

Review of the Literature

HPV-Positive Head and Neck Cancers: A Review of the Literature

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Introduction

Currently, over 110 million individuals are infected with sexually transmitted diseases (STDs), costing the U.S. health care system more than 16 billion dollars.¹ STDs caused by the human papillomavirus (HPV) are the most prevalent, affecting an estimated 79 million Americans.² It is predicted that annually another 14 million people will become newly infected with HPV.² This virus is so common that at least 50% of sexually active men and women contract it at some point in their lives.²

HPV is an etiologic factor in cervical cancer and has a strong association with oropharyngeal cancer (OPC). A causal relationship between cervical cancer and a sexually transmitted source was first hypothesized in 1842.³ Today, research shows that HPV is the main cause of cervical cancer.⁴ HPV is also linked with the risk of developing head and neck cancer (HNC), specifically OPC.⁵

Patient risk profiles for OPC and oral cavity cancer differ. Cancers limited to the oral cavity are most commonly carcinogen related and are typically found in older adults who smoke and consume alcohol.⁶ In contrast, OPC is increasingly prevalent in younger adult populations with no histories of smoking or drinking.⁷⁻⁹ Researchers report that HPV infection may explain the development of HNC in individuals who lack the typical risk factors for oral cancer.^{6,10} Certain sexual behaviors are related to greater risk for OPC. While some researchers state that the main risk factor for becoming infected with oral HPV is practicing oral sex,⁷ others also consider open mouth/deep kissing a risk factor.^{6,9}

Adolescents and young adults, aged 15 to 24 years, constitute only 25% of the sexually active population.¹¹ However, according to the Centers for Disease Control and Prevention (CDC), young adults have the highest prevalence of STDs.¹ Research shows that young adults represent over 65% of all

Abstract

Purpose: The human papillomavirus (HPV) is a sexually transmitted disease (STD) that is rampant among young adults and is linked with cervical and oropharyngeal cancers (OPC). As the preventive arm of oral health care, dental hygienists can take the lead in educating the young adult population about risk factors for HPV and OPC. Dental hygienists' active involvement in educational initiatives may help minimize the spread of HPV associated STDs, prevent transmission of HPV to the head and neck region, and decrease the development of OPC.

Keywords: human papillomavirus, oropharyngeal cancer, risk factors, at-risk behaviors, dental hygienists, sexually transmitted diseases

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reported sexually transmitted infections.^{12,13} Young adults may be more willing to engage in risky sexual behaviors, such as oral or anal sex, and thereby increase their risks for developing oral HPV.^{5,7,14} Since the suspected transmission of genital HPV to the oral cavity is due to high risk sexual practices, young adults may be a prime population with whom to discuss HPV and its associated risks.

As the preventive arm of oral health care, dental hygienists should be knowledgeable about oral HPV and its link to OPC. Dental hygienists can take the lead in educating the young adult populations they treat about risky sexual practices, HPV and OPC. Their active involvement in educational initiatives may help minimize the spread of HPV associated STDs, prevent transmission of HPV to the oral cavity and decrease the development of OPC.

Human Papillomavirus

HPV is a complex group of viruses that include over 100 strains. HPV infections are transmitted by direct skin-to-skin contact, with penetrative sex being the most frequent route of transmission.¹⁵ HPVs are categorized according to their ability to convert cells into cancer. Common low risk strains include HPV 2, 4, 6, 11, 13, 32 and those responsible for genital warts, benign cervical changes, recurrent re-

spiratory papillomatosis,¹⁶ and oral conditions, such as squamous cell papillomas, verruca vulgaris, condyloma acuminatum, and focal epithelial hyperplasia.¹⁷ Strains 16 and 18 are high risk and have been linked to cervical cancer and head and neck, particularly OPC.¹⁶ HPV associated conditions are of special interest to oral health care professionals due to the relationship between HPV and HNC.

