

Human Papillomaviruses and Cancer: Questions and Answers

Key Points

- Human papillomaviruses (HPVs) are a group of more than 100 related viruses (see Question 1).
- Genital HPV infections are very common and are sexually transmitted. Most HPV infections occur without any symptoms and go away without any treatment over the course of a few years (see Questions 1, 4, and 5).
- However, HPV infection sometimes persists for many years. Such infections are the primary cause of cervical cancer. HPVs may also play a role in cancers of the anus, vulva, vagina, penis, as well as oropharyngeal cancer (see Question 3).
- In 2006, the U.S. Food and Drug Administration approved Gardasil®, a vaccine that is highly effective in preventing infection with two high-risk HPVs that cause most cervical cancers and genital warts (see Question 6).
- The warts and other benign lesions caused by HPV infection 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 (HPVs) are a group of more than 100 related 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.

Genital HPV infections are very common and are sexually transmitted. Of the more than 100 types of HPV, more than 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. This can increase a woman's risk of developing cervical cancer.

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 acuminata) 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 of the cervix usually do not cause any symptoms.

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

Persistent HPV infections are now recognized as the major cause of cervical cancer. In 2007, it was estimated that 11,000 women in the United States would be diagnosed with this type of cancer and nearly 4,000 would 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 some cancers of the anus, vulva, vagina, and penile cancer (cancer of the penis) (2).

Studies have also found that oral HPV infection is a strong risk factor for oropharyngeal cancer (cancer that forms in tissues of the oropharynx, which is the middle part of the throat and includes the soft palate, the base of the tongue, and the tonsils) (2, 3). Researchers found that an oral HPV infection and past HPV exposure increase the risk of oropharyngeal squamous cell cancer, regardless of tobacco and alcohol use, two other important risk factors for this disease. However, combining HPV exposure and heavy tobacco and alcohol use did not have an additive effect (3).

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 cause lesions that 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 only the high-risk types of HPV lead to cancer. Sexually transmitted, high-risk HPVs include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 73 (4). These high-risk types of HPV cause growths on the cervix that are usually flat and nearly invisible, as compared with the external warts caused by low-risk types HPV-6 and HPV-11. HPV types 16 and 18 together cause about 70 percent of cervical cancers (4, 5). It is important to note, however, that the great majority of high-risk HPV infections go away on their own and do not cause cancer (5).

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 develop and progress to more severe abnormalities or cervical cancer. However, even among 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. As a general rule, the more severe the abnormal cell change, the greater the risk of cancer. 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 (5).

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 degree of protection provided by condoms in preventing HPV infection is unknown, condom use has been associated with a lower rate of cervical cancer.

In 2006, the U.S. Food and Drug Administration (FDA) approved Gardasil®, 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 (4), and types 6 and 11, which cause most (90 percent) genital warts (5).

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 at least 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 approved tests 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 can 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 human 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 (6). 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), a part of the National Institutes of Health (NIH), and elsewhere are studying how HPVs cause precancerous changes in normal cells and how these changes can be prevented (7). Scientists are also developing HPV vaccines that will be stable at room temperature and that protect against more HPV types.

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 (8). 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 infection and cervical cancer, the best way to communicate the latest research results to the public, and how doctors are talking with their patients about HPV infection. 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 HPV (Human Papillomavirus) Vaccines for Cervical Cancer Digest Page 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), another part of the NIH, 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
Web site: <http://www3.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/hpv/> on the Internet.

Selected References

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2. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *International Journal of Cancer* 2006; 118:3030–3044.
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5. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *The Lancet* 2007; 370:890–907.
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7. 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 Institute Monographs* 2003; 31:1–130.
8. 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. 6th ed. Philadelphia: Lippincott Williams and Wilkins, 2004.

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Related NCI materials and Web pages:

- National Cancer Institute Fact Sheet 4.21, *Human Papillomavirus (HPV) Vaccines* (<http://www.cancer.gov/cancertopics/factsheet/Prevention/HPV-vaccine>)
- National Cancer Institute Fact Sheet 5.16, *Pap Test* (<http://www.cancer.gov/cancertopics/factsheet/Detection/Pap-test>)
- NCI's HPV (Human Papillomavirus) Vaccines for Cervical Cancer Digest Page (<http://www.cancer.gov/cancertopics/hpv-vaccines>)
- *Understanding Cervical Changes: A Health Guide for Women* (<http://www.cancer.gov/cancertopics/understandingcervicalchanges>)
- *What You Need To Know About™ Cancer of the Cervix* (<http://www.cancer.gov/cancertopics/wyntk/cervix>)

How can we help?

We offer comprehensive research-based information for patients and their families, health professionals, cancer researchers, advocates, and the public.

- **Call** NCI's Cancer Information Service at 1–800–4–CANCER (1–800–422–6237)
- **Visit** us at <http://www.cancer.gov> or <http://www.cancer.gov/espanol>
- **Chat** using LiveHelp, NCI's instant messaging service, at <http://www.cancer.gov/livehelp>
- **E-mail** us at cancergovstaff@mail.nih.gov

- **Order** publications at <http://www.cancer.gov/publications> or by calling 1-800-4-CANCER
- **Get help** with quitting smoking at 1-877-44U-QUIT (1-877-448-7848)

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