HPV-Related Head and Neck Cancers (Slides With Transcript)

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Authors and Disclosures

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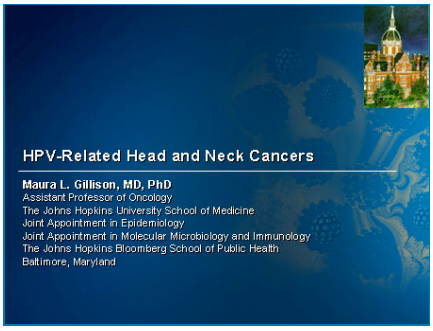
Overview of Head and Neck Cancer



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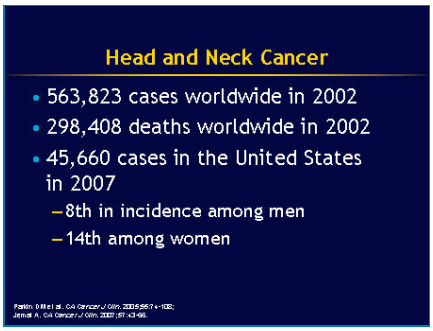
Head and neck cancer is a major cause of morbidity and mortality worldwide. If you look at these numbers, they're pretty similar in terms of worldwide incidence to cervical cancer, with over 560,000 cases diagnosed in 2002. Unfortunately, over 50% of individuals with head and neck cancer will succumb to the disease, so there are almost 300,000 deaths worldwide each year. In the United States, this is considered a rare cancer relative to, say, prostate, breast, or lung cancer. But there are a significant number of head and neck cancers in the United States; 46,000 cases are estimated to occur this year in the United States. It's eighth in incidence among men and 14th in incidence among women.



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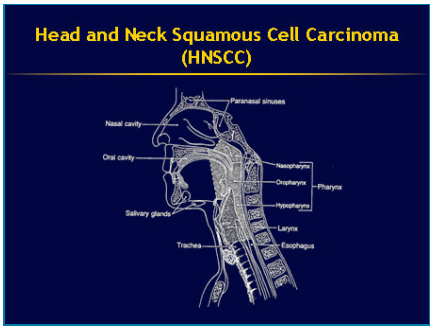
Head and neck squamous cell carcinoma, just to review your anatomy, is a cancer that arises from the upper mucosal surface of the aerodigestive tract and includes nasal cavity, oral cavity, nasopharynx, oropharynx, and hypopharynx cancers. Those of the larynx and sometimes the cervical esophagus are included in head and neck squamous cell carcinoma. Salivary gland cancers are largely not squamous cell carcinomas and account for most of the other cancers that occur in this region.



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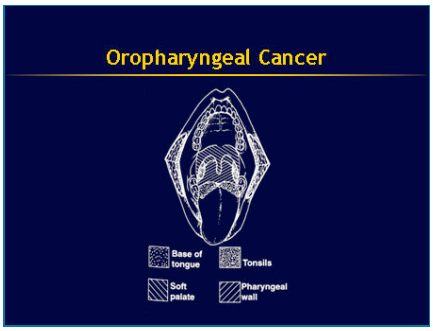
For reasons that will become clearer, I want to focus on oropharyngeal cancer. Those are cancers that arise from the back of the throat, including the base of the tongue, the tonsils in the back of your throat (the palatine tonsils) and the soft palate, and the posterior pharyngeal wall. It's important to note that there are actually tonsils in the base of your tongue. These are called the lingual tonsils. Most people are not aware of that. And these are not, of course, touched at all during a routine tonsillectomy because that could be associated with speech and swallowing difficulty.



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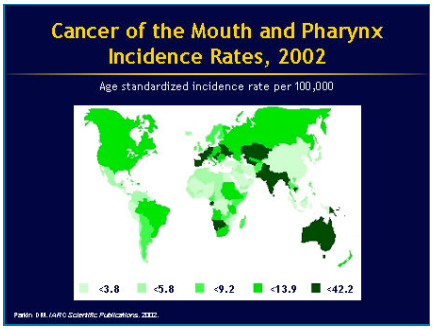
There is incredible geographic variation in the incidence rates of head and neck cancer worldwide. This is an example of cancer incidence rates for oral cavity and pharynx cancers. You see tremendous heterogeneity. In the United States, we're about in the middle of the road. But there are regions, for instance, Australia, driven by a very high incidence of lip cancers, and regions, including in Europe, that have very high incidence rates.



