



Brief Reports

Is Human Papillomavirus (HPV)-associated Esophageal Cancer due to Oral Sex?

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Abstract

Human papillomavirus (HPV) is one of the most common sexually transmitted infections. It is strongly linked with the development of cervical cancer, and studies are now focusing on HPV infection in extra-genital sites. There is increasing evidence implicating HPV as a risk factor in the development of esophageal squamous cell carcinoma. HPV are transmitted through micro-abrasions in the epithelial surface, and this occurs for oral and pharyngeal cancers. We hypothesize that oral sex (mainly cunnilingus) is the transmission route for the development of HPV-associated esophageal squamous cell carcinoma. In addition, we suggest that the use of a HPV vaccine administered to young adolescents in high risk populations would greatly reduce the incidence of esophageal cancer and other HPV-associated cancers.

Keywords: Esophageal cancer; Human papillomavirus; HPV; Oral sex; Vaccination

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Introduction

Human papillomavirus (HPV), one of the most common sexually transmitted infections (STI) [1], has been known to have oncogenic potential for over five

decades. Beginning with cervical cancer, research is now moving on to the implication of HPV infection in extragenital sites, such as the oral cavity, the oropharynx and the esophagus. The body of evidence implicating human papillomavirus as a risk factor in the development of esophageal squamous cell carcinoma

(SCC) is growing [2, 3]. We recently conducted a meta-analysis which demonstrated an almost three-fold increased risk of developing esophageal SCC if there is local HPV infection (unpublished data) and HPV infection has been found to be an even larger risk factor in the development of other cancer groups, for example oral SCC (OR: 12.3, 95% CI: 6.3 – 36.6) [1] and cervical SCC (OR: 158.2, 95% CI: 113.4 – 220.6) [4]. Knowing this, the next step in further understanding the pathogenesis of this subset of esophageal cancer is looking at the origin of HPV and the method of its transmission.

Human papillomavirus' are known to be transmitted through micro-abrasions in the epithelial surface, whereby the HPV virions have access to the basal cell layer, and are incorporated into the cells[2]. HPV 16 and 18 have been found to be 'high risk' strains, with an increased oncogenic potential when compared to the more common strains, 6 and 11, due to differences in the expression of certain viral oncogenes (eg. HPV E6 and E7) [3]. This step is vital to the oncogenic process and allows for mutation or interaction with tumour suppressor genes[4], in particular binding of HPV oncoproteins E6 to p53 and E7 to retinoblastoma protein (pRb) [3], and is a cause of cell immortality and thus is large part of the carcinogenic process. The friction involved in penetrative sexual intercourse is thought to be one of the main mechanisms for the development of cervical micro-abrasions[3], which allow the process to commence and HPV transmission to occur. In terms of HPV-associated oropharyngeal squamous cell carcinoma (OSCC) research is now being directed to the origin of HPV in the oral cavity, and the methods of transmission, in order to develop preventative measures to decrease the incidence of this disease.

Hypothesis

Along with its prerequisite role in cervical cancer development, HPV is increasingly being implicated in the development of upper aerodigestive cancers, such as oral, or pharyngeal, and, most recently, esophageal SCCs. Genital human papillomavirus is known to be

transmitted primarily through penetrative sexual intercourse which can cause micro-abrasions in the epithelial surface and allow for viral transmission. Considering the small amount of trauma needed to cause these micro-abrasions, it follows that coarse foods, hot drinks and repetitive swallowing, for example, could have the same effect in the esophagus. Given the increased genital HPV prevalence in females and the increased HPV-associated esophageal squamous cell carcinoma prevalence in males, we postulate that oral sexual intercourse, particularly cunnilingus, is a risk factor in the genital-esophageal transmission of the human papillomavirus and thus plays a part in the carcinogenesis of esophageal squamous cell carcinoma. We further hypothesise that due to the small percentage of people participating in oral sex who utilize barrier protection (i.e. condoms), countries with a high risk of HPV-associated esophageal squamous cell carcinoma should consider the introduction of public health immunization programs for people of both genders to decrease the risk for individuals and to aid in reducing the economic burden of disease.

