HPV: A major etiologic agent of head and neck cancer

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When American actor and producer Michael Douglas publicly announced in 2010 that his "throat" cancer was "probably" the result of having engaged in oral sex, his family and fans reeled with shock.[1] However, Douglas is to be lauded for giving the world a desperately needed wake-up call to the unpleasant fact that high-risk human papillomaviruses (HPVs) are not at all fastidious about which mucous membranes they can and will invade. In fact, the prevalence of oropharyngeal cancer among men has steadily risen more than 300 percent in the past 40 years.[2] Although tobacco and alcohol are contributory causes, controlled studies reveal that the primary blame rests upon HPV.

Careful investigation has further revealed that head and neck cancer is more prevalent in men and that they have a lower survival rate from these malignancies. It is also documented that men practice oral sex slightly more often than women, and that due to anatomical differences, men are exposed to HPV-infected mucous membrane tissue more than women.

Furthermore, the same study concluded that younger males (aged 35 to 45) were practicing oral sex more than their 60 year old cohorts, as more of the younger males tested positive for HPV 16 (the most prominent viral strain causing head and neck cancer).[3] Thus, changes in sexual behaviors may very well be fueling the previously mentioned 300 percent increase in oropharyngeal cancer over the past four decades.

How common is HPV and how is it contracted?

HPVs consist of more than 200 related DNA-containing strains that are the etiologic agents of everything from non-cancer-causing warts, to dangerous high-risk varieties such as strains 16, 18, and many more. HPVs are the most commonly sexually transmitted infection (STI) in the United States, today. High-risk HPVs are readily transmitted by vaginal, oral, and anal sex. Although barrier protection ameliorates the risk, it does not eliminate it entirely.[4]

Unlike hepatitis B, C, human immunodeficiency virus (HIV), and other retroviruses, papillomaviruses are decidedly not blood and body fluid-transmitted, although measurable viremia does occur during HPV infection. These viruses can be transmitted directly by skin-to-skin contact, thus any skin infected with HPV is directly "contagious."[5] Fortunately, this is not the case with HIV/AIDS.

HPV vaccine is recommended by the FDA for everyone from age nine to 45 with young boys and girls beginning vaccination at around age 11. Women are advised to remember their important prophylactic yearly cancer screening visit.

HPV infection is extremely common, and the Centers for Disease Control and Prevention (CDC) estimates that around 79 million Americans are now infected with the virus. About 14 million more are added to this number each year. Of these, 19,400 women and 12,100 men are projected to develop cancer. In fact, it is estimated that the majority of sexually active Americans will at some time during their lives contract HPV if they do not receive the vaccine at the recommended ages.[6] Of the vast number of HPV types, only 14 are known to be linked to a high prevalence of neoplasia and these are types 16 and 18. Most of the HPVs which do not cause malignancy are kept under control by the immune system.

Anatomic sites

HPV lesions and cancers can occur in the mouth, throat, at the base of the tongue, vulva, vagina, penis, and anus. The HPV virus is altogether different from herpes, which is also a virus, and which can likewise be transmitted by vaginal, oral, and anal intercourse.

Papilloma lesions are usually painless, flat, and wart-like. Advanced lesions are frequently described as dry and cauliflower-like, dissimilar from the blistered, crusty, and sometimes painful sores caused by herpes virus.

Where does HPV-derived head/neck cancer occur?

Head and neck cancers can arise in the following regions: Oral cavity including the tongue, salivary glands, and the larynx. They may be found in the nasal cavity including the paranasal sinuses. Malignant lesions can also arise in the pharynx including the nasopharynx, oropharynx, and hypopharynx.[7] HPV infects the squamous cells that line these organs and also those of the genital tract. Oropharyngeal cancer has become the most common HPV-related cancer in the U.S. and the number of cases being diagnosed each successive year is increasing.[8]

Symptoms

HPV-related cancer symptoms can include hoarseness or a change in voice quality, problems with swallowing, a lump in the neck or a sore in the mouth, a sore throat or earache that does not resolve with time, or a bleeding nose, mouth, or throat that occurs intermittently.[7] Vocal cord or glottis cancer has been very much on the rise in patients under 40 who have never smoked. In these patients, hoarseness was one of their most prominent symptoms. High-risk HPV was found in 100 percent of patients fitting this clinical profile in one study.[9]

Sub-cellular mechanisms of malignancy?

According to the CDC, HPV causes 70 percent of oropharyngeal cancers, which are those that arise at the base of the tongue, tonsils, and soft palate.[7] Malignant transformation probability due to infection with HPV 16 is proportional to the appearance of viral oncogene-coded gene products E6 and E7. These gene products inhibit p53 and retinoblastoma tumor suppressor actions. *In situ* hybridization techniques for integrated HPV 16 are highly specific but have low sensitivity,[8] nevertheless, the technology has been highly useful in proving the point that HPV is indeed

the "smoking gun." Husain and Ney have stated that high risk HPV 16 is responsible for 90 percent of oropharyngeal squamous cell carcinomas (OSCC).[8]

Viral oncogene products E6 and E7 are produced when the viral genome integrates with the host DNA. This increases the probability that the effects of p53 (tumor suppressor) and retinoblastoma tumor suppressor functions will be proportionately brought into play.