Risk Factors

Risk factors for HPV infection include high risk sexual behavior and age.⁷ Prevalence rates of HPV infection among sexually active young adults range from 29 to 39%.¹¹ From a representative sample of U.S. females 14 to 59 years of age, Dunne et al found that the prevalence of HPV was highest among those 20 to 24 years of age.¹⁶ Brown et al revealed that over 80% of their study participants, which consisted of females 14 to 17 years old, presented with evidence of HPV infection.¹²

The number of life-time sexual partners and frequency of sexual encounters, whether penetrative intercourse or other intimate skin-to-skin contact, are risk factors for HPV infection.^{7,15} Researchers support the premise that sexual intercourse is the primary route of genital HPV infection and that life-time number of sexual partners and HPV prevalence are associated.^{7,15,18} The chance of oral HPV infection also rises with an increased number of oral sex partners.⁸

HPV and Cervical Cancer

HPV is a main cause of cervical cancer.⁴ HPV 16 and 18, the most common high-risk HPV types, are found in approximately 90% of cervical cancers.¹⁹ More recently, these HPV types have been associated with OPCs, a subset of HNCs.^{7,10,16}

Head and Neck Cancers

HNCs commonly originate in squamous cells and include cancers of the oral cavity, oropharynx, hypopharynx, larynx, sinonasal tract and nasopharynx.²⁰ Globally, head and neck squamous cell carcinoma (HNSCC) is the sixth most common type of cancer,²⁰ with an annual incidence of approximately 400,000 worldwide.²¹ The American Cancer Society estimates that, in 2013, 53,640 new cases of HNSCC will be detected in the U.S. and that these cancers will be responsible for 11,520 deaths.²²

Oral Cancer/Oral Cavity Cancer

The most common oral cavity cancer sites include the anterior two-thirds of the tongue, floor of the

mouth, gingiva, lip vermillion and buccal and retro-molar mucosa, and the hard palate.⁵ The majority of head and neck tumors occur in the oral cavity.²³ In 2000, 300,000 of the 615,000 new cases of oral cavity tumors reported worldwide were squamous cell carcinomas.²⁴

Cancers limited to the oral cavity are most commonly carcinogen related, and are typically found in older adults.⁶ Historically, approximately 80 to 90% of U.S. oral cancer cases have been caused by tobacco and alcohol abuse.²⁵ Nearly 80% of patients with oral cavity squamous cell carcinoma are current or past tobacco users.²⁴ Compared with nonsmokers, these patients have a 5 to 7 times greater risk of developing malignant head and neck tumors.²⁴ Mu-wonge et al found that alcohol and tobacco create a synergistic effect which promotes mucosal permeability to carcinogens.²⁶

Early detection is the key to increased survival rates. Clinical signs and symptoms of oral cavity cancers are often generic and may be mistaken for other common conditions.²⁴ Nearly 80% of early-stage oral cancers are treatable, while individuals with advanced-stage cancers have survival rates of 21%.²⁴ The overall 5 year survival rate for patients with oral cavity squamous cell carcinoma is between 45 and 72%.²⁴ White males have a higher 5 year relative survival rate than African American males.²² Health care professionals must be aware of the possibility of oral cancer, understand the importance of conducting oral cancer exams and be knowledgeable about oral cancer signs and symptoms.

Oropharyngeal Cancer

OPC sites include the base of the tongue, soft palate, uvula, palatine tonsil fossa and oropharynx.⁵ The incidence of OPC is increasing worldwide.^{20,27} While previously a greater risk for OPC existed among individuals who smoked and consumed alcohol,²⁸ an increase of HPV-related OPC in nonsmokers and nondrinkers is currently reported.²⁷⁻²⁹ Younger individuals who lack the usual risk factors for oral cancer are presenting with OPC.^{9,10,30} Researchers examining the association between HPV and the typical risk factors for HNC, tobacco and alcohol use, found little indication that viral status was linked to either habit.⁵ Reports from a phase III cancer therapy trial stated that HPV-positive patients were younger and had less extensive tobacco exposure when compared with HPV-negative patients.³¹ Other studies attribute an HPV etiology to squamous cell carcinoma rather than smoking and alcohol.^{28,29} Pintos et al found an association between HPV and OPC, independent of smoking and alcohol consumption.³⁰ Others suggest that the increase in OPC is caused by an epidemic

of HPV-16 sexually transmitted disease.²⁰ Although previous risk factors for HNSCCs included tobacco smoking and alcohol consumption, HPV infection is a new addition.

