Published in final edited form as:

Curr Oncol Rep. 2014 March ; 16(3): 375. doi:10.1007/s11912-013-0375-8.

Counseling the Patient with Potentially HPV-Related Newly Diagnosed Head and Neck Cancer

John P. Finnigan Jr, BS^a and Andrew G. Sikora, MD, PhD^{a,b,c,d,e}

^aIcahn School of Medicine at Mount Sinai: Department of Otolaryngology

^bIcahn School of Medicine at Mount Sinai: Department of Oncologic Sciences

^cIcahn School of Medicine at Mount Sinai: Department of Immunology Institute

^dIcahn School of Medicine at Mount Sinai: Department of Dermatology

^eIcahn School of Medicine at Mount Sinai: Department of Tish Cancer Institute

Abstract

The recent emergence of a clinically distinct subset of head and neck cancers (HNC) caused by infection with the human papillomavirus (HPV) necessitates critical reevaluation of the existing counseling paradigm for patients with newly diagnosed HNC. Herein we propose a structural framework for patient counseling in which HPV testing is incorporated and the impact of HPV-status is discussed in the context of multiple medical and psychosocial domains. We strive to maintain a balance between making recommendations based on the best available scientific evidence and acknowledgment of uncertainty for both patients and providers. We anticipate that both the standard-of-care diagnostic workup and treatment, and counseling guidelines for these patients will change rapidly in the years ahead, as data from ongoing and planned prospective clinical trials become available.

Keywords

Head and neck cancer; Oncology; Human papillomavirus; HPV; Counseling; Diagnostic testing; Potentially HPV-related newly diagnosed head and neck cancer; HPV-related

Introduction

This article is intended to serve as a guide for clinicians treating patients with newly diagnosed head and neck cancer (HNC) potentially related to the human papillomavirus (HPV). This patient population includes patients with tumors of the oropharynx, primarily involving the tonsil and base of tongue, or tumors of unknown primary site with spread to

Contact: Andrew G. Sikora, One Gustave L. Levy Place, Box 1189, New York, New York, 10029, Office Phone: (212) 824-8431 (x58431), andrew.sikora@mssm.edu, John P. Finnigan, Jr., john.finnigan@mssm.edu.

Compliance with Ethics Guidelines

Conflict of Interest

John P. Finnigan and Andrew G. Sikora declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

the cervical lymph nodes. In light of a large and ever-expanding body of literature suggesting that HPV-mediated Head and Neck Cancers (HPV-HNC) have a distinct etiopathogenesis and clinical behavior when compared to “classical” tobacco/alcohol associated HNC, viral testing is an emerging component of the diagnosis and staging of tumors arising in certain anatomic sub-locations within the head and neck. Although current staging [1] and treatment guidelines do not yet distinguish between viral and non-viral HNC, this will change as guidelines are updated to reflect the existing scientific evidence, and as the results of clinical trials in this patient population become available. Absent formal recommendations from advisory bodies to guide the integration of HPV-testing into clinical practice, we propose a counseling strategy that is patient-centered and evidence-based, and that also acknowledges uncertainty where it exists, particularly when uncertainty may have implications affecting prognosis and therapeutic decision making. As part of the patient counseling process, it is important for providers involved in the care of patients with potentially HPV-mediated HNC to familiarize themselves with the aspects of this disease that differentiate it from non HPV-mediated HNC.

Emergence of HPV-HNC as a Distinct Clinical Entity

Squamous cell carcinoma of the head and neck (HNSCC) arises from the mucosal surfaces of lip, oral and nasal cavities, as well as the nasopharynx, oropharynx, and larynx. As a group, squamous cell carcinomas are the fifth most common cancer subtype worldwide [2, 3]; however, incidence rates vary considerably by region, with foci of high incidence in Southeast Asia, and Eastern Europe [4]. Eight-five to ninety percent of head and neck cancers are squamous cell carcinomas [5], and classically HNSCC was associated with exposure to alcohol and tobacco products [6], risk factors that have been casually associated with the disease [7, 8]. In addition, exposure to both agents in combination may act synergistically to increase risk significantly over that associated with either agent in isolation [9]. In the past, tobacco and alcohol accounted for upwards of 75–90 % [10] of HNSCC cases. The remaining 10 % of cases lacking attributable exposure were believed to be due to other minor risk factors, including diet [11] and/or micronutrient deficiencies [12], as well as poor oral hygiene [13] or a lack of consistent access to dental care [14]. It has also been shown that family history of head and neck cancer contributes to disease risk [15], suggesting the existence of genetic risk-modifying factors. In addition, individuals with heritable cancer risk or cancer-susceptibility syndromes, such as Li-Fraumeni syndrome, Fanconi’s anemia and Bloom-Machacek syndrome, are known to be at increased risk [16, 17].

The incidence of head and neck squamous cell carcinoma within the United States, particularly of the oral cavity, hypopharynx and larynx, rose steadily before reaching a plateau in the late twentieth century—an observation attributed to changes in the prevalence of alcohol consumption [18] and tobacco-use behaviors [19]. Thereafter, a significant decline in the disease incidence at these subsites was observed [20, 21]. However, during the same 20-year period, incidence of oropharyngeal cancer—particularly within the pharyngeal tonsil and base-of-tongue—increased dramatically both in the United States [22] and Europe [23], in dramatic contrast to the decreased or stable incidence of HNSCC at other oral and oropharyngeal subsites [24].

Demographics of this emergent population also differed substantially from those of patients with “classical” HNSCC, with less frequent history of alcohol and/or tobacco exposure [25], and patients were commonly white men of upper-mid social strata [26–28], presenting with lesions of the oropharynx an average of 3–5 years earlier [29] than the average “classical” head and neck cancer patient. An association between the human papillomaviruses and head and neck cancer was proposed based on unique epidemiologic and pathological features common to the patient cohort.

