REVIEW ARTICLE

Human Papilloma Virus Infection in Head and Neck Cancer

Silke Tribius, Markus Hoffmann

SUMMARY

Background: The causal link between cervical cancer and human papilloma virus (HPV) is well known. It is now becoming clear that some types of squamous-cell carcinoma of the head and neck, particularly oropharyngeal carcinoma (OPC), are also linked to HPV infection. The development of vaccines against certain HPV genotypes has changed the management strategy for HPV-associated diseases of the uterine cervix. An analogous approach is now being considered for the prevention of HPV-associated diseases of the head and neck.

Method: We review pertinent articles retrieved by a selective search of the literature for phase II and III trials providing evidence about a possible effect of HPV status on the survival rates of patients with OPC. Seven trials fulfilled our search criteria: four phase III trials with retrospective HPV analysis and three phase II trials with retrospective and prospective HPV analysis.

Results: Patients with HPV-positive OPC survive significantly longer than those with HPV-negative OPC. Tobacco smoking has been identified as a negative prognostic factor in patients with either HPV-negative or HPV-positive disease.

Conclusion: The established treatment strategy for OPC in patients with and without the traditional risk factors (tobacco and alcohol consumption) is now being reconsidered in the light of what we have learned about the role of HPV infection. Ongoing and projected clinical trials with risk-factor stratification may soon lead to changes in treatment. Further study is needed to answer the question whether HPV infection in the head and neck region is carcinogenic.

► Cite this as

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The causal association between cancers of the anogenital tract, especially cervical cancer, and infection with human papilloma virus (HPV) is widely known among physicians in Germany (1). The importance of immunizing the population by means of vaccination programs against HPV in the management of HIV-associated disorders is crucial in this context. Recently, the role of HPV in the pathogenesis of different squamous cell cancers in the head and neck region, especially of oropharyngeal cancer, has started to attract increasing attention.

HPV-associated oropharyngeal cancers

More than 90% of malignant neoplasias in the head and neck area are squamous cell carcinomas. They are the sixth most common type of tumors globally (1, 2). The carcinogenic effects of alcohol and tobacco have been recognized as the main risk factors in patients with head and neck cancer and play a part in more than 75% of patients (3, e1). The carcinogenic substances in tobacco smoke actually trigger a mutation of the tumor suppressor gene p53 (4).

In the current Globocan statistic, head and neck cancers of the lip and oral cavity are in 15th place (2.1%), carcinoma of the larynx is in 20th place (1.2%), and oropharyngeal cancer in 22nd place (1.1%). In Germany, the estimated incidence for 2008 of head and neck cancer has been reported to be 15 583 cases and 6100 deaths (2).

The number of newly diagnosed cancers of the oral cavity, larynx, and hypopharynx as classic nicotine- and alcohol-associated cancers is falling in many countries, but a rising incidence of oropharyngeal cancers has been reported worldwide (*Figure 1*). Epidemiological studies give rise to the assumption that the explanation is that HPV-positive oropharyngeal cancers are increasing on the one hand, and that tobacco consumption is falling on the other hand (5). This has been shown to be the case for the United Kingdom (6, e2), the Netherlands (7), the US (8), Denmark (9), Sweden (10), and Germany (11).

More than 180 types of papilloma virus are known; 150 of these occur in humans. In an international meta-analysis, HPV16 was found in up to 86.7% (95% confidence interval [CI]: 82.6 to 90.1) of cancers of the oropharynx, 68.2% (95% CI: 64.4 to 71.9) of cancers of the oral cavity, and in 69.2% (95% CI: 64.0 to 74.0) of laryngeal cancers (cervical carcinoma: 58% [1, 12, 13,

Department of Radiotherapy and Radio-Oncology, University Medical Center Hamburg-Eppendorf; Dr. med. Tribius