Similar to oral cavity cancer, most OPCs originate in squamous cell tissue. In OPCs, the tonsils are the most common site, with the base of tongue following.²⁰ These cancer sites comprise 90% of all OPCs.²⁰ In the U.S., tonsillar cancer accounts for 15 to 20% of all OPCs. Data collected between 1973 and 2001 reveal an increased risk of developing tonsillar cancer among white males aged 40 to 65 years.²⁹ From 1973 and 2004, Chaturvedi et al reported an increase in the percentage of HPV-related OPCs in the U.S.²⁹

In general, survival rates for HPV-related OPC are better than those for non-HPV-related neoplasms.³¹ The estimated 5 year relative survival rate for oropharynx/tonsil cancer stages I, II, III, and IV are 56, 58, 55, and 43%, respectively; and for tongue cancer stages I, II, III, and IV are 71, 59, 47, and 37%, respectively.³² Favorable survival rates for HPV-related OPC may be due to enhanced radiation sensitivity, higher response rates to chemotherapy and lack of field cancerization and cumulative patient exposure to tobacco and alcohol.^{33,34}

Causal Relationship Between HPV and OPC

During the past few decades, HPV DNA has been discovered in approximately 25% of individuals diagnosed with HNSCC.³⁵ In a recent study, researchers found a relationship between the detection of HPV-HR types in oral cells and the existence of HPV-HR types in tumor tissue; HPV-16 was the most frequent genotype detected.³⁶ HPV DNA was identified in 40 to 60% of OPC cases versus only 15% in oral cavity cancer cases.^{10,36}

As previously stated, several sexual behaviors increase the risk for developing OPC.¹⁰ These include number of sexual partners, age at first intercourse and the practices of oral-genital and oral-anal sex.¹⁰ It is reported that the chance of developing oral HPV infection substantially grows with an increased number of lifetime oral or vaginal sex partners.⁸ These findings corroborate results from a cross-sectional study of 2,065 females aged 18 to 29 years in which the number of sexual partners in the past 6 months and the number of lifetime sexual partners were independently related to higher risk for HPV infection and prevalence.¹⁸ Numerous cross-sectional and longitudinal studies report that the risk of HPV infection increases at early sexual debut or when a shorter time frame exists between sexual debut and the onset of the menstrual cycle.³⁷⁻⁴⁰ Compared to women 55 and older, individuals younger than 25 years are

more likely to have had their first intercourse experience before age 18.³⁷ Data from Smith et al revealed that younger patients had higher numbers of sexual partners compared to older patients and that younger-age OPC cases had a greater prevalence of HPV in tumors.⁵ Younger individuals also had a much higher likelihood of engaging in both oral-genital sex and oral-anal sex than did older individuals.⁵ Surveys of young adult sexual behavior suggest that most young adults engage in oral sex prior to vaginal intercourse.¹⁴ Young adults consider oral sex less risky than vaginal intercourse and report having more oral than vaginal sex partners.⁴¹ A U.S. survey found that 38.8% of males and 43.6% of females ages 15 to 19 years had performed oral sex.⁴²

An HPV vaccine is presumed to prevent HPV-related cervical cancer.⁴³ Currently, 2 HPV vaccines, Cervarix (Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant), GlaxoSmithKline Biologicals) and Gardasil (Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18) Vaccine, Recombinant), Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.), are available to protect against low and high-risk HPV types.⁴⁴ Both vaccines are effective against HPV 16 and 18,⁴³⁻⁴⁵ however, only Gardasil protects against HPV 6 and 11 and associated genital warts.⁴⁴ Initially, these vaccines were recommended for females aged 11 to 26 years;⁴⁶ today, one of the vaccines (Gardasil) is also recommended for males aged 11 to 21 years.⁴⁷ The HPV vaccine's ability to prevent OPC is possible but unknown.^{6,9,23}

Communication Regarding Sensitive Topics

Communication between health care providers and patients is essential; however, many health professionals lack the required skills to communicate effectively.⁴⁸ Patient education is a critical aspect of the dental hygienist's role and is the cornerstone of the profession. Consequently, dental hygienists must possess the necessary knowledge and skills to communicate with their patients about HPV.

