Oral sex and oropharyngeal cancer
The role of the primary care physicians

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Abstract
Background: We aimed to study the prevalence of oral sex and its possible association with human papillomavirus (HPV) 16 infection in the development of oropharyngeal cancer in the US population for possible prevention.

Methods: We conduct a systemic review on the prevalence of oral sex among Americans among different age groups, the prevalence of HPV 16 infection reported in oropharyngeal cancer, and correlation between oral sex and oropharyngeal cancer.

Results: Oral sex is prevalent among adolescents and sexually active adults. Sixty percent of oropharyngeal cancer reported in the United States is associated with HPV 16 infections. Individuals who practiced oral sex with multiple partners are at risk for developing oropharyngeal cancer and need to be informed about practicing safe sex or getting vaccination.

Conclusion: Family physicians will play a key role in prevention and educating the public about the risk of oral sex.

Abbreviations: CIN = cervical intraepithelial neoplasia, CIS = carcinoma in situ, HIV = human immunodeficiency virus, HPV = human papilloma virus, ISH = in situ hybridization, NHANES = national health and nutritional examination survey, PCR = polymerase chain reaction, SEER = Surveillance, Epidemiology, and End Results, STD = sexually transmitted disease.

Keywords: HPV 16, oral sex, oropharyngeal cancer, prevention

1. Introduction
In the United States, the number of people between 20 and 44 years of age is estimated to be 107 million in 2010. This number is projected to increase to 118 million in 2015 based on the United Nations Population Division. This specific age group constitutes the bulk of the work force supporting the American economy and its increasing number of retirees. Thus, any disease affecting this segment of the population is expected to have lasting and serious consequences on the US economy. Recently, a report from Surveillance, Epidemiology, and End Results (SEER) data demonstrated a statistically significant increase of oropharyngeal cancers affecting young people between the age of 20 and 44 years, encompassing all American ethnic groups. The incidence of tonsillar carcinoma increased at an alarming pace in the young (50 years or younger). Hence, oropharyngeal carcinoma is now recognized as a specific disease affecting the young.

The rise of oropharyngeal carcinoma in the United States has been reported to be linked with human papillomavirus (HPV) 16 infection, Presence of the virus DNA can be identified in oropharyngeal cancer biopsy specimens. Transmission of HPV 16 in head and neck cancer was reported to be through deep kissing and orogenital sex. The popularity of oral sex among young adults may have led to an increase of HPV 16 infection, which may be the cause for the current rise of HPV-associated oropharyngeal cancers in the United States and worldwide. The purpose of this review is to assess the prevalence of oral sex and the prevalence of HPV 16-associated oropharyngeal cancers in the United States and worldwide. Understanding the factors associated with HPV epidemiology in head and neck cancer may help clinicians develop strategies to cope with this specific clinical entity in terms of treatment and prevention.

2. Methods
2.1. Literature search strategy
Electronic searches were performed in the following databases: PubMed, Embase, ISI Web of Knowledge (Web of Science), and Google Scholar. In PubMed, the term “Oral Sex” as both key words and Medical Subject Headings (MeSH) term, and the results were combined with searches for the MsSH terms HPV16, oropharyngeal cancer, and US. All “Related Citations” for results
found in PubMed were searched as well. Embase, Web of Science, and Google Scholar were searched using the keywords noted earlier. All identified article titles were then entered into the Web of Knowledge individually, resulting in a list of articles citing the originally identified articles. This list was then culled for the inclusion in the set of articles to be reviewed.

2.2. Selection criteria

Eligible studies for the present review included those in which patients with histologically proven oropharyngeal cancer and HPV 16 infection were reported in the United States. All studies reporting the prevalence of oral sex in all age groups, heterosexual, and ethnic groups in the United States were reported. All studies reported outside of the United States were excluded. However, selected studies outside the United States may be relevant in the Discussion section but were not reported in the Results section. Abstract, case reports, conference presentations, editorials, and expert opinions were excluded. Studies reporting the prevalence of oral sex among homosexual and sexual workers were also excluded as the study targets the frequency of oral sex in the general US population. All duplicated studies were also excluded.

2.3. Data extraction and critical appraisal

The findings from the initial searches were used to decide the clinical outcome of the present review. The primary outcomes were to assess the prevalence of oral sex in the United States and the prevalence of HPV 16 infection in oropharyngeal cancer in the United States. Data was extracted to analyze each article for: the prevalence of HPV 16 infection in oropharyngeal cancer in the United States. As oral sex may be a taboo subject and may not be disclosed depending on age, cultural, ethnic, and socioeconomic groups, all studies reporting oral sex were analyzed to have a crude approximation of the frequency of oral sex in the United States. As oral sex may be associated with oropharyngeal cancer, all studies linking oral sex to HPV 16-induced oropharyngeal cancer are analyzed to identify individuals at risk for developing oropharyngeal cancer.

