**National Cancer Institute Research on Human Papillomavirus and Cervical Cancer**

**Statement of**
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**Before the House Committee on Government Reform Subcommittee on Criminal Justice, Drug Policy and Human Resources**

**March 11, 2004; 1:00 AM**

Chairman Souder and members of the House Subcommittee on Criminal Justice, Drug Policy and Human Resources, on behalf of Dr. Andrew von Eschenbach and the National Cancer Institute, would like to thank you for this opportunity to testify on HPV and cervical cancer. I am Dr. Edward Trimble, a gynecologist oncologist working in the Cancer Therapy Evaluation Program of the National Cancer Institute.

One hundred years ago, cervical cancer was the leading cause of cancer deaths among women in the United States. Since the identification and adoption of effective screening for cervical cancer with the Pap smear and based on our understanding of the natural history of precancerous changes in the cervix, we have been able to reduce both incidence and death rates from cervical cancer dramatically in the United States.

Over the past century, we have learned much about the natural history of cervical neoplasia or abnormal cell growth. We have learned that cervical cancer is preceded by precancerous changes in the cervix. We have learned that treatment of these precancerous changes can prevent the development of cancer. We have learned that a Pap test taken from the cervix can identify precancerous changes. More recently, we have identified human papillomaviruses (HPVs) as the major cause of cervical cancer. Studies also suggest that HPVs may play a role in cancers of the anus, vulva, vagina, and penis, and some cancers of the oropharynx (middle part of the throat including the soft palate), the base of the tongue, and the tonsils. There are more than 100 types of HPVs, of which only 30 types can be transmitted by sexual contact. HPV is one of the most common of the sexually transmitted viruses. Rarely can an infection with high risk HPV develop into precancer or cancer. The majority of HPV infections go away on their own and do not cause any abnormal cell growths.

The NCI has made a strong commitment to understanding the causes of cervical cancer and the relationship of HPV viruses to the development of cervical cancer. In fiscal year 2003, NCI spent $79 million for research on cervical cancer. NCI has funded extensive research to understand why most adults exposed to the HPV virus do not develop cancer or any other health problems resulting from that infection. NCI scientists have developed a new vaccine approach to prevent infection with HPV and are also working to develop a therapeutic vaccine to protect women already infected with the virus from developing

cancer. In addition, NCI has continuously worked to improve the reliability of Pap tests, to evaluate new methods of screening for cervical cancer, and to combine testing for HPV with Pap tests. NCI is also committed to working to improve treatment for women diagnosed with cervical cancer. In 1999, the NCI issued a clinical announcement to alert women and their doctors of a major treatment advance, combining chemotherapy and radiation therapy in cervical cancer. NCI investigators are also working to preserve fertility in women with early cervical cancer, as well as to preserve bladder, bowel, and sexual function after treatment for cervical cancer. Finally, NCI has increased its support for research to address the gaps in the delivery of research advances to all populations. NCI is building long-term relationships between research institutions and community-based programs to learn more about the causes of cancer disparities in minority communities and to develop ways to eliminate these causes.

As part of the National Cancer Institute's Challenge Goal *to eliminate the suffering and death due to cancer by 2015*, we are working to discover, develop, and deliver the interventions that will prevent many cancers, detect and eliminate many others, and modulate the behavior of the remainder so that, ultimately, no one has to suffer and die as a result of this disease. To this end, NCI is supporting research studies on HPV and cervical cancer as they align with Discovery, Development and Delivery.

**DISCOVERY**

**The Guanacaste Study of HPV Natural History** is being conducted in the Guanacaste Province, an area in Costa Rica with a very high incidence rate of cervical cancer. Cervical cancer is the leading cause of cancer death in regions without effective cytology programs and screening. This study involves women who live in a region where there is a lack of effective cervical cytology programs and screening. This prospective study of HPV infection and cervical neoplasia is based on the recruitment and 7-year follow-up of a random sample of approximately 10,000 women 18+ years of age, residing in Guanacaste. The study has permitted several studies of HPV infection, cytology, cervicography, and the whole spectrum of cervical neoplasia. The epidemiologic risk factors for each stage of neoplasia have been identified, controlling for the central role of type-specific HPV infection. Follow-up of the cohort at six month to yearly intervals depending on disease status is complete and data analysis will examine the origins of precancer and cancer.