Health Professionals' Communication

In general, health care providers have limited training in communication skills.⁴⁸ It appears that dentists, physicians, nurses and pharmacists need to improve their communication techniques.⁴⁹ Studies show that most physicians have had minimal education and practice regarding communication and compromised physician-patient communication has been documented.^{48,50} A 2007 study identified lack of time and heavy workloads as barriers to provider-patient communication.⁵⁰ Results from another study showed that several factors contributed to communication deficits: time pressures, fear of "opening a

can of worms," provider discomfort and avoidance, embarrassment, and lack of confidence and expertise.^{51,52}

Health care providers consider discussions regarding accepted health concerns part of their scope of practice, but for various reasons, many avoid discussions about sensitive topics. They may encounter situations where communication is stifled because of the sensitive nature of a topic.⁵¹ In a study aiming to describe health care providers' attitudes toward discussing sexuality-related issues with patients, researchers found that providers rarely discuss these topics with patients.⁵⁰ Lack of training and difficulty in discussing certain personal matters were the primary reasons for not addressing sexuality-related concerns.⁵⁰ Research on nurses' attitudes and beliefs towards discussing sexuality with patients shows that a majority feel that talking about sexuality is one part of their responsibilities.⁵³ Although most doctors and nurses feel that addressing sexual issues are part of their roles, most state they are poorly trained and, thus, unlikely to discuss them with patients.⁵⁴

Dental Hygienists and Patient Education

The main risk factor for oral HPV infection, unsafe sexual behavior, is a sensitive topic. Dental hygienists might avoid initiating conversations with young adult patients and their parents due to discomfort regarding the topic. Nonetheless, dental hygienists have an obligation to promote their patients' well-being by educating and addressing personal and public health concerns with them.

Although not as personal as sexual practices, dental hygienists have counseled patients regarding sensitive health topics, i.e., tobacco cessation.⁵⁵⁻⁵⁷ Many dental hygienists consider initiating conversations related to tobacco use part of their scope of practice, yet barriers exist to integrating a cessation plan into the dental hygiene maintenance appointment.⁵⁶ A survey of 58 dental hygienists reported a deficit in education and training with respect to smoking cessation.⁵⁷ Other barriers to integrating cessation plans into practice include those reported by medical professionals, e.g. too little time, financial limitations, no interest on the part of the patients, respect for individual freedom, lack of experience in providing smoking cessation advice and fear of losing patients.⁵⁶

Dental hygienists have a professional obligation to educate patients about preventing the transmission of oral HPV. A study conducted in 2011 found that while some dental hygienists were willing to initiate HPV-related communication with patients, others were hesitant because of discomfort regarding

the topic and concerns with confidentiality.⁵⁸ When educating young adults about oral HPV and sexual behaviors, dental hygienists must consider the sensitive nature of these topics. Stigmatization often is associated with them. According to McCormick et al, "Societal stigma associated with certain behaviors or conditions often infiltrate the medical encounter and may adversely impact provider communication skills."⁵¹

Given that HPV is the most common sexually transmitted disease among young adults,¹³ and that OPC is on the rise,²⁹ dental hygienists must be knowledgeable about oral HPV and OPC and be proactive in initiating discussions with their young adult patients and parents. Few studies have investigated practicing dental hygienists' knowledge and attitudes regarding oral HPV and OPC;⁵⁹ however, several investigations have addressed these topics with dental students, practicing dentists, nurses and physicians.⁶⁰⁻⁶³ Results from these studies show deficiencies in knowledge regarding oral HPV and OPC and avoidance by these professionals.⁶⁰⁻⁶³

