

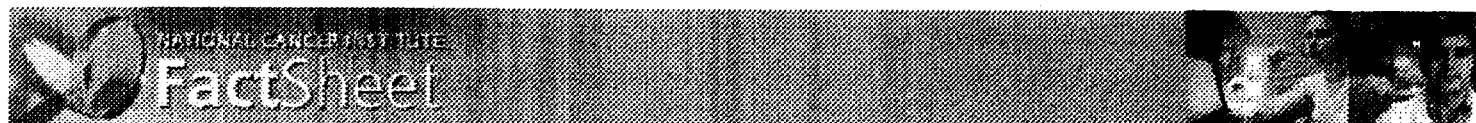


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## Human Papillomaviruses and Cancer: Questions and Answers

### Key Points

- Human papillomaviruses (HPVs) are a group of more than 100 types of viruses (see [Question 1](#)).
- Most HPV infections go away on their own (see [Questions 1, 4, and 5](#)).
- HPVs are the major cause of cervical cancer. HPVs may also play a role in cancers of the anus, vulva, vagina, and penis, and some cancers of the oropharynx (see [Question 3](#)).
- Although there is no cure for HPV infection, the warts and lesions these viruses cause can be treated (see [Question 10](#)).
- Researchers at the National Cancer Institute and elsewhere are conducting research on HPV-related cancers (see [Question 11](#)).

### 1. What are human papillomaviruses, and how are they transmitted?

Human papillomaviruses (HPV) are a group of more than 100 viruses. They are called papillomaviruses because certain types may cause warts, or papillomas, which are benign (noncancerous) tumors. The HPVs that cause the common warts which grow on hands and feet are different from those that cause growths in the throat or genital area. Some types of HPV are associated with certain types of cancer ([1](#)). These are called "high-risk" oncogenic or carcinogenic HPVs.

Of the more than 100 types of HPV, over 30 types can be passed from one person to another through sexual contact. Although HPVs are usually transmitted sexually, doctors cannot say for certain when infection occurred. Most HPV infections occur without any symptoms and go away without any treatment over the course of a few years. However, HPV infection sometimes persists for many years, with or without causing cell abnormalities.

### 2. What are genital warts?

Some types of HPV may cause warts to appear on or around the genitals or anus. Genital warts (technically known as condylomata acuminatum) are most commonly associated with two HPV types, HPV-6 and HPV-11. Warts may appear within several weeks after sexual contact with a person who is infected with HPV, or they may take months or years to appear, or they may never appear. HPVs may also cause flat, abnormal growths in the genital area and on the cervix (the lower part of the uterus that extends into the vagina). However, HPV infections usually do not cause any symptoms.

### 3. What is the association between HPV infection and cancer?

HPVs are now recognized as the major cause of cervical cancer. In 2006, an estimated 10,000 women in the United States will be diagnosed with this type of cancer and nearly 4,000 will die from it. Cervical cancer strikes nearly half a million women each year worldwide, claiming a quarter of a million lives. Studies also suggest that HPVs may play a role in cancers of the anus, vulva, vagina, and some cancers of the oropharynx (the middle part of the throat that includes the soft palate, the base of the tongue, and the tonsils) (1). Data from several studies also suggest that infection with HPV is a risk factor for penile cancer (cancer of the penis).

### 4. Are there specific types of HPV that are associated with cancer?

→ Some types of HPV are referred to as “low-risk” viruses because they rarely develop into cancer. HPV types that are more likely to lead to the development of cancer are referred to as “high-risk.” Both high-risk and low-risk types of HPV can cause the growth of abnormal cells, but generally only the high-risk types of HPV may lead to cancer. Sexually transmitted, high-risk HPVs include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, and possibly a few others. These high-risk types of HPV cause growths that are usually flat and nearly invisible, as compared with the warts caused by types HPV-6 and HPV-11. It is important to note, however, that the majority of high-risk HPV infections go away on their own and do not cause cancer (2). ←

### 5. What are the risk factors for HPV infection and cervical cancer?

→ Having many sexual partners is a risk factor for HPV infection. Although most HPV infections go away on their own without causing any type of abnormality, infection with high-risk HPV types increases the chance that mild abnormalities will progress to more severe abnormalities or cervical cancer. Still, of the women who do develop abnormal cell changes with high-risk types of HPV, only a small percentage would develop cervical cancer if the abnormal cells were not removed. Studies suggest that whether a woman develops cervical cancer depends on a variety of factors acting together with high-risk HPVs. The factors that may increase the risk of cervical cancer in women with HPV infection include smoking and having many children (3). ←

### 6. Can HPV infection be prevented?

The surest way to eliminate risk for genital HPV infection is to refrain from any genital contact with another individual.

