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A Brief Assessment on Cervical Cancer

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Abstract

The incidence of cervical cancer is most common in underdeveloped countries than developed countries. Cervical cancer is the third most common gynecologic malignancy worldwide. Cervix is the lower part of the uterus, the structure that dilates during childbirth to allow the baby to traverse the birth canal. This cancer is caused by human papilloma virus, a common sexually transmitted virus. Cervical cancers start in the squamous cells on the surface of the cervix. Cervical cancer can be prevented if precancerous lesions are identified early and treated promptly. Pap smears can help detect precancerous changes, which can be treated before they turn into cervical cancer. Treatment of cervical cancer relies upon on the stage of the cancer. Some Complications for the treatment of cervical cancer such as Surgery and radiation can create problems with sexual, bowel, and bladder function. Several preventive measures have been discussed in the present article.

Keywords: Cervical cancer; Human papilloma virus; Risk factors; Treatment; Prevention

Abbreviations: HPV: Human papilloma virus

Introduction

Cancer develops when normal cells in a particular part of the body begin to grow out of control [1]. Cervical cancer is the most common gynecologic malignancy worldwide. It is the third most common type of cancer in women. The cervix [2] is the lower part of the uterus, the structure that dilates during childbirth to allow the baby to traverse the birth canal. In some cases uterus may rupture with the mismanagement of labor [3]. Cancer of the cervix occurs when the cells of the cervix change in a way that leads to abnormal growth and invasion of other tissues or organs of the body. Cancer occurs in different cell types [4]. Cervical cancers start in the cells on the surface of the cervix [5]. There are two types of cells on the cervix's surface such as squamous and columnar cells. A cancer with both types of cells is called an adenocarcinoma with squamous differentiation. Most cervical cancers arise from squamous cells. Cervical cancer usually develops very gradually. It begins as a precancerous condition called dysplasia. Cervical dysplasia [6] refers to the presence of precancerous changes of the cells that make up the inner lining of the cervix.

This precancerous condition can be detected by a Pap smear. But the undetected precancerous changes can develop into cervical cancer and spread to the bladder, intestines, lungs, and liver. The progression of these precancerous changes to cervical cancer takes several years. Almost all cervical cancers are caused by HPV (human papilloma virus) which is a common sexually transmitted virus. Human Papillomavirus (HPV) is the primary cause of cervical, anal, vulvar, vaginal and penile cancers as well as genital warts [7]. Most of the women's bodies are able to fight HPV infection. The female lower genital is habited by various microorganisms as normal resident which help to protect the woman against various form of infections [8].The flora of the healthy vagina is usually dominated by one or a few species of lactobacilli [9] which maintain the acidity of the vagina and are critical for vaginal health.

Predominance of Human Papilloma Virus in cervical cancer

Infection with high-risk HPV plays a central role in the carcinogenesis and etiology of nearly all cases of cervical cancer, therefore HPV may also function to transform oral and breast tissue [10]. Human papilloma viruses (HPVs) are associated with cervix, vulva and penis cancers. Genital HPVs are transmitted sexually [11], as the central etiologic factor in cervical cancer worldwide. High-risk human papillomaviruses (HR-HPVs) are the causative agents of cervical cancer [12]. HPV infects the skin and mucous membranes of humans [13] and spreads from human to human through sexual contact [14]. There are approximately 130 HPV types that have been identified. There are more than 100 documented HPV types, and approximately 40 (high-risk HPVs) have the propensity to cause malignant changes, in varying degrees, in the anogenital epithelium [15].

HPV has been implicated as the causative agent in many intraepithelial neoplasias and invasive squamous cell carcinomas. In particular, HPV-16 and HPV-18 are the major established etiological agents of cervical cancer and are associated with two-thirds of all cases [16]. All the HPV infections do not show symptoms. Most sexually active persons will probably acquire a genital HPV [17] infection at some point during their lives. Patients with genital HPV infection are at risk for subclinical oral HPV infection [18]. The triggers of chronic inflammation increase cancer risk or progression include HPV infections [19]. The Choice of the Endpoint to Assess the Efficacy in Cervical cancer are response rate overall survival, progression free survival [20].

Risk factors for cervical cancer

Cancer kills or maims thousands of lives each day [21]. Complex cell interactions in the tumor and its microenvironment play an important role in tumorigenesis and cancer progression [22]. Several risk factors are associated with the incidence of cervical cancer. There is a strong

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inter connection between human papillomavirus (HPV) infection and cervical cancer. The association of environmental factors with cervical cancer is unclear and also that reflect the secondary associations attributable to confounding by HPV, if they are independent risk factors or whether they may act as cofactors to HPV infection in cervical carcinogenesis.

