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Prospects for prevention of HPV-driven oropharynx cancer

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Abstract

Prevention of HPV-associated cancers can take two forms—one through prevention of infection via prophylactic HPV vaccination, and one through interruption of disease progression through early identification (i.e.: screening) and treatment. Primary prevention via vaccination seems promising, as a proof-of-principal study demonstrated high vaccine efficacy against one-time detection of oral HPV16/18 infection. In addition to the direct benefit of vaccination, indirect protection from reduced genital HPV infection should also reduce oral HPV exposure at the individual level. Yet, for the current unvaccinated cohorts who will bear the burden of non-cervical HPV-associated cancers for the foreseeable future, no secondary prevention opportunities exist, as the field has not yet validated any screening methods for non-cervical HPV associated cancers. Serum HPV16 E6 antibody data suggest that this test might one day be able to detect many of the at-risk patients prior to tumor development. For any biomarker that proves valid and reliable, transitioning into clinical practice will require additional research focused on 1) diagnostics, 2) effective intervention, and 3) observed reductions in cancer mortality.

Keywords

prevention; human papillomavirus; HPV; oropharyngeal cancer

Introduction

HPV causes a varying proportion of cancer at several anatomic sites (1). HPV is a necessary cause of cervical cancer and causes most anal cancers as well (1). It causes a smaller proportion of cancers of the vulva, vagina, and penis (1). Over the last 20 years, HPV has been identified as a cause of oropharyngeal cancer (OPC); HPV types 16 and 18 are responsible for almost all HPV-positive OPCs (1).

The incidence of HPV-driven cancers is increasing worldwide, although the burden of these cancers differs by world region (2). Cervical cancer dominates the HPV-driven cancers in

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resource-poor areas, where 85% of cervical cancers occur (3). In such places, resources for prevention should focus on women. In more developed regions, the gender ratio for HPV-driven cancer incidence is becoming more evenly distributed because 1) the incidence of cervical cancer has been greatly reduced due to population-based screening and 2) the incidences of anal (4–6) and oropharyngeal cancers (7–9) are increasing, particularly in males. Recent data from the United States (US) shows that the number of cancers of the cervix is equivalent to the number of oropharynx cancers overall (at present the number of HPV-positive oropharynx cancers remains lower than the number of cervical cancers) (10). Thus, at least in the US, it may be appropriate to focus efforts for prevention of HPV-driven cancers on both males and females.

Prevention of HPV-driven OPC can be approached in two ways: 1) primary prevention is an intervention that prevents persistent HPV infections and resultant precancerous lesions from developing, and 2) secondary prevention is an intervention leading to the discovery and control of a precancerous or cancerous process while it is localized and therefore more readily amenable to curative treatment. For the latter, it is important that the disease not only be identified at an earlier stage, but that effective treatment of the lesion results in reduced mortality from the cancer.

The purpose of this chapter is to present the existing data on possibilities for primary and secondary prevention of HPV-driven OPC. Because optimal secondary prevention will rely on identification of an early lesion, precursors for HPV-driven OPC will be discussed. And, while theoretically, behavior modification and safer sexual practices (i.e.: dental dam or condom use) may prevent HPV transmission to the oral region given the strong association between sexual behavior and oropharyngeal cancer (11), this topic will not be covered in this chapter.

Primary prevention of HPV-driven OPC via prophylactic HPV vaccination

The discovery that the papillomavirus L1 major capsid protein self-assembles into virus-like particles (VLP) formed the foundation for a prophylactic HPV vaccine that generates neutralizing antibodies to virus capsid proteins (12). HPV L1 VLP vaccines induce high concentrations of neutralizing antibodies to L1 in the blood, and virtually all vaccinated subjects seroconvert after receiving three doses (13).