For those who choose to be sexually active, a long-term, mutually monogamous relationship with an uninfected partner is the strategy most likely to prevent genital HPV infection. However, it is difficult to determine whether a partner who has been sexually active in the past is currently infected.

HPV infection can occur in both male and female genital areas that are covered or protected by a latex condom, as well as in areas that are not covered. Although the effect of condoms in preventing HPV infection is unknown, condom use has been associated with a lower rate of cervical cancer.

Recently, the U.S. Food and Drug Administration (FDA) approved a vaccine that is highly effective in preventing infection with types 16 and 18, two “high-risk” HPVs that cause most (70 percent) cervical cancers, and types 6 and 11, which cause most (90 percent) genital warts (4).

### 7. How are HPV infections detected?

Testing samples of cervical cells is an effective way to identify high-risk types of HPV that may be present. The FDA has approved an HPV test as a follow-up for women who have an ambiguous Pap

test (a screening test to detect cervical cell changes and, for women over the age of 30, for general cervical cancer screening). This HPV test can identify 13 of the high-risk types of HPV associated with the development of cervical cancer. This test, which looks for viral DNA, is performed by collecting cells from the cervix and then sending them to a laboratory for analysis. The test can detect high-risk types of HPV even before there are any conclusive visible changes to the cervical cells. There are currently no tests approved to detect HPV infection in men.

#### 8. How are cervical cell abnormalities classified?

A Pap test is used to detect abnormal cells in the cervix. It involves the collection of cells from the cervix for examination under the microscope. Various terms have been used to describe the abnormal cells that may be seen in Pap tests.

The major system used to report the results of Pap tests in the United States is the Bethesda System. In this system, samples with cell abnormalities are divided into the following categories:

- **ASC—Atypical Squamous Cells.** Squamous cells are the thin, flat cells that form the surface of the cervix. The Bethesda System divides this category into two groups:
  1. **ASC–US—Atypical Squamous Cells of Undetermined Significance.** The squamous cells do not appear completely normal, but doctors are uncertain what the cell changes mean. Sometimes the changes are related to HPV infection. An HPV test may be done to clarify the findings.
  2. **ASC–H—Atypical Squamous Cells cannot exclude a High-grade squamous intraepithelial abnormality.** Intraepithelial refers to the layer of cells that forms the surface of the cervix. The cells do not appear normal, but doctors are uncertain what the cell changes mean. ASC–H may indicate a higher risk of being precancerous compared with ASC–US.
- **AGC —Atypical Glandular Cells.** Glandular cells are mucus-producing cells found in the endocervical canal (opening in the center of the cervix) or in the lining of the uterus. The glandular cells do not appear normal, but doctors are uncertain what the cell changes mean.
- **AIS —endocervical Adenocarcinoma In Situ.** Precancerous cells are found in the glandular tissue.
- **LSIL —Low-grade Squamous Intraepithelial Lesion.** Low-grade means there are early changes in the size and shape of the cells. The word lesion refers to an area of abnormal tissue. LSILs are considered mild abnormalities caused by HPV infection and are a common condition, especially among young women. The majority of LSILs return to normal over months to a few years.
- **HSIL —High-grade Squamous Intraepithelial Lesion.** High-grade means that the cells look very different in size and shape from normal cells. HSILs are more severe abnormalities and may eventually lead to cancer if left untreated.

Pap test results may also be described using an older set of categories called the “dysplasia scale.” Dysplasia is a term used to describe abnormal cells. Although dysplasia is not cancer, it may develop into very early cancer of the cervix. The cells look abnormal under the microscope, but they do not invade nearby healthy tissue.

There are four degrees of dysplasia: mild, moderate, severe, and carcinoma in situ. Carcinoma in situ is a precancerous condition that involves only the layer of cells on the surface of the cervix, and has not spread to nearby tissues. In the Bethesda System, mild dysplasia is classified as LSIL; moderate

or severe dysplasia and carcinoma in situ are combined into HSIL.

Cervical intraepithelial neoplasia (CIN) is another term that is sometimes used to describe abnormal tissue findings. Neoplasia means an abnormal growth of cells. The term CIN along with a number (1, 2, or 3) describes how much of the thickness of the lining of the cervix contains abnormal cells. CIN-3 is considered to be a precancerous condition that includes carcinoma in situ.