Critical to this association was the observation that within this new cohort of head and neck cancer patients, there was an increase in the prevalence of behavioral risk factors associated with transmission of sexually transmitted infections, including HPV [30]. This included an earlier age of sexual debut [31], increased numbers of total lifetime sexual partners, as well as an increase in the prevalence of sexual behaviors in which there was oro-genital contact [32]. Shortly thereafter, it was demonstrated that a history of oral HPV infection frequently preceded a later diagnosis of head and neck squamous cell carcinomas [33, 34]. Data from a number of large population-based studies show that 20–25 % of head and neck cancer patients show some evidence of HPV exposure [35]; as a group, these patients are significantly more likely to have been exposed to HPV than appropriately matched controls [36, 37]. Even more striking was the association between HPV infection and cancers of the oropharynx [25, 38], in which evidence of exposure is even more prevalent than sites elsewhere within the head and neck [9]. Evidence of HPV exposure is found in over 50–75 % of patients among this subset of head and neck cancers [39].

Virology and Molecular Biology of Oncogenic HPV

HPV are a family of epitheliotrophic DNA viruses, of which there are greater than 120 known genotypes. Over 40 genotypes are known to possess a tropism for mucosal surfaces [37], particularly within the human anogenital tract where they are nearly ubiquitous amongst sexually active adults [40]. The virus is known to be transmitted via direct contact with infected cutaneous or mucosal surfaces [41]. HPV is widely appreciated to be a sexually transmitted virus, with a large body of literature describing genital-genital, digital-genital, and oro-genital transmission. Cross-sectional data suggests that high-risk HPV genotypes are present in the saliva of 1–3 % [42] of adults, and yet precisely how HPV is introduced into the upper aerodigestive tract is a subject of some debate [4]; however, oro-genital [27] and even oro-oral transmission have been described [43]. It is also unclear what features of the oropharynx predispose it towards persistent viral infection resulting in transformation [37], and which features distinguish it from other sites within the head and neck in which HPV-mediated disease is rare. It is also widely appreciated that a subset of HPV are carcinogenic in humans, secondary to their causal association with a number of anogenital cancers in humans, including invasive cervical cancer, for which HPV is believed to be necessary for malignant transformation [38, 44].

Clinically relevant HPV genotypes are frequently subdivided into two groups based upon their capacity to induce transformation of normal squamous epithelial cells [45]. Those that are most commonly associated with benign papillomatous disease form the low-risk subgroup. Conversely, those that are associated with human malignancies and are capable of

inducing transformation in vitro are classified as high-risk—the group being typified by genotypes 16, 18, 31, 33, and 35 [46]. Genotypes 16 and 18 in particular are known to be capable of inducing transformation in both the genital, and upper aerodigestive tract [47]. In tumors bearing viral DNA, HPV16 is the most prevalent genotype [48], comprising upwards of 85–97 % of cases [26]. Genotype 18 is found both independently and in combination with HPV16 in approximately 2–5 % of cases—the other remaining high-risk genotypes are found in a minor fraction of cases [37].

HPV-HNC appear to have a distinct molecular phenotype, as defined by gene expression profiles [49], patterns of large-scale chromosomal abnormalities [50], copy number variation [51], and the absolute number of somatic abnormalities identified in a given tumor [52, 53]. More generally, HPV-positivity is inversely associated with molecular markers of poor prognosis [54, 55]. Establishing a mechanism whereby viral infection might conceivably lead to cancer in humans was necessary to demonstrate causality, and in the setting of HPV-associated cancers, the viral early proteins E6 and E7 are believed to contribute both to tumor initiation and maintenance of the malignant phenotype in HPV-HNC [56–60].

While it is recognized that expression of viral E6/E7 are necessary criteria for transformation, it is unknown whether the molecular rearrangements induced by the virus are sufficient to cause disease. Both proteins are frequently detected within the oropharynx of affected individuals [27] and within the body of HPV-associated tumors [41]. Considered “viral oncoproteins,” E6 and E7 are believed to inactivate p53 [61, 62] and the retinoblastoma (pRb) gene product [63], respectively, both of which then become targets for degradation [64, 65]. Loss of these critical regulatory proteins leads to dysfunction within multiple cellular pathways, including cell-cycle regulatory control, DNA damage repair, apoptosis [66], and reactivation of host telomerase [67].

HPV Testing in HNC: Rationale for Testing and Patient Counseling

As stated previously, published treatment guidelines do not yet distinguish between viral and non-viral HNC, and therefore do not consider HPV-testing a regular component of diagnosis, staging or treatment planning. However, it is the opinion of the authors that HPV-testing is sufficiently useful to justify routine use in high-probability cases, because of the significant impact of HPV status on patient prognosis. If one also considers the importance of stratifying patients by HPV-status when designing clinical trials, HPV testing is essential for patients to have the option of enrolling in existing or future trials. Thus, we consider HPV testing for potentially virally related HNSCC an emerging standard-of-care that is recommended for all patients presenting with HNSCC at a potentially HPV-related subsite (tonsil, tongue base, and—where feasible—lymph nodes from HNSCC of unknown primary). Depending on the institution, this usually involves identification of viral DNA by polymerase chain reaction (PCR) or in situ hybridization (ISH). While immunohistochemical staining for the cellular p16 protein is strongly upregulated in the majority of HPV-related oropharyngeal cancer (OPC), and can be used as an additional validation of HPV status, it is best used as an adjunct to, and not a replacement for, direct HPV testing (Table 1).

