The “HPV Discussion”: Effective Use of Data to Deliver Recommendations to Patients Impacted by HPV

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No sponsorships or competing interests have been disclosed for this article.

Abstract

Objective. The dramatic rise in oropharyngeal squamous cell carcinoma associated with the human papilloma virus (HPV) has brought significant change to the interaction between patients and head and neck oncologists. HPV-induced cancers are generally the result of elements from the patient’s sexual history, and otolaryngologists are generally less experienced than primary care physicians in addressing patient questions relating to sexual history and practices. This article addresses questions commonly posed by patients relating to HPV-induced head and neck cancers, issues related to HPV vaccination, and surveillance of HPV-related lesions. Supporting data are provided such that physicians may be better equipped to sufficiently address patient queries on this topic.

Data Sources. Available peer-reviewed literature and clinical practice guidelines.

Review Methods. Assessment and discussion of specific topics by authors selected from the Head and Neck Surgery Education Committee of the American Academy of Otolaryngology—Head and Neck Surgery Foundation.

Results. An educational “miniseminar” resulted in a notable increase in attendee knowledge and comfort regarding oropharyngeal squamous cell carcinoma counseling for patients in the setting of HPV-positive disease.

Conclusions and Implications for Practice. The dramatic increase in HPV-associated head and neck cancers has resulted in a changed paradigm of the physician-patient interaction. Care providers in today’s environment must be prepared to counsel patients regarding sexually transmitted diseases and high-risk sexual behaviors. Examination of the existing data provides the foundation with which to construct a framework in which physicians can effectively communicate information and recommendations as they pertain to HPV-related carcinoma.

Keywords

head and neck cancer, oropharyngeal cancer, human papilloma virus, HPV, patient counseling

Received March 16, 2015; revised April 27, 2015; accepted July 2, 2015.

The changing demographic of oropharyngeal cancer is well recognized. There has been a transition from the traditional risk factors of tobacco and/or alcohol use, with the majority of patients today having human papilloma virus (HPV)–related oropharyngeal squamous cell carcinoma (OPSCC). Indeed, HPV-associated OPSCC has increased by 225% from 1988 to 2004, while HPV-negative tumors of the oropharynx decreased 50% over the same period. As a result, it is projected that the number of HPV-associated OPSCC cancers will surpass the incidence of cervical cancer by 2020.¹

Patients with HPV-positive tumors generally lack the traditional risk factors of tobacco and alcohol use and more commonly are male than female. Their sexual histories are generally characterized by a greater number of past partners, with oral sex encounters being most prominent with regard to risk.² Not surprising, patients presenting with virus-induced, as opposed to tobacco-induced, tumors have many questions relating to the etiology of their disease, since data suggest that the current knowledge of this risk factor is lacking.³ As the HPV epidemic has developed, the desire among

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This article was presented as a miniseminar at the 2014 AAO-HNSF Annual Meeting & OTO EXPO; September 21-24, 2014; Orlando, Florida.

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Discussion

Transmission of HPV Infection

HPV is the most common sexually transmitted infection in the United States. Seventy-nine million Americans are currently infected, and 14 million become infected annually. Initial HPV infection is typically asymptomatic, as is the period of infectivity; indeed, the majority of infections are cleared by the immune system without the individual ever knowing about the infection. A minority of infections become chronic, and symptoms occur years, even decades, later (condylomata for low-risk infections and cancer for high risk infections).

Currently, the best evidence for how HPV is transmitted comes from the study of cervical and anogenital disease. HPV is most commonly spread via vaginal or anal sex, and worldwide, HPV remains a primarily cervical and anorectal subsite–oriented disease. The prevalence of oral HPV infection is 5- to 10-fold lower than that of genital infection. Globally, HPV malignant disease remains predominantly a disease of women, due largely to the worldwide burden of cervical disease; in countries with robust cervical cancer screening practices, the gap in incidence between genital and oral disease appears to be narrowing. The natural history of HPV malignancy appears to vary significantly by sex and by anatomic site. While the data mature for oral HPV infection and natural history, we base our knowledge and hypotheses on the data from anogenital disease while taking into account the emerging data on oral infection. One major point to consider is that individuals cannot know when they were infected, if they infected a partner, or if they may be currently infectious.