9. What tests are used to screen for and diagnose precancerous cervical conditions?

A Pap test is the standard way to check for any cervical cell changes. A Pap test is usually done as part of a gynecologic exam. The U.S. Preventive Services Task Force guidelines recommend that women have a Pap test at least once every 3 years, beginning about 3 years after they begin to have sexual intercourse, but no later than age 21.

Because the HPV test can detect high-risk types of HPV in cervical cells, the FDA approved this test as a useful addition to the Pap test to help health care providers decide which women with ASC-US need further testing, such as colposcopy and biopsy of any abnormal areas. (Colposcopy is a procedure in which a lighted magnifying instrument called a colposcope is used to examine the vagina and cervix. Biopsy is the removal of a small piece of tissue for diagnosis.) In addition, the HPV test may be a helpful addition to the Pap test for general screening of women age 30 and over.

10. What are the treatment options for HPV infection?

Although there is currently no medical cure for papillomavirus infection, the lesions and warts these viruses cause can be treated. Methods commonly used to treat lesions include cryosurgery (freezing that destroys tissue), LEEP (loop electrosurgical excision procedure, the removal of tissue using a hot wire loop), and conventional surgery. Similar treatments may be used for external genital warts. In addition, some drugs may be used to treat external genital warts (5). More information about treatment for genital warts can be found on the Centers for Disease Control and Prevention's (CDC) Sexually Transmitted Diseases Treatment Guidelines Web page at <http://www.cdc.gov/STD/treatment/> on the Internet.

11. What research is being done on HPV-related cancers?

Researchers at the National Cancer Institute (NCI) and elsewhere are studying how HPVs cause precancerous changes in normal cells and how these changes can be prevented (6). For example, scientists are developing HPV vaccines that will be stable at room temperature. The goal is to develop a vaccine that does not require refrigeration for storage and distribution, which could allow for its use in many climates and locations.

Laboratory research has indicated that HPVs produce proteins known as E5, E6, and E7. These proteins interfere with the cell functions that normally prevent excessive growth. For example, HPV E6 interferes with the human protein p53. This protein is present in all people and acts to keep tumors from growing (7). This research is being used to develop ways to interrupt the process by which HPV infection can lead to the growth of abnormal cells.

Researchers at the NCI and elsewhere are also studying what people know and understand about HPV and cervical cancer, the best way to communicate to the public about the latest research results, and how doctors are talking with their patients about HPV. This research will help to ensure that the public receives accurate information about HPV that is easily understood, and will facilitate access to appropriate tests for those who need them.

12. How can people learn more about HPV infection?

The following Federal Government agencies can provide more information about HPV infection:

The NCI's Digest Page about Human Papillomavirus (HPV) Vaccines for Cervical Cancer provides links to NCI materials about HPV vaccines as well as general information about HPV, cancer vaccines, and cervical cancer. This Web site can be found at <http://www.cancer.gov/cancertopics/hpv-vaccines> on the Internet.

The National Institute of Allergy and Infectious Diseases (NIAID) supports research on HPV infection and offers printed materials. NIAID can be contacted at:

**Organization:** National Institute of Allergy and Infectious Diseases  
**Address:** Office of Communications and Public Liaison  
6610 Rockledge Drive, MSC 6612  
Bethesda, MD 20892-6612  
**Telephone:** 301-496-5717  
**TTY:** 1-800-877-8339  
**Internet Web site:** <http://www.niaid.nih.gov>

The CDC-INFO Contact Center provides information on sexually transmitted infections, including HPV, and how to prevent them. The center can be reached by calling toll-free 1-800-CDC-INFO (1-800-232-4636). Both English- and Spanish-speaking specialists are available 24 hours a day, 7 days a week, 365 days a year. Staff provide information about sexually transmitted diseases (STDs) and referrals to free or low-cost clinics nationwide. Free educational literature about sexually transmitted infections and prevention methods is also available. More information from the CDC about sexually transmitted infections is available at <http://www.cdc.gov/std> on the Internet.

The CDC's Division of STD Prevention Web site also has information about HPV, including treatment guidelines and surveillance statistics. This Web site can be found at <http://www.cdc.gov/std/hpv/> on the Internet.