The University of Arizona Institutional Review Board approved the study as it is a review of the literature and does not require patient consent.

3. Results

3.1. Quantity of trials

A total of 359 references were reported worldwide during the period studied through the 4 search engines after exclusion of duplicate or irrelevant references. A total of 308 were excluded after reviewing the abstract. Fifty-one full papers were assessed. Sixteen articles assessed the prevalence of oral sex. Twenty-three reported the prevalence of HPV 16 in biopsy specimens and 9 linked the prevalence of oral sex to the development of oropharyngeal cancer. After applying the selection criteria, only 23 remained for assessment. A total of 74 references were reported worldwide about the presence of HPV 16 in the biopsy specimen. After applying the selection criteria, only 23 remained for assessment. A total of 9 references linking oral sex to HPV-induced oropharyngeal cancer were analyzed. Figure 1 summarizes the search. As all studies were retrospective, bias could not be excluded.

3.2. Prevalence of oral sex in the United States

In 1993, Janus et al[12] reported the first study of oral sex in America. A survey of 2765 adult men and women reported that 10% of men and 18% of women were engaged in oral genital sex. The following year, Laumann et al[13] conducted a survey of 3432 Americans aged between 18 and 59 years regarding their sexual practice. Only 27% of the men and 19% of women reported having oral sex during the last sexual event. In 2002, Mosher et al[14] conducted a similar survey of 12,571 people 15 to 44 years of age in the United States. This revealed that 90% of men and 88% of women had oral sex with an opposite sex partner. Orogenital sexual activity involved all ages and ethnicities. In another survey of 618 adolescents recruited from 2 California public high schools in 9th and 10th grade, 275 (44%) admitted to have oral sex only or both oral and vaginal sex. Oral sex can begin early, even in middle school children. In a study of 1279 students in this demographic, age 12 to 14 years, 101 (7.9%) reported to have oral sex. Thirty students (2.6%) had participated in oral sex when they were younger than 10 years. Among those engaged in oral sexual activity, two-third had >1 partner. Furthermore, oral sex increases progressively with age. In a survey of 12,571 American men and women aged 15 to 44 years, over 75% had oral sex. Oral sex prevalence was <50% and >80% for the 15- to 19-year-old group and older than 20 years’ group, respectively. Importantly, 10% of the people practicing oral sex used condoms regardless of the age group.[17] A recent trend among college age students is the hook up phenomenon wherein oral sex occurred in 38.4% sexual partners with no romantic attachment.[18,19] Other studies have corroborated the strong relationship between oral sex and age.[20–27] Table 1 summarizes oral sex prevalence according to age in the United States.[12–27]

3.3. Prevalence of HPV 16 infection in oropharyngeal carcinoma reported in the United States

Using ISH technique or PCR, HPV 16 DNA was demonstrated in oropharyngeal cancer biopsies.[6,8,11,28–47] Among 2824 oropharyngeal cancers reported in 23 US studies, HPV 16 was detected in 60.2% of the patients (range: 40%–87%). Table 2 summarizes the prevalence of HPV 16-induced oropharyngeal cancer in the United States.[6,8,11,28–47]
3.4. Correlation between oral sex and HPV16-induced oropharyngeal cancer

Oral sex has been implicated in the development of HPV16-induced oropharyngeal cancer. Individuals with a history of oral sex, multiple partners, and oral HPV 16 infection are at increased risk for developing cancer.[11,36,38,40,48–51] This is highlighted by a case study of 240 patients with oropharyngeal cancer. HPV 16-positive and HPV 16-negative patients had distinct risk factors profiles. Patients positive for HPV 16 had a history of oral sex and multiple oral sex partners. In contrast, HPV-negative patients had no history of oral sex and a strong history of smoking and drinking.[38] This is also corroborated in another study of 356 patients with oropharyngeal cancers. Among the ones who were HPV-positive (n = 315), mean life time oral sex partners were 12.8 compared to 6 for HPV-negative patients (n = 41).[42] Individuals with multiple life-time oral sex partners are particularly vulnerable to the development of HPV-induced oropharyngeal cancer. Using PCR, ISH, and serology to identify patients with and without HPV 16-induced oropharyngeal cancer, patients with viral-induced cancer had a history of ≥4 life-time oral sex partners compared to the ones without viral infection. Men may be at more risk for developing oropharyngeal cancer compared to women because of the higher number of life-time oral sex partner.[51]