Randomized trials have provided strong evidence for high efficacy of the two FDA-approved VLP vaccines: the bivalent HPV16/18 vaccine (Cervarix®, GlaxoSmithKline Biologicals) and the quadrivalent HPV 6/11/16/18 vaccine (Gardasil™, Merck Sharp and Dohme) against cervical, vaginal and vulvar HPV16/18 infections and related diseases, and against anal HPV16/18 infections in women (14–17). Among men, efficacy of the quadrivalent vaccine has been demonstrated against HPV-positive external genital lesions (18) and against anal HPV and intraepithelial neoplasia (AIN) among men who have sex with men (19) (Table 1).

Oral/oropharyngeal HPV infection is likely acquired from genital HPV infection during the process of sexual behaviour (or to a lesser extent, kissing or auto-inoculation) (20–22). Because the vaccine reduces the prevalence of genital HPV16/18 infection, vaccination

should indirectly reduce the incidence of oral/oropharyngeal HPV16/18 infection, independent of a direct effect of the vaccine on oral/oropharyngeal HPV16/18 infection. Yet, the fact that this parenterally administered vaccine prevents mucosal HPV infection at all genital sites makes it likely that a direct effect of the vaccine against oral/oropharyngeal HPV infection will be observed; in other words, the *a priori* hypothesis that vaccine efficacy (VE) against oral HPV will be similarly high is strengthened by the data from the anogenital sites.

Only one study to date has evaluated the prevention potential of the HPV vaccine against oral HPV infections (23). In this proof-of principle study, evaluation of VE against oral HPV infection was carried out in the Costa Rica Vaccine Trial (CVT), a randomized clinical trial (RCT) initially designed to evaluate VE against persistent cervical HPV16/18 infections and precancerous lesions (24). This value-added component was introduced at the final randomized blinded study visit four years following initial vaccination in response to the mounting evidence that HPV caused some oropharyngeal cancers. As a consequence, no pre-vaccination oral specimen was obtained, which would have allowed for exclusion from the analysis of women with prevalent oral HPV infection at the time of vaccination (as in a naïve cohort). Additionally, only one-time detection of oral HPV (and not persistent oral HPV) was evaluated as the endpoint. VE was estimated in an intention-to-treat analytic cohort (i.e.: among all women vaccinated regardless of baseline cervical HPV DNA or serology results, treatment for cervical precancer or number of vaccine doses). Among women who attended the study visit and accepted oral specimen collection (N=5834 women [2910 HPV arm; 2924 Control arm]), VE against oral HPV16/18 infection was 93% (one infection in vaccine arm, 15 in control arm, 95%CI 63 to 100%) (23). Type-specific VE was 92% against HPV16 (one and twelve women in vaccine and control arm, respectively, 95% CI=52 to 100%) and 100% against HPV18 (0 and 4 women in the vaccine and control arm, 95% CI= -12 to 100%)(23).

Despite the profound reduction in oral HPV16/18 prevalence among vaccinated woman observed in CVT, there are still many important questions in the field of prophylactic HPV vaccination and prevention of HPV-driven OPC. Most importantly, current vaccine administration recommendations are based on the epidemiology of cervical HPV infection. Specifically, since the attack rate of cervical HPV infection is highest shortly after sexual debut (for most populations, in the mid- to late- teens) (25), it is critical to vaccinate prior to sexual debut for the vaccine to be most effective against cervical HPV infection and related disease. Using the US as an example, the CDC's Advisory Committee on Immunization Practices (ACIP), the organization responsible for setting US immunization guidelines, recommends HPV vaccination for females and males between the ages of 11 and 12 years of age, as early as 9 years, and with a catch-up vaccination scheme until the ages of 26 and 21 for females and males, respectively. Catch-up vaccination will be terminated once the eligible cohorts have been vaccinated (in other words, when there are no longer adolescents who missed vaccination at the ideal window and require it at these older ages). Yet, data on the epidemiology of oral HPV infection show that the point prevalence of HPV does not peak in early ages as the cervix, but instead remains stable or increases with increasing age (Figure 1)(26, 27). If higher prevalence at older ages is masking increased acquisition at