Since many health care providers are reticent to explore sensitive topics, dental hygienists can take the lead in educating young adults about risky sexual behaviors, oral HPV and OPC. In contrast to medical professionals, dental hygienists see their patients more routinely, often every 3 to 6 months. Dental hygiene appointments emphasize prevention, and create an environment conducive to counseling patients about health behaviors, including risky sexual behaviors, HPV and OPC. Studies are needed to present empirical evidence that dental hygienists can help to reduce at risk behaviors of young adults by providing HPV and OPC related education.⁵⁹

Conclusion

HPV is a STD rampant among young adults.¹ It causes cervical cancer and is linked to the occurrence of OPCs.¹⁶ Young adults tend to engage in risky sexual behaviors, making them vulnerable to STDs. Given the reluctance to address sensitive topics among most health care professionals, it is important that dental hygienists adopt a proactive stance. Dental hygienists treat young adults and must be willing to intervene with at-risk patients and have the skill set to be comfortable performing this service. Dental hygiene educators need to consider including HPV-related information in their curricula.

Through educational interventions, hygienists may broaden young adults' knowledge base and shape their attitudes about HPV and OPC and at-risk behaviors. With respect to cervical cancer, HPV may

persist for more than 10 years before transforming from infection to malignancy.²⁷ It is unclear how long oral HPV may persist before transforming from infection to malignancy; however, the possibility of young adults developing OPC in their later adult-hoods exists. Dental hygienists' early interventions may prevent the development of oral HPV infection, OPCs and potentially decrease the incidence of subsequent neoplastic disease.

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References

1. Incidence, Prevalence, and Cost of Sexually Transmitted Infections in the United States. Centers for Disease Control and Prevention. 2013.
2. Sexually Transmitted Diseases (STDs): Genital HPV Infection Fact Sheet. Centers for Disease Control and Prevention. 2013.
3. Sexually Transmitted Diseases (STDs): Genital HPV Infection Fact Sheet. Centers for Disease Control and Prevention. 2013.
4. Rigoni-Stern D. Statistical facts relating to cancerous diseases. *Giorn, Prog Patol Therap.* 1842;2:507-517.
5. zur Hausen H. Papillomaviruses in the causation of human cancers - a brief historical account. *Virology.* 2009;384(2):260-265.
6. Smith EM, Ritchie JM, Summersgill KF, et al. Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers. *Int J Cancer.* 2004;108(5):766-772.
7. Psyrri A, DiMaio D. Human Papillomavirus in cervical and head-and-neck cancer. *Nat Clin Pract Oncol.* 2008;5(1):24-31.
8. Gillison ML. Human papillomavirus-related diseases: oropharynx cancers and potential implications for adolescent HPV vaccination. *J Adolesc Health.* 2008;43(4):S52-S60.
9. 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(9):1263-1269.
10. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol.* 2010;11(8):781-789.
11. 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.
12. Da Ros CT, Schmitt Cda S. Global epidemiology of sexually transmitted diseases. *Asian J Androl.* 2008;10(1):110-114.
13. Brown DR, Shew ML, Qadadri B, et al. A longitudinal study of genital human papillomavirus infection in a cohort of closely followed adolescent women. *J Infect Dis.* 2005;191(2):182-192.
14. Cates W Jr. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. American Social Health Association Panel. *Sex Transm Dis.* 1999;26(4):S2-S7.
15. Halpern-Felsher BL, Cornell JL, Kropp RY, Tschan JM. Oral versus vaginal sex among adolescents: perceptions, attitudes, and behavior. *Pediatrics.* 2005;115(4):845-851.