HPV specifically infects the basal keratinocytes of stratified squamous epithelium—hence, its propensity to infect and cause cancer or warts of the cervix, anus, penis, vulva/vagina, and upper aerodigestive tract. For infections of the anogenital region, the overlying stratified squamous epithelium protects the basal keratinocytes, and microabrasions of the epithelium, such as those produced by the friction of sexual intercourse, are required for the virus to have access to the underlying target cells. Interestingly, the basal keratinocytes of the palatine and lingual tonsils are naturally exposed in the base of the tonsillar crypts, perhaps explaining the proclivity of infection and subsequent cancer at these sites of the oropharynx. Additionally, it is hypothesized that tonsillar crypts may trap viral particles and allow for a longer period of exposure to target cells. Although not well described currently, there is a possibility that prophylactic tonsillectomy will become more common to address future risk. Regarding oral HPV infection, there is a reported 7% point prevalence, and most infections are eradicated by the immune system in 9 to 12 months. Oral infection demonstrates a bimodal age distribution, with the

Methods

A framework for navigating patient encounters with respect to HPV-positive cancers is presented here. Through analysis of the available peer-reviewed literature and published practice guidelines, selected authors solicited from the Head and Neck Surgery Education Committee of the American Academy of Otolaryngology—Head and Neck Surgery Foundation discussed HPV transmission, common patient questions, HPV vaccination, and surveillance of HPV-related lesions. The audience response system was used to identify attendee knowledge before and after the oral presentations.

Results

A recent miniseminar given at the Annual Meeting of the American Academy of Otolaryngology—Head and Neck Surgery Foundation polled audience members using the audience response system and revealed gaps in the knowledge of the attendees. Although 89% of physicians always or sometimes spoke with their OPSCC patients about HPV, only 26% felt that they had adequate knowledge of HPV (transmission, impact, etc) to counsel their patients (“The ‘HPV Discussion’: The Latest Data and How to Counsel Patients,” American Academy of Otolaryngology—Head and Neck Surgery Foundation Annual Meeting; September 24, 2014; Orlando, Florida). A follow-up question revealed that only 44% were aware of the current Centers for Disease Control and Prevention guidelines for HPV vaccination. The miniseminar discussed HPV transmission, vaccination, patient questions, and the management of benign lesions. Following the directed educational effort, 78% of the attendees felt that they had adequate knowledge of HPV to answer patient questions, and 82% felt comfortable about their knowledge of the current Centers for Disease Control and Prevention guidelines for HPV vaccination. Other educational deficits were identified as well, which were addressed by the speakers.
largest peak in infection occurring between 55 and 64 years of age and a second smaller peak between 30 and 34 years.10

HPV is transmitted through a number of sexual activities: vaginal sex, anal sex, oral sex, simple genital to genital contact, as well as possible autoinoculation; the latter includes possible digital transmission or transmission via other objects, such as sex toys.11 As such, while condom or other sexual barrier device use is advocated, it is by no means sufficient to prevent HPV infection, as the virus can infect areas not covered by the barrier method.13 The transmission of oral and genital HPV appears to be highly correlated with sexual activity, including early onset of sexual activity and increasing number of lifetime sexual partners. Oral infection also appears to be correlated with increasing number of oral sexual partners and possibly with open-mouth kissing. Finally, there is an increased risk of transmission of HPV associated with higher-risk behaviors, such as current tobacco use, marijuana use, and alcohol use.2,14

As mentioned before, oral HPV infection and subsequent disease is 2 to 3 times more likely in men than in women, in contrast to anogenital disease, which demonstrates a female preponderance. There are several hypotheses for this observation: (1) men appear to have more lifetime sexual partners than women; (2) mucosal epithelium may be more “infective” than keratinized epithelium, and thus men may be more at risk with respect to oral sexual activities with women than vice versa; and (3) there are likely yet-to-be-defined sex-based differences in the natural history and cofactors of HPV infection.11,15

HPV Vaccination

Given the prevalence of human papillomavirus in the general population and the corresponding benign, premalignant, and malignant diseases that can come from persistent infection, there is an obvious incentive to curtail the propagation of the disease through behavior modification and vaccination. The goal of vaccination is to generate a durable host immune response to the viral strains prior to exposure, therefore protecting the individual against infection. The downstream benefit would be to lessen the infection burden in the general population, reduce the risk of exposure, and theoretically diminish the rate of HPV-related tumors. The ideal vaccine would be not only safe and effective but easy to administer and would come at an acceptable cost. Within the United States, 2 current vaccines are approved by the Food and Drug Administration: Gardasil (Merck & Company) and Cervarix (GlaxoSmithKline).

