partitioning analysis showed that the HPV status of the tumor was the major determinant of OS, followed by the number of pack-years of tobacco smoking and then nodal stage for HPV-positive tumors, or tumor stage for HPV-negative tumors.

In a meta-analysis by O'Rorke et al. [23], the authors examined the difference in OS between the HPV-positive and HPV-negative patients with oropharyngeal cancer and found that the pooled HR was 0.47 (95% CI 0.35–0.62) (see Table 2).

***The prevalence of HPV in laryngeal cancer.*** In a meta-analysis stratified by anatomical site, Kreimer et al. [18] reported that the prevalence of HPV in laryngeal squamous cell carcinomas was 24.0% (of a total of 1435 cases) and found HPV-16 positivity in 69.2% of cases and HPV-

18 positivity in 17.0% of cases. Meta-analysis by Torrente et al. [29] demonstrated the same HPV prevalence (24.0%; 95% CI 21.8–26.3) in laryngeal cancer patients. The authors paid attention to the fact that the overall HPV prevalence in normal laryngeal mucosa was not determined because sampling methods for HPV detection in healthy cells were not standardized, and prevalence estimates remained inconsistent.

The reported incidence of HPV infection in normal laryngeal mucosa has been as high as 19.0% [30–33]. These results suggest that the number of HPV-positive cancers observed might reflect the prevalence of latent HPV infections in the vocal cord epithelium.

Li et al. [34] performed a systemic review and meta-analysis based on 55 studies that tested the presence of HPV in laryngeal cancer patients. It was reported that HPV DNA was detected in 28.0% of the 2559 cases of laryngeal carcinoma (95% CI 23.5–32.9%) (see Table 1). The prevalence of high risk HPV types was significantly higher than that of low risk HPV types (26.6% *vs* 3.7%). The most common HPV type was HPV-16, with a summary prevalence of 19.8% (95% CI 15.7–24.6). The remaining most frequently identified HPV types were HPV-18 (6.2% of cases; 95% CI 4.0–9.5), HPV-33 (3.3%; 95% CI 2.1–5.1), HPV-31 (2.4%; 95% CI 1.3–4.4), HPV-6 (4.3%; 95% CI 2.4–7.7) and HPV-11 (2.3%; 95% CI 1.2–4.4).

Analyses stratified by cancer location showed that laryngeal cancers in the glottis region had the highest HPV prevalence (35.2%; 95% CI 28.2–42.8), followed by those in the supraglottic region (30.5%; 95% CI 24.0–37.8) and the subglottic region (27.5%; 95% CI 17.5–40.4). The microenvironment of the glottis might favor HPV infection, because the squamocolumnar junction in the ventricle is similar to the cervical transformation zone.

The estimated HPV prevalence among laryngeal cancers might vary with respect to the analyzed population, HPV detection methods and tumor characteristics. The prevalence of high risk HPV was found to be much higher than that of low risk HPV types.

Various HPV prevalences in laryngeal cancers were observed in different geographical regions (range; 25.6–35.6%). Studies from South America reported a higher rate of HPV infection compared with that observed in Asia, North America and Europe.

In a meta-analysis based on 12 case-control studies, Li et al. [34] estimated the association between HPV infection and the risk of laryngeal cancer. A total of 638 patients with laryngeal cancer and 419 controls were enrolled. It was shown that HPV infection significantly increased the risk of laryngeal cancer (OR 5.39; 95% CI 3.25–8.94), this OR was higher than that for oropharyngeal cancer (OR 4.3; 95% CI 2.1–8.9) and oral cancer (OR 2.0; 95% CI 1.2–3.4) demonstrated by Hobbs et al. [22].

The OR of individual types indicated differences in the magnitudes of the association for HPV-16 (6.07; 95% CI 3.44–10.7) and HPV-18 (4.16; 95% CI 1.87–20.04). For low risk HPV (16 and 11 types) the OR were not statistically significant.

When estimating survival, O'Rorke et al. [23] showed that patients with HPV-positive laryngeal squamous cell carcinoma had a 50% lower risk of mortality compared to HPV-negative patients (HR 0.5; 95% CI 0.33–0.77) (see Table 2).

## CONCLUSION

The prevalence of HPV was found to be greater in HNC than in dysplasia and HPV virus was most frequently detected in oropharyngeal cancer among the different anatomical sites, HPV-16 was the most prevalent HPV type in HNC.

In spite of tumor location, the risk of dying was lower and survival was higher in HPV-positive patients than in HPV-negative patients, indicating that along with the carcinogenic effect, HPV is able to modulate the disease and influence on the prognosis.

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