The risk factors for cervical cancer commonly include the following:

- Having sex at an early age
- Multiple sexual partners
- Those who have multiple sex partners or who participate in high-risk sexual activities
- Women using the drug DES (diethylstilbestrol) during pregnancy to prevent miscarriage.
- Weakened immune system
- Smoking, nutrition, parity and oral contraceptive can also be considered as major environmental risk factors for cervical cancer [23,24]. Oral contraceptives contain hormone agents [25] such as estrogen and progestogen which are known to maintain female reproductive system and secondary sexual characteristics. These steroid hormones such as estrogen and progestogen are known to regulate immune responses [26].

Cervical carcinoma is the most common gynecologic malignancy associated with pregnancy; its occurrence is rare with an incidence of approximately 1 per 1,200 to 10,000 pregnancies [27].

Symptoms of cervical cancer

In early stages of cervical cancer symptoms do not appear in most of the cases but in advanced stages of cancer symptoms can be clearly observed. The symptoms in the early stages may appear in few cases. Those include abnormal vaginal bleeding during menses, after sexual intercourse, or after menopause, Abnormal vaginal bleeding, vaginal discharge with foul-smelling, Heavy and prolonged periods. Symptoms of advanced cervical cancer may include Back pain, Bone fractures, Single swollen leg, Fatigue, Heavy vaginal bleeding, Urinary Incontinence (Leaking of urine) or feces from the vagina, Reduction in weight, Leg pain, Loss of appetite, Pelvic pain [28]. In cervical cancer Lung, liver, and bones are the most common metastatic sites [29]. Cervical cancer in advanced stages certainly shows some symptoms. Microscopic invasion of cervix [30] is seen in endometrial or uterine cancer. The major symptoms of include:

- **Abnormal bleeding:** Women with cervical cancer may experience abnormal vaginal bleeding. This can be heavy or light bleeding during the menses.
- **Unusual heavy discharge:** An increased vaginal discharge is also a symptom of cervical cancer. It may be foul smelling, watery, thick, or contain mucus. It varies from woman to woman.
- **Pelvic pain:** Pelvic pain can also be a symptom for cervical cancer though it is not related to menstrual cycle. Many women describe them ranging from a dull ache to sharp pains that can last hours. It can be mild or severe.
- **Pain during urination:** Bladder pain or pain during urination can be a symptom of advanced cervical cancer. This cervical cancer symptom usually occurs when cancer has spread to the bladder. Malignancies of the upper urinary tract are rare malignancies. The carcinomas of the renal pelvis are specific of squamous cell carcinoma of the upper urinary tract [31].
- B**leeding between regular menstrual periods, after sexual intercourse, douching, or pelvic exam:** Bleeding after sexual intercourse, douching, or pelvic exam can be cervical cancer symptoms. This is due to the irritation of the cervix during these activities. While a healthy cervix may have a very small amount of bleeding, many conditions may cause bleeding after activities like sex [32].

Detection or identification of cervical cancer: George Papanicolaou identified Pap tests potential for early detection of cervical cancer. Colposcopy or endocervical curettage (ECC) can be used for testing the cervix from cancers. HPV infections can be currently screened using the Pap cytology and the HPV DNA testing.

Treatment for cervical cancer

Treatment of cervical cancer relies upon on the stage of the cancer, i.e., the size and shape of tumor, the woman's age and general health. Cervical cancer can be prevented if precancerous lesions are identified early and treated promptly. There are various surgical procedures to treat cancer without removing the uterus or damaging the cervix. Types of surgery for early cervical cancer include:

- **Laser therapy:** Also known as laser ablation. In this therapy laser light is used to destroy abnormal tissue. Laser surgery can only be used to treat preinvasive cervical cancer. Laser therapy is also used to destroy genital warts caused by HPV.
- **Loop electrosurgical excision procedure (LEEP):** This procedure uses low voltage electricity to remove abnormal tissue of the cervix. LEEP is also known as large loop excision of the transformation zone (LLETZ).
- **Cryotherapy or Cryosurgery:** generally involves killing of abnormal cells by freezing them [8,9]. Cryotherapy is recognized as the most advanced cost-effective and feasible approach in treating precancerous cervical lesions.

