Cervical Cancer

Cervical cancer forms in the interior lining of the cervix, the junction of the vagina and uterus. The development of cervical cancer is typically slow, and occurs over a period of years. The progression to cervical cancer begins with the development of precancerous changes in normal cells. Most of these changes, even if left untreated, will not progress to cancer. However, in 2018 the American Cancer Society estimates 13,240 women will be diagnosed with invasive cervical cancer and 4,170 will die of the disease in the United States. [1]

Cervical cancer is most often diagnosed in middle-aged women, with half of those diagnosed between the ages of 35 and 55. Cervical cancer is very rarely seen in women less than 20 years of age, but approximately 20% of cases occur in women over 65, demonstrating the necessity of continued screening procedures. The five year survival rate of invasive cervical cancer is currently 67% and improvements in screening and the development of prophylactic vaccines have decreased the incidence of late-stage cancer. [2]

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Teaching Materials:
- Cervical Cancer Curriculum
- Cervical Cancer Poster

Watch an interview with cervical cancer specialist Dr. Ira Horowitz.

Learn more about cervical cancer or make an appointment at the Winship Cancer Institute of Emory University.
Anatomy Of The Female Reproductive System

The cervix is part of the female reproductive tract that makes up the lower part of the uterus, also known as the womb. The upper endocervix connects to the uterus and the lower ectocervical region opens to the vagina. This connection allows for the passage of a fetus during delivery.

The graphic above depicts the major components of the female reproductive tract.

1. **Vagina** - female sex organ, passageway for menstrual blood and fetus during childbirth
2. **Cervix** - region connecting the uterus to the vagina; the muscles of the cervix support the weight of the fetus during pregnancy
3. **Uterus** (womb) - location where fertilized egg develops into a fetus and is nourished until birth. Note that the walls of the uterus are thick and lined with muscles
4. **Fallopian (uterine) Tube** - location of fertilization of an egg by a sperm cell
5. **Ovary** - produce and store gametes (eggs) and produce the female sex hormones, estrogen and progesterone

Types Of

The two types of cervical cancer are **squamous cell carcinoma** and **adenocarcinoma**, which are distinguished based on their appearance under a microscope. Both squamous cell and adenocarcinoma begin in the cells that line hollow organs, but squamous cells have a thin, flat appearance while adenocarcinomas involve cells with
secretory functions. Squamous cell carcinoma is far more common and makes up approximately 90% of cervical carcinoma cases. Both types have similar risk factors, prognoses and treatments.

Hear how cervical cancer survivor Lori Grice reacted to her diagnosis of adenocarcinoma by clicking on the image below. You can also watch the full interview with Lori and DeWayne Grice.

Risk Factors

There are several risk factors for the development of cervical cancer, both genetic and environmental. These include:

- Human Papillomavirus (HPV) Infection
- Family History of Cervical Cancer
- Age
- Sexual and Reproductive History
- Socioeconomic Status
- Smoking
- HIV Infection
- In Utero DES Exposure
- Long-term use of oral contraceptives

Human Papillomavirus (HPV) Infection:

HPV infection is associated with virtually all cases of cervical cancer. HPV is among the most common sexually transmitted diseases and most women clear the infection within two years without complications. Long term infection with high-risk strains of HPV can lead to the development of cervical dysplasia and cancer.

Because of the very high correlation between HPV infection and cervical cancer, the following paragraphs describe HPV in more detail.

The Human papillomaviruses are a family of sexually transmitted viruses consisting of over 100 different viral strains, 40 of which are known to infect the human genital tract and 15 of which have been associated with cervical cancer. Most patients with one of these infections show no symptoms, but some strains of HPV lead to the development of genital warts.

HPV contains a small, circular, double stranded DNA genome. The virus infects epithelial cells, one of the rapidly dividing cells that form the skin and mucous membranes. The virus reproduces within the host cell and when the cell dies, as part of natural cell turnover, the new virus particles (virions) are released and can infect other cells. The DNA of low-risk types of HPV remains separate from the host DNA, while high-risk forms are able to combine with (insert into) the host DNA. Insertion into the host genome is problematic because it interrupts the regulation of the viral genes. Without this control, the viral genome is transcribed at a much higher rate.

