

Cervical Cancer Curriculum

Table of Contents

I. Overview

- A. [What is Cancer](#)
- B. [Cancer Statistics from the American Cancer Society](#)

II. Causes of Cancer

- A. [Mutations](#)
- B. [Others](#)

III. Cervical Cancer

- A. [Anatomy of the Reproductive Tract](#)
- B. [Introduction to Cervical Cancer](#)
- C. [Risk Factors](#)
- D. [Cervical Cancer Development](#)
- E. [Types of Cervical Cancer](#)
- F. [Symptoms](#)
- G. [Detection](#)

IV. The Human Papillomavirus

- A. [What are Viruses?](#)
- B. [Introduction to the Human Papillomavirus](#)
- C. [Statistics](#)
- D. [Transmission](#)
- E. [Types](#)
- F. [How HPV Causes Cervical Cancer](#)
- G. [Prevention](#)
- H. [Vaccines](#)

V. Cervical Cancer Myths

- A. [Myths](#)

Cervical Cancer and the Human Papillomavirus

Grade Level: High School (9th-12th)

Georgia Standards: SCSH3, SCSH6, SCSH7, SCSH8, SCSH9, SB2, SB3

Science Characteristics of Science high School Standard

Science Biology Standard

Title: Choices Now, Consequences Later

Purpose of activity: Educate students about the human papillomavirus and cervical cancer and provide them with the knowledge to make informed decisions that will reduce their risk for both.

Goals/Objectives:

- Students will gain basic understanding of the cervix and cervical cancer
- Students will be able to define the link between the human papillomavirus and cervical cancer
- Students will gain basic understanding of viruses and vaccines
- Students will apply their knowledge to make healthy decisions that will reduce their risk for contracting the human papillomavirus and cervical cancer.

I. Overview

1. What is Cancer

- i. Cancer is a condition that develops when normal cells are damaged in ways that cause them to reproduce in an unregulated manner. The changes in cellular behavior are caused by mutations; changes to the DNA of a cell.

These mutations enable the cancer cell to divide continuously, without the need for normal signals. In some cancers the unchecked growth results in a mass, called a **tumor**. Cancerous cells may invade other parts of the body, interfering with normal body functions. If normal body functions are impaired significantly, death may occur.

Although cancer is often referred to as a single disease, it is really a group of diseases that affect many different organs and types of cells. The likelihood that a person will develop any particular type of cancer depends on their genes, environment and lifestyle. Of particular importance is that fact that some cancers may be prevented by wise lifestyle choices.

2. Cancer Statistics From the American Cancer Society (ACS)

i. The GOOD: **Some types of cancer can be prevented.**

The ACS estimates **170,000** US cancer deaths in 2008 are expected due to tobacco usage and another **185,000** are predicted due to other preventable cancers. That equals a grand total of **355,000** potentially preventable cancer deaths **YEARLY!**

i. The BAD: **Cancer is the second leading cause of death in the United States.**

1 in 4 deaths in the US is caused by cancer.

565,650 people are expected to die in 2008 from cancer.

ii. The UGLY: **In 2007, Cervical cancer was the leading cause of cancer death worldwide**

2007: ACS estimated **309,808** new cases of cervical cancer were diagnosed and **272,238** people will die from the disease worldwide.

2008: ACS estimates **11,070** new cases of cervical cancer leading to **3,870** deaths in the United States.

iii. The COST: Estimated yearly HPV and cervical cancer related costs...

The estimated economic burden of cervical HPV related disease ranges from **\$2.25 billion to \$4.6 billion yearly** in the US. Cervical cancer is estimated to account for between 181.5 million to 393 million in the United States.