## Selected References

1. Division of STD Prevention. *Prevention of genital HPV infection and sequelae: Report of an external consultants' meeting*. Atlanta, GA: Centers for Disease Control and Prevention, 1999.
2. Munoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New England Journal of Medicine* 2003; 348(6):518-527.
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4. Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. *New England Journal of Medicine* 2002; 347(21):1645-1651.
5. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002.

Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report* 2002; 51(RR-6):1-78.

6. National Cancer Institute. Future directions in epidemiologic and preventive research on human papillomaviruses and cancer. Proceedings of a workshop. Bethesda, Maryland, June 2002. *Journal of the National Cancer Institutes Monographs* 2003; 31:1-130.
7. Howley PM, Ganem D, Kieff E. Etiology of cancer: Viruses. Section 2: DNA Viruses. In: DeVita VT Jr., Hellman S, Rosenberg SA, editors. *Cancer: Principles and Practice of Oncology*. Vol. 1 and 2. 6 th ed. Philadelphia: Lippincott Williams and Wilkins, 2004.

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### **Related Resources**

**Publications (available at <http://www.cancer.gov/publications>)**

- \* National Cancer Institute Fact Sheet 3.79, *Human Papillomavirus Vaccines: Questions and Answers* <sup>1</sup>
- \* National Cancer Institute Fact Sheet 5.16, *The Pap Test: Questions and Answers* <sup>2</sup>
- \* *Understanding Cervical Changes: A Health Guide for Women* <sup>3</sup>
- \* *What You Need To Know About™ Cancer of the Cervix* <sup>4</sup>

### **National Cancer Institute (NCI) Resources**

#### **Cancer Information Service (toll-free)**

Telephone: 1-800-4-CANCER (1-800-422-6237)

TTY: 1-800-332-8615

#### **Online**

NCI's Web site: <http://www.cancer.gov>

*LiveHelp*, NCI's live online assistance:

<https://cissecure.nci.nih.gov/livehelp/welcome.asp>

## **Glossary Terms**

### **abnormal**

Not normal. An abnormal lesion or growth may be cancerous, premalignant (likely to become cancer), or benign.

### **adenocarcinoma (A-den-oh-KAR-sih-NOH-muh)**

Cancer that begins in cells that line certain internal organs and that have gland-like (secretory) properties.

**analysis**

A process in which anything complex is separated into simple or less complex parts.

**anus (AY-nus)**

The opening of the rectum to the outside of the body.

**benign (beh-NINE)**

Not cancerous. Benign tumors may grow larger but do not spread to other parts of the body.

**biopsy (BY-op-see)**

The removal of cells or tissues for examination by a pathologist. The pathologist may study the tissue under a microscope or perform other tests on the cells or tissue. When only a sample of tissue is removed, the procedure is called an incisional biopsy. When an entire lump or suspicious area is removed, the procedure is called an excisional biopsy. When a sample of tissue or fluid is removed with a needle, the procedure is called a needle biopsy, core biopsy, or fine-needle aspiration.

**cancer**

A term for diseases in which abnormal cells divide without control. Cancer cells can invade nearby tissues and can spread through the bloodstream and lymphatic system to other parts of the body. There are several main types of cancer. Carcinoma is cancer that begins in the skin or in tissues that line or cover internal organs. Sarcoma is cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemia is cancer that starts in blood-forming tissue such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the bloodstream. Lymphoma and multiple myeloma are cancers that begin in the cells of the immune system.

**carcinoma in situ (KAR-sih-NOH-muh in SYE-too)**

Cancer that involves only cells in the tissue in which it began and that has not spread to nearby tissues.

**cell**

The individual unit that makes up the tissues of the body. All living things are made up of one or more cells.

**cervical cancer (SER-vih-kul KAN-ser)**

Cancer that forms in tissues of the cervix (organ connecting the uterus and vagina). It is usually a slow-growing cancer that may not have symptoms, but can be found with regular Pap smears (procedure in which cells are scraped from the cervix and looked at under a microscope).

**cervical intraepithelial neoplasia (SER-vih-kul IN-truh-eh-pih-THEEL-ee-ul NEE-o-play-zha)**

CIN. A general term for the growth of abnormal cells on the surface of the cervix. Numbers from 1 to 3 may be used to describe how much of the cervix contains abnormal cells.

**cervix (SER-viks)**

The lower, narrow end of the uterus that forms a canal between the uterus and vagina.

**colposcope (KOL-puh-SKOPE)**

A lighted magnifying instrument used to examine the vagina and cervix.