Gardasil is a quadrivalent vaccine that protects against HPV 6, 11, 16, and 18, and it is the only current HPV vaccine that is Food and Drug Administration approved for use in both males and females. It is made up of virus-like proteins based on the L1 capsid of the virus structure. As a result, individuals receiving the vaccine are not at risk for developing a true viral infection, even in the setting of underlying immunocompromise. The immune protection occurs through the generation of serum IgG to the L1 capsid protein. For the vaccine to be effective, it needs to be instituted prior to infection by the virus. As a result, it is ideally administered prior to the initiation of sexual activity. Gardasil is recommended for use in girls and boys aged 11 to 12 years, but it can be given as early as 9 years. For girls aged 13 to 26 years having not received vaccination, it is recommended that a vaccination regimen be given.16 In boys, vaccination is recommended until age 21.17

For females, the goal of the vaccine is to decrease the risk for development of vulvar, vaginal, cervical, and anal cancer, as well as to decrease the risk of genital warts and benign and premalignant lesions. In males, the primary indication is to reduce anal and penile cancer, as well as genital warts and other benign and premalignant lesions. While HPV vaccination for prevention of oropharyngeal cancer is not currently a recognized indication by the Food and Drug Administration, it is believed that it will likely be a downstream benefit, and thus is endorsed by most health care professionals.

Gardasil is administered via an intramuscular injection at 0, 2, and 6 months. There have been no severe complications directly linked to HPV vaccine administration, but it is contraindicated in individuals with a yeast allergy. The most common side effect is headache, which occurs in up to one half of patients. In addition, there is a risk of syncope, which has been reported following other intramuscular vaccinations. As a result, it is recommended that a patient be observed for 15 minutes following administration. Additional severe side effects have not been reported, such as the development of Guillain-Barre syndrome, stroke, venous thromboembolism, seizures, and anaphylaxis.18

Cervarix is a recombinant bivalent vaccine against HPV 16 and 18. Unlike Gardasil, Cervarix is approved for use only in females. The recommended age of administration is the same as Gardasil, and it is administered as a 3-shot series given intramuscularly at 0, 1, and 6 months.18

Vaccine efficacy. Early studies confirm that both HPV vaccines are highly effective. Villa and colleagues demonstrated a 96% success rate at inducing a host immune response in individuals receiving all 3 doses.19 In looking at the at-risk population in the United States, Markowitz et al found that the rate of persistent HPV infection went from 11.5% in 2003-2006 (prevaccine era) to 5.1% in 2007-2010. In this cohort of patients, the efficacy rate was 82% for those who received at least 1 dose of the vaccine.20

There are at present very few data addressing the effectiveness of HPV vaccination at preventing oral and oropharyngeal infection. Herrero et al studied a group of 7466 women in Costa Rica who were randomized to receive either a bivalent vaccine against HPV 16 and 18 or a hepatitis A control vaccine. Ultimately, it was observed that the HPV vaccine was 93.3% effective at preventing oral and oropharyngeal HPV infection.21 However, due to the long latent period between infection and carcinogenesis, as well as the fact that other confounding variables exist (eg, tobacco exposure), studies looking directly at the reduction in oropharyngeal cancer due to vaccination are unlikely.
**Vaccine implementation.** Since its rollout in 2006, the utilization of HPV vaccination in the US population has been low but is improving. Based on 2010 data from the Centers for Disease Control and Prevention, 49% of girls aged 13 to 17 years had received 1 dose of the vaccine, and only 32% had received the full 3-dose regimen. In a follow-up assessment in 2012, 33.6% of girls in this age group had received all 3 doses, while only 6.8% of males completed the full course. The main reason cited for the lack of utilization was that physicians did not recommend it.

In summary, the currently available HPV vaccines are indicated for use in girls aged 9 to 26 and boys aged 9 to 21, with the goal of administering prior to the onset of sexual activity and potential viral exposure. Both vaccines have been shown to be safe and effective, but their utilization to date has been low, primarily due to the lack of endorsement by physicians. In an effort to increase implementation and substantially decrease the burden of HPV infection and HPV-related cancer in our population, educational initiatives aimed not only at children and parents but also their treating doctors will likely be necessary.