Department of Otorhinolaryngology, Head and Neck Surgery, University Medical Center Schleswig-Holstein; PD Dr. med. Hoffmann

e3, e4]). HPV infections of the anogenital tract are considered sexually transmitted, and anogenital cancers are therefore considered sexually transmitted diseases. By contrast, an association between sexual behavior and HPV infection in the head and neck region has not been satisfactorily confirmed. In Germany, three studies have investigated the HPV-DNA prevalence in head and neck cancer and reported a proportion of 20–60% (14–16), whereas the HPV-RNA prevalence as an indication of the biological activity of the infection in oropharyngeal cancer is low and clearly below that of the DNA prevalence in non-oropharyngeal cancers. A recent population-based study from the US (n = 271) described a rise in HPV-positive oropharyngeal cancers by 225% (0.8/100 000 to 2.6/100 000) to more than 70% between 1984 and 2004. Over the same time period, the incidence of HPV-negative oropharyngeal cancers has fallen by 50% (17, e5). The authors predict that in 2020 the annual incidence of HPV-positive oropharyngeal cancers will be higher than that of cervical cancer, which illustrates the increasing importance of this infection, especially in terms of socioeconomic relevance. Because of the relatively low number of cases that allow this conclusion, the data should be interpreted with caution and will need to be confirmed in further epidemiological studies.

A consequence of the epidemiological shifts of oropharyngeal cancer is the fact that HPV-positive oropharyngeal cancers can be distinguished from HPV-negative tumors as a separate tumor entity in terms of etiology and clinical presentation. The US study mentioned earlier (18) showed that patients with HPV-positive cancers are regularly younger than patients with HPV-negative cancers, which is presumed to be a function of the average increase in lifetime oral sexual partners and an early start of this sexual practice. The risk factors for HPV-positive and HPV-negative cancers are summarized in the *Box* (19). Data from Germany or Europe that confirm an association between sexual behavior and HPV infections in the head and neck region are lacking.

This review article aims to describe what is currently known regarding the role of HPV-infections in patients with oropharyngeal cancers in Germany, and to identify the importance for clinical practice. At the same time, we wish to outline the relevance of HPV immunization of men and women with the aim of preventing head and neck disorders, and even cancers in the best-case scenario.

Method

The article is based on a selective literature search. The authors searched for phase II and III trials that included data regarding an association between HPV infectious status and survival rates of patients with locally advanced oropharyngeal cancers. Seven studies met the search criteria, four are phase III studies with retrospective HPV analysis (20–23), and three are phase II studies with initial or retrospective determination of HPV status (24–26). The results therefore come from

BOX

Risk factors for HPV-positive and HPV-negative oropharyngeal cancer

- HPV-positive oropharyngeal cancers
 - Number of oral sex partners
 - Many vaginal sex partners
 - Younger age at first sexual contact
 - Anogenital warts
 - Consumption of marijuana
- HPV-negative oropharyngeal cancers
 - Consumption of nicotine
 - Consumption of alcohol
 - Older age
 - Poor oral hygiene

HPV, human papilloma virus

homogenous, prospectively collected patient cohorts with clearly defined inclusion and exclusion criteria, such as age, tumor stage, and general health. The patients were treated in a standardized fashion and received follow-up care. The *Table* shows a detailed overview of the study designs and results of the studies that will be discussed in this article.

Results

Prospective studies comparing the disease course in HPV-positive and HPV-negative oropharyngeal cancers

Initial indications of an association between HPV and head and neck cancer were published as early as in the 1980s (27, e6). Since the publications by Gillison and colleagues and Lindel and colleagues (28, 29), which support the assumption that HPV-associated head and neck cancer is an entity of its own, clinical studies have increasingly been published that investigated the therapeutic results in dependence of the tumor's HPV status (3). These studies show that patients with HPV-positive cancers have a much better prognosis. The explanation proffered for the survival advantage is better responsiveness to radiotherapy and chemotherapy, and thus better locoregional control (5). The underlying molecular mechanisms for a raised sensitivity to radiotherapy are currently not known and are the subject of intense research.