The HPV genome contains at least two genes whose protein products function as oncogenes, meaning that they can turn into cancer cells. These genes are called E6 and E7. The E6 and E7 proteins inhibit the tumor suppressor proteins p53 and pRb, respectively. By 'turning off' the p53 gene, cells will not die (this process is called immortalization). The inactivation of pRb leads to increased cell division. While either one of these mutations has the potential to lead to the development of cancer, the ability of HPV to inactivate both tumor suppressors further increases the efficiency of the transformation from normal to cancerous cells.
Infection with low-risk types of HPV generally produce benign lesions with a minimal chance of progression to dysplasia or cancer. However, high risk HPV strains (16, 18, 31, 33 and 35) are implicated in 99% of those diagnosed with cervical cancer. It is important to note that most women infected with high-risk strains of HPV infection will not develop cancer. The risk of developing dysplasia or cancer after HPV infection is, in part, dependent on the amount of virus present during infection and the length of time it takes to clear the infection.

There is no cure or treatment for HPV infection. Even without treatment, most infections are cleared by the immune system within two years. If the infection persists there is an increased chance of viral DNA integration and progression to cancer. Women can be tested to learn if they are infected with HPV. Even though there is currently no cure for HPV infection, the knowledge can help women make responsible choices regarding their sexual practices. Furthermore, it is possible to prevent HPV infection by receiving a vaccination. Vaccinations are recommended for young individuals—both female and male--within their early teens or late 20's.

More on Tumor Suppressors and Oncogenes

**Family History of Cervical Cancer:**
Women with a family history of cervical cancer, especially an affected mother or sister, have a two-fold risk of developing cervical cancer, suggesting an inherited susceptibility. However, there does not appear to be a correlation between a family history of other cancer types (i.e. colon cancer) and the risk of developing cervical cancer.

**Age:**
Very few women under the age of 20 are diagnosed with cervical cancer and more than half of those diagnosed are between the ages of 35 and 55. The risk decreases after age 55, but 20% of cases occur in women over 60 years old. The pattern seen is due to two conflicting factors, 1) changes in sexual behaviors and 2) the tendency of genetic mutations to accumulate over time.

**Sexual and Reproductive History:**
Epidemiological studies have shown an increased risk for invasive cervical cancer attributable to sexual and reproductive behavior. Increased numbers of sexual partners and lower age at first sexual act have both been associated with increased risk. Women who have had multiple pregnancies and are younger at the time of their first full-term pregnancy also demonstrate an increased risk. Long term use of oral contraceptives has been shown to increase risk in some studies, but this remains controversial. More recent studies have suggested that women who have used oral contraceptives for 5 or more years have a higher risk of cervical cancer than women who have never used contraceptives. While cervical cancer risk appears to increase the longer a woman uses contraceptives, the risk appears to gradually decline after use of oral contraceptives ceases.

Because HPV is a sexually transmitted disease, behaviors that increase sexual contacts are considered risk factors.

**Socioeconomic Status:**
Low socioeconomic status has proven to be a significant risk factor for invasive cervical cancer due to its large impact on education and medical resources. Results of the analysis of several epidemiological studies indicate that Hispanic and African-American women have a higher risk of invasive cervical cancer than Caucasian women.

Decreased risk is associated with increased education--women without a college degree have an increased risk, regardless of race. Therefore, it is possible that if access to screening and medical education were equalized, race would not prove to be a significant risk factor. The increased risk with low socioeconomic status is attributed to a lack of screening, failure to treat precancerous conditions, and lack of knowledge about prevention of HPV infection.
**Smoking:**
Current smoking is a risk factor for the development of cervical cancer due to the ability of carcinogens in cigarette smoke to cause mutations in DNA. This can also result in suppression of the immune system, which can allow HPV infections to persist and even progress into lesions or invasive cancer. In the epidemiological studies that have been conducted, smoking was associated with an increased risk of squamous cell carcinoma of the cervix, but not adenocarcinoma. Secondhand smoking also appears to increase risk of cervical cancer, even among non-smokers. A study examining the effects of secondhand smoking on cervical cancer risk found that non-smokers exposed to at least 2 hours of secondhand smoking per day tended to be at greater risk for CIN 1 cervical cancer.\(^{17,18}\)

