Natural History of HPV and Cervical Cancer

[Announcer] This podcast is presented by the Centers for Disease Control and Prevention. CDC – safer, healthier people.

[Dr. Saraiya] Hello, this is Dr. Mona Saraiya at the CDC. This is the first of a series of interviews that CDC is conducting with cervical cancer experts. Our guest today is Dr. Phil Castle. Dr. Castle is an intramural research scientist at the NIH. His research is on the natural history of human papillomavirus, or HPV infections, and cervical cancer and other anogenital cancers. He's particularly interested in the translation of the knowledge of HPV natural history into clinical medicine and prevention of cervical cancer. Welcome to the show, Phil.

[Dr. Castle] Nice to be here, Mona.

[Dr. Saraiya] Phil, tell us about the HPV virus and its relationship to the development of precancerous lesions, such as cervical intraepithelial neoplasia grade 3 (CIN3), or cervical cancer.

[Dr. Castle] HPV is a relatively simple capsid virus. It encodes only for eight genes. HPV is the most common of all sexually transmitted infections. Most if not all sexually active men and women have been infected by HPV at least once, and many have been infected more than once. Fortunately, most HPV infections are benign and go away on their own. HPV infections, except when they cause cancer, cause no symptoms.

Approximately 15 cancer-associated (carcinogenic) or high-risk HPV types cause virtually all cervical cancer and its immediate precancerous lesions worldwide. There is no place in the world this is not the case. HPV16 and 18, the two types targeted by HPV vaccines, are the most important HPV types everywhere in the world.

When HPV persists, women are at risk for precancer. If not treated, precancer develops into cancer over many years. The causal model is composed of four reliably measured carcinogenic steps or stages summarized as HPV acquisition, HPV persistence, progression to precancer, and invasion.

[Dr. Saraiya] Phil, you mention that HPV is a risk stratifier. Can you explain and give us an example to how this might be useful for the typical practitioner? And are there any tools practitioners can use to remember this?

[Dr. Castle] Simply put, women who test positive for high-risk HPV are at risk for precancer and cancer, whereas those who test negative are at very low risk for five to 10 years. As an example, the first approved application of high-risk HPV testing was for use with equivocal Pap smears or cervical cytology—that is, atypical squamous cells of undetermined significance, or ASCUS. Women with ASCUS cytology who test high-risk HPV positive are approximately 15 times more likely to have a precancerous lesion than those who test HPV negative. It is therefore recommended that HPV-positive ASCUS have a follow-up evaluation by colposcopy.

Guidelines for the use of HPV testing have been put forth by the American Cancer Society and the American Society for Colposcopy and Cervical Pathology. In particular, the ASCCP guidelines provide recommendations for the use of high-risk HPV and the clinical management of women following a non-normal cytology and/or positive HPV test. These guidelines have been published by the American Journal of Obstetrics and Gynecology and the Journal of Lower Genital Tract Disease. Written guideline materials are available on the American Society for Colposcopy and Cervical Pathology's Web site, asccp.org. In addition, several professional societies have come together to develop a consensus publication on the use of high-risk HPV testing in clinical practice. This will be published in several journals sometime in 2009.

[Dr. Saraiya] Why is HPV persistence so important in the development of cervical cancer?

[Dr. Castle] HPV is the necessary cause of cervical cancer. Without HPV, there can be no cervical cancer. HPV-negative cervical cancer can occur because of testing error. HPV causes cancer by permanently disrupting the infected cervical cell machinery.

[Dr. Saraiya] So, if someone has CIN1, what is the likelihood of this lesion progressing to a more serious lesion such as CIN2 or CIN3?

[Dr. Castle] CIN1 is not disease, but an indication of HPV infection only. Among women with equivocal or mildly abnormal Pap smears, the risk of CIN2 or CIN3 in the next two years following a CIN1 biopsy is approximately 13 percent. This is the same risk following a negative colposcopy and the same risk following a normal biopsy.

[Dr. Saraiya] How have some of your studies informed us about clinical practice and the natural history of cervical cancer?

[Dr. Castle] Our studies, fortunately, have been quite informative. Perhaps the most important finding has been the applicability of HPV testing to clinical practice. HPV testing is very useful in screening. A negative HPV test and Pap smear provides years of reassurance against cancer as compared to a Pap smear only. For example, in a study at Portland Kaiser, women who tested negative for both had only a 1 percent risk of precancerous lesions in 10 years. That kind of reassurance from a test is virtually unheard of in clinical medicine. High-risk HPV testing is also useful for deciding which women with equivocal Pap smears need immediate colposcopy.

Our data have also been useful in showing that women with HPV16 or HPV18 infections or persistent high-risk HPV infections have a very high risk of developing cervical precancer or cancer in the subsequent years. In contrast, some HPV types, so-called non-carcinogenic HPV types, are not clinically useful and should *never* be used in clinical practice.

[Dr. Saraiya] What is the one message you'd like clinical staff to walk away with today about the natural history of HPV and cervical cancer?

[Dr. Castle] High-risk HPV infections are typically benign. They usually go away on their own. It's not necessary for clinicians to react to a positive high-risk HPV test as if it meant cancer. Most women who test positive for high-risk HPV will not have cancer or even precancer. The

power of high-risk HPV testing is that women who test negative for high-risk HPV are very safe and don't need screening for another three years.

[Dr. Saraiya] Wow, that is really important. Can you also tell us about the relationship between age and HPV prevalence? How does this relate to when to start screening?

[Dr. Castle] HPV infection is extremely common in young women after they become sexually active. In the U.S., the median age of sexual debut is 17 years. As shown by the CDC and others, HPV prevalence declines sharply with age, so that the HPV prevalence is two- to five-fold less common in women aged 30 and older than in women under the age of 30. While HPV prevalence declines with age, the likelihood of CIN2 or CIN3 begins to rise in women in their mid 20s.

Fortunately, CIN2 or CIN3 typically takes many years before it becomes cancerous, such that cervical cancer is exceedingly rare in women under the age 25 and still very rare in women aged 25 to 29. Thus, screening with cervical cytology is recommended for women aged 21, or three years after sexual debut. However, high-risk HPV testing is only recommended for cervical cancer screening in women 30 and older.

[Dr. Saraiya] Phil, thank you so much for your time. This segment has been very informative.

[Announcer] For the most accurate health information, visit www.cdc.gov or call 1-800-CDC-INFO, 24/7.