16. Veldhuijen NJ, Snijders PJ, Reiss P, Meijer CJ, van de Wijgert JH. Factors affecting transmission of mucosal human papillomavirus. *Lancet Infect Dis.* 2010;10(12):862-874.
17. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. *JAMA.* 2007;297(8):813-819.
18. Garlick JA, Taichman LB. Human papillomavirus infection of the oral mucosa. *Am J Dermatopathol.* 1991;13(4):386-395.
19. Lenselink CH, Melchers WJ, Quint WG, et al. Sexual behavior and HPV infections in 18 to 29 year old women in the pre-vaccine era in the Netherlands. *PLoS One.* 2008;3(11):e3743.
20. Hariri S, Steinau M, Rinas A, et al. HPV Genotypes in High Grade Cervical Lesions and Invasive Cervical Carcinoma as Detected by Two Commercial DNA Assays, North Carolina, 2001-2006. *PLoS One.* 2012;7(3):e34044.
21. Ramqvist T, Dalianis T. Oropharyngeal cancer epidemic and human papillomavirus. *Emerg Infect Dis.* 2010;16(11):1671-1677.
22. Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics, 2002. *CA Cancer J Clin.* 2005;55(2):74-108.
23. Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2013. *CA Cancer J Clin.* 2013;63(1):11-30.
24. Shi W, Kato H, Perez-Ordonez 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.
25. Kademan D. Oral Cancer. *Mayo Clin Proc.* 2007;82(7):878-887.
26. Sturgis EM, Wei Q, Spitz MR. Descriptive epidemiology and risk factors for head and neck cancer. *Semin Oncol.* 2004;31(6):726-733.
27. Muwonge R, Ramadas K, Sankila R, et al. Role of tobacco smoking, chewing and alcohol drinking in the risk of oral cancer in Trivandrum, India: A nested case-control design using incident cancer cases. *Oral Oncol.* 2008;44(5):446-454.
28. D'Souza G, Dempsey A. The role of HPV in head and neck cancer and review of the HPV vaccine. *Prev Med.* 2011;53(1):S5-S11.
29. Angiero F, Gatta LB, Seramondi R, et al. Frequency and role of HPV in the progression of epithelial dysplasia to oral cancer. *Anticancer Res.* 2010;30(9):3435-3440.
30. 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.
31. Pintos J, Black MJ, Sadeghi N, et al. Human papillomavirus infection and oral cancer: a case-control study in Montreal, Canada. *Oral Oncol.* 2008;44(3):242-250.
32. Chung CH, Gillison ML. Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. *Clin Cancer Res.* 2009;15(22):6758-6762.
33. Oral Cavity and Oropharyngeal Cancer. American Cancer Society [Internet]. 2011. Available from: <http://www.cancer.org/acs/groups/cid/documents/webcontent/003128-pdf.pdf>.
34. 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.
35. 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.
36. Dahlstrand HM, Dalianis T. Presence and influence of human papillomaviruses (HPV) in Tonsillar cancer. *Adv Cancer Res.* 2005;93:59-89.
37. 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.
38. de Sanjose S, Cortés X, Méndez C, et al. Age at sexual initiation and number of sexual partners in the female Spanish population results from the AFRODITA survey. *Eur J Obstet Gynecol Reprod Biol.* 2008;140(2):234-240.