In high-risk HPV strains, E6 and E7 influence many cellular proteins which have an impact upon the outcome,[9] thus driving the neoplastic process. Protein p53 and E6 interact and push the cell's degradation while retinoblastoma (Rb) is inactivated by E7 upon linking with it.

Both p53 and Rb are tumor suppressors and are intimately involved in the repair of DNA and cell demise.[8] In brief, E6 and E7 are oncoproteins that are essential to the malignant process.[9,10] When E6 is bound to p53, the latter is destroyed and cannot control the all-important cell cycle. It is highly noteworthy that p53 is non-functional in at least 50 percent of all human cancers.[11]

The E6 HPV protein is also very important because it induces the expression of telomerase—the "immortality" enzyme—which continuously repairs the tips of chromosomes, and which is not normally present in adult somatic cells. This enzyme prevents the degradation of chromosomes and enables malignant cells to divide endlessly. Ultimately, HPV viral proteins E6 and E7 work together to essentially take over cell division and propel cell dynamics in the direction of malignancy.[11]

Diagnosis news

Some experts in the field hoped that they might be able to determine the efficacy of the HPV vaccine by conveniently scanning for the presence or absence of HPV 16 in saliva specimens at intervals post-immunization and then correlating that with the presence of tumors. However, in a study by Ramirez and Zelvallos, detection of HPV 16 in tumor specimens and saliva from the same patient was discordant in more than one quarter of patients tested.[12] It became clear that it would not be possible to base anti-HPV vaccine efficacy upon anything other than tumor sampling in conjunction with highly analytical examination of tumor tissue for this purpose to obtain reliable data. In its present state of technology, HPV derived from saliva would provide an interesting corollary. The same would apply for diagnostic situations.[13]

Liquid biopsies tracking HPV-DNA originating in OSCC in one prospective study had 100 percent accuracy in ruling out recurrence of malignance.[14] However, its positive predictive value for recurrence was only a disappointing 42 percent. Conclusions were formed that the test had promise, but it was far too expensive and provided potentially too many risky false negatives to be brought into use at this time.[14] There is work continually being done to perfect it.

NGS and HPV

We have recognized for several decades that the fundamental causation of cancer is somatically acquired mutations. Cancer is a disease of DNA and the result of a malfunctioning genome. However, we now have new technology, next generation sequencing (NGS), that enables us to localize the HPV DNA within the human genome that is causing the malignancy.

NGS permits the sequencing of an entire human genome within a reasonably short period of time. It is currently being used to personalize treatment in pilot pediatric cancer genome projects and in other studies around the world.[15] Individualized shot-gun metagenomic sequencing would offer enormous insight into the nature of HPV-induced cancers of the head and neck variety as well as other malignancies caused by this and certainly other viruses.[16] Much as we have learned to thwart HIV by designing integrase inhibitors that prevent the pro-viral DNA from integrating into the host cell DNA, learning where in the human genome various types of HPV are prone to insert might offer clues for treatment strategies.

In a noteworthy study reported by Morris, Chandramohan, and West et al, the "molecular landscape" of recurrent and metastatic head and neck cancers were examined and insights from a precision oncology sequencing platform were gained revealing the highly promising future of this unfolding technology.[17] They noted that to advance precision head and neck oncology, it was first necessary to produce a thorough catalog of molecular alterations in rare and incurable cancers. These are virtually always dramatically distinct from the primary tumors from which they arose. It will be critical to provide NGS profiles of all of these tumors and matched normal controls as well in order to develop rational therapies.[18]

In a far simpler format, NGS has already been employed to search for alpha, beta, and gamma sub-species of HPV 16 in saliva in a prospective study of over 95,000 cancer-free subjects. At a 3.9-year follow-up, 132 subjects were found to have head and neck squamous cell carcinoma (HNSCC) associated with type 16 HPV in saliva (males = 103; females = 29). Their average age was 66.5. Data was controlled for tobacco and alcohol use.[19]

Conclusion

In conclusion, we have made vast progress with HPV and stripped bare many of its ugly and very deadly secrets. We have become open to discussing HPV, removing it as a "taboo" topic, cloaked in ignorance. We're now armed with a powerful weapon capable of bringing it under control. It must be wielded aggressively for the protection of young people before they are ever exposed to the virus. We must educate parents, young people, and all who might derive benefit from immunity to the most dangerous strains of HPV. We have nothing to lose but a very deadly form of cancer itself, and many years of healthy life to gain.

Please visit mlo-online.com for references.

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