Hi. I’m Kristina Dahlstrom, an instructor in the Department of Head and Neck Surgery at The University of Texas MD Anderson Cancer Center. My lecture today will be on the epidemiology of oropharyngeal cancer.

The objectives of this lecture are to describe the epidemiology of oral HPV infection and the role of HPV in oropharyngeal cancer. I’ll also describe the trends and incidence and survival as well as methods for prevention of HPV-related oropharyngeal cancer.

HPV is the most common sexually transmitted infection in the world.

In the U.S., there are currently 70 --- 79 million individuals infected with 14 million new cases every year. Most individuals will have an infection during their lifetime. To date more than 150 types of HPV have been described. And about 40 of these infect the genital tract and potentially the oral cavity and the oropharynx.

HPVs are grouped based on their malignant potential. Low-risk types include HPV 6 and 11 which cause genital warts. And high-risk types are 16 and 18 which are responsible for most cancers. HPV is a small circular double-stranded DNA virus that targets the basal cells of the epithelial mucosa.

In order for malignant transformation to occur, there needs to be a persistent infection with a high-risk HPV type. HPV integrates into the host genome where viral proteins deregulate tumor suppressor function which results in defects in apoptosis, DNA repair, and cell cycle control and this leads to cellular immortalization.

Estimates for the prevalence of oral HPV infection vary by study. One large cohort study called the HPV in Men study includes men from Brazil, Mexico, and the U.S. And this study found an overall prevalence for any HPV type to be 4%. For high-risk types it was 1.3% and HPV 16 was the most common type found. Prevalence among U.S. males was about the same as the overall prevalence for all men.

Another large cohort study is the NHANES study which is representative of the U.S. population. And data from 2009 and 2010 found that 7% of the U.S. population are infected with an oral HPV infection with HPV 16 again being the most prevalent at 1%. HPV is much more common among men than women. In the NHANES study more than 10% of men were infected, but less than 4% of women were.

Risk factors for an oral HPV infection include higher age, being male, oral sexual behaviors, cigarette use, and host immunosuppression.

When modeled across age, we see that prevalence follows a --- a bi-modal distribution with peaks in the 20s and 30s as well as the 50s for both men and women although it always remains higher among men. And this distribution is especially apparent for the high-risk types.
And these are again results from the NHANES study. Among women ever being married or living with a partner was protective for an oral infection. While for both men and women increasing intensity of cigarette use as well as higher numbers of lifetime sex partners was associated with prevalent oral infections.

When we look at individual behaviors for sex we can see that both oral sex as well as vaginal sex, both are associated with prevalent infections; with individuals with higher numbers of partners being more likely to have prevalent infection.

Transmission of HPV to the oral tracts, there is limited data for this. But we do know that prevalence of oral infections are about 5-10 times lower than genital infections. And this could be due to reduced exposure and/or greater resistance to the virus at the oral tract. There is also evidence that HPV is sexually transmitted both oral to oral and oral to genital routes of transmission with higher numbers of deep kissing partners as well as frequency of oral sex and higher numbers of oral sex partners increasing the risk for a prevalent infection. Both men and women with a genital infection are also more likely to have an oral infection. And they are also more likely to have a partner with either an oral or a genital infection. To date we have inadequate methods to test for oral infections because this is mainly done in the oral cavity. But cancer actually develops further back in the oropharynx which is --- includes the tonsils and the base of the tongue.

Changes in sexual behavior over time are thought to be a contributing factor to the increased incidence of oropharyngeal cancer. Although there's limited longitudinal data, the current epidemic is likely a reflection of behaviors from the 1960s and 70s because there’s a long latency period of several decades between infection with the virus and cancer.

Smoking and immunosuppression are also risk factors for oral infections. Smoking has immunosuppressive effects. Among women with cervical infections, smokers had higher prevalence of infection, viral load, and disease progression. Smoking is also associated with both prevalent and incident oral HPV infection. And there is evidence for possible increased persistence of oral HPV among smokers.