**colposcopy (kol-POSS-koh-pee)**

Examination of the vagina and cervix using a lighted magnifying instrument called a colposcope.

**cryosurgery (KRY-o-SER-juh-ree)**

A procedure performed with an instrument that freezes and destroys abnormal tissues.

**cure**

To heal or restore health; a treatment to restore health.

**diagnosis**

The process of identifying a disease by the signs and symptoms.

**DNA**

Deoxyribonucleic acid. The molecules inside cells that carry genetic information and pass it from one generation to the next.

**drug**

Any substance, other than food, that is used to prevent, diagnose, treat or relieve symptoms of a disease or abnormal condition. Also refers to a substance that alters mood or body function, or that can be habit-forming or addictive, especially a narcotic.

**dysplasia (dis-PLAY-zha)**

Cells that look abnormal under a microscope but are not cancer.

**follow-up**

Monitoring a person's health over time after treatment. This includes keeping track of the health of people who participate in a clinical study or clinical trial for a period of time, both during the study and after the study ends.

**gland**

An organ that makes one or more substances, such as hormones, digestive juices, sweat, tears, saliva, or milk. Endocrine glands release the substances directly into the bloodstream. Exocrine glands release the substances into a duct or opening to the inside or outside of the body.

**gynecologic**



Having to do with the female reproductive tract (including the cervix, endometrium, fallopian tubes, ovaries, uterus, and vagina).

**high grade**

When referring to cancerous and precancerous growths, a term used to describe cells that look abnormal under a microscope. These cells are more likely to grow and spread quickly than cells in low-grade cancerous and precancerous growths.

**high-grade squamous intraepithelial lesion**

HSIL. A precancerous condition in which the cells of the uterine cervix are moderately or severely abnormal.

**human papillomavirus (HYOO-mun PA-pih-LOH-muh-VY-rus)**

HPV. A member of a family of viruses that can cause abnormal tissue growth (for example, genital warts) and other changes to cells. Infection with certain types of HPV increases the risk of developing cervical cancer.

**infection**

Invasion and multiplication of germs in the body. Infections can occur in any part of the body and can spread throughout the body. The germs may be bacteria, viruses, yeast, or fungi. They can cause a fever and other problems, depending on where the infection occurs. When the body's natural defense system is strong, it can often fight the germs and prevent infection. Some cancer treatments can weaken the natural defense system.

**intraepithelial (IN-truh-eh-pih-THEEL-ee-ul)**

Within the layer of cells that form the surface or lining of an organ.

**lesion (LEE-zhun)**

An area of abnormal tissue. A lesion may be benign (noncancerous) or malignant (cancerous).

**loop electrosurgical excision procedure (loop ee-LEK-troh-SER-jih-kul ek-SIH-zhun proh-SEE-jer)**

LEEP. A technique that uses electric current passed through a thin wire loop to remove abnormal tissue. Also called loop excision.

**low-grade squamous intraepithelial lesion**

LSIL. A condition in which the cells of the uterine cervix are slightly abnormal. LSIL is not cancer.

**mucus (MYOO-kus)**

A thick, slippery fluid made by the membranes that line certain organs of the body, including the nose, mouth, throat, and vagina.

**National Cancer Institute**

NCI. The National Cancer Institute, part of the National Institutes of Health of the United States Department of Health and Human Services, is the Federal Government's principal agency for cancer research. NCI conducts, coordinates, and funds cancer research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer. Access the NCI Web site at <http://www.cancer.gov>. Also called NCI.

**neoplasia (NEE-o-PLAY-zha)**

Abnormal and uncontrolled cell growth.

**oropharynx (or-o-FAIR-inks)**

The part of the throat at the back of the mouth. It includes the soft palate, the base of the tongue, and the tonsils.

**p53 gene**

A tumor suppressor gene that normally inhibits the growth of tumors. This gene is altered in many types of cancer.

**Pap test**

A procedure in which cells are scraped from the cervix for examination under a microscope. It is used to detect cancer and changes that may lead to cancer. A Pap test can also show noncancerous conditions, such as infection or inflammation. Also called a Pap smear.

**penis**

An external male reproductive organ. It contains a tube called the urethra, which carries semen and urine to the outside of the body.

**precancerous (pre-KAN-ser-us)**

A term used to describe a condition that may (or is likely to) become cancer. Also called premalignant.