**Human Immunodeficiency Virus (HIV):**
Women infected with HIV have been shown to have a five-fold risk of developing cervical cancer. HIV weakens the immune system, decreasing the ability to fight infection; therefore HPV infections are more likely to persist. This is thought to provide more time for the HPV to induce cancer. The high correlation between HIV infection and HPV infection is also partly due to the fact that both are sexually transmitted diseases and behaviors that put women at risk for one also put them at risk for the other.\(^{17,18}\)

**In Utero Diethylstilbestrol (DES) Exposure:**
DES is a synthetic estrogen used from the 1930s to the 1970s to reduce complications during pregnancy. Use of this drug was discontinued after it was demonstrated that the drug could harm the developing baby. Elevated risk of cervical cancer is just one of the potential health effects for women who were exposed to DES while they were in their mothers womb; others include a variety of gynecological cancers, reproductive tract irregularities, infertility and complications during pregnancy.\(^{19}\)

Learn more about cervical cancer or make an appointment at the [Winship Cancer Institute of Emory University](http://www.wshipcancer.org).

**Prevention**
As described previously, the major risk factor for developing cervical cancer is infection with the human papillomavirus (HPV).

Abstinence is the only sure way to prevent infection with the virus. For sexually active women, the use of a condom can reduce, but not eliminate, risk of infection.

Two vaccines are available that prevent infection with the forms of the virus most associated with cervical cancer.

Visit the cancer prevention section to learn more about cervical cancer vaccines.

Watch the full interview with Dr. Ira Horowitz

In 2017, a study of 12,000 women demonstrated a link between the use of intrauterine devices (IUDs) and a reduction in cervical cancer rates. Women using the device had a one-third reduction (33%) in their rate of cervical cancer. The study was not designed to show that IUD use caused the reduction, but the link was identified. Researchers suggest that the presence of the IUD in the uterus causes changes in the immune system that help users fight off HPV infection.\(^{20}\)

**Symptoms**

**Symptoms:**
Typically, early cervical cancer is asymptomatic (no symptoms), but abnormal vaginal bleeding can occur once the cancer becomes invasive.  

Watch the video to learn about HPV infection symptoms from cervical cancer specialist Dr. Kevin Ault. Click here to watch the full interview with Dr. Ault.

Click here for information about cervical cancer treatment and services at the Winship Cancer Institute of Emory University.

**Detection And Diagnosis**

**Detection:**

Since early cervical cancer is asymptomatic, regular screening by a Pap smear is important in order to avoid the progression of precancerous lesions or noninvasive cancer. Current US guidelines, released March 2012, recommend Pap smears for women over 21. Screening should then be repeated every three years until at least age 65. If you have had a history of normal Pap smears and a radical hysterectomy, in which the cervix has been removed due to non-cancerous reasons (i.e., fibroids), routine screening via Pap smear may not be necessary. The American Cancer Society recommends screening with Pap smear and HPV DNA testing every five years from age 30-65 but finds a Pap smear every three years acceptable. Women with prenatal exposure to diethylstilbestrol (DES), a prior history of cervical cancer, or a disease/condition that weakens their immune system, should continue screening past age 65. Although cancers of the ovaries, cervix, and uterus may be difficult to detect at an early stage, there are several detection options currently in use.

There is some evidence that testing for HPV may be a better way to prevent the development of cancer than Pap smears, but these results need to be confirmed before any recommendations are changed.

Important tests for detecting cancers of the female reproductive tract include:

- **Pap Smear** for detecting cervical and vaginal cancer.
- **Ultrasound** for detecting ovarian and uterine cancer.
- **CA-125** for detecting ovarian cancer.

If the diagnostic tests indicate the presence of cancer, additional imaging (CT, MRI, etc.) may be performed to determine the location and extent of the disease.