Despite the current lack of guidelines regarding pre-test and post-test counseling, once testing is undertaken, the potential emotional impact of the information provided—both in terms of impact on patient prognosis and identification of sexually transmitted etiology—suggests that counseling should be provided. While little literature addresses the need for counseling directly in the subset of patients with HPV-HNC, we may consider relevant examples from similarly affected populations (reviewed comprehensively in [68]). In patients with HPV-unrelated HNC, disease-related anxiety and emotional distress are both common and known to negatively affect quality of life [69, 70]. However, it appears that interventions designed to mitigate disease-associated distress are underutilized or ineffective, as patients frequently report worsening anxiety during the course of their treatment [71]. Consider also that women with HPV-associated cervical dysplasia or invasive carcinoma may suffer from feelings of confusion, fear, and guilt in response to their diagnosis [72, 73]. It has also been demonstrated that feelings that contribute to self-blame and isolation may negatively affect information-seeking behaviors during physician–patient interactions, and may impair patient adherence to treatment recommendations [74]. Finally, a questionnaire-based study of patients with HPV-HNC treated at a major cancer center revealed significant gaps in patient understanding of HPV’s contribution to their cancer, transmission of the virus, and potential precautions [75]. Over one-third of patients in this study specifically desired more information about HPV from caregivers. Thus, counseling should address the major areas of patient concern: HPV biology, HPV transmission and transmissibility, impact on prognosis and treatment planning and post-diagnosis harm reduction. It is important to acknowledge that our current knowledge base is unable to answer all of the questions that a patient may have, and to reiterate that this is a field of active and ongoing research. Counseling strategies must provide ample opportunities for the patient to identify areas of concern and to ask questions of the provider.

Specific Aspects of Patient Counseling: Biology, Transmission and Transmissibility

Before HPV-testing is performed, the provider should offer a brief discussion of the potential mechanisms of carcinogenesis (viral vs. environmental), emphasizing that while HPV-related cancer has a generally better prognosis, both types of cancer are treatable. It is also important that before HPV testing is performed, patients have a clear understanding of what information will be provided and its potential implications, in order to decide who they are comfortable sharing this information with. If a patient’s test results are consistent with HPV-HNC, the provider should engage in a frank discussion of the most common modes of transmission and the natural history of the virus. While the information about biology of HPV presented above is likely more detailed than necessary for most patients, many patients may be quite unfamiliar with the mechanisms by which viruses can cause cancer, or even what a virus is. The clinician should assess both the patient’s initial knowledge base and desire for detailed information to determine in what depth to explain the topic. It is also important for the clinician to understand the patient’s starting assumptions about HPV and HPV-related cancer, since these topics are often sensationalized or misrepresented by the lay media.

With regard to viral transmission, the patient should be made aware that the virus is very common [42], and is known to be transmitted via contact with infected body areas [41]. This includes vaginal, anal and oral sexual behaviors; oro-oral contact, which is taken to include deep “French-style” kissing has also been implicated [43]. Most infections are asymptomatic, and therefore an individual in the community may not know that he/she is infected, and therefore capable of transmitting the virus to others. Epidemiologic evidence suggests that there is a significant “latent period,” between infection and the onset of HPV-associated cancers, which makes it impossible to conclusively define when, where, and from whom any individual acquired a high-risk HPV. The vast majority of HPV infections are transient, and most healthy individuals will effectively clear the virus. However, there may be significant person-to-person variability in the time required complete viral clearance.

Despite the fact that HPV-HNC is causally related to an acquired infectious agent, it is important to communicate clearly that the patient’s cancer is not transmissible by any known mechanism. The patient should be made aware that his or her partner is potentially at increased risk of subsequently developing HPV-HNC or other HPV-related cancers; however, the exact magnitude and even the certainty of this risk is unknown. There is currently no evidence to suggest behavioral modification to decrease the risk of transmission, and there are no recommendations or regulations requiring partner notification in documented cases. However, in some instances, the patient or his/her partner may inquire about means to further decrease the risk of viral transmission, including the utility of existing vaccines. Since most partners of patients with head and neck cancer have already been exposed to HPV in the past, there is currently no recommendation for use of prophylactic HPV vaccines in partners who do not meet conventional CDC guidelines [76–78]. However, while not supported by specific clinical studies, in the absence of other preventative measures, the partners of patients with HPV-HNC may find it reassuring to undergo periodic surveillance exams of the oral cavity and oropharynx, and should be encouraged to follow any age-appropriate and gender-appropriate established screening guidelines (such as for cervical cancer) where applicable.

Specific Aspects of Patient Counseling: Prognosis and Treatment Planning

Historically, the prognosis of patients with newly diagnosed head and neck cancer has been dependent upon the following criteria: age at the time of diagnosis [25]; response to treatment (for those patients treated with nonsurgical therapy); and for patients treated with surgery, radiologic and surgical-pathologic criteria used to assess disease stage at the time of treatment and the completeness of surgical excision [44], including: tumor size, extent of nodal metastases within the lymphadenectomy specimen, and extent of locoregional and neurovascular invasion. However, it has become increasingly clear that HPV-positivity is also an independent prognostic factor associated with significantly improved prognosis in patients with newly diagnosed HPV-HNSC [79, 80]—an observation that is relevant regardless of the anatomic location of the tumor within the oropharynx [81], histologic grade of the primary lesion [35], or clinical stage at the time of diagnosis [82, 83]. Specifically, it appears that HPV-positivity is associated with significantly reduced risk of recurrence [84] and improved disease-free and progression-free survival [26, 35, 39]. HPV-positivity is also associated with a significant reduction in disease-specific mortality [25, 39], and all-cause

mortality [26]. All-told, HPV-positivity—as determined by direct measures, or inferred via p16-status—is independently associated with a 40–50 % reduction in the risk of death from all causes when compared with HPV-unrelated OPC [85–88]. Improved prognosis within this cohort of patients appears to be attributable to enhanced treatment responsiveness, although decreased risk of second primary cancers may also play a role [89]. An expanding body of literature suggests that HPV-HNC, relative to HPV-unrelated disease, is more responsive to primary surgical therapy [90], as well as several adjuvant radiotherapy [10, 88] and/or chemoradiotherapy protocols [91, 92]. A number of hypotheses have been suggested as to why HPV-HNC appears to respond favorably to treatment, but at this time none have been confirmed [29, 93].