**protein (PRO-teen)**

A molecule made up of amino acids that are needed for the body to function properly. Proteins are the basis of body structures such as skin and hair and of substances such as enzymes, cytokines, and antibodies.

**risk factor**

Something that may increase the chance of developing a disease. Some examples of risk factors for cancer include age, a family history of certain cancers, use of tobacco products, certain eating habits, obesity, lack of exercise, exposure to radiation or other cancer-causing agents, and certain genetic changes.

**screening**

Checking for disease when there are no symptoms.

**soft palate (PAL-et)**

The back, muscular (not bony) part of the roof of the mouth.

**squamous cell (SKWAY-mus)**

Flat cell that looks like a fish scale under a microscope. These cells cover inside and outside surfaces of the body. They are found in the tissues that form the surface of the skin, the lining of the hollow organs of the body (such as the bladder, kidney, and uterus), and the passages of the respiratory and digestive tracts.

**surgery (SER-juh-ree)**

A procedure to remove or repair a part of the body or to find out whether disease is present. An operation.

**symptom**

An indication that a person has a condition or disease. Some examples of symptoms are headache, fever, fatigue, nausea, vomiting, and pain.

**throat (throate)**

The hollow tube inside the neck that starts behind the nose and ends at the top of the trachea (windpipe) and esophagus (the tube that goes to the stomach). The throat is about 5 inches long, depending on body size. Also called the pharynx.

**tissue (TISH-oo)**

A group or layer of cells that work together to perform a specific function.

**tonsil**

One of two small masses of lymphoid tissue on either side of the throat.

**tumor (TOO-mer)**

An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancerous), or malignant (cancerous). Also called neoplasm.

**uterus (YOO-ter-us)**

The small, hollow, pear-shaped organ in a woman's pelvis. This is the organ in which a baby grows. Also called the womb.

**vaccine**

A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. A vaccine can help the body recognize and destroy cancer cells or microorganisms.

**vagina (vuh-JY-nuh)**

The muscular canal extending from the uterus to the exterior of the body. Also called birth canal.

**virus (VYE-rus)**

A microorganism that can infect cells and cause disease.

**vulva**

The external female genital organs, including the clitoris, vaginal lips, and the opening to the vagina.

**wart**

A raised growth on the surface of the skin or other organ.

## **Table of Links**

**1** <http://cancer.gov/cancertopics/factsheet/risk/HPV-vaccine>

**2** <http://cancer.gov/cancertopics/factsheet/Detection/Pap-test>

**3** <http://cancer.gov/cancertopics/understandingcervicalchangesPDF>

**4** <http://cancer.gov/cancerinfo/wyntk/cervix>



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## Recent Studies Regarding HPV and Cervical Cancer: Questions and Answers

### Key Points

- ALTS (ASCUS/LSIL Triage Study for Cervical Cancer) and Portland Kaiser Permanente studies allowed researchers to examine whether testing for specific human papillomavirus (HPV) types -- HPV16 and HPV18 -- was more effective at predicting risk for precancerous conditions or cervical cancer than testing for a broad pool of cancer-causing, or oncogenic, HPV types (Question 5).
- The study authors found that women who tested positive for HPV16 or HPV18 had an increased risk for precancerous conditions and cervical cancer compared to those women who tested positive for another oncogenic HPV type and to those who tested negative for HPV (Question 6).
- Future research will help to demonstrate whether women who test negative for HPV16 and HPV18 can be followed and treated less aggressively than women who test positive for these HPV types (Question 9).

### Background

Cervical infections due to a group of about 15 oncogenic, or cancer-causing, human papillomavirus (HPV) types cause virtually all cervical cancers. They also are the cause of their immediate precursor, cervical intraepithelial neoplasia grade 3 (CIN3), a precancerous condition. Overall, about 10 percent of women at any one time have an oncogenic HPV infection, and they are more common in young women than in older women. Most cervical infections by even oncogenic HPV types go away on their own and do not cause cancer. In some women, oncogenic HPV infections persist and can progress over several years to CIN3, and may even progress to invasive cervical cancer. Most women, however do not progress to the precancer stage. Cervical cancer itself is extremely rare in the United States; there are about 11,000 new cases diagnosed and about 4,000 related deaths reported annually.

### Understanding Pap Smears and Other Cervical Cancer Screening and Management Techniques

#### 1. What is a Pap smear? What is a colposcopy?

A Pap smear is a procedure in which cells are scraped from the cervix (the lower, narrow end of the uterus that serves as a channel between the uterus and the vagina) and examined under a microscope. A Pap smear is used to detect cancer and cellular changes that may lead to cancer, as well as non-cancerous conditions like infection or inflammation.