The **Genetic Supplementation Study** is nested within the Guanacaste Study (see above) in Costa Rica. It is a case control study intended to systematically evaluate the role of both viral variants and host immune response genes in cervical carcinogenesis. Biological specimens are being collected from women enrolled in the Guanacaste Study and detailed genotyping of the viral genome as well as genotyping of genetic polymorphisms in the genome of those women will be performed. A major focus will be the study of immune genes, particularly those known to interact with HPV and an assessment of genes potentially modifying other HPV cofactors.

**Study to understand Cervical Cancer Early Endpoints and Determinants (SUCCEED)** is a study to comprehensively assess biomarkers of risk for each

progressive stage of cervical neoplasia (normal, HPV-infected, precancer, cancer) and to discover a new set of biomarkers that can distinguish those at highest risk of cervical cancer from those with benign HPV infection. Over 1000 women will be recruited into the study and a subsequent 2-year prospective component will be conducted to validate the most promising candidate biomarkers and their key outcomes for HPV clearance, persistence, and progression to precancer.

**The Alternatives in Women's Health Care Immunology Study (nested within ALTS, described under Delivery)**, has enrolled approximately 900 women in a prospective study to identify biomarkers associated with permissive versus protective immune response to low-grade cervical lesions. Women with low-grade cervical disease are being followed at six month intervals for two years. Cellular and immunological parameters at entry will be correlated with progression, persistence or regression of low-grade lesions during follow-up.

A longitudinal study of HPV Infection and Cervical Neoplasia in Sao Paulo, Brazil was conducted on 2404 women, in which cervical specimens from Pap smears were tested for cytology and HPV genotyping every 4-6 months over a period of 8 years. Actuarial and non-actuarial analyses were used to measure time and rates of lesion progression and regression according to status and type of HPV infection. The study found that precursor lesions of the cervix persist longer and progress more quickly in women with oncogenic HPV infections than in women with non-oncogenic infections or without HPV. The study concluded that testing cervical lesions for oncogenic HPVs may help identify those lesions that are likely to progress rapidly. Results of this study are published in: N.F. Schlecht, R.W. Platt, E. Duarte-Franco, M.C. Costa, J.P. Sobrinho, J.C.M. Prado, A. Ferenczy, T.E. Rohan, L.L. Villa, E.L. Franco 2003 Human Papillomavirus Infection and Time to Progression and Regression of Cervical Intraepithelial Neoplasia JNCI 95: 1336-43.

**DEVELOPMENT**

A high priority of the NCI is to prevent cervical cancer by developing a vaccine that prevents and treats HPV infection and premalignant disease. There is growing evidence that a VLP-based (virus-like particle) HPV vaccine will be effective in preventing genital HPV infection. A large randomized **Vaccine Trial** is planned in Costa Rica to evaluate the efficacy of two virus-like particle (VLP)-based prophylactic human papillomavirus (HPV) vaccines developed at NCI. Volunteers in the trial will be screened for cervical disease at entry and will receive three VLP or three placebo vaccinations over the course of six months. Participants will be followed for four years and information collected on side effects of the vaccine (safety), immune reduction by the vaccine, and the occurrence of cervical disease.

Another high priority area is the development of affordable, second-generation DNA-based tests for the diagnosis of HPV infection. A partnership with the Gates Foundation and the Program for Appropriate Technology in Health (PATH) is an initiative, still in the planning stages, to create a low-cost test in two to three years for field testing.

**Optical Technologies for Cervical Neoplasia** is a Program Project Grant, sponsored by the **Cancer Imaging Program/National Cancer Imaging Program (CIP/NCI)** that uses a method of technology assessment that will guide the development of new and existing optical technologies to detect and diagnosis early cervical cancer. Evaluation of these optical technologies will provide improved screening and detection methods for cervical intra-epithelial neoplasia that are both sensitive and cost-effective in both developing and developed countries. The relationship between optical signatures and the underlying cancer biology is not well understood. Preliminary studies demonstrate that this imaging approach accurately detects the intracellular changes that occur as cells become abnormal and can be applied to developing mathematical models for distinguishing normal and neoplastic tissue. Recent clinical trials have shown that the imaging technique is feasible for use in large populations and can be adapted for simple, inexpensive imaging systems for use in screening trials worldwide. NCI investigators will continue to develop this promising new technology in a large randomized trial comparing fluorescence and reflectance screening with standard cervical cancer screening techniques.