The Eastern Cooperative Oncology Group (ECOG) 2399 study

The ECOG 2399 study was one of the first studies to investigate the treatment results of patients with oropharyngeal or laryngeal cancers at stages III/IV in dependence on the tumor's HPV status (24). The patients received two cycles of paclitaxel and carboplatin, and if they responded well this was followed by

FIGURE 1

Trend for the incidence rates of oropharyngeal cancers in men in Germany, the United Kingdom, and the United States between 1996 and 2005

Data sources: Germany: analysis from the Thuringian cancer registry database (oropharyngeal cancers), from (11); Guntinas-Lichius O, Wendt T, Buentzel J, et al.: Head and neck cancer in Germany: a site-specific analysis of survival of the Thuringian cancer registration database. *J Cancer Res Clin Oncol* 2010; 136: 55–63, reproduction of the figure with permission from Springer Science and Business Media). (UK [all head and neck tumors; 22.5% of head and neck tumors in men in 2007 were oropharyngeal cancers]: Cancer Research UK [6]). US data: SEER 13; <http://seer.cancer.gov/faststats> [8])

radiochemotherapy with paclitaxel. Of the 105 patients included in the study, 60 (66%) had oropharyngeal cancers whose tissue was examined for HPV-DNA and p16^{INK4A} expression (a cellular tumor suppressor protein that is often overexpressed in oropharyngeal cancer because of HPV activity). 38 of these patients (63%) were positive for HPV-DNA and 22 (37%) were negative for HPV-DNA. Overall survival at 2 years was significantly better in patients with HPV-DNA positive cancers compared to patients with HPV-negative cancers (95% versus 62%; $p = 0.005$).

TAX 324

Posner and colleagues also investigated the treatment result retrospectively relative to the HPV-DNA status in the randomized phase III study TAX 324 (20). Of a total of 264 patients with oropharyngeal cancer, tumor specimens for the purpose of HPV diagnostic testing were available from 111 patients (42%). Of these, 56 (50%) tested positive for HPV-DNA and 55 (50%) tested negative. Patients with HPV-DNA positive tumors had comparable TNM stages to HPV-DNA negative patients but were younger (54 versus 58 years; $p = 0.02$), had an ECOG performance status of 0 (77% versus 49%; $p = 0.003$) and mostly small primary tumors (T1/2; 49% versus 20%; $p = 0.001$).

Two-year overall survival was significantly better in HPV-DNA positive patients (89% versus 48%; $p = 0.0001$; Figure 2a). After 2 years, 83% of patients

with HPV-DNA positive tumors and 35% of patients with HPV-DNA negative tumors were free from recurrences ($p < 0.0001$; Figure 2b).

Trans Tasman Radiation Oncology Group (TROG) 02.02

The prognostic importance of HPV-DNA status has also been evaluated in the randomized phase III Head-START study, in which patients were treated with radiochemotherapy (cisplatin) with or without tirapazamine (21). Of the 861 patients who were included in the study, 172 had oropharyngeal cancers from which tissue specimens were available for HPV and p16^{INK4A} analysis. 106 patients (61.2%) tested positive and 79 (45.9%) tested negative for p16^{INK4A}. The two year survival rate was significantly better in the group of patients with for p16^{INK4A} overexpression than in patients with for p16^{INK4A}-negative tumors (91% versus 74%; hazard ratio 0.36; 95% CI 0.17 to 0.74; $p = 0.004$).

