ORAL CANCER, AN EMERGING PARADIGM SHIFT

Cancer of the oral cavity and oropharynx accounts fro approximately 85% of all head & neck cancers. This is a cancer group that arises in the mucosal surfaces of the upper aerodigestive tract and is almost exclusively squamous cell carcinoma. The overall incidence of this form of cancer has not changed in decades and recent statistics are about 37,000 new cases annually.

Historically, oral cancer has been associated with tobacco and alcohol exposure and poor oral hygiene. Men were 6 times more likely to have this type of cancer and blacks twice as likely as whites. There has always been a high incidence of local and regional recurrence with an overall 5-year disease-free survival of only about 50%.

Since the 1980's, there has been about a 50% decline in the incidence of tobacco and alcohol related oral cancers but the overall incidence of the disease has not declined due to the growing number of Human Papilloma Virus (HPV) related oral cancers. In fact, the incidence of HPV + oral cancer has risen by 270% in the past 20 years. The overall male to female ratio has dropped to 2:1 and females now out-number males in the less than 35-year age group.

HPV is one of the most common virus groups in the world today with over 130 different types identified. These viruses can infect any cutaneous or mucosal surface. Most are harmless, producing no disease or harmless skin lesions. Transmission can be from solid surfaces such as a shower floor or gym mat, skin to skin, saliva or other body fluids.

HPV is now considered a sexually transmitted disease (STD) and certain strains of this virus group are directly linked to causing cancer. This viral-cancer link was first established with cervical cancer and is now well-established with oral, rectal and genital cancers. The risk of infection increases with the number of lifetime sex partners and the risk of oral cancer is directly proportional with the number of lifetime oral sex partners. One to five lifetime oral sex partners doubles the risk of developing an HPV + oral cancer and there is a 5-fold increased risk with 6 or more partners throughout one's life.

The strains of this virus family that are most commonly sexually transmitted includes HPV strains 6 and 11, which are the viruses responsible for condyloma (genital warts), and strains 16,18, 31 and 45 which are considered the most oncogenic strains and responsible for the majority of cervical, genital, rectal and oral cancers.

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Interestingly, contact with the virus does not mean that one will become infected and most people will clear the virus without infection. It appears that repeated exposure increases the risk of infection and once infected the virus gets incorporated into the host DNA and human cells begin producing the virus. It is possible for an infected host's immune system to clear the virus but the how's and why's of this are not yet fully understood. It is believed the less than 1% of those who come into contact with an oncogenic strain of this virus and/ or become infected will ultimately go on to form a cancer. It has been hypothesized that a genetic immune system defect may be responsible for certain individuals' inability to clear the virus. There has been no link with age or any identified synergism with tobacco and/or alcohol and HPV + cancers.

Cervical cancer was the second most common cause of cancer deaths in women in the 1950's. Pap smear technology which identifies women with an increased risk of developing cervical cancer reduced this cancer type to the 7th most common cause of cancer death in women by the 1960's. Subsequent identification of the human papilloma virus as the etiologic agent for cervical cancer was the ground breaker for subsequent investigation into the cancer causing potential of this virus family. We now know that all cervical cancer is HPV+ with types 16 and 18 being most common.

HPV 16 is also the most common virus identified in oral cancer. Primary lesions are small, hard to see and are usually asymptomatic. The most common locations are the tonsils, base of tongue, oropharynx and nasopharynx. Due to these difficult to see locations and lack of symptoms, most patients present with advanced stage disease. Studies have shown that patients presenting with large malignant cervical lymph nodes can have very small (1-2 mm) primary lesions. In the past, these were considered "unknown primary" head and neck cancers, but with advanced imaging technology and heightened awareness of common HPV primary sites, the origin of the cancers are becoming less of a mystery.

Oral cancer screening should be a part of every annual medical and dental examination. There is a >90% 5-year survival with early stage diagnosis of oral cancer but most are late-stage diagnoses which reduces the 5-year survival to about 50%. The history should be directed to elicit any warning signs such as a sore or lesion that does not heal within 2 weeks, lumps or thickening, white or red patches, persistent soreness or fullness in throat, pain or difficulty chewing or swallowing and chronic hoarseness. The most common abnormal physical finding will be a painless neck mass obviating the need for a careful and thorough soft tissue neck examination.

Some ancillary tests have been marketed to medical and dental professions to facilitate the early detection of HPV and oral cancer. There are saliva tests to detect

HPV but the implications of a positive test in the absence of any visible lesion is not fully understood since statistically >99% of people who come in contact with the virus will not go on to form any cancer and results may increase anxiety and additional unnecessary testing and healthcare expenses. There are colored light devices —"scopes" which are designed to detect abnormal mucosal changes, but these are not specific for cancer and have very high false positive and negative results so they are not considered valuable screening tools by most oral cancer experts. Older methods of scraping the oral mucosal surface for cytologic evaluation, a technique which mimics the Pap smear, never proved as successful in the mouth due to the keratinizing nature of oral cancer and the inability of this technique to yield sections of the basement membrane necessary to make a cancer diagnosis. The new oral brush cytology techniques are proving to be much more effective and reliable since they do sample basement layer tissue where these cancers originate and is a technology which is growing in popularity and availability.

Any persistent mucosal abnormality should be referred for surgical evaluation. A common abnormal finding is the benign oral papilloma which is an HPV-related disease. These lesions are excised and HPV screening is routinely done; they are rarely caused by one of the oncogenic strains of HPV. Recurrence after excision is uncommon but monitoring is indicated for higher risk HPV strains. Other suspicious lesions can be brush biopsied which is a simple and painless office procedure and provides adequate information to determine if additional diagnostic procedures are indicated.

Once an oral cancer diagnosis is made, a staging work-up is necessary and, if fortunate enough to have an early stage oral cancer, surgical excision is frequently possible. Radiation is considered for early stage disease only if clear surgical margins cannot be obtained. As stated previously, the vast majority of these cancers are late stage diagnoses and most treatment protocols employ both chemotherapy and radiation therapy reserving surgery for treatment failures.

Bob Chaloner and Kevin Braat, MD during the recent SEA-TV taping.

Can this cancer be prevented? HPV prevention through vaccination has been in the media forefront for the past few years. In 2006, the FDA approved Gardasil, a vaccine which protects against HPV strains 6, 11, 16 and 18. The CDC subsequently recommended immunization for females age 9-26 years. There have been subsequent studies showing reduced cervical cancer rates in women who are immunized up to 45 years of age but the CDC guidelines on this recommended age range for immunization have not yet been changed. In October 2011 the CDC did update their recommendation to include male vaccination. The field of cancer vaccines has been energized by the clinical success and public acceptance of this technology which will undoubtedly lead to a lot more on this topic in the not too distant future.

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In summary, our generation is facing a relatively new malignant lesion which is sexually transmitted, has a predilection for a younger and more affluent patient population and carries a significant morbidity and mortality. That's the bad news, but there may be a "silver lining" in all of this. Anti-smoking campaigns have been effective in reducing the incidence of all forms of smoking related cancer, especially cancers of the upper aerodigestive tract. Screening for many different types of cancers has reduced cancer deaths in properly selected patient populations. Although HPV + oral cancers are on the rise, specific risk factors have been identified and these cancers are significantly more responsive to therapy and have a longer disease-free survival compared to same stage HPV – cancer, so with time and optimization of treatment protocols, outcomes are anticipated to improve. HPV is potentially curable with aggressive immunization programs and education has the potential to impact transmission. Heightened awareness in oral and primary care medical communities can contribute to earlier stage detection and better treatment outcomes.

- Kevin Braat, MD