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Why is there so much geographic heterogeneity in incidence rates? That is because head and neck cancer is largely a disease of environmental and behavioral exposures. Very few of the main risk factors are nonmodifiable risk factors such as family history of head and neck cancer, age, gender, or race. The majority of them have to do with personal health, hygiene, and exposures. The main risk factors for head and neck cancer worldwide remain alcohol and tobacco use. Oral hygiene is a very important and unappreciated risk factor for head and neck cancer. Diets poor in fruits and vegetables, very clearly from study to study, are associated with increased risk of head and neck cancer. And over the last 10 years or so, there is overwhelming evidence that human papillomavirus is a very important risk factor for head and neck cancer. When you look at the worldwide literature, it's clear that HPV does not act, at least in humans, by a hit-and-run mechanism. It's spread by directhuman-to-human contact. And the virus is essential for the maintenance of the malignant phenotype. All data in humans indicate that. So when you look at the worldwide literature, the most important thing to demonstrate, if you hypothesize that a cancer is caused by HPV, is that the virus is present in the tumor, and not just by standard qualitative polymerase chain reaction (PCR). It's important to demonstrate it by a number of different mechanisms because they provide very important critical pieces of the puzzle.

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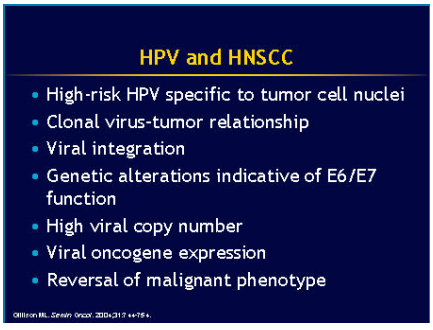
HPV and Head and Neck Cancer

This is what has been demonstrated for HPV in a subset of head and neck cancers. The viral genome, largely of high-risk HPV types, almost exclusively 16, is specific to tumor cell nuclei. A clonal relationship between the virus and the tumor has been demonstrated. Viral integration to these tumors has been demonstrated by a number of different mechanisms. We have demonstrated, as have others, that there are genetic alterations indicative of E6 and E7 viral oncogene function in these cancers that are not found in HPV-negative head and neck cancers. The virus can be present in very high copy number, about 500 copies per cell, but, of course, you only require 1 copy per cell. Viral oncogene expression has clearly been



demonstrated, and in very nice work presented this year at the American Society of Clinical Oncology Annual Meeting, and not yet published, Amanda Psyrri's group at Yale grew out HPV-positive head and neck cancer cell cultures from patients and demonstrated that if,through molecular mechanisms, you decrease E6 and E7 expression in the tumors, you see reversal of the malignant phenotype, indicating that the presence of the virus is very critical to the tumor and it's acting as a tumor.

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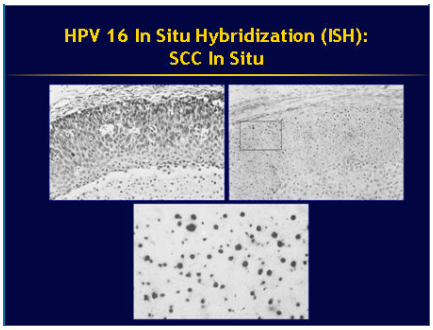
In our laboratory and in our work we focus on in situ hybridization because we've developed the assay technique so that it has sensitivity down to 1 viral copy per tumor cell. It gives you an extraordinary amount of information in terms of the specificity of the virus to the tumor cell nucleus. This is an example of an in situ and microinvasive squamous cell carcinoma, where you see on the top left an H&E stain. And here you see the in situ hybridization, the specificity of the viral signal, which are these little dots to the tumor cell, and down here you even see a specificity to the small microinvasive component. Here is this area in this box blown up. It gives you a beautiful picture of the specific association of the virus to the tumor. And that's now the standard in our work.