Due to the anatomic complexity of the head and neck region and the aggressive nature of HNSCC, multi-modality therapy is often required. Combination therapies, such as chemoradiation, are associated with risk of serious morbidity, including short-term and long-term complications due to sacrifice or dysfunction of structures critical for normal speech, deglutition, and maintenance of the upper airway. As the association between HPV and head and neck cancers has only recently gained wide acceptance, there are as yet few prospective therapeutic clinical trials that have stratified patients based upon HPV-status. In the absence of these data, treatment guidelines do not yet distinguish between HPV-mediated and unrelated disease. However, this does not mean that the diagnosis of HPV-HNC has no bearing on treatment decisions, which are made by consensus after discussion between the patient and caregivers. While providers should not advocate for treatment de-intensification on an ad hoc basis in the absence of clinical trials supporting this approach, a patient who is knowledgeable about the uniquely good treatment response and survival associated with HPV-HNC will bring this understanding to the assessment of risks and benefits involved in choosing between different treatment options [94]. This highlights the importance of ensuring HPV-HNC patients have a thorough and realistic understanding of the unique epidemiologic and clinical characteristics of their disease. Conversely, patients with HPV-unrelated HNSCC should be reassured that their cancer is treatable, and be given a realistic assessment of their prognosis.

Specific Aspects of Patient Counseling: Harm Reduction

It is clear that behavioral risk factors play an important role in the development of head and neck cancer. Perhaps most important amongst the known risk factors, especially with regards to HPV-HNC, is tobacco use. It is clear that historical and ongoing tobacco use affects clinical outcomes in patients with HPV-HNC. A clear dose-response relationship exists between the intensity and duration of tobacco exposure and individual risk of developing HNC. Additionally, tobacco-use behaviors at the time of diagnosis, or tobacco use that continues during treatment in patients with HPV-HNC, are independently associated with worse prognosis [95, 96], particularly in response to adjuvant radiotherapy [97]. Counseling strategies should therefore incorporate an assessment of tobacco exposure at the time of diagnosis, and ongoing environmental factors contributing to maintenance of this behavior [98]. It is well established that brief, intensive, counseling sessions delivered by a physician can be effective in reducing tobacco use [99, 100]. They should explain the risk associated with continued tobacco use, with regards to disease-specific and all-cause

mortality [¹⁰¹]. Relapse events are common, and repeat approaches by the provider are often required. The patient may also require additional support, and the provider must be prepared to discuss existing behavioral, pharmacologic, and combinatorial treatment regimens, or make appropriate referrals [^{102, 103}].

Patients should be counseled that post-therapy follow-up care is an essential part of their treatment, and that all patients are at risk of recurrence or second primary cancers, despite favorable HPV status. Additional interventions, while not necessarily supported by clinical evidence, may promote patient wellbeing and a sense of control. Promotion of a sound diet, patient-appropriate exercise regimen, and stress reduction is a common-sense recommendation for all cancer patients. Hard evidence regarding participation in HNC-specific patient support groups is limited by the retrospective nature of existing studies and small sample sizes [^{104, 105}]; however, anecdotal experience suggests that many patients find them helpful.

Conclusion

By 2020, the yearly incidence of HPV-HNC is expected to pass that of invasive cervical cancer; concurrently, HPV-HNC is expected to become the most common form of HNC [²²]. Head and neck cancer care providers eagerly await the results of high-quality, prospective, randomized clinical trials that take into account the unique aspects of HPV-HNC which distinguish it from classical tobacco/alcohol-induced head and neck cancer. Absent this data, however, current treatment guidelines do not distinguish between patients with HPV-mediated and unrelated disease, and therapeutic de-escalation should not be performed on an ad hoc basis. Therefore, providers who care for HPV-HNC patients should develop a concise, evidence-based, and patient-centered counseling strategy in order to insure that required information is effectively communicated to patients in a way that allows them to effectively navigate a complex and evolving treatment paradigm.

References

1. Patel SG, Shah JP. TNM staging of cancers of the head and neck: striving for uniformity among diversity. *CA Cancer J Clin.* 2005; 55(4):242–258. quiz 261–242, 264. [PubMed: 16020425]
2. Parkin DM, Ferlay J, Curado MP, et al. Fifty years of cancer incidence: CI5 I-IX. *Int J Cancer.* 2010; 127(12):2918–2927. [PubMed: 21351270]
3. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005; 55(2):74–108. [PubMed: 15761078]
4. Franceschi S, Munoz N, Bosch XF, Snijders PJ, Walboomers JM. Human papillomavirus and cancers of the upper aerodigestive tract: a review of epidemiological and experimental evidence. *Cancer Epidemiol Biomarkers Prev.* 1996; 5(7):567–575. [PubMed: 8827362]
5. Mehanna H, Paleri V, West CM, Nutting C. Head and neck cancer--Part 1: Epidemiology, presentation, and prevention. *BMJ.* 2010; 341:c4684. [PubMed: 20855405]
6. Rothman K, Keller A. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. *J Chronic Dis.* 1972; 25(12):711–716. [PubMed: 4648515]
7. Franceschi S, Talamini R, Barra S, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. *Cancer Res.* 1990; 50(20):6502–6507. [PubMed: 2208109]