II. Causes of Cancer

1. Mutations

i. Cancer is caused by mutations resulting from internal or external factors

Internal: inherited mutations, spontaneous mutations

External: tobacco, chemicals, radiation, infectious organisms

2. Others

ii. Some agents, such as viruses, can induce cancer without altering cellular DNA

III. Cervical Cancer

1. Anatomy of the Reproductive Tract

i. Vagina

The vagina is a passageway for menstrual blood during menstruation and the fetus during childbirth

ii. **Cervix**

The cervix is the lower portion of the uterus and it plays an important role in reproduction. The narrow cervical canal connects the uterus to the vagina and allows passage of menstrual fluid. During pregnancy the muscles of the cervix support the weight of the fetus. When childbirth occurs the muscles relax and the opening of the cervix widens (dilates) allowing the fetus to pass through the cervical canal and out of the vagina.

Note: Cervical abnormalities can result in miscarriage

iii. **Uterus (womb)**

The uterus houses and nourishes a fertilized egg (zygote) until birth. Note that the walls of the uterus are thick and lined with muscles

iv. **Fallopian (uterine) Tube**

The fallopian tubes are the site of fertilization of an egg (female gamete) by a sperm cell (male gamete)

v. **Ovaries**

The ovaries produce and store eggs and produce the female sex hormones, estrogen and progesterone

2. Introduction to Cervical Cancer

Cervical cancer is a slow developing cancer that starts in the interior lining of the cervix. Almost all cases begin with changes in normal cells caused by the human papillomavirus (HPV), a sexually transmitted infection.

Cervical cancer is most often diagnosed in middle-aged women, with half of those diagnosed between the ages of 35 and 55. It is rarely seen in women younger than 20 and approximately 20% of cases are in women over 65.

3. Risk Factors

- i. The number one risk factor for developing cervical cancer is infection with the **Human Papillomavirus**. HPV is implicated in over 90% of cervical cancer cases. HPV is discussed in more detail later in this document.
- ii. Other risk factors include:
 - Family history of cervical cancer
 - Smoking cigarettes
 - a. Nicotine (the addictive compound found in cigarettes) has been found in the cervical mucus of women that smoke.
 - b. Studies have shown that women who previously smoked or currently smoke (ever-smokers) tend to have significantly longer HPV infections than women who never smoked (never-smokers). The median duration for ever-smokers was 10.7

months and the median for never-smokers was 8.5 months. (Guiliano)

- c.
 - Age
 - a. In the US HPV infection is most prevalent in women aged 20-24 and cervical cancer is most prevalent in women aged 35-55.
 - Sexual history
 - a. Younger age at first intercourse has been found to be a main risk factor for developing advanced pre-cancerous conditions that may progress on to invasive cancer. (Deacon)
 - b. Increased number of sexual partners is associated with higher incidence of
 - Reproductive history
 - Socioeconomic status
 - HIV co-infection
 - *In utero* exposure to diethylstilbestrol (DES)

4. Cervical Cancer Development

i. There are 3 steps necessary for cervical cancer development:

1. HPV infection. Most common in women aged 20-24 and it is thought that a majority of women will be infected at some point in their life. HPV infects cells by entering cracks or small wounds in the skin.
2. HPV persistence. Less common. In most women (~80%), HPV infections are cleared or suppressed by the immune system within 1-2 years of exposure. If HPV infection is not cleared and persists for a long period of time a condition called cervical intraepithelial neoplasia (CIN) can develop. See below for more about CIN.
3. Cell transformation and invasion. Rare in comparison to the number of women infected by HPV. Transformation is the process by which viral proteins alter the behavior of infected cells. Transformed cells have different division capabilities and can ultimately lead to cancer. Invasion is the spread of the altered cells in the cervical epithelium and usually occurs after a long period of infection. It is thought that severe dysplasia does not occur without certain co-factors. (e.g. Smoking, HIV co-infection, Immunosuppression)

ii. **Cervical Intraepithelial Neoplasia (CIN)**

The duration of an HPV infection is heavily dependent on the immune system and in most cases infection is successfully cleared within 1-2 years. If HPV

infection persists for a long period, years or decades, a condition called cervical intraepithelial neoplasia may develop. CIN is an abnormal condition characterized by excessive cell division and changes to cells within the lining of the cervix. It is the result of long term HPV infection of these cells. CIN is classified into three stages based on the severity of the condition (CIN, 1, 2, and 3).