these ages, then individuals may require the protection afforded by HPV vaccination to reduce oral HPV in their 20s to 30s; recent prospective data on oral HPV incidence confirms this concern of continued acquisition at older ages (28). If the vaccine is initially administered at the age of 11 to 12, the conferred protection will need to last at least two decades to prevent acquisition of oral HPV infection that may result in HPV-driven OPC. At present, there are published data on the duration of protection out to 8 years, although no waning of systemic antibodies reassures us that protection will be long lived (29). Yet, whether possible waning of immunity will be differential by anatomic site is unknown. If protection is found to wane, a booster vaccine can be given albeit with cost implications.

Any future RCT designed to evaluate the efficacy of the HPV vaccine against oral HPV16/18 would need to address the following design considerations: 1) collection of a pre-vaccine oral specimen to remove from the analysis individuals infected with oral HPV at the time of vaccination (i.e.: to create and according-to-protocol analytic cohort); 2) use a more meaningful biologic endpoint than one-time detection of oral HPV infection such as persistent oral HPV16/18 infection, since the quantitative relationship between one-time detection of HPV in oral exfoliated cells and risk of future HPV-driven OPC is unknown; and 3) given the rarity of oral HPV infection and its propensity to clear within one year, such a future trial would need to be large. The rarity of oral HPV16/18 infection, the absence of a precancerous phase that could serve as a surrogate endpoint and the putatively long interval between oral HPV infection and HPV-driven OPC indicates that future studies will experience similar limitations as those experienced in the CVT. Finally, results from a formal RCT may not affect the current vaccine recommendations of the CDC's ACIP; a prospective oral HPV natural history study that documents oral HPV16 acquisition and persistence in later decades of life may have policy implications, and this would only be in the setting of waning immunity. It should be noted that a formal trial might inform policy recommendations in other countries which have not recommended male vaccination.

The prospects for primary prevention of HPV-driven OPC and all HPV-driven cancers via prophylactic HPV vaccination are dampened by the fact that relatively few people worldwide are being vaccinated. Even in resource-rich settings such as the US, uptake of even a single dose remains insufficient. As of 2011, the MMWR data indicate 53% and 7% of 13–17 year old girls and boys received at least one dose, respectively (30); to achieve herd immunity, the vaccination rate may need to be higher. In Australia, where a nationally-funded vaccine program has achieved 70% vaccine coverage for the full three-dose vaccine regimen, a significant decrease was observed in genital warts among young females and males (the latter were likely unvaccinated) suggesting herd immunity (31). Recent data suggested that even with lower vaccine coverage, there was still substantial decreases in the prevalence of cervical HPV16/18 infections (32) and genital warts (33).

Secondary prevention of HPV-driven cancers will remain necessary for several decades not only due to inadequate vaccine uptake, but also because current generations at risk for cancer will not experience the benefit from vaccination (as it is established that the prophylactic HPV vaccine does not treat HPV infections [34]). While the field has validated methods for screening for cervical cancer, at present, there are no validated secondary prevention measures for HPV-driven cancers beyond the cervix.

Secondary prevention of HPV-driven OPC

Most researchers believe there is a long lag time between HPV infection and OPC development, making these cancers amenable to secondary prevention. From the cervix, we understand that the HPV infection persists during the entire interval, and the two main viral oncogenes, E6 and E7, continue to be expressed in tumors. We can use these characteristics of the virus to develop screening tools for secondary prevention.

Effective secondary prevention of cancer requires several components: 1) availability of a test that can detect the cancer before the appearance of symptoms, 2) diagnostic measures to identify the precancer, 3) effective treatment for the early stage cancer, 4) evidence that early detection reduced the cancer-specific mortality, or at least incidence of the cancer, and 5) confirmation that the benefits of screening outweigh the risks.