Table 1

| Study                                      | No. of subjects | Age, y | Prevalence | Period of study |
|--------------------------------------------|-----------------|--------|------------|-----------------|
| Janus and Janus[12]                        | 2765            | >18    | 10%–18%    | 1993            |
| Lauman et al[13]                           | 3432            | 18–59  | 19%–27%    | 1994            |
| Mosher et al[14]                           | 12,571          | 15–44  | 88%–90%    | 2002            |
| Brady and Halpern-Felsher[15]              | 618             | Adolescents (NS) | 44% | 2007 |
| Markham et al[16]                          | 1279            | 12–14  | 7.9%       | 2009            |
| Loefler et al[17]                          | 12,571          | 15–44  | 75%        | 2007            |
| Lewis et al[18]                            | 1468            | 18–25  | 38.4%      | 2010            |
| Fielder et al[19]                          | 483             | 18–21  | 40%        | 2012            |
| Gates and Sonnenst[20]                     | 1237            | 15–19  | 49%        | 2000            |
| Bumsamin and Walker[21]                    | 1105            | 12–16  | 10.9%      | 2006            |
| Lindberg et al[22]                         | 2271            | 15–19  | 54%–55%    | 2008            |
| Halpern-Felcher et al[23]                  | 580             | 14.54 (mean) | 19.6% | 2005 |
| Boekeloo and Howard[24]                    | 335             | 12–15  | 18%        | 2002            |
| Hars et al[25]                             | 477             | 18–41  | 89%        | 2007            |
| Chandhara et al[26]                        | 13,495          | 15–44  | 82%        | 2008            |
| Coppen et al[27]                           | 42,099          | 15–24  | 66% (females), 65% (males) | 2010 |

NS = not specified.

Table 2

| Study                                      | No. of patients | Age, y | Technique | Prevalence | Year reported |
|--------------------------------------------|-----------------|--------|-----------|------------|---------------|
| Emnster et al[8]                           | 72              | mean 53.6 | PCR | 69%        | 2007          |
| D’Souza et al[9]                           | 100             | NS     | PCR | 72%        | 2007          |
| Smith et al[10]                            | 67              | NS     | PCR | 34%        | 2004          |
| Nichols et al[11]                          | 44              | NS     | ISH | 61%        | 2009          |
| Westra et al[12]                           | 21              | mean 53 | ISH | 57%        | 2008          |
| Strome et al[13]                           | 52              | mean 61 | PCR | 40%        | 2002          |
| Kong et al[14]                             | 49              | NS     | POR | 67%        | 2009          |
| Ji et al[15]                               | 97              | NS     | POR | 72%        | 2009          |
| Cohen et al[16]                            | 35              | mean 55.8 | POR | 68%        | 2008          |
| Kumar et al[17]                            | 42              | median 55 | PCR | 64%        | 2007          |
| Weinberger et al[18]                       | 107             | median 61 | POR | 61%        | 2004          |
| Beigum et al[19]                           | 45              | NS     | ISH | 82%        | 2005          |
| Ritchie et al[20]                          | 45              | mean 52 | PCR | 42%        | 2003          |
| Gillison et al[21]                         | 240             | NS     | ISH | 38%        | 2008          |
| Singh and Westra[22]                        | 175             | NS     | ISH | 87%        | 2010          |
| Sivathamparam et al[23]                    | 43              | mean: 57 | ISH | 74%        | 2013          |
| Jordan et al[24]                           | 235             | NS     | PCR | 67%        | 2012          |
| Dahlstrom et al[25]                        | 355             | median: 56 | ISH, PCR | 67%        | 2015          |
| Salazar et al[26]                          | 65              | median: 64 | PCR | 35%        | 2014          |
| Worham et al[27]                           | 118             | NS     | POR | 43%        | 2013          |
| Iyaya et al[28]                            | 102             | NS     | ISH, POR | 55%        | 2013          |
| Liu et al[29]                              | 185             | median: 55 | POR | 40%        | 2015          |
| Goodman et al[30]                          | 529             | NS     | PCR | 71%        | 2015          |
| Total                                     | 2824           |        |    | 60.2%      |               |

ISH = in situ hybridization, NS = not specified, PCR = polymerase chain reaction.
between oral sex and HPV 16-induced oropharyngeal cancer.\cite{11,36,38,40,42,48–51}

4. Discussion

To our knowledge, this is the first review on prevalence of oral sex and the emergence of oropharyngeal cancer affecting young American adults through HPV 16 infection. From 1993 to 2002, the percentage of American men and women who admitted to having oral sex increased from 10% to 18% to 88% to 90%. The reported increase in oral-genital contacts affects all ethnic groups, regardless of age, sex, and rural or urban areas.\cite{12–27} Hooking up, that is, sexual interaction between partners who are not dating or in a romantic relationship often involves oral sex because of its convenience. In a study of 483 female college students, 34% admitted to hooking up before college admission. During their first college year, 40% had hooking experience involving oral sex.\cite{19} More ominously, oral sex is becoming popular among adolescents and middle school children who are still psychologically immature and do not grasp the full consequences of their action.

