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The Contagious Head and Neck Cancer: The Role of Human Papillomavirus HPV

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Summary

Squamous cell cancer of the head and neck (HNSCC) is an evolving area of clinical and research focus with a rising prevalence of the disease in the female population. Some human papillomavirus (HPV) types act as carcinogens that contribute to the development of HNSCC. The purpose of this article is to discuss the role of HPV in the rise of HNSCC in women, with a focus on shifting clinical practice guidelines.

Commentary

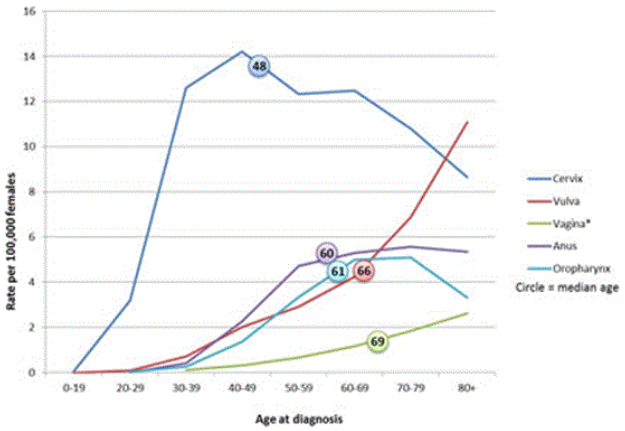
Head and neck cancers of the oropharynx (hereafter abbreviated as HNSCC) typically originate within the moist squamous cell linings of the nasal cavity, lips, oral cavity, salivary glands, tongue, soft palate, pharyx, and larynx [1]. There were over 12,000 new cases of laryngeal cancer and nearly 40,000 new cases of oral and pharyngeal cancer diagnosed in the United States 2014, with 3,610 deaths [2]. HNSCC is the fifth deadliest cancer worldwide [3] with survival rates ranging from 30% for cancers of the oral cavity and pharynx to 50% for laryngeal cancers. Combined 5 year survival rates for all HNSCC cancers are 60.8% [4].

Gender

While men have historically been more likely to develop HNSCC, rates among females are on the rise over recent decades. The incidence by gender varies according to anatomic location however the incidence gap between men and women has been changing over recent decades as the number of female smokers has increased. The male-female ratio is currently 3:1 for oral cavity and pharyngeal cancers. Rising prevalence of HNSCC among women poses a legitimate area of concern [5].

Age

The incidence of HNSCC increases with age, with most patients diagnosed between the fifth and seventh decade of life [6]. Historically, HNSCC has been associated with older males with a history of heavy tobacco and alcohol use [7]. However, emerging data surrounding the incidence and prevalence of HNSCC among younger adults (e.g. 45 years of age and younger) demonstrates that 25% of those affected have no history of significant tobacco or alcohol use [8]. In fact, rates of certain cancers of the oropharynx have increased over the last 30 years among young adults who have never smoked or used tobacco products [9]. In contrast with historical profiles of patients with HNSCC, patients carrying a diagnosis of HPV-associated HNSCC are often non-smokers and non-drinkers and on average 5 years younger than their tobacco-use-associated counterparts [10] (Figure 1).



*The vaginal cancer statistic for women between the ages of 20 and 39 is not shown because there were fewer than 16 cases.

Figure 1: Rates of HPV-associated cancers and median age at diagnosis among women in the United States, 2004-2008.

External Risk Factors

Gender and age aside, most risk factors for the development of HNSCC are environmental in nature and include all forms of tobacco products (loose tobacco, cigarettes, cigars, chewing tobacco, and snuff), ethanol products, laryngopharyngeal reflux (LPR), chemicals (asbestos, chromium, nickel, arsenic, and formaldehyde) and other factors such as ionizing radiation [11]. In spite of growing public awareness and tobacco control efforts resulted in reducing rates of smoking prevalence over recent years in the United States [12] a strong association between tobacco use and onset of HNSCC remains. An additional risk factor, and one of particular importance to women, is the human papillomavirus or HPV. HPV is emerging as a contributor for the shift in HNSCC trends. Presently, the majority of

HNSCC are linked to HPV infection, with similar incident rates of HPV-related HNSCC found in males and females [13]. Oncogenic HPV DNA is found in the majority of oropharyngeal cancers, including a high proportion of those who are non-smokers and do not drink [14]. Currently, of the 7% of adults with oral HPV infections, approximately 3.6% of those are women [4,15]. The remainder of this clinical commentary will discuss issues surrounding increases in HPV-associated HNSCC in women.

What is HPV?

Over 100 different HPV genotypes have been identified, comprising some of the most common viruses in existence. Current CDC estimates are that over 20 million Americans are infected with some form of the virus, with an incidence of over 6 million new infected individuals each year [16]. Rates of infection typically peak among older adolescents and adults, then decline with age. Among sexually active adults, 1 in 2, or 50%, will at some point in their adult lives acquire an HPV infection, with 80% of women acquiring the infection in their lifetime [16-17]. While over 100 different strains or genotypes of the virus have been identified, they are collectively and globally referred to as HPV. Some strains produce visible manifestations, primarily on skin and mucosal membrane regions of the body, including wart like growths on the hands, arms, legs, genitalia, and other areas [16].