39. Kahn JA, Rosenthal SL, Succop PA, Ho GY, Burk RD. The interval between menarche and age of first sexual intercourse as a risk factor for subsequent HPV infection in adolescent and young adult women. *J Pediatr.* 2002;141(5):718-723.
40. Collins SI, Mazloomzadeh S, Winter H, et al. Proximity of first intercourse to menarche and the risk of human papillomavirus infection: a longitudinal study. *Int J Cancer.* 2005;114(3):498-500.
41. Khan JA, Rosenthal SL, Succop PA, Ho GY, Burk RD. Mediators of the association between age of first sexual intercourse and subsequent human papillomavirus infection. *Pediatrics.* 2002;109(1):E5.
42. Prinstein MJ, Meade CS, Cohen GL. Adolescent oral sex, peer popularity, and perceptions of best friends' sexual behavior. *J Pediatr Psychol.* 2003;28(4):243-249.
43. Mosher WD, Chandra A, Jones J. Sexual behavior and selected health measures men and women 15-44 years of age, United States, 2002. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. 2005.
44. Mammas IN, Sourvinos G, Spandidos DA. Human papilloma virus (HPV) infection in children and adolescents. *Eur J Pediatr.* 2009;168(3):267-273.
45. HPV Vaccine - Questions & Answers. Centers for Disease Control and Prevention. 2012.
46. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection disease in males. *N Engl J Med.* 2011;364(5):401-411.
47. Committee On Infectious Diseases. HPV vaccine recommendations. *Pediatrics.* 2012;129(3):602-605.
48. CDC Press Briefing Transcript: ACIP recommends all 11-12 year-old males get vaccinated against HPV. Centers for Disease Control and Prevention. 2011.
49. Back AL, Arnold RM, Baile WF, Tulsky JA, Fryer-Edwards K. Approaching difficult communication tasks in oncology. *CA Cancer J Clin.* 2005;55(3):164-177.
50. Rozier RG, Horowitz AM, Podschun G. Dentist-patient communication techniques used in the United States: The results of a national survey. *J Am Dent Assoc.* 2011;142(5):518-530.
51. Hautamaki K, Miettinen M, Kellokumpu-Lehtinen PL, Aalto P, Lehto J. Opening communication with cancer patients about sexuality-related issues. *Cancer Nurs.* 2007;30(5):399-404.
52. McCormick KA, Cochran NE, Back AL, Merrill JO, Williams EC, Bradley KA. How primary care providers talk to patients about alcohol. *J Gen Intern Med.* 2006;21(9):966-972.
53. McNulty CA, Freeman E, Bowen J, Shefras J, Fenton KA. Barriers to opportunistic chlamydia testing in primary care. *Br J Gen Pract.* 2004;54(504):508-514.
54. Saunamäki N, Andersson M, Engstrom M. Discussing sexuality with patients: nurses' attitudes and beliefs. *J Adv Nurs.* 2010;66(6):1308-1316.
55. Haboubi NH, Lincoln N. Views of health professionals on discussing sexual issues with patients. *Disabil Rehabil.* 2003;25(6):291-296.
56. Parker DR. A dental hygienist's role in tobacco cessation. *Int J Dent Hyg.* 2003;1(2):105-109.
57. Ramseier CA, Fundak A. Tobacco use cessation provided by dental hygienists. *Int J Dent Hyg.* 2009;7(1):39-48.
58. Edwards D, Freeman T, Roche AM. Dentists' and dental hygienists' role in smoking cessation: an examination and comparison of current practice and barriers to service provision. *Health Promot J Austr.* 2006;17(2):145-151.
59. Daley E, DeBate R, Dodd V, et al. Exploring awareness, attitudes, and perceived role among oral health providers regarding HPV-related oral cancers. *J Public Health Dent.* 2011;71(2):136-142.

60. Bigelow C, Patton LL, Strauss RP, Wilder RS. North Carolina dental hygienists' view on oral cancer control. *J Dent Hyg.* 2007;81(4):83.
61. Cannick GF, Horowitz AM, Drury TF, Reed SG, Day TA. Assessing oral cancer knowledge among dental students in South Carolina. *J Am Dent Assoc.* 2005;136(3):373-378.
62. Maybury C, Horowitz AM, Yan AF, Green KM, Wang MQ. Maryland dentists' knowledge of oral cancer prevention and early detection. *J Calif Dent Assoc.* 2012;40(4):341-350.
63. Kwan TT, Lo SS, Tam KF, Chan KK, Ngan HY. Assessment of knowledge and stigmatizing attitudes related to human papillomavirus among Hong Kong Chinese healthcare providers. *Int J Gynaecol Obstet.* 2012;116(1):52-56.
64. Applebaum E, Ruhlen TN, Kronenberg FR, Hayes C, Peters ES. Oral cancer knowledge, attitudes and practices: A survey of dentists and primary care physicians in Massachusetts. *J Am Dent Assoc.* 2009;140(4):461-467.