Even though the prevalence of HPV 16 oral infection remains unknown among sexually active adolescents, epidemiologic studies in cervical cancer suggest that they are at highest risk to develop cancer as vaginal sex at young age predisposes to viral infection and development of cervical cancer.\cite{152}

Behavioral studies of adolescents and young adults suggest that this age group is the most vulnerable to sexually transmitted diseases because they tend to have both multiple and older partners and do not practice safe sex.\cite{53–54} In a study of 18,984 adolescents aged 13 to 17 years, 56% of the respondents reported ≥2 partners, 54% had concurrent partners, 69% had sex with older partners, and 35% had sex outside of their ethnic group.\cite{53} The risk of HPV genital infection is also much higher for males who started vaginal intercourse at a young age compared to older males, thus exposing their partners to oral infections if they also practiced oral sex.\cite{15} Condom use was infrequent among adolescents who had multiple partners and a previous history of a sexually transmitted disease.\cite{152–154} Therefore, it is not surprising that among youths who practiced oral sex regularly, condom use was practically nonexistent perhaps because of the misconception that oral sex is relatively safe.\cite{56} In a study of 867 adolescents attending a New York City public high school, 91.8% had a high knowledge about HIV transmission and prevention. However, 40% of these students thought that sexually transmitted disease (STD) germs were harbored only in the vagina or the penis and 20% did not know that condoms could prevent transmission of venereal diseases.\cite{56} Increased awareness of HIV transmission through vaginal intercourse and the low risk of HIV infection through saliva make oral sex a convenient method to engage with multiple partners without the added fear of pregnancy.\cite{25–28} Casual attitudes among adolescents and young adults that oral sex is not real sex leads to carelessness, engaging in cunnilingus–fellatio acts with ≥1 partner with no or little protection.\cite{16,17} Among 12,571 Americans of all ethnic groups aged 15 to 44 years, only 6.4% of the men and 5.7% of the women recalled of using condoms at their last oral sex encounter.\cite{17} Married men and women, individuals with nonmonogamous partners or a higher number of sex partners in one’s life time were less likely to use condoms during oral sex.\cite{17} Male sexual partners of women with genital HPV infection and carriers of HPV 16 are often asymptomatic.\cite{17} If these individuals engage in oral sex with multiple partners without protection, the risk of HPV transmission increases significantly. Conversely, men with multiple sex partners will most likely acquire HPV infection creating a vicious circle linked to sexual promiscuity.\cite{198}

Despite multiple studies on HPV infection in the genital area, little is known about the prevalence of oral HPV infection. D’Souza et al.’s\cite{60} is the first study demonstrating that oral HPV infection rates increase with deep kissing and multiple sex partners suggesting that saliva is a favorable medium for HPV transmission. Even though HPV infection is usually self-limited, in individuals with recent (<6 months) history of oral sex with multiple partners, the infection may not clear up.\cite{199} As an illustration, the prevalence of oral HPV infection is low (0.9%) among 334 patients with genital HPV infection.\cite{60} However, the rate of oral infection can increase significantly if one practice oral sex. In a study of 43 women with genital HPV 16 infection, 53% developed oral infection if they provided (fellatio) and received (cunnilingus) oral sex from their partners suggesting a strong correlation between oral sex and oral HPV infection.\cite{61} Long-term follow-up of women diagnosed with oral HPV infection demonstrated that 55% to 60% of the individuals infected remained infectious at 6 months’ follow-up.\cite{62} The risk of long-term persistent HPV infection is also corroborated in a study of 148 female college students who had persistent genital infection 12 to 28 months later if they had ≥1 sexual partners.\cite{63} Thus, individuals who practice unprotected oral sex with multiple partners may be at risk for persistent infection. To date, the most compelling evidence linking oral sex and persistence of HPV 16 in the oral mucosa comes from the National Health and Nutritional Examination Survey (NHANES). The study included 2116 men and 2140 women aged 20 to 69 years who answered a survey on
sexual behavior and provided oral-rinse sample for HPV 16 detection. Oral sexual behavior was the primary determinant for oral HPV infection regardless of age, race, sex, or sexual preference. Interestingly, young men (30–44 years) had the most lifetime oral sexual partners and had the highest risk of HPV 16 oral infection compared to women, which raises the hypothesis that performing oral sex on a woman increased the chance for infection. More studies need to be done to investigate whether there is a relationship between oral sex, oral HPV 16 infection, and late development of cancer.

HPV 16 has a special predilection for the tonsillar crypts. Its DNA becomes integrated in the host cells inducing tonsillitis. The mechanism of malignant transformation has yet to be elucidated but has been postulated to occur through dysregulation of cell cycle check points in head and neck cancer studies. Among oropharyngeal cancers reported in the United States, 59.7% contained HPV 16 virus. If one postulates that oral sex started to gain popularity in the 90’s because of HIV fear and the average time from HPV infection to cancer development is 12 years, one should see an increased incidence of oropharyngeal cancer in early 2000’s, which would rise rapidly in the next decades as the number of people infected with oral HPV increases.