A colposcopy is a procedure in which the vagina and cervix are examined using a lighted magnifying instrument called a colposcope. The vagina and cervix may be biopsied during a colposcopy so that tissue

samples can be examined under a microscope for abnormal cells. A colposcopy may be prescribed if a Pap smear detects certain abnormal cellular conditions.

## **2. What is human papillomavirus (HPV)?**

There are more than 100 types of human papillomaviruses (HPV). HPV is one of the most common sexually transmitted diseases (STDs), and more than 30 of the different types of HPV can be transmitted through sexual contact. While some types of HPV may cause warts to appear around the genitals, HPV infections also may occur without any obvious symptoms.

The U.S. Food and Drug Administration (FDA) has approved the use of a test for HPV as a screening tool for cervical cancer in conjunction with a Pap smear or cytology. Oncogenic HPV DNA testing (or "trriage") for patients with ASCUS has proven to be a useful alternative to referring patients for immediate colposcopy to detect CIN3 and cancer (greater or equal to CIN3). A 2004 conference of the International Agency for Research on Cancer concluded that there was sufficient evidence that HPV DNA testing could be used as a primary screening test in women age 30 and older.

## **3. Why are HPV16 and HPV18 important?**

Of the types of HPV that increase risk for certain types of cancer, HPV16 is the most common among women in the general population. Large case studies have shown that approximately 50 percent of women with CIN3 or cervical cancer are infected with HPV16. Additional research suggests that 60 percent to 70 percent of cervical cancer cases worldwide are caused by either HPV16 or HPV18. Virtually all remaining cases of cervical cancer are caused by other oncogenic HPV types.

## **4. What are ASCUS and LSIL?**

ASCUS and LSIL are acronyms for two mild abnormalities detected by Pap tests. ASCUS stands for "Atypical Squamous Cells of Undetermined Significance", and LSIL stands for "Low-grade Squamous Intraepithelial Lesion".

A diagnosis of ASCUS means that the nature of the abnormality is uncertain or equivocal. A diagnosis of LSIL means that there is a more definite, but still mild, abnormality.

## **Study Findings**

### **5. What were the goals of the ALTS and the Portland Kaiser Permanente studies?**

The National Cancer Institute (NCI) organized and funded ALTS (the ASCUS/LSIL Triage Study for Cervical Cancer) to help resolve the controversy over what physicians and women should do about ASCUS (equivocal) and LSIL (mildly abnormal) Pap test results\*. Most of these abnormalities will go away without treatment, but some may lead to a precancerous condition or cancer. This analysis of the ALTS data provided the opportunity for researchers to determine whether women with equivocal Pap smear results, who also tested positive for HPV16, had a greater risk for CIN3 or cervical cancer than women with equivocal Pap smear results who tested positive for other oncogenic types of HPV.

The Portland study was designed to examine the natural history of HPV infection and cervical neoplasia (abnormal and uncontrolled cell growth)\*\*. Additionally, this study allowed analysis of whether testing specifically for HPV16 and HPV18, in addition to overall testing for all HPV oncogenic types, might help identify women at particularly high risk for CIN3 or cervical cancer.

### **6. What were the results of these studies?**

In their analysis of ALTS data, Castle et al. found that 542 women in the study group developed CIN3 or cervical cancer. Those who tested positive for HPV16 had 38 times the risk for CIN3 or cervical cancer than women in the study who were HPV negative. Women who tested positive for other oncogenic HPV types had seven times the risk for these conditions than women who tested HPV negative. The authors concluded that patients with a positive HPV16 diagnosis may require more aggressive management than those who test positive for another oncogenic HPV type or who are HPV negative.

Khan *et al.* found that women in the Portland study who tested positive for HPV16 or HPV18 were diagnosed with CIN3 or cervical cancer more often than women who tested positive for another oncogenic HPV type, or women who tested negative for HPV. Additional analysis of women with normal Pap smear results at study enrollment provided further evidence for the observed risk differences. The authors concluded that screening for HPV16 and HPV18 separately from other oncogenic HPV types may identify women at the greatest risk of CIN3 and cervical cancer, while allowing for less aggressive management of cases of other oncogenic HPV infections.