Radiation Therapy Oncology Group (RTOG) 0129

Another study is the randomized phase III study of RTOG 0129, in which patients with locally advanced head and neck cancers were treated with simultaneous radiochemotherapy (cisplatin 100 mg/m² body surface area) according to a conventional or accelerated fractionation scheme (22). Ang and colleagues described retrospectively the HPV-DNA status of a total of 323 patients as the most important prognostic marker for patients with oropharyngeal cancer (64% of the total study population, $n = 206$). As was also reported by Posner and colleagues, the patients with HPV-DNA positive tumors were younger in the RTOG 0129 study; their general health was better, they were mostly male and of Caucasian origin. Three-year survival for patients with HPV-positive tumors was 84.2%; it was 57.1% for patients with HPV-negative tumors ($p < 0.001$). The three-year rate for locoregional control was also significantly better in the group of HPV-positive patients ($p < 0.001$).

The authors emphasize that smoking tobacco had a negative effect on the disease course in both groups (19, 22). Depending on four risk factors, the risk of patients to die from their tumor has been categorized as low, intermediate, and high: HPV-DNA status, pack years (definition of pack years: the number of consumed packs of cigarettes per day multiplied by the number of years for which consumption was maintained); T- and N-stage. The authors conclude from these results that smoking tobacco and a more advanced tumor stage counteract at least in part the better therapeutic response in HPV infection, which means that the mortality risk in such patients rises to a comparable level as that of HPV-negative non-smokers.

Danish Head and Neck Cancer Study Group (DAHANCA) 5

195 patients who had received radiotherapy alone were randomized into the placebo arm of this study (23). HPV status was determined in 156 patients, of whom 74 (47%) had oropharyngeal cancers. Of these, 24 (32%) were HPV-positive and 50 (68%) were

TABLE

Prospective studies that compared the disease course of patients with HPV-positive and HPV-negative oropharyngeal cancers (prospective and retrospective)

Study	Design	n	Study period	Tumor localization	Tumor stage	Test method	Therapy	Result
TAX324 Posner et al. 2011 (20)	Randomized phase-III study, retrospective HPV analysis	111	1999–2003	Oropharynx	T1/2 (35%) T3/4 (65%)	E6/E7 PCR	TPF or PF, followed by carboplatin + RT	Overall survival better in HPV-positive vs -negative patients (HR 0.20; $p < 0.0001$)
TROG 02.02 Rischin et al. 2010 (21)	Randomized phase-III study, retrospective HPV analysis	206	2002–2005	Oropharynx	T1/2 (28%) T3/4 (72%)	p16 IHC, ISH	RT + cisplatin ± tirapazamine	2-year survival better in patients with p16 ^{INK4A} -positive vs -negative tumors (HR 0.36; $p = 0.004$)
RTOG 0129 Ang et al. 2010 (22)	Prospective phase-III study, retrospective HPV analysis	721	2002–2005	Oral cavity (6%) Oropharynx (60%) Hypopharynx (8%) Larynx (26%)	T2 (23%) T3 (45%) T4 (31%)	ISH	Cisplatin + accelerated RT or normofractionated RT	3-year survival better in patients with HPV-positive vs -negative tumors (HR = 0.38; $p < 0.001$)
ECOG 2399 Fakhry et al. 2008 (24)	Prospective phase-II study	96	NA	Oropharynx (65%) Larynx (35%)	T2 (43%) T3/4 (57%)	p16 IHC, ISH	Paclitaxel + carboplatin followed by paclitaxel + RT	2-year overall survival better in patients with HPV-positive vs -negative tumors ($p = 0.005$)
DAHANCA 5 Lassen et al. 2009 (23)	Randomized phase-III study, retrospective HPV analysis	156	1986–1990	Oropharynx (47%) Larynx (30%) Hypopharynx (13%) Nasopharynx (10%)	T1/2 (46%) T3/4 (54%)	p16 IHC, ISH	RT	Locoregional control ($p = 0.0005$) and overall survival ($p = 0.0003$) significantly better in p16 ^{INK4A} -positive patients
Gilbert et al. 2012 (25)	Prospective phase-II study	42	2007–2009	Oropharynx (71%) Other (29%)	T1/2 (50%) T3/4 (50%)	p16 IHC	Pemetrexed + oxaliplatin	Median survival 20.3 months for p16 ^{INK4A} -negative and 34.1 months for p16 ^{INK4A} -positive patients ($p = 0.039$)
Jo et al. 2009 (26)	Prospective phase-II study	24	2000–2003	Oropharynx (58%) Other (42%)	T1/2 (54%) T3/4 (46%)	E6/E7 PCR	Docetaxel + cisplatin and 5-FU/LV followed by surgery+ RT	Trend for better overall survival (HR = 0.14; $p = 0.10$) in HPV-positive vs -negative patients