Epidemiologic studies in the United States support that hypothesis. Both SEER data from and 1973 to 2004 have confirmed the rise of oropharyngeal carcinoma, particularly tonsillar carcinoma, affecting all ethnic groups in the United States compared to other head and neck sites. Compared to older individuals, young patients (younger than 50 years) are at increased risk of developing tonsillar carcinoma. The incidence of tonsillar carcinoma increased from 15% in 1974 to 1983 to 55% in 1994 to 2003 for young patients compared to 26% and 37% for older patients over the same time period. Improvement in cancer-specific survival for tonsillar cancer patients younger than 50 years suggests that the rise in oropharyngeal cancer in the young may be associated with HPV infection. In another study, the rise of tonsillar carcinoma from 1998 to 2003 in the United States was associated with a decrease of head and neck cancer in other sites. As the rate of HPV-positive oropharyngeal cancer increased by 22.5% from 1988 to 2004, it was estimated that the annual number of HPV-positive oropharyngeal cancers in the United States will exceed the annual number of cervical cancers by the year 2020 if the current trend continues. If one considers that the cost owing to HPV-related cervical cancer in women is already prohibitive because of years of life lost and mortality-related productivity cost, the cost owing to HPV-associated oropharyngeal cancer would be much higher because it affects both sexes and the lack of awareness that it may be associated with oral sex.

There could be a worldwide epidemic linked to oral sex as HPV-associated oropharyngeal cancer is also increasing in other countries. Nasman et al reported a steady increase in HPV-associated tonsillar carcinoma in Sweden. The incidence of HPV-positive tumors were respectively 68%, 77%, and 93% for the period reported in 2000 to 2002, 2003 to 2005, and 2006 to 2007. The increase in HPV-positive tumors was also associated with a decrease in prevalence of HPV-negative tumor in the same period suggesting an epidemic of virus-associated carcinoma.

Increased popularity of oral sex and infrequent use of condoms during fellatio may be associated with HPV infection and other orally transmitted sexual disease. A survey of 1373 students aged 16 to 18 years in the United Kingdom revealed that 56% had experienced fellatio or cunnilingus. Only 2% of individuals engaged frequently in oral sex reported consistent use of condom. As a result, the incidence of other sexually transmitted disease is also rising through oral sex. A survey of European countries demonstrated a steady rise of oral syphilis from 1999 to 2007. An international study of 5642 head and neck cancer patients confirmed the hypothesis that oropharyngeal cancers were associated with the practice of oral sex. Individuals with ≥4 lifetime oral sex partners were at increased risk for developing oropharyngeal cancer. Men with an earlier age at sexual debut (<18 years) were particularly vulnerable of developing tonsillar cancer. Women who practiced oral sex were at risk for developing base of tongue cancer. Therefore, unless public health measures are taken to educate the public about the risks of oral sex, prevention of oral HPV transmission, and possibly the need of HPV vaccination for both males and females adolescents, we predict a steady rise of oropharyngeal cancers in the United States and internationally. Simple measures such as use of condoms should significantly reduce the risks of HPV transmission and cancer development. Vaccination should be considered in young individuals practicing oral sex as it has been proven effective in reducing the risk of HPV-induced genital warts. Family physicians will play an increasing role in educating patients about the danger of oral sex and for possible vaccination of individuals at risk. In a study of 2775 females aged 9 to 59 years, only 15.2% of individuals aged 11 to 26 years received vaccination. If efforts for HPV prevention were to be successful, both sexes should get vaccination at a young age if they practice oral sex.

HPV 16 vaccination has been proven effective to reduce the rate of genital infection and subsequent development of cervical carcinoma in situ (CIS), which is often the precursor of invasive cervical carcinoma in young women. A meta-analysis of 20,583 sexually active women aged 15 to 23 years who were randomized between placebo (n = 10,292) or vaccine (n = 10,291) demonstrate a significant reduction of grade 2 to 3 cervical intraepithelial neoplasia (CIN) and CIS among patients who received the vaccine. Other studies also corroborated the vaccine efficacy to reduce pathogenic HPV infection and cervical cancer in young women of all ethnic groups. In the United States, a significant reduction of HPV-associated high-grade CIN has been observed in the period following the introduction of the vaccine. Vaccination was most effective to prevent grade 3 CIN among the age group 15 to 17 years suggesting that if a similar policy is to be implemented for prevention of oropharyngeal HPV infection and cancer development, adolescents of both sexes would benefit the most from the vaccination. Preliminary study suggests that HPV 16 vaccination may decrease the risk of persistent HPV oral infection. Herrero et al reported a study of 7466 women aged 18 to 25 years who were randomized to receive HPV 16/18 vaccine or hepatitis A as placebo. Among 5840 participants who provided an oral sample for HPV 16 infection, only 1 had infection in the vaccine group compared to 15 in the control group, for an estimated vaccine efficacy (VE) of 93.3%. Corresponding efficacy against prevalent cervical HPV 16 infection for the same cohort was 72% suggesting that the vaccine may be effective to prevent both oral and cervical HPV infection. Even though the primary endpoint of the study was to assess VE for prevention of cervical carcinoma, the study raised interesting question whether it may also be effective for oropharyngeal carcinoma as 3611 participants who gave oral sample for HPV testing admitted to have oral sex with single (n = 2105) or multiple lifetime oral sex partners (n = 1516). Future
The prevalence of oral sex has become a threat for both the American population and worldwide because of the risk of oropharyngeal carcinoma associated with HPV 16 infection. Unless public health measures are taken to educate the public about the risks of oral sex, an epidemic of oropharyngeal cancer affecting the young may ensue with serious outcomes. Family physicians will play a crucial role in the fight against oropharyngeal cancer.