**Surveillance and Management of Benign HPV Lesions**

After completion of definitive treatment for OPSCC, the National Comprehensive Cancer Network recommends posttreatment baseline imaging of the primary and neck and a structured regimen of evaluations based on history and physical examination. Neck and/or chest imaging is recommended as clinically indicated (not explicitly defined), and surveillance imaging of the chest is suggested in patients at high risk for lung cancer—which includes patients (1) an age of 55 to 74 years and a 30–pack year history of smoking and a duration of smoking cessation <15 years or (2) an age >50 years and a >20–pack year history of smoking and 1 additional risk factor of radon exposure, occupational exposure, cancer history, family history of lung cancer, or pulmonary disease history.

Positron emission tomography (PET)–computed tomography (CT) is routinely used as a surveillance tool in patients with head and neck squamous cell carcinoma treated with chemoradiation. Timing of this modality posttreatment remains controversial, with recommendations varying from 6 to 16 weeks. A negative posttreatment PET-CT result has the potential to identify patients who are at low risk of early recurrence. A recent study examined the reliability of 3-month posttreatment PET-CT in patients with HPV-associated OPSCC. This study found the sensitivity of a 3-month posttreatment PET-CT to be 33% for the primary site and 63% for the regional site of recurrence.

To screen patients for second primary cancer and distant metastasis, the value of PET-CT scanning has also been put under question, since the majority of patients presenting with recurrent disease are symptomatic and/or are noted to have physical findings at presentation. In view of these characteristics, Crandley et al reported that the combination of a thorough physical examination and chest CT would have detected 92.6% of distant metastasis and second primary cancer. In their retrospective analysis looking at patterns of distant metastasis and second primary cancer, patients with stage 3 and 4 HPV-related OPSCC would be best assessed following treatment with chest CT every 4 to 6 months for the first 2 years posttreatment and afterward with chest CT every 12 months for years 3 to 5.27

A number of recent publications have examined the use of laboratory testing methods to study disease recurrence and prognosis. HPV polymerase chain reaction testing, HPV in situ hybridization analysis, immunohistochemical staining for p16, and other techniques have been studied in this regard. When using pretreatment HPV 16 status to screen for HPV 16–positive OPSCC, Ahn et al found that HPV 16 DNA detection in both plasma and saliva rinse samples demonstrated 88% specificity and 100% positive predictive value. When saliva HPV DNA status was combined with plasma HPV DNA status, patients with HPV-positive status in either source had significantly worse recurrence-free survival and overall survival. Thus, quantitative polymerase chain reaction detection of HPV DNA in post-treatment surveillance saliva and plasma samples could function as a valuable prognostic biomarker of recurrence-free survival and overall survival in patients with HPV-positive OPSCC.

**Management of benign disease.** One of the aspects of patient management relates to the assessment of new oral lesions noted in the head and neck in examination of patients following treatment. Much of the literature relating to HPV genotypes has focused on the relationship of this group to anogenital warts as well as benign cutaneous lesions. At least 40 HPV genotypes can infect genital skin and mucosa. As such, HPV genotypes are divided into those that carry a high risk of causing high-grade dysplasia and those that do not. The latter group, resulting in low-grade dysplasia, condylomata, and other warts, is described as low risk.

In this regard, it is important for the clinician to be familiar with the following commonly noted lesions in the oral cavity: verruca vulgaris (common wart), multifocal epithelial hyperplasia (Heck disease), condyloma acuminatum (venereal wart), and oral squamous papilloma. See Laskaris30 for an excellent atlas of images of the lesions described here.

**Verruca vulgaris.** Verruca vulgaris is principally caused by HPV 2 and HPV 4, and this cutaneous lesion is most commonly observed in children on the hands and fingers. Verruca vulgaris is uncommon in the mouth. When present in the mouth, this wart is a well-circumscribed growth of squamous epithelium with prominent hyperkeratosis, giving it a white pebbly or papillary surface. Histologically, it is characterized by having a heavy granular layer and koilocytes. The oral lesions resemble those on the skin both clinically and microscopically, and they occur via autoinoculation of fingers to mouth.