For HPV-driven OPC, an obvious consideration for a screening test would be for oral HPV16 DNA or related cytological abnormalities, analogous to HPV DNA testing and cytology in cervical cancer prevention programs. One study (35) reported on whether a “Pap-test equivalent” would be useful for early detection of HPV-driven oropharyngeal cancer. The authors investigated oral HPV16 infection and oropharyngeal cytologic abnormalities in: 1) patients with oropharyngeal abnormalities, of whom 70% had been diagnosed with invasive oropharyngeal cancer, and 2) patients infected with the human immunodeficiency virus (HIV) and with no clinical symptoms of oropharyngeal disease (a group at increased risk of HPV-driven oropharyngeal cancer). In group 1, HPV16 infection and abnormal cytology were strongly associated with the presence of oropharyngeal cancer, indicating that cytologic evaluation of visible lesions in the oropharyngeal region could detect invasive oropharyngeal cancer. Unfortunately, the results in group 2 (non-symptomatic HIV-infected patients) showed that the presence of tonsillar cytologic abnormalities was not associated with oral HPV16 infection. The results from this study indicated that screening akin to cervical cancer prevention strategies had limited utility as a screening modality for populations without visible lesions. Therefore, at present, while research-based assays exist to detect oral HPV16 DNA, there are no clinically-validated tests that predict risk of HPV-driven oropharyngeal cancer. Advances in this field should focus development of new tests and biomarkers not only for oral HPV16 detection and traditional cytology, but also promising new biomarkers in the cervical cancer screening domain, including p16 or dual-stain with p16/Ki67 (36, 37).

An alternative strategy to direct sampling and/or visualization of the oral region would be a blood-based biomarker for detection of HPV-driven OPC. From what is known about HPV-induced carcinogenesis, antibody markers against HPV E6 and E7 oncoproteins should occur in response to an underlying HPV-driven neoplastic process and would be expected at very low levels among cancer-free individuals. For oropharyngeal cancer, case-control studies have validated this hypothesis and shown: 1) HPV16 E6 antibodies are rare in individuals without cancer, at between 0.5 and 1%, and 2) HPV16 E6 antibodies are present among oropharynx cancer cases in Europe and US (~30%) (38, 39). Yet, a tumor biomarker should be present prior to cancer diagnosis to be amenable to screening. Recent data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a cohort of

over 500,000 adults in 10 European countries (40), confirmed that HPV16 E6 seropositivity was present in less than 1% of controls and in 35% of oropharyngeal cases. Importantly, given the prospective design of the study, the authors were able to investigate this potential biomarker in blood samples collected years prior to cancer diagnosis: in this work, HPV16 E6 seropositivity was present on average 6 years prior to diagnosis of oropharyngeal cancer and in some cases, more than 10 years prior to diagnosis (Figure 2) (41). The robust presence of antibody positivity independent of the time between blood specimen collection and subsequent diagnosis of oropharyngeal cancer suggests that oropharyngeal cancer may be detected at a preclinical stage and raises the possibility of a blood-based screening marker for HPV-driven oropharyngeal cancer. Such an HPV16 E6 screening marker would be beneficial if it identified individuals at risk for oropharyngeal cancer prior to cancer development, or even if it detected cancer at an earlier stage that was more amenable to treatment.

It will be important to confirm these results in other large population cohorts and further evaluate its sensitivity, specificity, predictive value, true latent period, and implications for those who test positive.