### References

1. Population division of the department of Economics and Social Affairs of United Nations Secretariat. World Population Prospects: the 2008 Revision. Available at: http://esa.un.org/unpp.
2. Shiboski CH, Schmidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the U.S population ages 20–44 years. Cancer 2005;103:1843–9.
3. Brown LM, Chock DP, Devesa SS. Oropharyngeal cancer incidence trend: diminishing racial disparities. Cancer Causes Control 2011;22:753–63.
4. Nguyen NP, Ly BH, Bets M, et al. Importance of age as a prognostic factor for tonsillar carcinoma. Ann Surg Oncol 2010;17:8742–9.
5. Nguyen NP, Chi A, Nguyen LM, et al. Human papillomavirus-associated oropharyngeal cancer: a new clinical entity. QJM 2010;103:229–36.
6. Erster JA, Sciutro CG, O’Brien MM, et al. Rising incidence of oropharyngeal cancer and the role of oncogenic human papilloma virus. Laryngoscope 2007;117:2115–28.
7. Ryerson AR, Peters ES, Coughlin SS, et al. Burden of potentially human papilloma virus-associated cancers of the oropharynx and oral cavity in the US, 1998–2003. Cancer 2008;113:2901–9.
8. D’Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papilloma virus and oropharyngeal cancer. N Eng J Med 2007;356:1944–56.
9. 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;135:180–8.
10. D’Souza G, Agrawal Y, Halpern J, et al. Oral sexual behaviours associated with prevalent oral human papillomavirus infection. J Infectious Dis 2009;199:1263–9.
11. Smith EM, Ritchie JM, Summervill KE, et al. Age, sexual behavior, and human papilloma virus infection in oral cavity and oropharyngeal carcinomas. Int J Cancer 2004;108:766–72.
12. Janus SS, Janus CL. The Janus report on sexual behavior. New York: Johnson Wiley & Sons; 1993.
13. Laumann E, Gagnon JH, Michael RT, et al. The social organization of sexuality: sexual practices in the United States. Chicago:University of Chicago Press; 1994.
14. Mosher WD, Chandra A, Jones J. Sexual behavior and selected health measures: men and women 15–44 years of age, United States 2002. Advanced Data 2005;360:1–35.
15. Brady SS, Halpern-Felsher BL. Adolescents’ reported consequences of having oral sex versus vaginal sex. Pediatrics 2007;119:229–36.
16. Markham CM, Peskin MF, Addy RC, et al. Patterns of vaginal, oral, and anal sexual intercourse in an urban seventh-grade population. J School Health 2009;79:193–200.
17. Leichliter JS, Chandra A, Liddon N, et al. Prevalence and correlates of heterosexual anal and oral sex in adolescents and adults in the United States. J Infect Dis 2007;196:1832–9.
18. Lewis MA, Granato H, Blayney JA, et al. Predictors of hooking up sexual behaviors and emotional reactions among college students. Arch Sex Behav 2012;41:1219–29.

### Table 4

| Cancer development sequence | Interventions |
|----------------------------|--------------|
| Personal belief: oral sex is not real sex leading to promiscuity. Individuals at risks: multiple partners, genetic HPV 16 infection, couples practicing both fellatio and cunnilingus, young age (<18 y). Oral HPV 16 infection with special predilection for tonsillar crypts | Public education: oral sex is real sex with the dangers of sexually transmitted diseases. |
| Latency period | Protection during oral sex (example: condoms) |
| Development of oropharyngeal cancer in young individuals | Physician awareness for early detection and treatment. Oral sex history should be elicited in young patients with tonsillar mass or neck nodes. |

HPV = human papilloma virus.
[19] Fielder RL, Carey KB, Carey MP. Are hookups replacing romantic relationship? A longitudinal study of first year female college students. J Adolesc Health 2013;52:657–9.

