

# Cervical Cancer is Curable if Detected on Time

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## ABSTRACT

Cervical cancer is the second most common cause of cancer in the world by the incidence of tumors in the female population. It occurs most often in an age where women are working and economically active, in which they play a key role in family care and can give the most in business. Cancer occurs when the cells of the cervix, in the presence of high-risk viruses and with a weakened immune response of the host, change and start to grow uncontrollably. Fortunately, the changes have been going on for years and regular gynecological examinations can be detected on time.

**Key words:** Cervic, cancer, screening, treatment

## INTRODUCTION

Cervical cancer is the second leading cause of cancer death in women.<sup>[1]</sup> Worldwide, more than 288,000 women die each year. At least 80% of these deaths occur in low-resource settings, with most occurring in the poorest regions of South Asia, sub-Saharan Africa, and parts of Latin America. In many of these countries, cervical cancer is the most common cause of cancer death. As tumor registries in low- and middle-income countries are not well developed, the true numbers may be higher. Despite these limitations, deaths from cervical cancer in resource-poor settings are predicted to increase to over 90% by 2020. Health care providers in developing countries regularly see women with advanced, incurable cervical cancer. Deaths often occur in relatively young women, who are raising children, caring for their families, and contributing to the communities.

### Characteristics

There are approximately 400,000 new cases of cervical cancer worldwide annually.<sup>[2]</sup>

A. The most common symptom of cervical cancer is abnormal vaginal bleeding—specifically, postcoital and intermenstrual bleeding, menorrhagia, and postmenopausal bleeding. Other symptoms include

pelvic fullness/pain, unilateral leg swelling, bladder irritability, and tenesmus. Cervical cancer is also commonly asymptomatic, found only following an abnormal Pap smear, colposcopic exam, or cervical biopsy.

- B. Common signs of advanced cervical cancer are a fungating cervical mass, unilateral leg edema, and obstructive renal failure.
- C. Cervical cancer results from persistent infection with high-risk human papillomavirus (HPV) types (most commonly 16 and 18). Risk factors associated with cervical cancer are: Prior history of sexually transmitted diseases (STDs), early age of first coitus, multiple sexual partners, multiparity, nonbarrier methods of birth control, and smoking.
- D. Cervical cancer primarily spreads by direct extension from the cervix to the parametria, vagina, uterine corpus, and the pelvis. Other routes of spread include lymphatic and hematogenous dissemination, as well as direct peritoneal seeding.
- E. Lymph node (LN) metastasis usually occurs in a sequential fashion, traveling first to the parametrial LNs, then to pelvic (obturator, internal, and external iliac), common iliac, para-aortic, then scalene LN.

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## Risk

Most cervical cancers are caused by the HPV, a STDs.<sup>[3]</sup> HPV is common, does not have outward symptoms like warts, and is easily transmitted. Use of a condom – and possibly also use of a diaphragm and spermicide – can reduce the transmission of HPV but cannot eliminate it. The virus lives on areas surrounding the genitals and the anus and can be transmitted without penetration.

Early engagement in sexual intercourse has also been shown to increase susceptibility to HPV, and therefore an increased risk of developing cervical cancer. Cervical cancer is the final stage of a long process because this form of cancer has a long “pre-invasive” period. Most pre-invasive lesions do not progress to cervical cancer – they either stop progressing or they actually regress back to the original normal state. Studies have found an increased association between use of birth control pills and both pre-invasive cervical lesions and invasive cervical cancer. It is very difficult to determine if this increased association can be translated into an increased risk.

HPVs are DNA viruses associated with genital warts (condyloma acuminata), intraepithelial neoplasia and cancer of the female external genital tract (cervix, vagina, and vulva), and the male external genital tract (penis and anus).<sup>[4]</sup> Approximately 40 of the >100 HPVs affect the external genital tract; the four most common are HPV 6, 11, 16, and 18. More than 80% of high-grade intraepithelial neoplasia and cancers of the external genital tract are caused by HPV 16 or 18. Most genital warts (condyloma acuminata) are caused by HPV 6 or 11. Most HPV infections are transient with most men and women clearing their infection in 6–8 months.