Obstacles for screening for HPV-driven OPC

Even if a screening test for HPV-driven OPC was identified that had acceptable clinical performance, there remain limitations to implementation of a screening program aimed at HPV-driven OPC. First, for the case of HPV-driven OPC, the question still remains whether there is an identifiable precancerous lesion akin to the intra-epithelial lesions at other HPV-driven cancer sites (i.e.: cervical intraepithelial neoplasia [CIN]). For head and neck cancers resultant from tobacco and alcohol use (and not HPV infection), there are the established precursors of leukoplakia and erythroplakia. Logically, HPV-driven cancers in the oropharynx do not erupt *de novo* and there must be a continuum of detectable cancerous growth before invasive cancer. While no study to date has effectively described this lesion, the presence of HPV16 E6 antibodies 10 years prior to cancer diagnosis raises the possibility that a precursor lesion or early cancer is present, and that this long lead time would be amenable to screening. Second, the sites at which HPV causes cancer in the head and neck region—tonsil, base of tongue, and other parts of the pharynx—are less accessible than are anogenital sites for conventional diagnostic measures (i.e.: exploratory surgery including diagnostic biopsy). A less invasive approach, such as ultrasound or imaging of the oropharyngeal region, may be an alternative for identification of a validated precursor lesion. At least in principle, one might imagine exposing the oropharynx to a labeled tracer that could get into cells and bind E6 protein, E7 protein, or p16, because the tracer contained a sequence with high affinity for one of those proteins, and could then be visualized by a digital camera. Third, while there is treatment for OPC, it is associated with profound morbidity and the survival rates for OPC have not increased over time, suggesting that new, less invasive treatments are necessary. And finally, large-scale RCTs would be needed to provide evidence that early detection of HPV-driven OPC reduced the mortality from the disease. Confirmation that the benefits of screening outweigh the risks and costs would be an important public health consideration. This is particularly true for HPV-driven OPC, which is a rare cancer (annual incidence <10/100,000) and largely has no clear risk factors

(beyond male gender and sexual behaviour) that one could use to target an enriched population for screening. As a consequence, the numbers needed to screen in order to detect one cancer are likely to be large.

Strategy for prevention of HPV-driven OPC

A strategy for prevention of HPV-driven OPC should incorporate all available tools. Certainly, public health practitioners must continue to expand prophylactic HPV vaccination to recommended individuals with the goal of preventing all HPV-driven cancers. We will need to continue to monitor the long-term duration of protection, and a booster vaccine, if needed, could overcome waning protection albeit with cost implications. In the future, we should observe vaccine-related reductions in HPV-driven OPC resultant from 1) the direct benefit of vaccination, 2) the indirect benefit from reduced genital HPV infection, which should reduce oral HPV exposure at the individual level, and 3) the reduction in the prevalence of HPV vaccine types at the population level (i.e., herd immunity). For the interceding cohorts who will not benefit from vaccination, secondary prevention will remain important for the next several decades. Serum HPV16 E6 antibody data suggest that an optimized version of this test might one day be able to detect many of the at-risk patients before they develop their tumors and that future research may be able to develop and validate a test that can detect a precursor lesion in these at-risk patients.

Summary

At present, there are no validated prevention measures for HPV-driven OPC, a cancer with documented increases in incidence in many developed countries around the world. Yet, there are several promising opportunities on the horizon. For primary prevention, the prophylactic HPV vaccine will directly and indirectly prevent oral HPV16/18 infection, and likely its downstream lesions. A key question is whether the underlying oral HPV epidemiology, specifically acquisition of oral HPV16/18 infection in people in their mid-30s, will undermine current vaccination approaches where adolescents are vaccinated at 11–12 years of age. For secondary prevention, the discovery of HPV16 E6 antibody positivity a decade before cancer development may eventually lead to the use of serum antibodies as a screening test for HPV-driven oropharyngeal cancer. For any biomarker that proves valid and reliable, transitioning into clinical practice will require development of a clinically-usable test, and then additional research focused on 1) diagnostics, 2) effective intervention, and 3) observed reductions in cancer mortality. In the best of scenarios, because HPV-driven OPC is a fraction of head and neck cancer overall, even if all the HPV-driven OPCs were prevented there would still remain a burden of tobacco-related head and neck cancers. In addition to targeting HPV infection, prevention strategies also need to focus on tobacco and alcohol use, as they remain major risk factors for head and neck cancers worldwide.