While most strains of HPV are considered harmless, spontaneously resolving within two years of onset and with no associated malignancy, a small subset of viruses contributes to the formation of cancerous lesions. Among those infected with some strain of HPV in the United States, approximately 33,000 will develop an HPV-related malignancy each year. Of these, approximately 12,000 will manifest as HNSCC. The two most prevalent strains worldwide are HPV16 (3.2%) and HPV18 (1.4%) [17]. Oncogenic HPVs include these strains, which are responsible for the majority of HPV-related cancers. HPV-16 is responsible for 70 percent of HPV-positive cases of oropharyngeal squamous cell cancer. A 224-gene signature has been found to discriminate HPV16-induced oropharyngeal squamous cell carcinomas. HPV-related oropharyngeal cancers retain HPV16 expression with recurrence [18].

A Contagious Cancer

Anogenital associations

The majority of HPV-associated malignancies affect anal and genital regions. HPV infection accounts for the vast majority of cervical (99.7%) and anal (90%) cancers. Initial evidence supporting ties between HPV and cervical cancer emerged in 1976 [19]. As early as 1933, HPV-associated malignancies were identified in animals [20]. Since that time, research has continued to elucidate ties between the various viral strains and development of cancer. HPV infection is linked to cancers of the cervix, penis, vulva, vagina, and anus [21].

Oral cancer associations

Emerging research has revealed that HPV plays a significant role in the development of HNSCC (Figure 2).

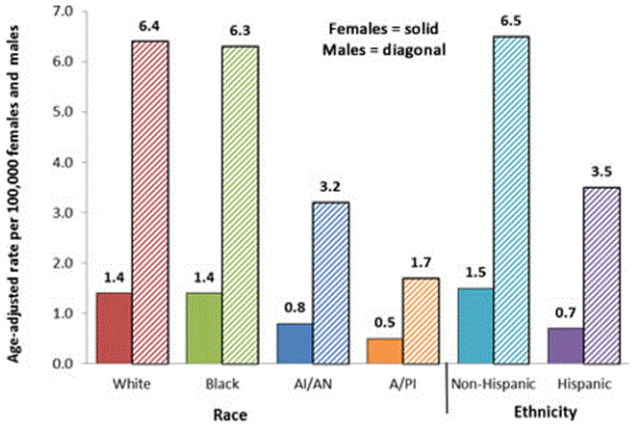


Figure 2: Centres for Disease control data. HPV-assiociated oropharyngeal cancer rates by race, ethnicity and sex. United States 2004-2008.

In 1983 the strictly anogenital associations of HPV infection were challenged when the HPV virus was linked to various forms of HNSCC, with up to 22.5% of HNSCC malignancies sampled during an early investigation testing positive for HPV [22]. More recently, oncogenic HPV DNA was obtained from half of all new HNSCC, even among non-smokers and non-drinkers [23]. Between 1988 and 2004 the incidence of HPV-related cancers of the head and neck increased by a full 225% while, at the same time, rates of non-HPV head and neck cancers fell by over 50% [3]. This new epidemic of HPV-associated HNSCC is projected to increase, and according to the National Cancer Institute, "more than half of the cancers diagnosed by 2020 will be oropharyngeal (i.e. HNSCC) rather than cervical in the U.S" [24]. Data released by the National Cancer Institute revealed that, in 2011, approximately 40% of all head and neck cancers in the United States tested positive for HPV [25]. These HPV strains dismantle tumour suppressor genes within the affected epithelial membranes, leaving the infected cells vulnerable to the development of deadly malignancies. One example of the increasing emergence of HPV-associated malignancies of the oral cavity is illustrated in a 2009 study tracking the prevalence of HPV related tonsillar cancer among Swedish patients [26]. Here, prevalence of HPV among all recorded cases of tonsillar cancer was seen to increase sharply, from 23% of malignancies examined between 1970 and 1979, to 57% of malignancies examined between 1990 and 1999, and as high as 93% of malignancies present in 2007 [27]. This issue was popularized in the media in 2013 through public statements made by actor Michael Douglas when he revealed to the Guardian newspaper that his throat cancer was caused by an HPV infection, transmitted to him as a result of performing oral sex on an individual with an HPV infection of the anogenital regions [27].

Transmission

While oral HPV infection may be transmitted mouth to mouth or vertically from an infected mother to her child, oral HPV infection is typically transmitted sexually [28]. Epidemiological ties between HPV and HNSCC are believed to have strengthened following changes in societal attitudes toward sexual expression, which began to emerge in the 1960's.

At present there is strong evidence supporting a positive correlation between a "high" number of lifetime vaginal (26) or oral (6) sex partners and risk of HNSCC [29]. Married women diagnosed with cervical neoplasms are five times more likely to have a husband with over 20 lifetime sexual partners than those without cervical neoplasms. Further evidence supporting HPV-related malignancies as a sexually communicable cancer is evidenced by higher rates of cervical cellular dysplasia among women married to men carrying a diagnosis of bladder cancer [30-31]. There is an association between HPV infection in bladder transitional cell carcinoma in men and cervical dysplasia in their spouses [32]. Men whose wives carry a diagnosis of cervical cancer demonstrate increased incidence of oral and pharyngeal cancers (particularly of the palatine tonsils) as well as cancers of the hypopharynx and larynx [33].