This smoking and HPV association remains after adjustment for sexual behaviors. HIV-positive patients also have higher prevalence of oral HPV infection. They are at increased susceptibility to infection and also have increased persistence of infections.

There are 35,000 cases of HPV associated cancers every year in the U.S.

About a third of these are cervical cancers and almost 40% are oropharyngeal cancers. The distribution varies between men and women. For men almost 80% of the total cases are oropharyngeal cancers. And there’s more than 10,000 cases among men every year. While for women we see that a little more than half are cervical cancers and just 12% are oropharyngeal cancers. Among women there’s about 2,500 cases per year.
HPV has consistently been identified in head and neck tumors since the 1990s with the oropharynx being the main site. Of tumors that test positive for HPV, HPV 16 is by far the most common type and is found in at least 85% of those tumors. There's been an increase in prevalence of HPV in tumors over time with less than 50% testing positive in the 1990s to about 80% currently.

This figure shows the increasing prevalence over time in HPV in tumors. And as you can see the most dramatic increase has been from studies from North America and Europe.

The role for HPV in oropharyngeal cancer comes mainly from case-control studies. Mork reported in 2001 that antibodies to the HPV 16 capsid protein increased the risk for cancer. Seropositivity increased the risk for oropharyngeal cancer by 4 --- by a factor of 14 and tongue cancer by a factor of 3. An International Agency for the Research on Cancer multicenter study found that antibodies to the HPV 16 E6 or E7 oncoproteins also were associated with an increased risk for cancer with odds ratios of 9 for oropharyngeal cancer and 3 for oral cavity cancer.

D'Souza looked at different methods of --- to test for HPV, oral HPV infection as well as serology and found that serology was the strong --- was more strongly associated with the risk for cancer. Cases were 32 times more likely to be positive for antibodies to the capsid protein and 58 times more likely to be positive for antibodies to the E6 or E7 oncoproteins.

Compared with HPV-negative patients, HPV-positive oropharyngeal cancer patients are more likely to be younger males that are non-smokers and non-drinkers. They have higher numbers of lifetime sex partners as well as oral sex partners and are more likely to present with a tonsil or base of tongue tumor site.

This figure shows the risk factor profiles for HPV-positive patients versus negative patients. HPV-positive patients shown at the top are associated with oral sex and marijuana use while the bottom panel shows HPV-negative patients with an association with inc --- higher intensity of smoking, alcohol drinking as well as poor dental status.

The incidence for oropharyngeal cancer is much higher among men than women in the U.S.

Currently there are eight cases per 100,000 men while only two cases per 100,000 women. Incidence is especially high among white males and lowest among American Indians and Asian-Pacific Islanders.

Here this is SEER data and we see the trends over time in incidence where the bottom line in green shows oropharyngeal cancer increasing over time with the most dramatic increase in the last period studied between 2000 and 2004 with a 5% increase per year. For oral cavity cancer which is considered HPV-unrelated and is shown in orange there's been a decrease in incidence over time, 2% every year since the 1980s. And this can
be attributed to a decrease in smoking prevalence in the population along with an increase in oral HPV prevalence.

So when tumors were tested for HPV from a cohort going back to the 1980s we see that the prevalence of HPV-positive tumors has increased from 16% to 73% between 1988 and 2004 while --- and this has led to a 225% increased incidence in HPV-positive cancers along with a 50% decreased incidence in HPV-negative cancers.

So this increase in incidence is real --- mainly seen among white men and to a lesser extent white women. And in fact incidence among black men has been decreasing. And there haven't been any significant differences in incidence over time for the other ethnic groups.

Comparing oropharyngeal cancer to cervical cancer you see that cervical cancer incidence is decreasing due to good screening programs while as we saw before oropharyngeal cancer is increasing. So in 2010 the incidence for cervical cancer was equal to the incidence for oropharyngeal cancer among men. And it’s estimated that by 2020 there will be more HPV-positive oropharyngeal cancer cases than cervical cancers.