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References

1. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens--Part B: biological agents. *Lancet Oncol.* 2009; 10:321–322. [PubMed: 19350698]
2. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol.* 2012; 13:607–615. [PubMed: 22575588]
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010; 127:2893–2917. [PubMed: 21351269]
4. Johnson LG, Madeleine MM, Newcomer LM, Schwartz SM, Daling JR. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973–2000. *Cancer.* 2004; 101:281–288. [PubMed: 15241824]
5. Brewster DH, Bhatti LA. Increasing incidence of squamous cell carcinoma of the anus in Scotland, 1975–2002. *Br J Cancer.* 2006; 95:87–90. PMC2360500. [PubMed: 16721368]
6. Nielsen A, Munk C, Kjaer SK. Trends in incidence of anal cancer and high-grade anal intraepithelial neoplasia in Denmark, 1978–2008. *Int J Cancer.* 2012; 130:1168–1173. [PubMed: 21469144]
7. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011; 29:4294–4301. PMCID 3221528. [PubMed: 21969503]
8. Nasman A, Attner P, Hammarstedt L, Du J, Eriksson M, Giraud G, et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma? *Int J Cancer.* 2009; 125:362–366. [PubMed: 19330833]
9. Hong AM, Grulich AE, Jones D, Lee CS, Garland SM, Dobbins TA, et al. Squamous cell carcinoma of the oropharynx in Australian males induced by human papillomavirus vaccine targets. *Vaccine.* 2010; 28:3269–3272. [PubMed: 20226244]
10. Jemal A, Simard EP, Dorell C, Noone AM, Markowitz LE, Kohler B, et al. Annual Report to the Nation on the Status of Cancer, 1975–2009, featuring the burden and trends in human papillomavirus(HPV)-associated cancers and HPV vaccination coverage levels. *J Natl Cancer Inst.* 2013; 105:175–201. PMC3565628. [PubMed: 23297039]
11. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med.* 2007; 356:1944–1956. [PubMed: 17494927]
12. Kirnbauer R, Booy F, Cheng N, Lowy DR, Schiller JT. Papillomavirus L1 major capsid protein self-assembles into virus-like particles that are highly immunogenic. *Proc Natl Acad Sci U S A.* 1992; 89:12180–12184. PMC50722. [PubMed: 1334560]
13. Stanley M. Immunobiology of HPV and HPV vaccines. *Gynecol Oncol.* 2008; 109:S15–S21. [PubMed: 18474288]
14. Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsague X, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol.* 2012; 13:89–99. [PubMed: 22075171]
15. Munoz N, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. *J Natl Cancer Inst.* 2010; 102:325–339. [PubMed: 20139221]
16. Schiller JT, Castellsague X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. *Vaccine.* 2012; 30(Suppl 5):F123–F138. [PubMed: 23199956]
17. Kreimer AR, Gonzalez P, Katki HA, Porras C, Schiffman M, Rodriguez AC, et al. Efficacy of a bivalent HPV 16/18 vaccine against anal HPV 16/18 infection among young women: a nested analysis within the Costa Rica Vaccine Trial. *Lancet Oncol.* 2011; 12:862–870. PMCID 3172992. [PubMed: 21865087]
18. Giuliano AR, Palefsky JM, Goldstone S, Moreira ED Jr, Penny ME, Aranda C, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. *N Engl J Med.* 2011; 364:401–411. PMC3495065. [PubMed: 21288094]