HPV, human papilloma virus; CRT: radiochemotherapy; TPF: docetaxel + cisplatin + 5-fluorouracil; IHC: immunohistochemistry; ISH: in-situ hybridization; NA = not available; PCR: polymerase chain reaction; PF: cisplatin + 5-fluorouracil; LV: leucovorin; RT: radiotherapy. HR: hazard ratio

HPV-negative. Survival rates were significantly better in patients with p16^{INK4A}-positive tumors (5-year survival: 58% versus 28%; $p = 0.0005$).

Two further, single-center, prospective, phase II studies that investigated the efficacy of induction chemotherapy dependent on the patient's HPV status also showed an advantage for patients with HPV-positive tumors:

The study reported by Gilbert and colleagues (25) included 47 patients, 27 (57%) of whom had oropharyngeal cancers. Patients with HPV-positive tumors showed a better response to treatment and their mean survival was 34.1 months, compared with 20.3 months for patients with HPV-negative tumors ($p = 0.039$).

Jo and colleagues published a further phase II study (26). They investigated a smaller patient cohort

($n = 31$) with 14 (45%) oropharyngeal cancers, of whom 13 were p16^{INK4A}-positive. Patients with HPV-positive tumors had better overall survival, but this did not reach statistical significance. It is worth mentioning that this was the only study in which the surgery that followed induction chemotherapy was part of the therapy.

Discussion

The increasing incidence of oropharyngeal cancers worldwide is often explained with the similarly increasing prevalence of HPV infections in the head and neck region (31). Patients with HPV-positive cancers differ from patients whose carcinogenesis is due to classic risk factors, such as consumption of nicotine and alcohol. HPV-positive cancer patients seem to be younger

Kaplan-Meier curves for (a) overall survival and (b) progression-free survival for patients with HPV-DNA positive and HPV-DNA negative tumors who were treated in the TAX 324 study. HPV=human papillomavirus. From: Posner et al.: Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial. *Ann Oncol* 2011; 22: 1071–7 (20). Reproduction with permission from Oxford University Press

and have better treatment results after radio(chemo)therapy (5). The prevailing opinion is increasingly that such patients should be referred to individual therapeutic regimens that are adapted to their HPV-status, which differs from therapeutic strategies for HPV-negative patients and those for patients with the classic risk factors.

The current therapeutic approach for locally advanced head and neck cancers is multimodal and consists of a combination of surgery and

radio(chemo)therapy or radioimmunotherapy (EGFR-antibody cetuximab). The risk of complications has increased fivefold with the more intensive treatment regimens (32). Especially in patients with HPV-positive oropharyngeal cancers with a very good prognosis, the value of intense therapy and its expected negative long-term sequelae, especially in terms of quality of life, is understandably the subject of critical scrutiny. The hope is that all future prospective studies of the treatment of head and neck cancers, especially oropharyngeal cancers, will consider the risk factors shown by Ang and colleagues and stratify these accordingly (22).

The global introduction of prophylactic HPV vaccination programs has resulted in a reduced incidence of cervical intraepithelial neoplasias (CIN) of stages I–III in vaccinated women compared with unvaccinated women. This supports the hope placed on the vaccine, that it will contribute to reducing cervical and uterine cancers. No studies assessing the efficacy of the vaccine regarding the reduction of HPV-positive disorders of the head and neck region have been undertaken as yet.