**Multifocal epithelial hyperplasia.** Heck disease most commonly presents in children as multiple small, slightly elevated, and minimally keratinized papules located mainly on the tongue as well as labial and buccal mucosa. They are caused by HPV 13 and HPV 32, with the lesions occurring in a tight cluster, giving a cobblestone appearance to the
mucosa. The risk factors for infection include crowded unhygienic living conditions and the HLA-DR4 allele. These lesions have also been reported in immunosuppressed patients. Spontaneous regression of the lesions, like verrucae, is common after months to years.

**Condyloma acuminatum.** Venereal warts are regarded as a sexually transmitted disease and are most common in the anogenital region. Most are caused by low-risk genotypes 6 and 11 but may harbor high-risk HPV genotypes 16 and 18. Oral condylomata are more common in adolescents and young adults but are not limited to that age group. The resulting oral lesions are sessile or pedunculated, with papillary projections. On histopathologic sections, they have the typical papillary pattern where koilocytes may also be observed.

Because of the presence of intraepithelial neoplasia (dysplasia) in anogenital condylomata, high-grade dysplasia and squamous cell carcinoma in the anogenital region are often found. Condylomata show low-grade dysplasia that may progress to high-grade dysplasia or carcinoma, particularly if infected with a high risk genotype. Compared with the number of benign squamous papillomas and condylomata diagnosed in an oral pathology laboratory, dysplastic papillomatous lesions are distinctly uncommon (<1%) with many occurring in immunosuppressed individuals.

**Oral squamous papilloma.** Squamous papillomas occur over a wide age range, with an estimated prevalence of 1 per 250 adults. They appear as an exophytic, sessile, or pedunculated growth of squamous epithelium, with papillary projections and can appear pink or white, depending on the degree of keratinization. Due to this broad range of features, squamous papillomas are often difficult to distinguish from condyloma acuminata or verruca vulgaris clinically and pathologically. Squamous papillomas are presumed to be caused by low-risk types of HPV, and genotypes 6 and 11 have been detected in approximately 50% of lesions.

Oral verruca vulgaris, multifocal epithelial hyperplasia, squamous papilloma, and condyloma acuminatum are also infectious, and because only a few oral squamous papillomas and condylomata can be dysplastic, surgical excision is the recommended treatment. Recurrence of these types of warts is unusual and is believed to be caused by incomplete removal of infected epithelium at the base of the lesion. Continued reformation or the transition of an ongoing subclinical lesion to a clinical lesion causes new lesions to appear. Malignant transformation has not been reported in verrucae or multifocal epithelial hyperplasia. Oral condylomata and squamous papillomas that harbor high-risk HPV genotypes are associated with increased risk for dysplasia and development of squamous cell carcinoma. Similar to dysplastic leukoplakia, dysplastic papillomatous lesions require continued periodic follow-up to rule out recurrence of dysplasia. There is no method to treat subclinical oral infection other than prevention.

**Common Patient Questions**

This section reviews appropriate evidence-based answers to questions commonly posed by patients seeking to gain more information about HPV-related infections and cancer.

“I Have Never Smoked—How Did I Get Cancer in the Throat?”. Patients must be counseled that HPV is a sexually transmitted disease that has the potential to create mutations in cells that eventually cause malignant tumors. This is a very different mechanism from chronic exposure to inhaled/ingested carcinogens that occurs with chronic tobacco and/or alcohol use. It is not possible to establish when or from whom infection was first contracted. Data regarding transmission of infection are somewhat limited. The Centers for Disease Control and Prevention suggests that oral sex is a likely mechanism of transmission while open-mouth kissing is considered a possible mode of transmission as well. Still, the likelihood of contracting HPV when engaging in these activities with someone who is infected is not known. A case-control analysis demonstrated an increased risk of infection with an increased number of vaginal sex partners (>26; odd ratio = 3.1) or oral sex partners (>6; odd ratio = 3.4). Furthermore, some data suggest a 2- to 3-fold increased risk of HPV-positive OPSCC in partners of cervical cancer patients.

Regarding incidence and clearance of infection, a study of >1600 healthy men was performed in Brazil, Mexico, and the United States. Acquisition of oral oncogenic HPV was associated with smoking and nonmarried status but was not associated with reported sexual behaviors. Median duration of infection was 7 months, and most infections were cleared within 1 year. Of note, only 4.4% of men in this study acquired an oral infection during the study period.