19. Palefsky JM, Giuliano AR, Goldstone S, Moreira ED Jr, Aranda C, Jessen H, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med*. 2011; 365:1576–1585. [PubMed: 22029979]
20. D'Souza G, Agrawal Y, Halpern J, Bodison S, Gillison ML. Oral sexual behaviors associated with prevalent oral human papillomavirus infection. *J Infect Dis*. 2009; 199:1263–1269. [PubMed: 19320589]
21. Pickard RK, Xiao W, Broutian TR, He X, Gillison ML. The prevalence and incidence of oral human papillomavirus infection among young men and women, aged 18–30 years. *Sex Transm Dis*. 2012; 39:559–566. [PubMed: 22706220]
22. Edelstein ZR, Schwartz SM, Hawes S, Hughes JP, Feng Q, Stern ME, et al. Rates and determinants of oral human papillomavirus infection in young men. *Sex Transm Dis*. 2012; 39:860–867. [PubMed: 23064535]
23. Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, et al. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. (Submitted).
24. Herrero R, Hildesheim A, Rodriguez AC, Wacholder S, Bratti C, Solomon D, et al. Rationale and design of a community-based double-blind randomized clinical trial of an HPV 16 and 18 vaccine in Guanacaste, Costa Rica. *Vaccine*. 2008; 26:4795–4808. PMC2652516. [PubMed: 18640170]
25. de Sanjose S, Diaz M, Castellsague X, Clifford G, Bruni L, Munoz N, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infect Dis*. 2007; 7:453–459. [PubMed: 17597569]
26. Kreimer AR, Villa A, Nyitray AG, Abrahamsen M, Papenfuss M, Smith D, et al. The epidemiology of oral HPV infection among a multinational sample of healthy men. *Cancer Epidemiol Biomarkers Prev*. 2011; 20:172–182. PMID 3027138. [PubMed: 21148755]
27. Gillison ML, Broutian T, Pickard RK, Tong ZY, Xiao W, Kahle L, et al. Prevalence of Oral HPV Infection in the United States, 2009–2010. *JAMA*. 2012 NIHMS450330.
28. Kreimer AR, Pierce Campbell C, Lin H, Fulp W, Papenfuss M, Abrahamsen M, et al. Natural history of oral human papillomavirus infection in men: the HIM cohort study. *The Lancet*. (In press).
29. Roteli-Martins CM, Naud P, De Borja P, Teixeira JC, De Carvalho NS, Zahaf T, et al. Sustained immunogenicity and efficacy of the HPV-16/18 AS04-adjuvanted vaccine: up to 8.4 years of follow-up. *Hum Vaccin Immunother*. 2012; 8:390–397. [PubMed: 22327492]
30. National and state vaccination coverage among adolescents aged 13–17 years--United States, 2011. *MMWR Morb Mortal Wkly Rep*. 2012; 61:671–677. [PubMed: 22932301]
31. Donovan B, Franklin N, Guy R, Grulich AE, Regan DG, Ali H, et al. Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data. *Lancet Infect Dis*. 2011; 11:39–44. [PubMed: 21067976]
32. Kahn JA, Brown DR, Ding L, Widdice LE, Shew ML, Glynn S, et al. Vaccine-type human papillomavirus and evidence of herd protection after vaccine introduction. *Pediatrics*. 2012; 130:e249–e256. PMC3408690. [PubMed: 22778297]
33. Bauer HM, Wright G, Chow J. Evidence of human papillomavirus vaccine effectiveness in reducing genital warts: an analysis of California public family planning administrative claims data, 2007–2010. *Am J Public Health*. 2012; 102(5):833–835. [PubMed: 22420808]
34. Hildesheim A, Herrero R, Wacholder S, Rodriguez AC, Solomon D, Bratti MC, et al. Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: a randomized trial. *JAMA*. 2007; 298:743–753. [PubMed: 17699008]
35. Fakhry C, Rosenthal BT, Clark DP, Gillison ML. Associations between oral HPV16 infection and cytopathology: evaluation of an oropharyngeal "pap-test equivalent" in high-risk populations. *Cancer Prev Res (Phila)*. 2011; 4:1378–1384. PMC3380432. [PubMed: 21836021]
36. Cuschieri K, Wentzensen N. Human papillomavirus mRNA and p16 detection as biomarkers for the improved diagnosis of cervical neoplasia. *Cancer Epidemiol Biomarkers Prev*. 2008; 17:2536–2545. PMC2900792. [PubMed: 18842994]