Specific tests for Human Papillomavirus (HPV) DNA may be administered annually to women over 30, which lessens the necessity of Pap smears to once every five years. HPV screening involves a Polymerase Chain Reaction (PCR) based test that is able to detect DNA sequences common to all HPV strains. Because this sequence can be disrupted when the virus inserts itself into cellular DNA, other genes (E6 and E7) are often also identified. This allows the tests to reliably detect the presence of high-risk HPV strains. In a recent study, the addition of HPV DNA tests to traditional Pap smears reduced the incidence of grade 2/3 cervical intraepithelial neoplasia (CIN) by 40%. Since HPV infections are frequently transient, it is possible that risk for cervical dysplasia or cancer may exist even with negative test results.
Diagnosis:

If a Pap smear reveals abnormal cells, further diagnostic tests are performed to determine a diagnosis. Irregular cells could indicate:

- Human Papillomavirus Infection
- Cervical Intraepithelial Neoplasia (CIN)
- Cervical Cancer

Watch the full interview with cervical cancer advocates Lori and DeWayne Grice.

Further tests are necessary to make a diagnosis. Additional tests that may be performed include:

- **Colposcopy** - a camera is inserted into the vagina and the cervix is examined.
- **Biopsy** - removal of a small sample of tissue for examination by a pathologist. The procedure is typically done without anesthesia and is associated with minimal pain or bleeding. It is possible to perform the biopsy during a colposcopy.

Pathology Report And Staging

**Cervical Intraepithelial Neoplasia:**
Cervical intraepithelial neoplasia (CIN) is an abnormal condition that is detectable by Pap smears and other cervical exams. CIN is the growth of abnormal cells in the lining of the cervix. Though CIN it is not cancerous, it has the potential to progress to cancer if left untreated. There are three stages (or grades) of CIN: CIN 1, CIN 2 and CIN 3. The stages are define by how abnormal the cells appear, slight, moderate and high. The risk of cancer development increases with increasing CIN grade. CIN is relatively common, with 1.4 million low grade and 330,000 high grade cases diagnosed in the United States in 2006. Cervical lesions are treated depending on the degree of severity. CIN 1 lesions may be removed or closely monitored; CIN 2/3 lesions are usually surgically removed. In either case, careful follow-up screening is performed to ensure that there is no recurrence. Despite the high incidence of CIN, if these irregularities are treated, progression to cancer is very rare. The image below shows microscopic images of normal cervical tissue, CIN 1, CIN 2 and CIN 3.

![Microscopic images of cervical tissue](image)

Image courtesy of Talaat S Tadros MD, Emory University School of Medicine.

**Cervical Cancer Staging:**
If a lesion is determined to be cancerous, the disease is staged. Staging is typically based on guidelines produced by the Federation Internationale de Gynecologie et d' Obstetrique (FIGO). In this system tumors are classified by their size and location. An alternative system is used by the American Joint Committee on Cancer (AJCC).
Staging of the cancer helps the clinicians to design an appropriate plan of treatment. View the FIGO guide to cervical cancer staging. Visit the AJCC website.

**Treatment**

Depending on the stage and location of the cancer, several different treatments are used for cervical cancer. Common treatment methods are listed below.

**Surgery:**

*Cryosurgery* - used for pre-invasive cancer; kills cancer cells by freezing them with a metal probe that has been cooled by liquid nitrogen.

*Laser Surgery* - used for pre-invasive cancer; laser beams are used to burn off abnormal cells or remove tissue for further study.

*Cone Biopsy* - used to preserve fertility in women with early stage cancer or to obtain a sample for further study; a cone-shaped section of tissue is taken from the cervix.

*Simple Hysterectomy* - the uterus and cervix are removed either through the vagina or the abdominal wall; results in infertility.

*Radical Hysterectomy and Pelvic Lymph Node Dissection* - the uterus, upper vagina and lymph nodes are removed through the vagina or the abdominal wall; results in infertility.

*Pelvic Externation* - for recurrent cancer; radical hysterectomy is accompanied by removal of the bladder, vagina, rectum and part of the colon; results in infertility. For details on surgical treatment view the section on Surgery.