8. Mashberg A, Boffetta P, Winkelman R, Garfinkel L. Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans. *Cancer*. 1993; 72(4):1369–1375. [PubMed: 8339227]
9. Herrero R, Castellsague X, Pawlita M, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *J Natl Cancer Inst*. 2003; 95(23): 1772–1783. [PubMed: 14652239]
10. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol*. 2008; 26(4):612–619. [PubMed: 18235120]
11. Kreimer AR, Randi G, Herrero R, Castellsague X, La Vecchia C, Franceschi S. Diet and body mass, and oral and oropharyngeal squamous cell carcinomas: analysis from the IARC multinational case-control study. *Int J Cancer*. 2006; 118(9):2293–2297. [PubMed: 16331628]
12. Garrote LF, Herrero R, Reyes RM, et al. Risk factors for cancer of the oral cavity and oropharynx in Cuba. *Br J Cancer*. 2001; 85(1):46–54. [PubMed: 11437401]
13. Talamini R, Vaccarella S, Barbone F, et al. Oral hygiene, dentition, sexual habits and risk of oral cancer. *Br J Cancer*. 2000; 83(9):1238–1242. [PubMed: 11027440]
14. Bundgaard T, Wildt J, Frydenberg M, Elbrond O, Nielsen JE. Case-control study of squamous cell cancer of the oral cavity in Denmark. *Cancer Causes Control*. 1995; 6(1):57–67. [PubMed: 7718736]
15. Suarez C, Rodrigo JP, Ferlito A, Cabanillas R, Shaha AR, Rinaldo A. Tumours of familial origin in the head and neck. *Oral Oncol*. 2006; 42(10):965–978. [PubMed: 16857415]
16. Foulkes WD, Brunet JS, Sieh W, Black MJ, Shenouda G, Narod SA. Familial risks of squamous cell carcinoma of the head and neck: retrospective case-control study. *BMJ*. 1996; 313(7059):716–721. [PubMed: 8819440]
17. Trizna Z, Schantz SP. Hereditary and environmental factors associated with risk and progression of head and neck cancer. *Otolaryngol Clin North Am*. 1992; 25(5):1089–1103. [PubMed: 1408193]
18. Schantz SP, Yu GP. Head and neck cancer incidence trends in young Americans, 1973–1997, with a special analysis for tongue cancer. *Arch Otolaryngol Head Neck Surg*. 2002; 128(3):268–274. [PubMed: 11886342]
19. Devesa SS, Blot WJ, Fraumeni JF Jr. Cohort trends in mortality from oral, esophageal, and laryngeal cancers in the United States. *Epidemiology*. 1990; 1(2):116–121. [PubMed: 2073497]
20. Canto MT, Devesa SS. Oral cavity and pharynx cancer incidence rates in the United States, 1975–1998. *Oral Oncol*. 2002; 38(6):610–617. [PubMed: 12167440]
21. Shiboski CH, Shiboski SC, Silverman S Jr. Trends in oral cancer rates in the United States, 1973–1996. *Community Dent Oral Epidemiol*. 2000; 28(4):249–256. [PubMed: 10901403]
22. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011; 29(32):4294–4301. [PubMed: 21969503]
23. Hammarstedt L, Lindquist D, Dahlstrand H, et al. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. *Int J Cancer*. 2006; 119(11):2620–2623. [PubMed: 16991119]
24. Shiboski CH, Schmidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20–44 years. *Cancer*. 2005; 103(9):1843–1849. [PubMed: 15772957]
25. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst*. 2000; 92(9):709–720. [PubMed: 10793107]
26. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010; 363(1):24–35. [PubMed: 20530316]
27. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med*. 2007; 356(19):1944–1956. [PubMed: 17494927]
28. Sikora AG, Morris LG, Sturgis EM. Bidirectional association of anogenital and oral cavity/pharyngeal carcinomas in men. *Arch Otolaryngol Head Neck Surg*. 2009; 135(4):402–405. [PubMed: 19380365]