**Rapid Access to Preventive Intervention Development (RAPID)** provides funding and resources to develop agents that prevent, reverse, or delay cancer development. RAPID is designed to quickly move novel preventive molecules, such as HPV vaccines for cervical cancer, from the laboratory into clinical studies.

**The Gynecologic Cancer Intergroup (GCIG)** is an organization of international cooperative groups for clinical trials in gynecologic cancers that is identifying active treatments for cervical cancer.

**DELIVERY** The **ASCUS/LSIL Triage /Study for Cervical Cancer (ALTS)** is a clinical trial to find the best way to help women and their doctors decide what to do about abnormal Pap test results that are diagnosed in about three million women in the United States each year. ASCUS stands for atypical squamous cells (abnormal cells lining the cervix) of undetermined significance and LSIL for low-grade squamous intraepithelial lesions. Most of these abnormalities are mild and will go away without treatment, but some may signal a precancerous condition or, rarely, cancer.

The motivation for this trial was to use the information about the role of HPV to design better treatment and prevention strategies to reduce the burden of cervical cancer and its precursors. The study consisted of three management strategies: (1) immediate colposcopy of all women; (2) repeat cytology with colposcopy only if the results show a high grade lesion; and (3) HPV testing and repeat cytology in combination, with referral to colposcopy if either the HPV test is positive or the cytology shows a high grade lesion. Four Clinical Centers - University of Alabama, Birmingham AL; Magee-Womens Hospital, Pittsburgh PA; University of Oklahoma, Oklahoma City OK; and University of Washington, Seattle WA - enrolled approximately 5,000 women with a recent diagnosis of ASCUS or LSIL. Participants were followed at six month intervals for a total of 2

years and the efficacy and cost-effectiveness of the different strategies in the early detection of high-grade lesions were compared.The findings were as follows:

- HPV testing is sensitive in detecting underlying precancerous lesions among women with a Pap test diagnosis of ASCUS
- Neither cytology nor HPV testing is useful for triaging women with a Pap test diagnosis of LSIL
- A single colposcopic-directed biopsy procedure is not completely sensitive in detecting precancers

The **Bethesda System for Cervical Cytology** was developed under the auspices of the NCI to provide a coherent framework for reporting Pap test results. Currently over 90% of cytology laboratories in the U.S. and many countries internationally use this system. The standardized terminology has facilitated correlation among different research studies and has become the basis for professional societies to develop patient management guidelines.

The **Portland Kaiser Cohort Study** has enrolled almost 24,000 women obtaining a routine Pap smear screening at any of the seven Portland Kaiser-Permanente clinics for the purpose of conducting a prospective study of HPV infection and cervical neoplasia. This is a companion study for the Guanacaste Study (described above under Discovery). The enrollment phase has yielded a prevalent case-control comparison which has demonstrated that HPV is the primary risk factor for cervical intraepithelial neoplasia. The study also has shown that HPV testing can be used to clarify borderline Pap smears. The full cohort based on up to 10-years of follow-up showed the usefulness of combined Pap tests to improve the detection of cervical cancer. The use of HPV DNA testing as an adjunct to Pap tests was approved in 2003 by the Food and Drug Administration, and several groups have modified screening recommendations accordingly.

The **Cancer Research Network** is a consortium of researchers affilitated with eleven major not-for-profit HMOs that is providing the mechanism for NCI to quickly obtain better data on patterns of cancer care from multiple perspectives. One of their recent findings indicates that the majority of breast and cervical cancer cases appear to be associated with an absence of screening and failures in detection.

For the purpose of **broadening our understanding of the causes of cancer disparities**, the NCI has implemented a partnership demonstration project in eight states to increase screening for breast and cervical cancer among women who have never or rarely been screened (in collaboration with CDC, USDA and ACS). Despite a three-fold reduction in cervical cancer mortality nationwide, many counties from Maine through Appalachia, many of the southeastern states, the Texas/Mexico border, and in the Central Valley of California have experienced higher cervical cancer mortality rates. To address these high rates, the partnership will use NCI analyses of county mortality rates to identify high-rate counties and will work to train staff of CDC's Breast and Cervical Cancer Early Detection Program; USDA's Cooperative State Research, Education, and Extension

Service; ACS's regional cancer control programs; and NCI's Cancer Information Service to increase screening among high-risk women.

In the future, NCI plans to continue its close collaboration with its sister agencies in DHHS to make available effective vaccines for HPV to reduce the emotional and economic cost of screening for cervical cancer, to improve the accuracy of screening, and to find more effective treatment for cervical cancer.