Approximately 35 HPV subtypes infect the genital tract.<sup>[5]</sup> Sexually transmitted, high-risk types of HPV (HPV 16 and HPV 18) are said to be present in about 70% of all squamous cervical cancers and 80% of all adenocarcinomas; type 18 is more frequently associated with adenocarcinoma of the cervix and type 16 with squamous cancer. HPV causes a disease that will develop in the transformation zone. The transformation zone is that area on the cervix that undergoes squamous metaplasia, which develops mainly during the adolescent years.

About 20 million Americans and 630 million people worldwide are infected with HPV. In the United States, about 6.2 million will acquire a new infection every year. Infection with high-risk HPV is necessary or required but is not a sufficient factor for the development of squamous cervical neoplasia and nearly all types of cervical cancer. Only a small fraction of women infected with HPV will develop high-grade cervical abnormalities and cancer. The current model of cervical carcinogenesis suggests that HPV infection results in either transient or persistent infection. Fortunately,

for most women, particularly those who are young, their immune system is effective and clears the infection. In most cases, they are cleared within 1–2 years without producing neoplastic changes. The risk of neoplasia increases in those women in whom the infection persists. There does appear to be a high prevalence of the infection in teenagers, peaking in the 30 s with subsequent decrease. Most lesions present in teenagers spontaneously regress.

## Prevention

Cervical cancer is a preventable disease, either by detection and treatment of precancerous lesions or vaccination against HPV.<sup>[1]</sup> Due to the long pre-invasive phase, regular screening with Pap smears and treatment of pre-invasive lesions has led to a 75% decrease in the incidence and mortality of cervical cancer in industrialized countries over the past 50 years. Physical examination with Pap remains the mainstay of cervical cancer screening around the world.

Screening programs, however, require financial and medical resources. Trained practitioners with basic supplies such as exam rooms, speculums, and microscope slides are needed to perform exams, and facilities with trained cytopathologists are needed to analyze the Pap smears. For resource-poor areas, this screening strategy may be difficult to secure financially.

The recent development of vaccines against the most common oncogenic types of the HPV may someday eliminate the need for screening with Pap smears. Until then, the natural history of HPV infection will continue to follow that of other STDs—poor women are more likely to become infected, more likely to develop pathologic sequelae, and more likely to die from the sequelae.

## Screening

Screening is testing for a health problem or risk factor when there are no recognized signs or symptoms that would indicate the presence of that problem or risk factor.<sup>[6]</sup> It is important to remember that the goal of screening is not merely to find problems, however. The goal of screening is to identify asymptomatic people for whom an intervention will help reduce the progression of early disease or prevent an adverse health event. An example of screening is sampling the ectocervix (performing a Pap smear) on asymptomatic sexually active adult women with the goal of detecting early cervical cancer. When early precancerous or cancerous changes are discovered, treatment effectively reduces a woman’s risk of cervical cancer and reduces mortality. Remember that performing tests in patients who already have symptoms is not screening. For example, a Pap smear for a woman with abnormal bleeding, lower abdominal pain, and weight loss would instead be a diagnostic test performed as part of a workup.

## Pap smear

Positive Pap smears are more often associated with invasive disease in older women.<sup>[7]</sup> A significant percentage of women over age 65 have never had a Pap smear. There is some debate as to what age to discontinue Pap screening. For women who have a cervix, the U.S. Preventive Service finds no solid evidence to impose an upper age limit, but suggests testing be discontinued after age 65 for those who have up until that time had regular and normal screenings. For women at higher risk of cervical cancer (including older patients with a personal or family history of cervical cancer, previous abnormal smears, or high-risk sexual behavior), testing should continue annually. Medicare covers annual cervical cancer screening for women at higher risk for cervical cancer; screening for all other female beneficiaries is covered every 3 years.