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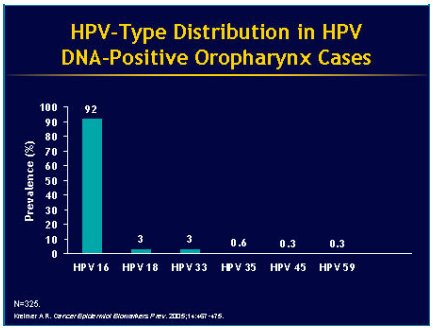
HPV and Oropharyngeal Cancer

When you look at the worldwide literature based on PCR of HPV in oropharyngeal cancers, this is the type of HPV-type distribution that you see. As with cervical cancer, HPV 16 accounts for the overwhelming majority. But in contrast to cervical cancer, it is considerably higher. Dr. Palefsky showed you data showing that 62% of cervical cancers are associated with HPV 16. From all studies so far of HPV-positive head and neck cancers, 90% to 95% of them are HPV 16. In our work and looking at the most important molecular evidence, it's really for HPV 16 and related types in the A9 clade. We don't see much HPV 18 in our work, and that was really demonstrated by oncogene expression rigorously enough for HPV 18. So the most important type is HPV 16 and its related types.



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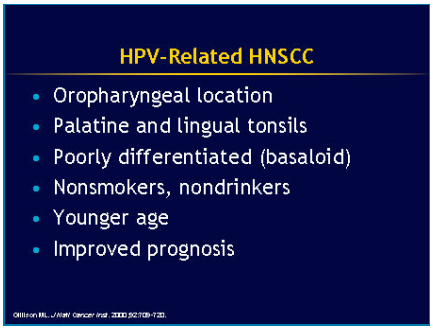
When you look at the worldwide literature, there is specificity now of the type of head and neck cancers that are caused by HPV, and they are largely oropharyngeal cancers, and in particular palatine and lingual tonsils. That's why I pointed that out so carefully, the anatomy, to remind you of the location of these tumors. When you look at them under the microscope, they have a characteristic histopathology, a basaloid histopathology, which interestingly enough is also associated with penile, anal, and vulvar squamous cell carcinomas that are HPV-positive. These cancers occur in nonsmokers and nondrinkers but not exclusively so. HPV is an important cause of head and neck cancer also in smokers and drinkers. It's just that the proportion of the cancers that can be attributed to HPV is higher in nonsmokers and nondrinkers. These cancers occur largely in individuals at a younger age than classical head and neck cancer that is HPV-negative. A number of studies have now shown that it isan important prognostic factor in terms of outcome to standard-of-care therapy, with individuals with HPV in their tumor having about a 70% to 80% reduction in the risk of dying from their cancer when compared with an HPV-negative head and neck cancer. We've recently demonstrated that and confirmed it in a prospective clinical trial of uniformly staged and treated patients that's in press.



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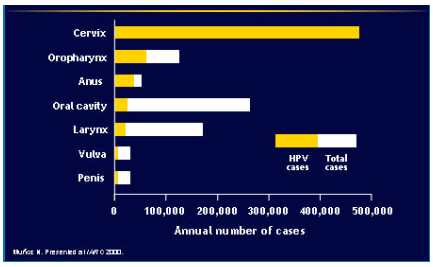
When you look at the incidence and distribution of cancers attributable to HPV, the head and neck cancers that are associated

with HPV are like all other cancers associated with HPV except cervical cancer in that the HPV is associated with a subset of these cancers. Cervical cancer is actually the exception to the rule in that HPV is necessary for the development of cancer at that site. But now, head and neck cancer clearly is an important contributor to the worldwide burden of HPV-associated malignancies.



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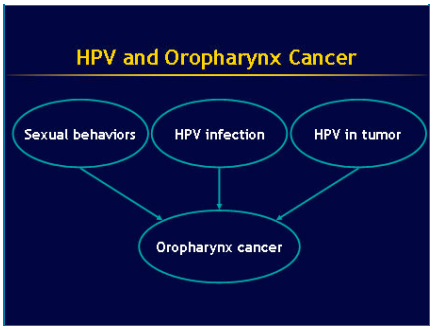
When you consider all of those cancers that are caused by HPV, you see common associations. Number 1 is that all of the data would suggest that HPVs are largely sexually transmitted. So when we had our first manuscript showing this strong association with oropharyngeal cancer largely on a molecular level, we thought it would be important to demonstrate that sexual behavior is associated with risk of oropharyngeal cancer. Another important factor is HPV infection, whether measured by exposure or by serology, the presence of antibodies to the virus indicating that at some point in the life of that individual they have had a mucosal HPV infection somewhere in their body. You should see that associated with risk of oropharyngeal cancer if the cancer is indeed caused by HPV. And you should also see an association, as has been shown in a number of case-control studies for cervical cancer, that the presence of the virus at that site is associated with increased risk. That would be animportant association to demonstrate with oropharyngeal cancer. Of course, there is no evidence that this virus acts by a hit-and-run mechanism, so clearly you would have to demonstrate that HPV is present in the tumor. When we demonstrated that HPV was largely associated with oropharyngeal cancer, it became clear to us that we needed to find these 3 critical factors in order to provide some conclusive evidence that HPV is associated with oropharyngeal cancer.