“Is my spouse at risk for cancer? Can we engage in sexual activity?”. Existing evidence does not support a need for abstinence of sexual activity between stable partners. A study of 163 patients with HPV-positive OPSCC along with 93 partners was recently conducted. In this cohort, the rate of oncogenic oral HPV infection in partners was 1.2%, whereas the rate in the general population is 1.3%. A study directly examining the incidence of HPV-positive OPSCC occurring in spouses/partners of those afflicted with HPV-positive OPSCC has not yet been performed. However, given the relatively low rate of tumor development among those with a history of infection and/or applicable risk factors, it seems reasonable to expect that the rate of incidence of HPV-positive OPSCC among spouses/partners of patients diagnosed with OPSCC is very low. Furthermore, ceasing sexual activity after diagnosis of cancer would not seem to affect the sharing of HPV that has already occurred. However, it should be noted that stable couples are not infrequently found to have concomitant genital infections of similar HPV genotypes. Finally, persistent oral HPV infection in one spouse is associated with persistent infection in the other spouse.

With regard to new/future partners, there is presumably a risk of transmission to future partners, although this risk is not yet characterized. The inconsistent use or nonuse of barrier methods has been associated with an increased risk of oral HPV infection and HPV-positive OPSCC, and the use of barrier methods may decrease the risk of disease transmission.
"Is there a test for oral/oropharyngeal HPV infection?". Although detection of HPV through polymerase chain reaction is commonly performed for purposes of pathologic analysis and scientific study,6 there is currently no Food and Drug Administration–approved test for oral/oropharyngeal HPV infection. However, the study of HPV 16 E6 antibodies may hold promise as a future marker of oncogenic infection. Recent data demonstrated that approximately one-third of patients developing a HPV-positive cancer have detectable levels of E6 antibodies prior to diagnosis.42

"Can the infection be passed to my children?". Hugging, bathing, light kissing, and general family contact do not result in virus transmission.5 Thus, passing of the infection to children is highly unlikely.

"Do I need to inform my past partners?". Given that nearly 80% of sexually active individuals will have contact with HPV at some point, there is no need to inform past partners of an HPV-positive tumor.5 As noted above, most infections disappear spontaneously, and the rate of carcinoma development in those who have been infected is very low.

"Will the cancer come back since the tissue is infected?". Two recent studies provided compelling evidence that HPV infection in the oropharynx is generally localized in nature.43,44 In both studies, examination of oropharyngeal subsites outside of that affected by the carcinoma did not have detectable HPV present. Therefore, the “field cancerization” effect that is commonly present in chronic tobacco users does not appear to occur in chronic HPV infection. This finding is borne out in additional data demonstrating a lower rate of second primary tumors in patients treated for an HPV-positive OPSCC.45,46 However, it must be noted that the lower rate of second primary tumors in this patient population is demonstrable only among nonsmokers. Regarding smokers, the rate of second primary tumors approaches that of HPV-negative patients. Given all these data, nonsmoking patients with HPV-positive tumors may be counseled that their risk of a second tumor is lower than that of a patient with tobacco-induced cancer.

"Does vaccination help after the diagnosis of HPV-induced Carcinoma?". There is currently no evidence that HPV vaccination provides any benefit after diagnosis of HPV-positive OPSCC. However, some limited data suggest that vaccination may decrease the severity of HPV-related recurrent respiratory papillomatosis.47

Conclusion

The evolution of OPSCC necessitates evolution in the practice of head and neck cancer therapy. It is imperative that head and neck oncologists of all specialties be aware of contemporary information regarding the transmission, prevention, and vaccination practices pertinent to HPV. Structured educational activities and manuscripts summarizing this information are important adjuncts to continuing education regarding HPV-related disease in the head and neck. It is also critical that head and neck oncologists educate their patients with HPV-related disease to alleviate fear and empower them with the knowledge.

Author Contributions

Samir S. Khariwala, data analysis, drafting, final approval, accountability for all aspects of the work; Michael G. Moore, data analysis, drafting, final approval, accountability for all aspects of the work; Kelly M. Malloy, data analysis, drafting, final approval, accountability for all aspects of the work; Benoit Gosselin, data analysis, drafting, final approval, accountability for all aspects of the work; Richard V. Smith, data analysis, drafting, final approval, accountability for all aspects of the work.

Disclosures

Competing interests: None.

Sponsorships: None.

Funding source: None.

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