**Radiation:**

Either internal (also called brachytherapy) or external radiation may be used to treat cervical cancer. For details on these treatments view the section on Radiotherapy.

**Chemotherapy:**

Several different drugs may also be used to treat primary or recurrent cervical cancer. For details on specific chemotherapy treatments view the section on Chemotherapy.

NOTE: Sometimes radiation and chemotherapy are given at the same time. The rationale is that the low levels of chemotherapy given make the cancer cells more sensitive to the radiation. The technique is called chemoradiotherapy or radiosensitization. If a woman is pregnant at the time of diagnosis, a decision must be made, based on the stage of the cancer, whether to continue the pregnancy to term. Treatment for cervical cancer cannot be administered during pregnancy, and aggressive cancers often require immediate treatment.

Learn more about cervical cancer treatment at the Winship Cancer Institute of Emory University.

Watch the entire interview with cervical cancer survivor Lori Grice and her husband DeWayne Grice.

Information about clinical trials:

- General clinical trial information from CancerQuest
- Click here for information about clinical trials at the Winship Cancer Institute of Emory University
- Click here for information about clinical trials from Georgia Clinical Trials Online.
- Click here for information about clinical trials from the National Cancer Institute.

The Society of Gynecologic Oncology has produced a series of educational publications on cervical cancer, ovarian cancer, endometrial cancer and vulvar cancer. Their materials include planning guides and survivorship care plans.

**Cervical Cancer Resources**
Introduction

- The cervix is the junction of the vagina and the uterus.
- Cervical cancer forms on the interior lining of the cervix.
- Typically, cervical cancer development is slow, occurring over a period of years.
Types of Cervical Cancer

- There are two main types of cervical cancer: squamous cell carcinoma and adenocarcinoma.
- Squamous cell carcinoma is the most common type.

Risk Factors

- Human papillomavirus (HPV) infection is associated with virtually all cases of cervical cancer.
- HPV is sexually transmitted, but only 15 of over 100 strains are implicated as causing cervical cancer.
- A family history of cervical cancer doubles the risk for developing the cancer.
- Most cases of cervical cancer occur after the age of 20.
- Increased numbers of sexual partners and lower age at first sexual act have both been associated with increased risk.
- Smoking has been associated with an increased risk of squamous cell carcinoma of the cervix.
- Women infected with HIV have been shown to have a five-fold risk of developing cervical cancer.
- The long-term use of oral contraceptives has been shown to increase the risk.

Symptoms

- Early cervical cancer is asymptomatic.
- Abnormal vaginal bleeding can occur once the cancer becomes invasive.

Detection and Diagnosis

- Cervical cancer can be detected by a Pap smear.
- HPV tests are available to detect the presence of viral DNA.
- More tests are carried out if the Pap smear reveals abnormal cells.
- A colposcopy can be used to view the tissue of the cervix.
- A tissue biopsy can be done and a pathologist can then examine the sample.
- Additional imaging (CT, MRI, etc.) may be performed.

Pathology Report and Staging

- Cervical intraepithelial neoplasia (CIN) is a non-cancerous, abnormal growth of cells lining the cervix.
- The risk of cancer development increases with increasing CIN grade.
- Cervical cancer staging is determined by the size and location of the tumor.

Treatment

- Different types of surgery can be performed depending on the stage of the cancer: cryosurgery, laser surgery, cone biopsy, simple hysterectomy, radical hysterectomy, and pelvic exteration.
- Internal or external radiation and chemotherapy are possible treatments for cervical cancer.

Cervical Cancer Vaccine

- The vaccine Gardasil® has been approved in the U.S. for males and females aged 9-26 for the prevention of infection by HPV 6, 11, 16, and 18.
- The vaccine Cervarix® has been approved in the U.S. for females aged 10-25 for the prevention of infection by HPV 16 and 18.
- The vaccines prevent new infections and are not effective against pre-existing HPV infections.

Know The Flow

Know the Flow is an educational game for you to test your knowledge. To play:

- Drag the appropriate choices from the column on the right and place them in order in the boxes on the left. Note that you will only use five of the six choices to complete the game.
- When done, click on 'Check' to see how many you got correct.
- For incorrect answers, click on 'Description' to review information about the processes.
- To try again, choose 'Reset' and start over.