[20] Gates GJ, Sonenstein FL. Heterosexual genital sexual activity among adolescent males: 1988 and 1995. Fam Plan Persp 2000;32:295–7.

[21] Bersamin MM, Walker S. Correlates of oral sex and vaginal intercourse in early and middle adolescence. J Res Adolesc 2006;16:59–68.

[22] Lindberg LD, Jones R, Santelli JS. Nonsexual social activities among adolescents. J Adolesc Health 2008;43:231–8.

[23] Halpern-Felsher BL, Cornell JL, Kropp RV, et al. Oral versus vaginal sex among adolescents: perceptions, attitudes, and behavior. Pediatrics 2003;115:845–51.

[24] Boekeloo BO, Howard DF. Oral sexual experience among young adolescents receiving general health examination. Am J Health Behav 2002;26:306–14.

[25] Hans JD, Gillen M, Akande K. Sex redefined: the reclassification of oral-genital contact. Perspect Sex Reprod Health 2011;42:74–8.

[26] Chandra A, Mosher WD, Copen C, et al. Sexual behavior, sexual attraction, and sexual identity in the United States: data from the 2006–2008 national survey of family growth. Natl Health Stat Rep 2011;36:1–36.

[27] Copen CE, Chandra A, Martinez G. Prevalence and timing of oral sex with opposite sex partners among females and males age 15–24 years: United States, 2007–2010. National Health Statistics Reports 2012;56:1–2.

[28] Nichols AC, Faquin WC, Westra WH, et al. HPV-16 infection predicts treatment outcome in oropharyngeal carcinoma. Otolaryngol Head Neck Surg 2009;140:226–34.

[29] Westra WH, Taube JM, Poeta ML, et al. 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;14:366–9.

[30] Strome SE, Sarva A, Brissett AE, et al. Squamous cell carcinoma of the tonsils: a molecular analysis of HPV association. Clin Cancer Res 2002;8:1093–100.

[31] Kong CS, Narasimhan B, Cao H, et al. The relationship between human papillomavirus status and other molecular prognostic markers in head and neck squamous cell carcinomas. Int J Radiat Biol Phys 2009;7:533–61.

[32] Ji X, Sturgis EM, Zhao C, et al. Association of p73 G4C14 to A4T14 repeat length in human papillomavirus-associated head and neck squamous cell carcinomas. Int J Radiat Biol Phys 2009;74:100–7.

[33] Dahlstrom KR, Bell D, Hanby D, et al. Socioeconomic characteristics of patient smoking status, and sexual behavior. Oral Oncol 2015;51:862–9.

[34] Goodman MT, Saraiya M, Thompson TD, et al. Human papillomavirus genotype and oropharyngeal cancer survival in the United States of America. Eur J Cancer 2015;51:2759–67.

[35] Furniss CS, McLean MD, Smith JF, et al. Human papillomavirus 16 and head and neck squamous cell carcinoma. Int J Cancer 2007;120:1366–72.

[36] Schwart SM, Dalinge JR, Moody DR, et al. Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. JNCI 1998;90:1626–36.

[37] Herrero R, Castellsague X, Pawlita M, et al. Human papillomavirus and oral cancer: The International Agency for Research on Cancer Multicenter study. JNCI 2003;95:1772–83.

[38] Chaturvedi AK, Graubard BI, Brousnan T, et al. NHANES 2012 findings: association of sexual behavior with higher prevalence of oral oncogenic human papillomavirus infection in US men. Cancer Res 2013;73:2468–77.

[39] Louie KS, de Sanjose S, Diaz M, et al. International agency for research on cancer multicenter cervical cancer study groupEarly age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries. Br J Cancer 2009;100:1191–7.

[40] Ford K, Sohn W, Lepkowski J. American adolescents: sexual mixing patterns, bridge partners, and concurrency. Sex Trans Dis 2002;29:13–9.

[41] Diclemente RJ, Wingoog GM, Stonean C, et al. Association of adolescents history of sexually transmitted disease and their current high risk behavior and STD status. Sex Trans Dis 2002;29:503–9.

[42] Giulano AR, Lazcano E, Villa LL, et al. Circumcision and sexual behavior: Factors independently associated with human papillomavirus detection among men of the HIM study. Int J Cancer 2009;124:1251–7.

[43] Cohall A, Kassots J, Parks R, et al. Adolescents in the age of AIDS: myths, misconceptions, and misunderstandings regarding sexually transmitted diseases. J Natl Med Assoc 2001;93:64–9.

[44] Nicolau S, Camargo CG, Stavale JN, et al. Human papillomavirus DNA detection in male sexual partners of women with genital human papillomavirus infection. Urology 2005;65:251–4.