Prevention

The emergence of the vaccine Gardasil (Merck) in 2006 and later Cervarix was successful in shifting the focus toward prevention of HPV [34]. Although these vaccines are unable to eradicate existing HPV infections, evidence exists that they can prevent the development of HPV-associated malignancies associated with the HPV-16 and 18 strains. Gardasil is approved for both males and females ages 9 to 26, while Cervarix is approved for females only, age 9 to 25. In spite of growing awareness of the vaccines' availability and potential benefit, at present only around one third of girls and 6.8 percent of boys complete the recommended three shot vaccine series by their thirteenth birthdays [35]. Due to existing recommendations that vaccination occur early in life, prior to any genital-genital or oral-genital contact, ideally parents or guardians of unvaccinated individuals must be extremely proactive in pursuing the full vaccination course while the individual being vaccinated is still an adolescent [35].

Detection and Diagnosis

Early detection and diagnosis are crucial to the effective management of HPV-related malignancies and widely adopted screening procedures exist for cervical and anal cancers. However, there is no standard screening for oropharyngeal cancers, placing those at risk for HPV associated HNSCC at increased risk for late detection of the disease. One method, salivary testing, has variable accuracy. Even if HPV is found to be present in saliva, the risk of developing an HPV-associated HNSCC is unknown at this time [36]. Accordingly, questions remain as to the clinical utility of this technique and merits further investigation.

The emphasis on early detection of cervical cancer in women has led to emerging insights into the links that exist between cervical and oral HPV. In particular, the presence of HPV related lesions such as warts and oral papilloma in children has inspired interest in non-sexual modes of viral transmission [37]. The potential for perinatal infection between mother and child is an area of continued investigation. A recent investigation involving 70 women carrying a diagnosis of cervical cancer and 46 of their biological children, all of whom were born via vaginal delivery, revealed that only four (5.71%) of the women tested positive for oral HPV (via oral swabbing). Among the children only one (2.17%) tested positive for oral HPV. Of note, the young adult "child" who tested positive for oral HPV was also sexually active, therefore non-perinatal (sexual) transmission could not be ruled out [38]. Based on these results, the authors speculated that HPV might play a less significant role in oral cancer (as opposed to cervical cancer where nearly all cases are directly linked to the presence of HPV). Reasons for this disparity may include (1) exposure of the oral cavity to alternative carcinogenic factors such as alcohol or tobacco products (2) the presence of protective enzymes produced by the immune system in saliva (3) the protective action of antibodies produced in response to the primary (cervical) infection and (4) antimicrobial properties inherent to saliva [38]. Alternatively, it is possible that anogenital strains of HPV are transmitted exclusively via sexual routes later in life [39]. Future research should examine the specific strains, communication modalities, and protective properties of antibodies and saliva against HPV.

Treatment

Surgery, chemotherapy and/or radiotherapy are the standard of care for most cancerous tumors. Patients with HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) have a better clinical response to therapy than HPV-negative OPSCC patients, suggesting that an intensive chemo-radiotherapy may not be necessary [40]. In spite of this, questions remain as to the risk benefit ratio of reduced doses of chemo-radiotherapy or radiotherapy alone. Although the benefits of dose reduction are persuasive (e.g. decreased cost and resource utilization, reduced inconvenience to patients, potential for reduced side effects), these benefits remain uncertain when viewed within the context of potential risks including reductions in survival rates, patient resistance to receiving "less" treatment, a reduced focus on prevention, and obligation of clinical research resources to study dose reduction in a population of patients who already, as a group, demonstrate an excellent response to standard treatment [41]. Radiotherapy may be particularly effective for the treatment of HPV-associated malignancies as these tumors demonstrate more rapid regression following onset of radiotherapy compared with non-HPV-associated malignancies [42]. An emphasis on smoking cessation remains central to treatment considerations for those diagnosed with HPV-associated HNSCC, as current smokers with HPV-associated HNSCC have the highest risk of tumor recurrence (37%) compared to those who are similarly diagnosed but with a remote (17%) or no (6%) smoking history [43].

Recommendations

HPV-associated HNSCC, as a virus-related cancer epidemic, requires serious attention in the area of public awareness and prevention practices, particularly within the younger population who have not been vaccinated for HPV. Emphasis on the benefits of vaccination as a precaution against the "contagious cancer" may be a helpful strategy in improving vaccination rates. The long-term goal of developing educational resources explaining the facts about HPV in HNSCC may be a consistent way for the public to understand the potential implications of HPV as well as help direct the treatment selection for these patients [44]. Early screening for presenting signs of HNSCC in patients who are positive for HPV will allow for earlier diagnosis and treatment. Likewise, HPV testing for patients carrying an established diagnosis of HNSCC may assist in further delineating the incidence and prevalence of HPV-related malignancies as well as provide prognostic guidance.

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