The validity of the Pap test as a screening instrument varies with the technique of the individual physician, sample method used, and laboratory interpretation; sensitivity ranges from 30% to 87% while specificities range from 86% to 100%. Obtaining a proper specimen can sometimes be difficult in older women for a number of reasons, including vaginal atrophy and narrow cervical os. Musculoskeletal disorders can make lying in the usual supine position with legs in stirrups quite difficult. Using the left lateral position may be preferable. For these reasons, if a primary care clinician is not experienced in performing Pap smears in older women, referral to a gynecologist is appropriate.

Since the development of the Pap test in the 1940s, the incidence of cervical cancer in the United States and deaths from it has declined by 80%.<sup>[8]</sup> In the United States, Latinas and African American women tend to develop cervical cancer more than their white counterparts. While teenage Latinas and African Americans have higher rates of unplanned pregnancy than their white counterparts, it is women over 30 who get cervical cancer at higher rates than younger women. Cervical cancer is most often found in women who have either never had a Pap smear or who did not have one in the previous 5 years. Patterns in both the United States and the Global South (with the highest rates of cervical cancer) show the link between the diseases and women's lack of consistent access to reproductive health care. Globally, about 500,000 women develop cervical cancer each year and about 270,000 die. Other countries where cervical cancer and deaths are rampant include sub-Saharan and Eastern Africa, Central America, and north and western Latin America including Venezuela, Colombia, Ecuador, Peru, and Bolivia.

## Diagnosis

As with any type of cancer, cervical carcinoma is a histologic diagnosis.<sup>[9]</sup> The Pap test is a screening procedure only and false negatives in the presence of invasive cancer may be as high as 20%. Due to this, all lesions of the cervix require biopsy. Biopsies should be taken from the center of

an ulcerative lesion, as this is the area most likely to yield adequate tumor for diagnosis. Cone biopsy is contraindicated in the presence of overt carcinoma. Whenever, the endocervix is palpably abnormal, even in the presence of a normal pap smear, it is advisable to perform an endocervical curettage or core biopsies of the endocervix before assuming that the diagnosis is cervical fibroids.

## Treatment

Cervical cancer treatment is dependent on the stage at diagnosis.<sup>[10]</sup> Treatment modalities for cervical cancer consist of surgery or radiotherapy. Since cervical cancer grows locally, surgery is acceptable if surgical margins free of disease are obtainable. Surgical management can include fertility-sparing procedures, such as a cold knife conization of the cervix for microinvasive disease, or radical trachelectomy (where the uterine cervix and upper portion of the vagina are removed) with pelvic lymphadenectomy for early disease. If fertility preservation is not desired than an extrafascial (simple) hysterectomy is performed for microinvasive disease. If the cancer stage is greater than microinvasive (1A1), more extensive surgery is required. Compared to a simple hysterectomy, a radical hysterectomy requires excision of the uterosacral ligaments and ligation of the uterine artery at its origin so that the cardinal ligaments can be removed. These maneuvers allow for complete dissection of the parametrium. A radical hysterectomy with pelvic lymphadenectomy is a treatment option if the tumor is confined to the cervix. Although LN status does not affect staging, pelvic lymphadenectomy is performed at the time of radical hysterectomy to determine the need for further therapy.

Cervical cancer is a radiosensitive disease. Randomized controlled trials have shown that the concurrent use of chemotherapy and radiation, known as chemoradiation, increases the sensitivity of cervical cancer to radiation effects. Consequently, chemoradiation reduces cervical cancer recurrence rates and improves overall survival compared to radiation alone. Radiation therapy for cervical cancer consists of external beam radiation to the whole pelvis followed by brachytherapy. Brachytherapy is a method of radiation therapy where the source of radiation is placed in the upper vagina, which allows for the delivery of high doses of radiation to the cervix.

Cervical cancer is the most common gynecologic malignancy among women worldwide.<sup>[11]</sup> However, due to its indolent development, the clear understanding of its molecular progression, and the widespread implementation of the Pap smear as a screening method, early cervical cancer is almost entirely preventable, treatable, and even curable. Yet this cancer remains a significant cause of mortality in poor women. The infrastructure and funding required to execute successful, nationwide Pap smear screening and treatment of precancerous lesions is extensive, and many countries simply do not have

the means to develop or implement such a program. For these reasons and many others, women in low-resource countries often present in the late stages of cervical cancer. Although early stages can be treated with surgery or radiotherapy, later stages are treated almost exclusively with radiotherapy and concurrent chemotherapy where available.