Supporting evidence

Oral-genital transmission of sexually transmitted infections is possible and has been implicated as a route of transmission for both viral and non-viral infections. Viral infections like HIV, Hepatitis C, Herpes Simplex Virus as well as bacterial infections like gonorrhea, syphilis and Chlamydia thachomatis have all been shown to be transmitted via oral-genital sex [5, 6], thus opening up the possibility of other viruses, for example HPV, being transmitted in a similar manner.

Current research suggests that oral-genital transmission of HPV can occur, and thus oral sex may be a factor in the development of oral and or pharyngeal squamous cell carcinoma. Chatterjee *et al.* demonstrated oral-genital transmission of HPV in 1998, when they found that 41.6% of infants born to cervical HPV positive mothers had HPV DNA in the buccal mucosal cells [7]. A study of 452 Swedish patients in 2005 then showed that high-risk oral HPV infection is significantly associated with oral sex [8]. It has also

been revealed that the risk of developing HPV independently, rises with increases in the number of lifetime oral sex partners ($p=0.007$ for trend) [9]. Patients with pharyngeal squamous cell carcinoma have been found to be 3.5 times more likely to have engaged in oral-genital sex than patients with SCC of other head and neck sites [10]. Therefore, it can be seen that oral sex is a factor in oral-genital transmission of HPV and

thus the development of oral and or pharyngeal squamous cell carcinoma. Given the similar strains of HPV being found present in esophageal SCCs as in oropharyngeal SCCs (table 1), we suggest that oral sex is a method of transmission in the development of esophageal mucosal HPV infection and thus esophageal SCC.

Table 1 HPV-associated cancers and the most types of HPV detected in each cancer.

Cancers in which HPV DNA has been detected	Most predominant HPV type
<i>Anogenital Squamous Cell Carcinomas</i>	
Cervix	16, 18
Vagina	16, 18
Vulva	16, 18
Anus	16, 18
Penis	16, 18
<i>Upper Aerodigestive Tract Squamous Cell Carcinomas</i>	
Oral cavity	16, 18
Oropharynx	16, 18
Larynx	16, 18
Tonsil	16
Esophageal	16, 18
<i>Other</i>	
Squamous cell skin carcinoma	Epidermodysplasiaverruciformis-associated HPV
Periungual squamous cell skin carcinoma	
Squamous cell carcinoma of the eye conjunctiva	16, 18

Oral sex is the most common type of non-coital sexual practice, being practiced by over 50% of people over the age of 18 [11]. It has been shown that of the 11% of females and 15% of males aged 15-17 years who had ever engaged in oral sex reported the use of a condom in their most recent oral sex experience. However, even for these young people using condoms, a meta-analysis conducted in 2002 showed that condoms may not prevent genital HPV transmission [12], and though more research must be conducted, it follows that the use of male condoms may not prevent oral-genital HPV transmission either. Conversely, studies have shown that the use of female condoms confers as much protection from STIs as male condoms, and considering the higher prevalence of genital HPV in females and thus, the increased risk to males during oral

sex, this could be an effective method of reducing transmission however, more research is needed to explore this option. However, for the small number of people practicing 'safe' oral sex, the use of male condoms may not prevent the acquisition of oral or esophageal HPV.

Given the possibility of oral-genital HPV transmission, and the possibly ineffective nature of condoms as a preventative measure, it is necessary to develop other preventative strategies to decrease the transmission of HPV and thus decrease the incidence of HPV-associated esophageal squamous cell carcinoma. In 2006, a quadrivalent vaccine (Gardasil) targeting HPV 6, 11, 16 and 18, was introduced in several countries and since then a bivalent vaccine (Cervarix), targeting HPV 16 and 18, has also been introduced.

Together, these vaccinations have demonstrated >90% efficacy against persistent HPV 16 and 18 infection [13].

Economic burden of primary prevention

Given that China is one of the highest risk countries for HPV-associated esophageal squamous cell carcinoma (unpublished data), we assessed the benefit of implementing a vaccination program in Chinese people aged 10-14 years.