29. Nguyen NP, Ly BH, Betz M, Vinh-Hung V. Importance of age as a prognostic factor for tonsillar carcinoma. *Ann Surg Oncol*. 2010; 17(10):2570–2577. [PubMed: 20559738]
30. Kreimer AR, Alberg AJ, Daniel R, et al. Oral human papillomavirus infection in adults is associated with sexual behavior and HIV serostatus. *J Infect Dis*. 2004; 189(4):686–698. [PubMed: 14767823]
31. Heck JE, Berthiller J, Vaccarella S, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. *Int J Epidemiol*. 2010; 39(1):166–181. [PubMed: 20022926]
32. Schwartz SM, Daling JR, Doody DR, et al. Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. *J Natl Cancer Inst*. 1998; 90(21):1626–1636. [PubMed: 9811312]
33. Hansson BG, Rosenquist K, Antonsson A, et al. Strong association between infection with human papillomavirus and oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. *Acta Otolaryngol*. 2005; 125(12):1337–1344. [PubMed: 16303684]
34. Smith EM, Ritchie JM, Summersgill KF, et al. Human papillomavirus in oral exfoliated cells and risk of head and neck cancer. *J Natl Cancer Inst*. 2004; 96(6):449–455. [PubMed: 15026470]
35. Reimers N, Kasper HU, Weissenborn SJ, et al. Combined analysis of HPV-DNA, p16 and EGFR expression to predict prognosis in oropharyngeal cancer. *Int J Cancer*. 2007; 120(8):1731–1738. [PubMed: 17236202]
36. Hafkamp HC, Speel EJ, Haesevoets A, et al. A subset of head and neck squamous cell carcinomas exhibits integration of HPV 16/18 DNA and overexpression of p16INK4A and p53 in the absence of mutations in p53 exons 5–8. *Int J Cancer*. 2003; 107(3):394–400. [PubMed: 14506739]
37. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev*. 2005; 14(2):467–475. [PubMed: 15734974]
38. Mork J, Lie AK, Glatte E, et al. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2001; 344(15):1125–1131. [PubMed: 11297703]
39. O'Rourke MA, Ellison MV, Murray LJ, Moran M, James J, Anderson LA. Human papillomavirus related head and neck cancer survival: a systematic review and meta-analysis. *Oral Oncol*. 2012; 48(12):1191–1201. [PubMed: 22841677]
40. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol*. 2003; 157(3):218–226. [PubMed: 12543621]
41. Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. *Semin Oncol*. 2004; 31(6):744–754. [PubMed: 15599852]
42. Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009–2010. *JAMA*. 2012; 307(7):693–703. [PubMed: 22282321]
43. Rintala M, Grenman S, Puranen M, Syrjanen S. Natural history of oral papillomavirus infections in spouses: a prospective Finnish HPV Family Study. *J Clin Virol*. 2006 Jan; 35(1):89–94. [PubMed: 16112613]
44. Haddad RI, Shin DM. Recent advances in head and neck cancer. *N Engl J Med*. 2008; 359(11):1143–1154. [PubMed: 18784104]
45. Munger K, Howley PM. Human papillomavirus immortalization and transformation functions. *Virus Res*. 2002; 89(2):213–228. [PubMed: 12445661]
46. Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med*. 2003; 348(6):518–527. [PubMed: 12571259]
47. McDougall JK. Immortalization and transformation of human cells by human papillomavirus. *Curr Top Microbiol Immunol*. 1994; 186:101–119. [PubMed: 8205836]
48. Gillison ML, Lowy DR. A causal role for human papillomavirus in head and neck cancer. *Lancet*. 2004; 363(9420):1488–1489. [PubMed: 15135592]
49. Lohavanichbutr P, Houck J, Fan W, et al. Genomewide gene expression profiles of HPV-positive and HPV-negative oropharyngeal cancer: potential implications for treatment choices. *Arch Otolaryngol Head Neck Surg*. 2009; 135(2):180–188. [PubMed: 19221247]

50. Klussmann JP, Mooren JJ, Lehnen M, et al. Genetic signatures of HPV-related and unrelated oropharyngeal carcinoma and their prognostic implications. *Clin Cancer Res.* 2009; 15(5):1779–1786. [PubMed: 19223504]
51. Braakhuis BJ, Snijders PJ, Keune WJ, et al. Genetic patterns in head and neck cancers that contain or lack transcriptionally active human papillomavirus. *J Natl Cancer Inst.* 2004; 96(13):998–1006. [PubMed: 15240783]
52. Stransky N, Egloff AM, Tward AD, et al. The mutational landscape of head and neck squamous cell carcinoma. *Science.* 2011; 333(6046):1157–1160. [PubMed: 21798893]
53. Agrawal N, Frederick MJ, Pickering CR, et al. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. *Science.* 2011; 333(6046):1154–1157. [PubMed: 21798897]
54. Poeta ML, Manola J, Goldwasser MA, et al. TP53 mutations and survival in squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2007; 357(25):2552–2561. [PubMed: 18094376]
55. Westra WH, Taube JM, Poeta ML, Begum S, Sidransky D, Koch WM. Inverse relationship between human papillomavirus-16 infection and disruptive p53 gene mutations in squamous cell carcinoma of the head and neck. *Clin Cancer Res.* 2008; 14(2):366–369. [PubMed: 18223210]
56. Schwarz E, Freese UK, Gissmann L, et al. Structure and transcription of human papillomavirus sequences in cervical carcinoma cells. *Nature.* 1985; 314(6006):111–114. [PubMed: 2983228]
57. Crook T, Morgenstern JP, Crawford L, Banks L. Continued expression of HPV-16 E7 protein is required for maintenance of the transformed phenotype of cells co-transformed by HPV-16 plus EJ-ras. *EMBO J.* 1989; 8(2):513–519. [PubMed: 2542020]
58. Howley PM. Role of the human papillomaviruses in human cancer. *Cancer Res.* 1991; 51(18 Suppl):5019s–5022s. [PubMed: 1653110]
59. Nasserri M, Gage JR, Lorincz A, Wettstein FO. Human papillomavirus type 16 immortalized cervical keratinocytes contain transcripts encoding E6, E7, and E2 initiated at the P97 promoter and express high levels of E7. *Virology.* 1991; 184(1):131–140. [PubMed: 1651587]
60. Rampias T, Sasaki C, Weinberger P, Psyri A. E6 and e7 gene silencing and transformed phenotype of human papillomavirus 16-positive oropharyngeal cancer cells. *J Natl Cancer Inst.* 2009; 101(6):412–423. [PubMed: 19276448]
61. Werness BA, Levine AJ, Howley PM. Association of human papillomavirus types 16 and 18 E6 proteins with p53. *Science.* 1990; 248(4951):76–79. [PubMed: 2157286]
62. Scheffner M, Huibregtse JM, Vierstra RD, Howley PM. The HPV-16 E6 and E6-AP complex functions as a ubiquitin-protein ligase in the ubiquitination of p53. *Cell.* 1993; 75(3):495–505. [PubMed: 8221889]
63. Munger K, Werness BA, Dyson N, Phelps WC, Harlow E, Howley PM. Complex formation of human papillomavirus E7 proteins with the retinoblastoma tumor suppressor gene product. *EMBO J.* 1989; 8(13):4099–4105. [PubMed: 2556261]
64. Wiest T, Schwarz E, Enders C, Flechtenmacher C, Bosch FX. Involvement of intact HPV16 E6/E7 gene expression in head and neck cancers with unaltered p53 status and perturbed pRb cell cycle control. *Oncogene.* 2002; 21(10):1510–1517. [PubMed: 11896579]
65. Wilczynski SP, Lin BT, Xie Y, Paz IB. Detection of human papillomavirus DNA and oncoprotein overexpression are associated with distinct morphological patterns of tonsillar squamous cell carcinoma. *Am J Pathol.* 1998; 152(1):145–156. [PubMed: 9422532]
66. Galloway DA, McDougall JK. The disruption of cell cycle checkpoints by papillomavirus oncoproteins contributes to anogenital neoplasia. *Semin Cancer Biol.* 1996; 7(6):309–315. [PubMed: 9284523]
67. Veldman T, Horikawa I, Barrett JC, Schlegel R. Transcriptional activation of the telomerase hTERT gene by human papillomavirus type 16 E6 oncoprotein. *J Virol.* 2001; 75(9):4467–4472. [PubMed: 11287602]
68. Chu A, Genden E, Posner M, Sikora A. A patient-centered approach to counseling patients with head and neck cancer undergoing human papillomavirus testing: a clinician's guide. *Oncologist.* 2013; 18(2):180–189. [PubMed: 23345545]