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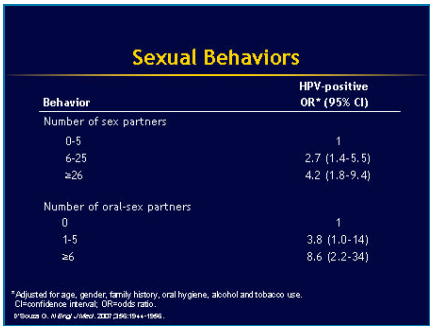
When we completed the case-control study, we focused initially on sexual behaviors and found that every sexual behavior that was associated with risk of cervical cancer in the literature was associated with oropharyngeal cancer, for instance, age of onset of sexual behavior and number of lifetime sexual partners. There were strong increases in risk with significant trends. But the most important risk factor appeared to be the number of oral sexual partners that you'd had in your lifetime, that is, the number of individuals on whom you had performed oral sex. This was independent of sexual orientation or the gender of your partner. We saw strong trends with strong increases in risk, with individuals who reported 6 or more lifetime oral sexual partners having almost a 9-fold increase in risk after adjustment for all the other factors that we found in this study to be associated with risk of oropharyngeal cancer.



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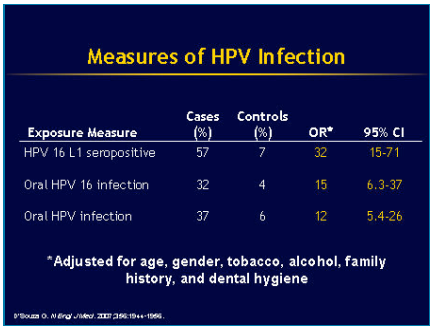
When we looked at measures of HPV infection, we found, of course, that HPV 16 L1 seropositivity, a lifetime measure of exposure to HPV 16, was strongly associated with oropharyngeal cancer risks. But then, of course, people could argue, "Well, you don't really know the site of infection. These infections are site specific. They don't transmit through the blood. They're not hematogenously spread. So how do you know that the site is actually in the oral cavity?" So we went ahead and measured HPV 16 infection by real-time PCR in the oral cavity in cases and controls. Individuals who had an HPV 16 infection had a 15-fold increase in their risk after adjusting for other factors. The presence of any of the 37 HPV types inclusive of HPV 16 was also strongly associated with risk of oropharyngeal cancer.



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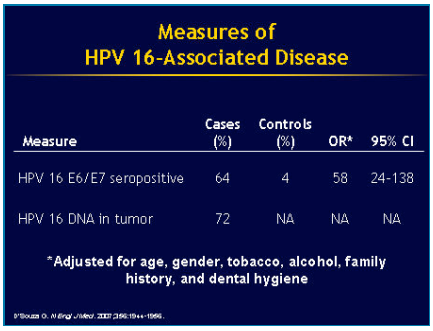
When we looked at measures of HPV 16-associated disease, obviously the most important thing was looking for the presence of the virus in the tumor. In these cases of oropharyngeal cancer enrolled from 2000 to 2005, we found a 72% prevalence of HPV 16 by in situ hybridization, showing the specificity of the virus to the tumor cell nucleus. And in our ECOG (Eastern Cooperative Oncology Group) study, we performed HPV 16 detection by in situ hybridization in our laboratory. This was an unselected patient population in a national study, and the prevalence was 63% in that study -- not too far off from this. But we were surprised by how high that was. We didn't expect it to be that high. We were reassured that we were able to confirm this by another mechanism, which was looking at the presence of antibodies to the viral oncoproteins in the cases and comparing that to controls, because antibodies to E6 and E7 are highly specific to the presence of an invasive squamous cell carcinoma. Butnot everybody who has a cancer will seroconvert. We were able to show that 64% of cases had E6 and E7 antibodies present in their serum, so there were very strong associations between HPV 16-associated disease measures and oropharyngeal cancer.