Looking at other head and neck cancer sites these also are decreasing in incidence: the oral cavity, the larynx and the pharynx. So by 2030 it’s estimated that half of all head and neck cancers will be HPV-positive oropharyngeal cancers.

So along with this increase in incidence there has als --- also been improvement in the five-year survival rates for oropharyngeal cancer.

This is shown in red and goes from 1975 to 2005 and this is from SEER data.

And this improvement in survival is due to the increase in HPV-positive tumors. HPV-positive patients have much better survival than HPV-negative patients which are shown in blue. And when we look at survival trends over time we see that HPV-positive patients have had a significant improvement is survival over time. This hasn't been seen for HPV-negative patients.

At MD Anderson we looked at more than 2,000 patients diagnosed between 1955 and 2004 and saw significant increases in survival especially in the last decade that we looked at from 1995 to 2004.

When we looked at survival by stage we saw that for patients diagnosed before 1995 the current staging --- TNM staging system adequately predicts survival; stage 1 and 2 having the best and stage 4 having the worst. But when we looked at patients diagnosed since 1995 we see that the staging system no longer is predictive for survival. Stage 3 and 4 patients have better survival than stage 1 and 2 and this is likely because HPV-positive patients tend to present with stage 3 and 4 disease.
So looking at the most important factors for survival in patients diagnosed before 1995 those factors that correspond with the traditional TNM staging system, TNM category are the most important predictors of survival. But since 1995 smoking was the most important. Young never smokers had the best survival and these are patients that tend to be HPV-positive while patients with the worst survival are smokers with large tumors and they tend to be HPV-negative. And we didn’t have HPV status available for this cohort but the phenotypes do correspond with HPV status.

So no far --- so far no precursor lesion for oropharyngeal cancer…

…has been identified. There’s currently no screening test available to --- to catch cancers at an early stage but we do have prophylactic vaccines available to prevent HPV infections. The quadrivalent vaccine protects against HPV type 6 and 11 which cause genital warts and 16 and 18 which cause cancer. The bivalent vaccine protects against type 16 and 18. The FDA just approved a nonavalent vaccine which protects against five additional types and all together these types are responsible for 90% of cervical cancers.

The CDC does recommend the HPV vaccine for routine vaccination for 11 and 12-year-old girls and boys as well as those who are age 13 to 26 who haven’t previously been vaccinated. Vaccination of both boys and girls is very important to prevent HPV-associated cancers. The WHO Strategic Advisory Group of Experts met in April of 2014 and issued a recommendation for a 2-dose schedule for girls if vaccination is initiated prior to their 15th birthday and the 3-dose schedule should remain if immunization is after the girl is 15. The CDC’s current recommendation still remains the 3-dose schedule for both boys and girls.

Compared to other developed countries the U.S. has low rates of HPV vaccination. Less than 40% of girls have received all three doses and only 14% of boys have.

The reasons that parents give for not having their child vaccinated include a lack of knowledge; they don’t think it’s necessary, they have safety concerns, it’s not recommended by the pediatrician, or their child is not sexually active. And, in fact, the number one reason for parents of boys to not have their son vaccinated is that it’s not recommended by the pediatrician. The --- There needs to be an effort by healthcare providers to recommend the vaccine to get the vaccination rates higher.

So, to summarize this lecture, HPV is the most common sexually transmitted infection worldwide and most individuals will be infected. The oropharynx is the main site for HPV-related head and neck cancer and are associated with younger aged male sex, a high number of sex partners and a tonsil or a base of tongue tumor. The incidence of HP --- HPV-related oropharyngeal cancer is increasing while the incidence of HPV-unrelated head and neck cancer is decreasing. There’s currently no screening strategy available for HPV-related oropharyngeal cancer. And primary prevention of HPV-related disease including oropharyngeal cancer is through HPV vaccination which is crucial for both boys and girls. CDC does recommend routine vaccination of boys and girls. There needs to
be an effort by healthcare providers to recommend the HPV vaccine in order to reach the Healthy People 2020 target of 80% coverage.

This concludes my lecture. If you have any questions or comments, please let us know.