69. De Boer MF, McCormick LK, Pruyn JF, Ryckman RM, van den Borne BW. Physical and psychosocial correlates of head and neck cancer: a review of the literature. *Otolaryngol Head Neck Surg.* 1999; 120(3):427–436. [PubMed: 10064650]
70. Kugaya A, Akechi T, Okuyama T, et al. Prevalence, predictive factors, and screening for psychologic distress in patients with newly diagnosed head and neck cancer. *Cancer.* 2000; 88(12): 2817–2823. [PubMed: 10870066]
71. Verdonck-de Leeuw IM, de Bree R, Keizer AL, et al. Computerized prospective screening for high levels of emotional distress in head and neck cancer patients and referral rate to psychosocial care. *Oral Oncol.* 2009; 45(10):e129–e133. [PubMed: 19362038]
72. Kwan TT, Cheung AN, Lo SS, et al. Psychological burden of testing positive for high-risk human papillomavirus on women with atypical cervical cytology: a prospective study. *Acta Obstet Gynecol Scand.* 2011; 90(5):445–451. [PubMed: 21306349]
73. Daley EM, Perrin KM, McDermott RJ, et al. The psychosocial burden of HPV: a mixed-method study of knowledge, attitudes and behaviors among HPV+ women. *J Health Psychol.* 2010; 15(2): 279–290. [PubMed: 20207671]
74. Fortenberry JD. The effects of stigma on genital herpes care-seeking behaviours. *Herpes.* 2004; 11(1):8–11. [PubMed: 15115631]
75. Milbury K, Rosenthal DI, El-Naggar A, Badr H. An exploratory study of the informational and psychosocial needs of patients with human papillomavirus-associated oropharyngeal cancer. *Oral Oncol.* 2013; 49(11):1067–1071. [PubMed: 23953777]
76. Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2007; 56(Rr-2):1–24. [PubMed: 17380109]
77. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2010; 59(20):626–629. [PubMed: 20508593]
78. Recommendations on the use of quadrivalent human papillomavirus vaccine in males--Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep.* 2011; 60(50):1705–1708. [PubMed: 22189893]
79. Ragin CC, Taioli E. Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis. *Int J Cancer.* 2007; 121(8):1813–1820. [PubMed: 17546592]
80. Dayyani F, Etzel CJ, Liu M, Ho CH, Lippman SM, Tsao AS. Meta-analysis of the impact of human papillomavirus (HPV) on cancer risk and overall survival in head and neck squamous cell carcinomas (HNSCC). *Head Neck Oncol.* 2010; 2:15. [PubMed: 20587061]
81. Weinberger PM, Yu Z, Haffty BG, et al. Prognostic significance of p16 protein levels in oropharyngeal squamous cell cancer. *Clin Cancer Res.* 2004; 10(17):5684–5691. [PubMed: 15355894]
82. Paz IB, Cook N, Odom-Maryon T, Xie Y, Wilczynski SP. Human papillomavirus (HPV) in head and neck cancer. An association of HPV 16 with squamous cell carcinoma of Waldeyer's tonsillar ring. *Cancer.* 1997; 79(3):595–604. [PubMed: 9028373]
83. Vila, P. Decreased Impact Of Nodal Positivity On Oropharyngeal Cancer Survival In The HPV Era: A Population Based Study. In: Genden, E.; Morris, L.; Posner, M.; Boffetta, P.; Sikora, A., editors. *European Archives of Oto-Rhino-Laryngology and Head and Neck.* (In press).
84. Jain KS, Sikora AG, Baxi SS, Morris LG. Synchronous cancers in patients with head and neck cancer: risks in the era of human papillomavirus-associated oropharyngeal cancer. *Cancer.* 2013; 119(10):1832–1837. [PubMed: 23423883]
85. Fakhry C, Gillison ML. Clinical implications of human papillomavirus in head and neck cancers. *J Clin Oncol.* 2006; 24(17):2606–2611. [PubMed: 16763272]
86. Weinberger PM, Yu Z, Haffty BG, et al. Molecular classification identifies a subset of human papillomavirus--associated oropharyngeal cancers with favorable prognosis. *J Clin Oncol.* 2006; 24(5):736–747. [PubMed: 16401683]
87. Schlecht NF. Prognostic value of human papillomavirus in the survival of head and neck cancer patients: an overview of the evidence. *Oncol Rep.* 2005; 14(5):1239–1247. [PubMed: 16211291]