For any hope of increased survival, remission, or cure at later stages, treatment must include radiation therapy. Brachytherapy, an important type of radiation treatment for cervical cancer, is an extremely sophisticated technique which requires extensive training and equipment and large power sources. Some central hospitals in developing countries may have one or two radiotherapy machines and may have only one, if any, radiation oncologists available. Some of the poorest countries have no radiotherapy machines at all.

Cervical cancer continues to be a major public health issue. Both the World Health Organization and the International Atomic Energy Agency play an important role in cancer control and quality assurance and have developed countless initiatives to help reduce the prevalence of cervical cancer. While chemoradiation is the current standard of care in the United States, most women in low-resource countries have limited or no access to radiation therapy. Many of the challenges low-resource areas face in providing radiotherapy are simply insurmountable. By applying alternative strategies in managing cervical cancer in addition to working toward acquiring new and better resources, more patients will be able to get some form of effective treatment. This will save lives and improve the quality of life for countless women worldwide.

Most women with cervical cancer are diagnosed early through Pap smears or because they have unexplained vaginal bleeding.<sup>[12]</sup> There are two options for the treatment of Stage I cervical cancer. One is radiation therapy, which is quite effective. The other is radical pelvic surgery, which involves removing the uterus and taking out the LNs next to it.

Surgery as a treatment for cervical cancer has the advantage that it does not interfere with the ovaries because they are not involved with the disease; estrogen, made by the ovaries, does not stimulate cervical cancer. Most women who get the disease are fairly young and have functioning ovaries, which can continue to work normally after the surgery. Radiation therapy, on the other hand, will shut down the ovaries forever and cause artificial menopause, which is not desirable in younger women. The surgical approach can usually maintain normal sexual function by keeping the top of the vagina intact and unscarred.

Many physicians recommend some radiation therapy in addition to surgery, due to the risk of involvement of LNs that have not been taken out. Moreover, some new approaches involve chemotherapy.

## Therapy

The two main particles used in radiation therapy are photons and gamma rays.<sup>[11]</sup> Photons are produced when electron-containing beams collide with a heavy metal. Gamma rays, in contrast, are radioactive particles emitted by the decay of a radioisotope; Cobalt-60 is the most common radioisotope used. Both photons and gamma rays cause ionizing events as they travel through tissue. Damage results when ionizing radiation interacts with water molecules to form destructive free radicals. These particles cause damage to DNA, which then triggers cellular death, i.e., apoptosis. Abnormal cancer cells are more susceptible to this damage than healthy, noncancerous cells.

The two main categories of radiation therapy are external beam radiation therapy (EBRT) and brachytherapy. EBRT is used to irradiate a large area around the tumor including LNs. Brachytherapy, which employs the use of small radioactive implants or “seeds,” is a more targeted approach and is recommended as an integral part of the first-line treatment of cervical cancer.

EBRT methods are more precise when aided by the use of radiation simulators where patients are positioned and marked for treatment, and treatment planning systems (TPS) with which a radiation oncologist can calculate contours and dosimetry on imaging before performing the actual procedure. However, both simulators and TPS require extra cost, equipment, and personnel. Many centers in developing countries have to perform radiation therapy without these assistive devices, putting patients at risk for improper dosing. In article examining worldwide radiotherapy resources, it was observed that, globally, only 19% of countries had simulators and only 45% had TPS, meaning many radiotherapy procedures are being performed without any prior planning.

## CONCLUSION

Cervical cancer rarely shows symptoms and is also called “silent” disease. However, it is important to emphasize that it is a cancer that can be easily detected and prevented. A regular gynecological examination is very reliable, and a simple measure to detect cervical cancer on time. Thanks to Pap smear screening, cervical cancer can be avoided. If discovered on time, it can be treated with great success.

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