CIN 1: only about 1% of cases of CIN 1 will progress to invasive cervical cancer. Approximately 20% will progress to CIN2. CIN 1 is not considered a pre-cancer. If discovered, CIN 1 is closely watched.

CIN 2: approximately 30% of CIN2 will progress to more severe neoplasia. CIN 2 lesions are usually removed and follow-up screening is performed to detect recurrence.

CIN 3: abnormal cells make up 2/3 of the cervical epithelium and approximately 40% of these cases will progress to cancer. Often develops after persistent infection with HPV types 16 or 18. Most cases of CIN 3 do not develop from CIN 1 (pinto!2). CIN 3 lesions are usually removed and follow-up screening is performed to detect recurrence.

5. Types of Cervical Cancer

- i. Adenocarcinoma
 - Adenocarcinomas are cancers that begin in glandular (secretory) tissue.
 - Makes up ~10% of cervical cancer cases
- ii. Squamous Cell Carcinoma
 - Cancer that develops in the squamous cells, cells that line the outer layer of the cervix. Squamous cells get their name from their scale-like appearance; *squama* describes the scales of a fish in Latin.
 - More common form of cervical cancer, makes up ~90% of all cases

6. Symptoms

- i. Early cervical cancer has no symptoms (asymptomatic) in most cases, but abnormal vaginal bleeding may occur once the cancer is invasive.

7. Detection

- i. Because cervical cancer is generally asymptomatic, regular screening is the best way to avoid the progression of precancerous lesions or noninvasive cancer and detect cervical cancer.
- ii. **Pap Tests**

Pap tests are the key method used in cervical cancer screening and are recommended yearly for all women over 21 or within three years of onset of sexual activity.

How it works: During a routine pelvic exam the doctor inserts a broom shaped brush or spatula through the vagina. Cells are wiped from the surface of the cervix and placed on a slide or in a vial. Cell samples are sent to a laboratory and examined under a microscope for abnormalities. Women with abnormal results may be asked to have additional procedures. These include a repeat Pap test, an HPV test and a visual inspection of the cervix (colposcopy). As with any medical test, the Pap test is not 100% accurate.

iii. **HPV Test**

The HPV DNA test is used in conjunction with the Pap test in cervical cancer screening. It is recommended for women over the age of 30 to reduce the need for yearly pap tests.

How it works: Whereas a Pap test can detect cellular abnormalities, the HPV test can detect the presence of high risk HPV DNA. An HPV test uses the same method as a Pap test to obtain a cervical sample, but a different test is run on the cells that can determine whether or not high-risk HPV infection is present. As with any medical test, the HPV test is not 100% accurate.

iv. **Colposcopy**

A colposcopy is used after an abnormal Pap smear or when a physician sees something abnormal during a pelvic exam.

How it works: A colposcopy is done using an instrument called a colposcope. A colposcope is a type of microscope that can magnify the cervix up to 16 times its normal size. It allows the physician to visually examine the linings and other structures of the cervix. It is a very safe procedure that should not cause any pain.

IV. **The Human Papillomavirus (HPV)**

Main Risk Factor for Cervical Cancer

1. **What are Viruses, “a kind of borrowed life” (7th Report)**

- i. Viruses are very small particles, the smallest being only 20 nanometers across (a nanometer is about 35-millionths of an inch). For comparison, a human hair is about 80,000 nanometers in diameter or ~4,000 times larger. Viruses come in all different shapes and sizes, but are usually composed of just two components; a **genome** and **capsid**.
 - The genome is the genetic information carried by the virus. It is either double or single stranded DNA or RNA. Viral genomes are organized as linear or circular molecules of nucleic acid (DNA or RNA).
 - The capsid is a protein shell that surrounds and protects the viral genome. It is made up of various protein subunits called **capsomeres**.
 - Some viruses have accessory structures that aid them in survival, infection, and reproduction. Viruses such as Influenza (cause of the flu) and HIV have lipid envelopes surrounding the capsid.