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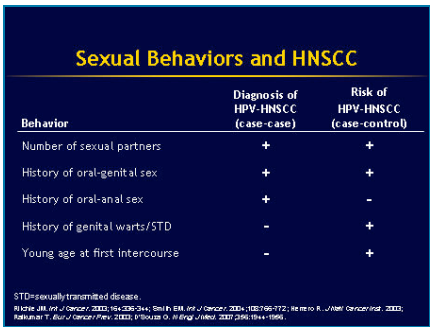
Supporting Studies

We were pretty convinced with these data. When you look at the worldwide literature, you will see that other groups, who have done excellent work, have also demonstrated associations between sexual behaviors in case-case comparisons -- individuals who have an HPV-positive cancer, compared with HPV-negative cancers, have higher reports of number of sexual partners, a history of oral-genital sex, and a history of oral-anal sex. When you look at the worldwide literature existing in case-control studies, you see strong associations in a couple of studies looking at number of sexual partners and, in our study, oral-genital sex and history of genital warts or STDs, and young age at first intercourse.



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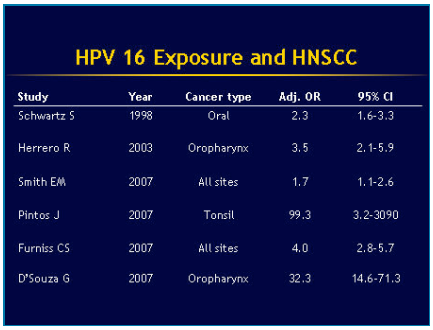
Looking at HPV 16 exposure measured serologically, we're also starting to see strength and consistency from study to study. Of course, the adjusted odds ratios vary depending on the eligibility of the cases. For instance, Elaine Smith's recently published paper showed a small but significantly elevated adjusted odds ratio associated with HPV 16 exposure. Then again, oropharyngeal cancer patients only comprised a small proportion of the cases in that study, whereas if you look at our associations with oropharynx cancer exclusively and then the paper by Pintos et al where they focused exclusively on tonsils, you start to see an extraordinarily high odds ratio -- a 99-fold increase in risk.



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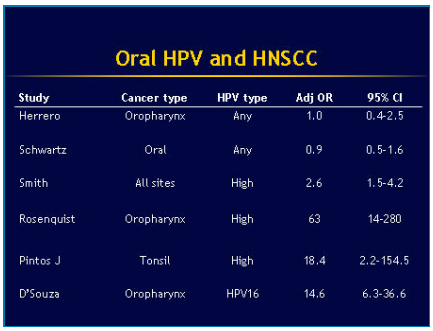
Looking at oral HPV infection in risk of head and neck cancer, we're also starting to see strength and consistency from study to study in the literature with the same heterogeneity from study to study, largely because the heterogeneity of the underlying patient population. Of course, if you're mixing apples and oranges and looking for associations, they will be weakened if you have more apples than oranges, with the oranges being the HPV-positive head and neck cancers. But there are very strong increases in risk associated with high-risk types and, of course, very strong associations with HPV 16 in particular.



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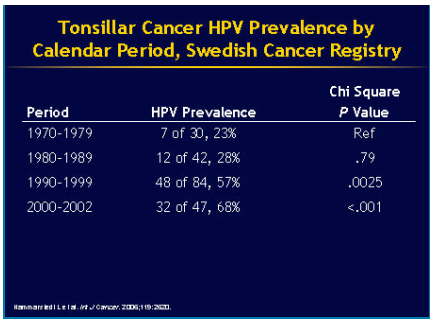
In Sweden, they saw the same increase in tonsillar cancer incidence there, and they were able to go back because of their tumor registry and test the tumors for HPV. They saw a significant increase, from 23% of the tumors in the 1970s being HPV-positive to almost 70% in 2000 to 2002, very similar to our numbers.



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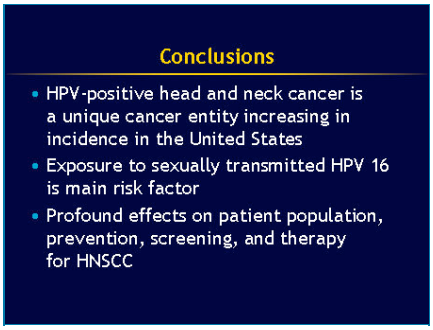
Conclusions

In conclusion, HPV-positive head and neck cancer is a unique cancer that is increasing in incidence in the United States. It's really changing the character of head and neck cancer in the United States. My clinical practice has changed incredibly in the last 10 years since I've been seeing exclusively head and neck cancer patients. Exposure to sexually transmitted HPV 16 is the main risk factor, and this is having profound effects on our patient population in the United States.



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