Vaccination using the quadrivalent HPV-4 vaccine (33) and the bivalent vaccine (34) confers effective protection against HPV infections on women. For the quadrivalent HPV-4 vaccine, effectiveness has been confirmed for men (35, e7), and the vaccine has been licensed in the US beyond its previous approval for preventing cervical, vaginal, and vulvar cancers in women to include use in men to protect against anogenital warts. In Europe, on the other hand, the quadrivalent HPV-4 vaccine is licensed only for girls for the prevention of cervical cancer and other disorders caused by HPV strains 6, 11, 16, and 18, whereas the bivalent vaccine has license approval for premalignant and malignant cancers of the cervix. The Standing Vaccination Committee at the Robert Koch Institute recommends for Germany that girls aged 12–17 should be vaccinated, before their first sexual intercourse. HPV vaccination has therefore been included in the national vaccination program for girls.

The vaccination rate in Germany is estimated at 25–45% (e8) of patients in the target group who have received three doses of the vaccine, which is low. The reasons for this low uptake have not been explored in Germany; in the US, however, resistance among parents to having their daughters immunized against a potential sexually transmitted infection and reasons of expense in case the health insurers do not cover the vaccination have had a negative effect on people's readiness to be vaccinated. In contrast to Germany, uptake in the United Kingdom—three doses of the bivalent vaccine—is high. An explanation for this is the national immunization program in schools, which has been in force since 2008, which offers the vaccine to all girls aged 12–13 on an opt-out basis. Additionally, a catch-up program allows for the immunization of all girls up to the age of 18. More than 84% of girls aged 13–14 in the UK have by now received all three doses of the vaccine (e9).

In Germany, the prevalence of HPV infections of the cervix/uterus in women with normal Pap tests is currently reported to be 6.3% (1, 36, 37). If the rate of HPV infection in Germany rises to a similar extent as in the US, it will be important to intensify the acceptance of the vaccine among 12–17 year old girls and open up the discussion to include at least young males at risk in the program (38–40).

Conclusion

Treatment strategies for cancers of the oropharynx are currently being put to the test because of the prognostic importance of HPV infection on the pathogenesis and disease course in patients with and without classic risk factors (such as nicotine and alcohol). If future clinical studies consider HPV status and smoking status in addition to the classic risk factors, the results of such studies could prompt a change to the current therapeutic strategies in Germany. In our opinion, awareness of the importance of HPV vaccination—with the aim of lowering the incidence of HPV-related disorders—should be raised in Germany. To this end, better information about HPV needs to be made available to the population and to physicians, and this should include the range of associated disorders and the option of having the HPV vaccine.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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KEY MESSAGES

- There are indications that the carcinogenesis of oropharyngeal cancer as a result of infection with human papilloma virus (HPV) is a possibility.
- HPV-positive oropharyngeal cancers are a separate tumor entity and carry a better prognosis than squamous cell cancers of the head and neck region, which are associated with the classic risk factors. Smoking has a negative effect on survival independently of HPV status.
- HPV vaccination lowers the incidence of benign and premalignant lesions of the anogenital tract, possibly also of HPV-associated diseases of the anogenital tract and oropharynx.
- Extending the recommendation for vaccination to include men entails an opportunity to lower the incidence of HPV-associated disorders in the male population.
- Patients with head and neck cancers without classic risk factors should be referred to specialized centers even for the diagnostic evaluation.

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Corresponding author

Dr. med. Silke Tribius
Klinik für Strahlentherapie und Radioonkologie
Universitätsklinik Hamburg-Eppendorf
Martinistr. 52
20246 Hamburg, Germany
tribius@uke.uni-hamburg.de

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REVIEW ARTICLE

Human Papilloma Virus Infection in Head and Neck Cancer

Silke Tribius, Markus Hoffmann

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