[45] Lu B, Wu Y, Nielson CM, et al. Factors associated with acquisition and clearance of human papillomavirus in a cohort of US men: A prospective study. J Inf Dis 2009;199:52–9.

[46] Beachler DC, Weber KM, Margolick JB, et al. Risk factors for oral HPV infection among a high prevalence population of HPV-positive and at risk HIV-negative adults. Cancer Epidemiol Biomarkers Prev 2012;21:122–33.

[47] Kellokouski J, Syrjanen S, Syrjanen K, et al. Oral mucosal changes a subset of human papillomavirus-associated oropharyngeal carcinogenesis. Hum Pathol 2014;45:92–100.

[48] Sanchez-Vargas LO, Diaz-Hernandez C, Martinez-Martinez A. Detection of human papillomavirus archived clinical tissue and its associated head and neck squamous cell carcinoma survival: a comparison by tumor site and initial treatment. Head and Neck Pathol 2014;8:77–87.

[49] Worsham MJ, Stephen JK, Chen KM, et al. Improved survival with HPV among Africans Americans with oropharyngeal cancer. Clin Cancer Res 2013;19:2486–92.

[50] Iseyeva T, Xu J, Dai Q, et al. Africans Americans with oropharyngeal carcinoma-mediated carcinogenesis. Hum Pathol 2014;45:310–9.

[51] Souza G, Fakhry C, Sugar AE, et al. Six months natural history of oral HPV infection and cervical human papillomavirus in oral mucosa of women with cervical lesions and their relation to oral sex practice. Int J Cancer 2009:124:1251–7.

[52] Sanzana-Vargas LO, Diaz-Hernandez C, Martinez-Martinez A. Detection of human papillomavirus in oral mucosa of women with cervical lesions and their relation to oral sex practice. Int J Cancer 2010;5:255.

[53] D’Souza G, Fakhry C, Sugar AE, et al. Six months natural history of oral versus cervical human papillomavirus infection. Int J Cancer 2007;121:143–50.

[54] Oksenholt P, Aghaizu A, Reid F, et al. Frequency and risk factors for prevalent, incident, and persistent genital carcinogenic human papillomavirus infection in sexually active women: community based cohort study. BMJ 2012;344:e1468.

[55] D’Souza G, Cullen K, Bowie J, et al. Differences in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection. PLoS One 2014;9:e86023.

[56] Kim SH, Koo BK, Kang S, et al. HPV integration begins in the tonsillar crypt and leads to the alteration of P16, EGFRI, and c-myc during tumor formation. Int J Cancer 2007;120:1418–25.

[57] Begum S, Cao D, Gillison M, et al. Tissue distribution of human papillomavirus 16 DNA integration in patients with tonsillar carcinoma. Clin Cancer Res 2005;11:1694–9.
Chaturvedi AK, Engels EA, Anderson EF, et al. Incidence trends for human papillomavirus (HPV) 16-positive oropharyngeal cancer cells. J Natl Cancer Inst 2009;101:412–23.

Ylilato N, Josefsson A, Melbye A, et al. A prospective study showing long-term infection with human papillomavirus 16 before the development of cervical carcinoma in situ. Cancer Res 2000;60:6027–32.

Chaturvedi AK, Engels EA, Anderson EF, et al. Incidence trends for human papillomavirus (HPV) 16-positive oropharyngeal cancer cells. J Natl Cancer Inst 2009;101:412–23.

Ryerson AB, Peters ES, Coughlin SS, et al. Burden of potentially human papillomavirus-associated cancers of the oropharynx and oral cavity in the US, 1998–2003. Cancer 2008;113:2901–9.

Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011;29:4294–301.

Ekweueme DU, Chesson HW, Zhang KB, et al. Years of potential life lost and productivity costs because of cancer mortality and for specific cancer sites where human papilloma virus may be a risk factor for carcinogenesis—United States. Cancer 2008;113:2936–45.

Nasman A, Attnér P, Hammarstedt L, et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-associated carcinoma? Int J Cancer 2009;125:362–6.

Stone N, Hatherall B, Ingham R, et al. Oral sex and condom use among young people in the United Kingdom. Persp Sex Reprod Health 2006;38:6–12.

Vinals-Iglesias H, Chimenos-Kustner E. The reappearance of a forgotten disease in the oral cavity: Syphilis. Med Oral Patol Oral Cir Buc 2009;14:e416–20.

Heck JE, Berthiller J, Vaccarella S, et al. Sexual behaviours and the risk of head and neck cancer: a pooled analysis in the international head and neck cancer epidemiology (INHANCE) consortium. Int J Epidemiol 2010;19:166–81.

Winer RL, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. N Engl J Med 2006;354:2645–54.

Baldwin SB, Wallace DR, Papenfuss MR, et al. Condom use and other factors affecting penile papillomavirus detection in men attending a sexually transmitted disease clinic. Sex Transm Dis 2004;31:601–7.