The U.S. Census Bureau reported that in 2012 the number of people in China aged 10-14, being the target-group for HPV vaccination [14], is 80,407,556 [15]. Using an estimated cost of vaccinating one person in a school-based program of US\$300 [14], we calculated that the cost of vaccinating the entire target group would be just over US\$24 billion.

We also found the aged standardized risk of esophageal cancer in China is 16.7/100,000 in 2012 [16], and given that the current population in China is estimated at 1,343,240,000 [15], it can be extrapolated that the yearly incidence of esophageal cancer in China would be approximately 224,321. Given the prevalence of HPV DNA in esophageal SCC in China is estimated to be 46.9% [19], we calculated that the yearly incidence of HPV-associated esophageal cancer in China would be approximately 105,206. Using methodology from Sanders *et al.* the vaccine efficacy against high-risk HPV type was estimated at 75% [14], though actually it has been found to be much higher [17]. However, using this 75% estimate, we found that an estimated 78,905 cases of esophageal cancer would be prevented should the vaccine be implemented.

Given that the 5-year survival rate of esophageal cancer patients is 12.5% [18], based on data published by Yabroff *et al.* in 2008, we estimated that the cost of treating each esophageal cancer patient for five years is US\$117,325 [18]. Therefore, given the incidence, the cost of treating esophageal cancer patients in China is estimated to be over US\$26.3 billion. Should the vaccine be implemented and over 78,000 of these cases be prevented, the cost of treating esophageal cancer patients would be reduced to just over US\$17 billion.

Consequently, it can be extrapolated that while the cost of vaccinating all Chinese people aged 10-14 is approximately US\$14.8 billion more than that saved by its implementation, over 78,000 cases of esophageal cancer would be prevented. While the cost difference appears to be large, this is not the only cancer type the vaccine would target – implementation of the vaccine has been shown to prevent up to 98% of cervical intraepithelial neoplasia (CIN) grade 2 or worse [19]. Given that current estimates indicate that 75434 Chinese women are diagnosed with cervical cancer each year [20], implementation of the vaccine would potentially prevent 73925 of these. Using the same method as for esophageal cancer, we calculated the amount saved in the treatment of cervical cancer should be vaccine be implemented at over US\$4.2 billion [18]. Therefore the total amount saved on the treatment of esophageal and cervical cancer patients should the vaccine be implemented would be over US\$19 billion, and over 150,000 patients would be prevented from developing cancer. In addition, the vaccine, given the association between HPV and other cancer types (table 1), has the potential effect the lives of many more people who may have developed other HPV-associated cancers.

Limitations

The evaluation of cost-effectiveness is limited by the assumption that in most cases, HPV is a direct cause of esophageal carcinoma. It is a basic demonstration of the financial implications of implementing the vaccine, and would have different results given the population and incidence HPV and esophageal carcinoma in the country being analysed.

Conclusion

In 2010, it was reported that esophageal cancer is one of only three types of cancer (the others being liver and intrahepatic bile duct and melanoma of the skin), which, between 1990 and 2006, had an overall rise in the mortality rate among males, increasing by 9.7% [21].

This increase demonstrates the need for further research into the causes of esophageal cancer and thus prevention, screening, and treatment options. Should more research be conducted, we believe that it would prove that oral sex, particularly cunnilingus, is a factor in the implantation of HPV DNA into the esophageal mucosa through micro-abrasions in the epithelial surface. This knowledge could facilitate the development of an advocacy program with the aim of changing the perception of oral sex as a 'safe' form of sexual intercourse, and preventing the transmission of many STIs.

The introduction of vaccination programs as a primary preventative measure in high-risk areas for the development of HPV-associated esophageal squamous cell carcinomas, like Asia, and in particular China, could have a huge impact on the number of incident cases of this cancer diagnosed each year. However, the vaccine would also target other HPV-associated cancer groups, and in effect have a much greater influence on incidence rates of over 10 different types of cancer. Should the program be implemented in a country like China, for example, the implementation of a vaccination program would impact on the lives of over 150,000 Chinese people – and considering this is only taking into account esophageal and cervical cancer patients, this is a conservative estimate and the number would, in fact, be much larger.

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