Bacteriophages (virus that infect bacteria) have the most complex structures of all viruses.

- Viruses are strange entities; they don't fit neatly into a category of living or non-living. They have some characteristics of living things, but are not composed of cells and lack metabolic enzymes and equipment for making proteins. Because of this, they can only reproduce within a host cell.
- Different virus types can only infect particular host species (i.e. chickens, dogs, humans, fish, etc.). Viruses attach to their target cells using surface proteins that bind to receptor molecules on the surface of host cells. Once the virus binds to the host cell the viral genome makes its way inside to complete the infection process.
- After infection the host's cellular machinery begins to replicate the viral genome and produce viral proteins. The newly produced viral molecules self-assemble into new viruses (virions) and exit the cell, often damaging or destroying the host cell in the process. A single infecting virus can produce large amounts of progeny, often hundreds or thousands at a time. When the viruses exit the host cell they are capable of infecting other cells, spreading the infection. Cellular death or damage and the body's immune response are responsible the symptoms of viral infection.

2. Introduction to the Human Papillomavirus

- i. HPV is part of the *Papillomaviridae* family of viruses
- ii. HPV is a double-stranded DNA virus with a circular genome. The genome consists of about 8,000 base pairs that encode for only 8 genes. Two of those 8 genes are E6 and E7. These are the genes primarily responsible for HPV's cancer causing potential. The HPV capsid consists of a major coat protein and a minor coat protein.

3. Statistics

- i. A 2007 study performed in the US on over 2000 women aged 14-59 showed HPV prevalence to be 26.8% overall, with women aged 20-24 having the highest prevalence (44.8%).
- ii. Age breakdown
 - 14-19 – 24.5%
 - **20-24 – 44.8%**
 - 25-29 – 27.4%
 - 30-39 – 27.5%
 - 40-49 – 25.2%
 - 50-59 – 19.6%

4. Transmission

- i. The human papillomavirus is transmitted via skin-skin contact. Sexual intercourse is not necessary for transmission, but is the most common route. The probability of acquiring HPV from a single sexual encounter is not known, but is most likely quite high.

5. Types

- i. There are over 200 known genetically different strains of human papillomavirus. Some strains of the virus are responsible for common warts and warts on the bottom of the feet (plantar warts). Other strains can infect the inner lining of the cervix; these strains are divided into low risk and high risk strains. The high risk strains are those strongly associated with cervical cancer. Two high risk strains, 16 and 18, are thought to be responsible for over 70% of cervical cancer cases. Low risk strains 6 and 11 are responsible for a large percentage of genital warts.

6. How HPV Causes Cervical Cancer

- i. HPV invades the skin or mucosa by entering tiny breaks in the surface (even those not visible to the naked eye). Once inside, HPV infects host epithelial cells, tricking them into producing new viruses. In the process of normal cell replacement, the infected cells are shed, releasing viral particles. High risk strains of HPV can integrate viral DNA into the host genome, although this is not a normal part of the HPV life cycle. Viral integration may give infected host cells a selective advantage, leading to a longer infection time. The longer the infection lasts, the more time there is for cancer to develop. After integration, two viral genes (E6 and E7) may be over-expressed. The E6 and E7 proteins are responsible for the ability of HPV to cause cancer.
- ii. E6, E7, and Cervical Cancer
The E6 and E7 proteins prevent the activity of key tumor suppressors. E6 inhibits p53, a protein that controls responses to different types of cellular stress including DNA damage and viral infection. E7 inhibits Rb, a protein that can prevent cell division by blocking the activity of transcription factors. The combined effects of E6 and E7 put cells at risk for undergoing uncontrolled division that can lead to cancer.