The authors note that an elevated risk for HPV16 also was observed in a natural history study in Guanacaste, Costa Rica (Schiffman, *Virology*, 2005)\*\*\*.

### **7. How were these studies performed?**

The ALTS study compared three different management strategies for 5,060 women with Pap tests that either showed ambiguous cytologic abnormalities (ASCUS, 3,488 women), or low-grade squamous intraepithelial lesions (LSIL, 1,572 women). The study referred one-third of the women to an immediate colposcopy, regardless of their Pap test results; one-third to colposcopy if their initial HPV test was positive or if their Pap test showed high-grade squamous intraepithelial lesions (HSIL); and one-third to colposcopy if their Pap test showed HSIL at their enrollment in the study or during follow-up. All three groups received additional tests every six months for two years of follow-up and a colposcopy at the end of the trial. Women whose test results showed cervical intraepithelial neoplasia grade 2 (CIN2) or higher received treatment for the condition.

The Portland study examined data on 20,514 women who received routine cytologic screening through a prepaid health plan in Oregon. Women included in this analysis had negative, equivocal, or mildly abnormal baseline cervical Pap smears; suitable samples for HPV testing; and type-specific HPV test results. Study participants received regular follow-up cytology testing for up to 10 years following their enrollment. Practice guidelines at the time of the study mandated treatment for women whose Pap smears showed CIN2 or higher, but some physicians also treated some patients with cervical intraepithelial neoplasia grade 1 (CIN1).

### **8. What were the limitations of these studies?**

ALTS was a clinical trial and, consequently, the participants in the trial may have been screened more regularly than patients in everyday clinical management. Additionally, the women in this study were relatively young, with a median age of 25. A population of older women might lead to different results.

Women with cellular abnormalities in the Portland study received very aggressive treatment -- more than was mandated by clinical standards at the time or today. Thus, results in this study may actually underestimate the risk attributable to HPV16 and to HPV18 because of over-treatment. Additionally, there were relatively few cases to analyze despite the study size, possibly leading to some imprecise estimates of risk.

### **9. What are the next steps in this area of research?**

Twenty organizations - including the American Society for Colposcopy and Cervical Pathology (ASCCP),

the American Cancer Society, and the National Cancer Institute (NCI) - will participate in a conference in September 2005 to discuss the use of HPV DNA testing for screening and for triage of equivocal (ASCUS) Pap smears. One of the topics of discussion is likely to be the utility of HPV genotype detection in screening and clinical management.

The data from these recent two studies should be confirmed in other larger studies and in other populations, perhaps even in some of the clinical trials that are evaluating HPV DNA tests to develop more precise estimates of risk. Also, subsequent evaluations will need to examine this question in women who are newly infected.

To perform HPV genotyping, a reliable, FDA-approved test to distinguish these specific HPV types will need to be developed and validated. When FDA-approved tests that provide genotype information become available, researchers will be better able to identify women with persistent infection, an important risk factor for the development of precancer and cancer. Understanding the risks associated with a persistent HPV infection and the appropriate clinical management of these women is critical to preventing cervical cancer.

Future research will help to demonstrate whether women who test negative for HPV16 and HPV18 can be followed and treated less aggressively than women who test positive for these HPV types, thereby reducing the number of clinical visits, potential over-treatment of these women, and increasing the cost effectiveness of such testing.

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For more information about cancer, please visit the NCI Web site at <http://www.cancer.gov> or call NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237).

\*Castle PE, Solomon D, Schiffman M, Wheeler CM for the ALTS Group. Human papillomavirus type 16 infections and 2-year absolute risk of cervical precancer in women with equivocal or mild cytologic abnormalities." *Journal of the National Cancer Institute*, Vol 97, No. 14, July 20, 2005.

\*\*Kahn MJ, Castle PE, Lorincz AT, Wacholder S, Sherman ME, Scott DR, Bush BB, Glass AG, Schiffman M. The elevated 10-year risk of cervical neoplasia in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice." *Journal of the National Cancer Institute*, Vol. 97, No. 14, July 20, 2005.

\*\*\* Schiffman M, Herrero R, DeSalle R, Hildesheim A, Wacholder S, Rodriguez AC, Bratti MC, Sherman ME, Morales J, Guillen D, Alfaro M, Hutchinson M, Wright TC, Solomon D, Zigu C, Schussler J, Castle PE, Burk RD. The carcinogenicity of human papillomavirus types reflects viral evolution. *Virology*, Vol. 337, 2005.