37. Wentzensen N, Schwartz L, Zuna RE, Smith K, Mathews C, Gold MA, et al. Performance of p16/Ki-67 immunostaining to detect cervical cancer precursors in a colposcopy referral population. *Clin Cancer Res.* 2012; 18:4154–4162. [PubMed: 22675168]
38. Ribeiro KB, Levi JE, Pawlita M, Koifman S, Matos E, Eluf-Neto J, et al. Low human papillomavirus prevalence in head and neck cancer: results from two large case-control studies in high-incidence regions. *Int J Epidemiol.* 2011; 40:489–502. [PubMed: 21224273]
39. Smith EM, Rubenstein LM, Haugen TH, Pawlita M, Turek LP. Complex etiology underlies risk and survival in head and neck cancer human papillomavirus, tobacco, and alcohol: a case for multifactor disease. *J Oncol.* 2012; 2012:571862. PMC3270416. [PubMed: 22315596]
40. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey MC, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr.* 2002; 5:1113–1124. [PubMed: 12639222]
41. Kreimer AR, Johansson M, Waterboer T, Kaaks R, Chang-Claude J, Drogen D, et al. An evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer. *Journal of Clinical Oncology.* (In press).

Figure 1. Modeled carcinogenic HPV prevalence across age in the US population aged 14 to 69 years

Reprinted with the journal's permission (Source of the data and legend: Gillison ML *et al*, JAMA 2012; reference 27). Per the authors, age was modeled using restricted cubic splines with 5 knots (age and 3 spline terms). To evaluate the influence of covariates on human papillomavirus (HPV) prevalence across age, the model was adjusted for sex, race, smoking, marital status, and lifetime number of (any) sex partners. Given the standardization for covariates included in the multivariate models, the HPV prevalence curves obtained from the adjusted models are presented at the mean levels of the covariates (sex, race, smoking, marital status, and lifetime number of any sex partners) and aligned with the HPV prevalence curve in the unadjusted models to enable visual display of the data.

Figure 2. Proportion of HPV16 E6 seropositive oropharyngeal cases by lead-time from blood draw to oropharyngeal (OP) cancer diagnosis

Black bars indicate the proportion of oropharyngeal (OP) cases that were HPV16 E6 seropositive; vertical lines indicate 95% confidence interval. Numbers of cases for each time interval are as follows: <5 years, N=54; 5 to 10 years, N=55; >10 years, N=26; Source of the data: adapted from Kreimer AR *et al* Journal of Clin Oncol 2013; reference 41.

Table 1

Sites of HPV-attributable cancers: Proportion of cancer due to HPV, presence of HPV-induced premalignant lesion, and HPV vaccine efficacy.

Cancer Site	% attributable to HPV infection	HPV-induced premalignant lesion	Vaccine efficacy against persistent HPV16/18 infection or premalignant lesion, when available *
Cervix	100	Cervical intraepithelial neoplasia (CIN)	>95%
Anus	90	Anal intraepithelial neoplasia (AIN)	95%
Penis	40	Penile intraepithelial neoplasia (PeIN)	90% [†]
Vagina	40	Vaginal intraepithelial neoplasia (VaIN)	100%
Vulva	40	Vulvar intraepithelial neoplasia (VIN)	100%
Oropharynx	12–72	Unknown	Unknown ^{**}

* In an according-to-protocol or per-protocol susceptible analytic cohort, which is typically restricted to individuals who were HPV DNA–negative and seronegative at baseline and through the vaccination phase.

[†] Against a composite endpoint of penile, perianal, or perineal intraepithelial neoplasia.

** While vaccine efficacy against persistent oral HPV infection is unknown, vaccine efficacy against one-time detection of oral HPV16/18 infection was 93%.