Know the Flow: Cervical Cancer

Processes in order
Processes

- Learn more
  Exposure to HPV by sexual contact
- Learn more
  HPV infects cervical cells
- Learn more
  HPV infection persists for more than one year
- Learn more
  HPV infection creates 'CIN'
- Learn more
  Cervical Cancer Develops and Invades Nearby Areas
- Learn more
  HPV Infection is Cleared by the Immune System

Check answers  Reset

You did it!

The process is in the correct order!

Play again

Pick A Part: Female Reproductive System

Pick A Part is an educational game for you to test your knowledge. To play:

- Drag the appropriate choices from the column on the bottom and place them in order in the boxes on the left. Note that you will only use five of the six choices to complete the game.
- When done, click on 'Check' to see how many you got correct.
- For incorrect answers, click on 'Description' to review information about the processes.
- To try again, choose 'Reset' and start over.

Pick a Part: Female Reproductive System
The GRID is an educational quiz game, covering cancer related topics. The format of the game is similar to a popular TV quiz show, where the clues are phrased as an answer and the response os phrased in the form of a question. For example:

**Clue:** This website won the 2007 "Cancer on the Internet” award.

**Response:** What is CancerQuest?
How to play:

**For one person:**
Enter your name and begin the game. Choose a category and a point value, the clue will open. To check your response, click and hold the "Ans" button. If your response was correct click the "Check", the point value will be added to your total. If your response was incorrect click the "X", the point value will be subtracted from your total (you lose points for incorrect responses).

**For two or more:**
Enter player’s names and begin the game (click the "make active" box to add players). Choose a category and a point value, the clue will open. Each player uses a different keyboard key to "ring in"

- Player 1 - use "z" key
- Player 2 - use "." (period) key
- Player 3 - use "enter" key on far right of keyboard

To check response click and hold the "Ans" button. If a correct response is given, click the "Check". The point value will be added to the responding player's total. If an incorrect response is given, click the "X". The point value will be subtracted from responding player's total (an incorrect response results in a loss of points). The player with the correct response chooses the next clue. Continue until all clues are uncovered, the player with the most points wins the game.

**The Grid: Cervical Cancer**

Game Over
The Winner Is
Player
0
Points

![Restart button](image)

Please Select the Number of Players

1 2 3

Enter player names

<table>
<thead>
<tr>
<th>Player 1</th>
<th>Player 2</th>
<th>Player 3</th>
</tr>
</thead>
</table>

Submit

has buzzed in!

View Answer | Answered Correctly | Answered Incorrectly

Q

Player 1, Buzz In!

B

Player 2, Buzz In!

P

Player 3, Buzz In!

Pap "Quiz"

100 If I have an abnormal Pap, that means I have cervical cancer

200 I am not currently sexually active, so I do not need to have a Pap test

300 If I have HPV with no visible symptoms, I still need anual Pap tests

400 I cannot have a Pap test while pregnant

Treatment

100 Evaluation and treatment of abnormal cells of the cervix will affect my fertility and ability to have children

200 Treatment for precancerous cells in my cervix will interfere with my sex life

300
If I have had treatment for abnormal cells, I do not need to have any follow-ups.

If I am treated for abnormal cervical cells, they can come back in the future

Some Cancer Answers

Cervical cancer is passed down from your parents

Everybody that has HPV will get cervical cancer

A virus that causes simple lesions like warts can cause cancer

Even though I have always been monogamous, I may still develop cervical cancer

HPV is only transmitted by vaginal intercourse

HPV is not treated with antibiotics

HPV is the same thing as HIV

There is no cure for HPV

Potpourri

There is no cure for HPV

HPV is a very common sexually transmitted disease.

If I am pregnant and I have abnormal cells of the cervix, it will affect the baby

The use of condoms will protect me 100% against HPV

I’ll need to get Pap tests after menopause


10. American Cancer Society (accessed 9/5/07) [http://www.cancer.org]