7. Prevention

- i. **Abstinence!** (not having sex) is the only 100% effective method of HPV prevention
- ii. Other Ways to Reduce Risk
Use a Condom! Condoms will not provide complete protection against HPV, but they will reduce the chance of getting it.
Remember: condoms also help reduce the risk of unwanted pregnancy and

other sexually transmitted infections, including: HIV, gonorrhea, Chlamydia, herpes, hepatitis, and syphilis, among others.

Low Number of Sexual Partners! The chances of getting HPV increase with increasing numbers of sexual partners. Studies have shown that women with multiple (>1) sexual partners have an increased risk for HPV and for CIN.

8. Vaccines

i. The Immune Response

The human immune system is a complex collection of cells and proteins that function to protect the body from foreign matter, both living and nonliving. There are two main types of immune cells involved in protection against viruses, T cells and B cells. Upon activation by the appropriate object (like a virus), a B cell produces millions of copies of a particular antibody (a protein) directed against that object. The antibodies then move throughout the circulatory system binding their specific target.

ii. Vaccines

Vaccines consist of an injection of attenuated (severely weakened) virus that poses no danger, a 'killed' virus, or purified components of a virus. The goal of a vaccine is to enhance the immune response against a virus should the infectious version be encountered. Thus, the body develops a tool to fight viruses without being exposed to the potential dangers of an actual infection.

iii. HPV Vaccines

Gardasil® is approved by the Food and Drug Administration (FDA) to protect against infection by four types of HPV: 6, 11, 16, and 18. It is approved for use in girls and women aged 9-26. HPV types 16 and 18 are considered high-risk because they are implicated in over 70% of all cervical cancers diagnosed. Types 6 and 11 are considered low-risk types that are not known to cause cervical cancer, but they do cause genital warts. Studies have shown Gardasil® to be almost 100% effective in preventing diseases caused by the 4 types of HPV it covers. Importantly, Gardasil® is not known to prevent the development of disease in women already infected with HPV.

Cervarix™ is an HPV vaccine that has not yet been approved by the FDA, but it has been approved in Australia and Europe. Cervarix™ protects against infection by high risk HPV types 16 and 18.

V. Cervical Cancer Myths

Cervical cancer is not preventable

FALSE! While not having sex (abstinence) is the only 100% effective way to prevent HPV infection, other options that reduce the risk of infection include vaccination and the consistent use of condoms.

HPV infection is rare

FALSE! It is estimated that in the U.S., almost 27% of women aged 14-59 are infected with HPV.

Only women with multiple sex partners or unfaithful partners can get infected by HPV

FALSE! HPV may be transmitted in a single sexual experience. Even people who have had only one sexual partner may be infected.

Young women do not need Pap tests

FALSE! Anyone who has been sexually active needs to be examined by a healthcare professional. It is recommended that women start getting tested three years after sexual activity begins.

Men do not get infected with HPV

FALSE! Men DO get infected with the virus and, like women, are responsible for the transmission of the virus to their sexual partners. Both men and women can get genital warts from some types of HPV.

HPV is the same as HIV or Herpes

FALSE! The viruses that cause HIV and herpes are not related to the human papillomavirus.

VI. References

1. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. "Human papillomavirus and cervical cancer." *Lancet*. 2007 Sep 8;370(9590):890-907. Review
2. zen Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. *Nature Reviews. Cancer*. 2002; 2(5):342-50
3. Dunne EF, Unger ER, Sternberg M, McQuillan G, Swan DC, Patel SS, Markowitz LE. Prevalence of HPV infection among females in the United States. *JAMA*. 2007;297(8):813-9.

4. Schiffman M, Castle PE. Human papillomavirus: epidemiology and public health. *Archives of Pathology and Laboratory Medicine*. 2003; 127(8):930-4.
5. Pett M and Coleman N. Integration of high-risk human papillomavirus: a key event in cervical carcinogenesis? *Journal of Pathology*. 2007; 212: 356–367.
6. Harald zur Hausen . Papillomaviruses and cancer: from basic studies to clinical application. *Nature*. 2002; 2: 342-350.