88. Lindel K, Beer KT, Laissue J, Greiner RH, Aebersold DM. Human papillomavirus positive squamous cell carcinoma of the oropharynx: a radiosensitive subgroup of head and neck carcinoma. *Cancer*. 2001; 92(4):805–813. [PubMed: 11550151]
89. Morris LG, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. *J Clin Oncol*. 2011; 29(6):739–746. [PubMed: 21189382]
90. Licitra L, Perrone F, Bossi P, et al. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. *J Clin Oncol*. 2006; 24(36):5630–5636. [PubMed: 17179101]
91. de Jong MC, Pramana J, Kneijens JL, et al. HPV and high-risk gene expression profiles predict response to chemoradiotherapy in head and neck cancer, independent of clinical factors. *Radiother Oncol*. 2010; 95(3):365–370. [PubMed: 20346528]
92. Posner MR, Lorch JH, Goloubeva O, 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(5):1071–1077. [PubMed: 21317223]
93. Lacy PD, Piccirillo JF, Merritt MG, Zequeira MR. Head and neck squamous cell carcinoma: better to be young. *Otolaryngol Head Neck Surg*. 2000; 122(2):253–258. [PubMed: 10652400]
94. Vu HL, Sikora AG, Fu S, Kao J. HPV-induced oropharyngeal cancer, immune response and response to therapy. *Cancer Lett*. 2010; 288(2):149–155. [PubMed: 19628331]
95. Hafkamp HC, Manni JJ, Haesevoets A, et al. Marked differences in survival rate between smokers and nonsmokers with HPV 16-associated tonsillar carcinomas. *Int J Cancer*. 2008; 122(12):2656–2664. [PubMed: 18360824]
96. Mayne ST, Cartmel B, Kirsh V, Goodwin WJ Jr. Alcohol and tobacco use prediagnosis and postdiagnosis, and survival in a cohort of patients with early stage cancers of the oral cavity, pharynx, and larynx. *Cancer Epidemiol Biomarkers Prev*. Dec; 2009 18(12):3368–3374. [PubMed: 19959684]
97. Gillison ML, Zhang Q, Jordan R, et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. *J Clin Oncol*. 2012 Jun 10; 30(17):2102–2111. [PubMed: 22565003]
98. West R. Assessment of dependence and motivation to stop smoking. *BMJ*. 2004 Feb 7; 328(7435):338–339. [PubMed: 14764501]
99. Lancaster T, Stead L. Physician advice for smoking cessation. *Cochrane Database Syst Rev*. 2004; (4):Cd000165. [PubMed: 15494989]
100. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. *Am J Prev Med*. 2008; 35(2):158–176. [PubMed: 18617085]
101. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med*. 2005; 142(4):233–239. [PubMed: 15710956]
102. Cummings KM, Mahoney M. Current and emerging treatment approaches for tobacco dependence. *Curr Oncol Rep*. 2006; 8(6):475–483. [PubMed: 17040625]
103. Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev*. 2012; 10:Cd008286. [PubMed: 23076944]
104. Vakharia KT, Ali MJ, Wang SJ. Quality-of-life impact of participation in a head and neck cancer support group. *Otolaryngol Head Neck Surg*. 2007; 136(3):405–410. [PubMed: 17321868]
105. Mowry SE, Wang MB. The influence of support groups on quality of life in head and neck cancer patients. *ISRN Otolaryngol*. 2011; 2011:250142. [PubMed: 23724251]
106. Singhi AD, Westra WH. Comparison of human papillomavirus in situ hybridization and p16 immunohistochemistry in the detection of human papillomavirus-associated head and neck cancer based on a prospective clinical experience. *Cancer*. 2010; 116(9):2166–2173. [PubMed: 20186832]
107. Clavel C, Masure M, Bory JP, et al. Hybrid Capture II-based human papillomavirus detection, a sensitive test to detect in routine high-grade cervical lesions: a preliminary study on 1518 women. *Br J Cancer*. 1999; 80(9):1306–1311. [PubMed: 10424730]

108. Clavel C, Masure M, Bory JP, et al. Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: a study of 7932 women. *Br J Cancer*. 2001; 84(12): 1616–1623. [PubMed: 11401314]
109. Lindquist D, Romanitan M, Hammarstedt L, et al. Human papillomavirus is a favourable prognostic factor in tonsillar cancer and its oncogenic role is supported by the expression of E6 and E7. *Mol Oncol*. 2007; 1(3):350–355. [PubMed: 19383307]
110. Shi W, Kato H, Perez-Ordóñez B, et al. Comparative prognostic value of HPV16 E6 mRNA compared with in situ hybridization for human oropharyngeal squamous carcinoma. *J Clin Oncol*. 2009; 27(36):6213–6221. [PubMed: 19884544]

Table 1
Summary of available HPV testing modalities, their specific attributes and drawbacks for use in patient counseling

HPV testing methods

HPV DNA in situ hybridization [106]	The current <i>gold standard</i> , along with PCR analysis. Requires a high degree of technical expertise.
HPV DNA PCR [107, 108]	Modern DNA PCR technique that is extremely sensitive, but can be affected by contamination. Can readily be used to distinguish among oncogenic HPV types. Along with in situ hybridization, a <i>gold standard</i> technique.
HPV E6/E7 mRNA rt-PCR [109]	Detects biologic activity/ongoing viral oncogene production required for maintenance of malignant phenotype. Currently a research technique.
Immunohistochemistry [106, 110]	Host p16(INK4a) expression highly correlated with HPV-positivity. Therefore, frequently used as surrogate for direct HPV-testing, particularly in research studies.