Treatment for cervical cancer in advanced stage includes:

- **Radical hysterectomy:** Radical hysterectomy [33], sometimes called Wertheim's hysterectomy is an operation that is performed for cancer of the cervix. This means excision of the uterus, fallopian tubes, ovaries, cervix, lymph glands in the pelvis and the upper part of the vagina. The ovaries may also be removed. If they are removed, depending on your age, Hormone Replacement may be required.
- **Pelvic exenteration:** It is a radical surgical treatment for advanced and recurrent cervical cancer. This is an extreme type of surgery in which all of the organs of the pelvis, including the bladder and rectum, are removed. Pelvic exenteration continues to be the only curative option in certain patients with centrally recurrent cervical, vaginal, or vulvar cancers.

The mainstay of treatment in cancer cervix is radiotherapy [34]. Use of radiation therapy in cancer treatment is one of the important treatment modalities [35]. In some cases radiation may be used to treat cancer that has spread beyond the pelvis, or recurrent cancer. Radiation therapy is either external or internal. Internal radiation therapy uses a device filled with radioactive material, which is placed inside the woman's vagina and is removed after treatment. Selective internal ra-

diation therapy (SIRT) [36], otherwise known as radio embolization [37] is used for colorectal cancers. External radiation therapy beams radiation from a large machine onto the body where the cancer is located. Intensity-modulated radiation therapy (IMRT) in used in many pelvic cases. Deformable dose accumulation is an emerging method to accumulate the radiation dose from each fraction and evaluate the final dose distribution from radiation therapy [38].

Neoadjuvant chemotherapy (NACT) and radical surgery (RS) have emerged as a possible alternative to conventional radiation therapy (RT) in locally advanced cervical carcinoma [39]. The essential conditions for Neoadjuvant chemotherapy are low-grade toxicity and high antitumor activity [40]. Continuous hyperfractionated accelerated radiotherapy (CHART) is an altered fractionation scheme used to reduce overall treatment time, overcome tumor repopulation thus could be an option in cervical carcinoma. Chemotherapy uses anticancer or cytotoxic drugs to kill cancer. Some of the drugs used for cervical cancer are 5-FU [41], cisplatin [42], carboplatin, ifosfamide, paclitaxel, and cyclophosphamide. Chemotherapy drugs kill cancer cells but also damage some normal cell causing side effects. Once into the target site, anticancer drugs cannot distinguish between healthy and cancer cells [43]. Although most trails of concurrent chemoradiation have used cisplatin in combination with 5-fluorouracil (5-FU), there is at present no evidence that this combination performs better than cisplatin alone [44].

Cisplatin is well-known anticancer drug often been used for treatment of various human malignancies [45]. The cancer-specific survival rate at 5 years was 78 % for all patients and 77 % for patients who received a 5-fluorouracilbased treatment. Sometimes radiation and chemotherapy are used before or after surgery called concurrent chemoradiation. Finally hysterectomy is not often performed for cervical cancer that has not spread. It may be done in women who have repeated LEEP procedures. Fluorouracil is a constituent in most combined chemotherapy [46] and radiation studies in cervical cancer [47]. With the chemotherapy-related neutropenia, a rare complication called Neutropenic enterocolitis can occur in some of the cancer patients [48]. Nanoparticles have been of significant interest over the last decade as they offer great benefits for drug delivery to overcome limitations in conventional chemotherapy. Using targeted nanoparticles to deliver chemotherapeutic agents in cancer therapy offers many advantages to improve drug/gene delivery and to overcome many problems associated with conventional chemotherapy [49].

Some Complications for the treatment of cervical cancer such as Surgery and radiation can create problems with sexual, bowel, and bladder function. Some types of cervical cancer do not respond well to treatment and the cancer may recur after treatment. The recurrence of cancer is high in those women who had treatment to save the uterus [50]. Cervical cancer treatments, such as chemotherapy, radiation and surgical procedures, can cause side effects in women. Chemotherapy and radiation can lead to adverse side effects that include skin irritation, dryness of vagina, nausea, vomiting, diarrhea, loss of hair, recurrent infections. Radiation dermatitis [51] occurs to some degree in most of the patients who receive radiotherapy. Surgical or radiotherapy cancer treatment options can lead to complications involving bowel or bladder function. These cervical cancer complications of treatment can be uncomfortable and may have a significant impact on a woman's daily life and activities [52].

Prevention of cervical cancer

Cervical cancer can be prevented if preventive measures are followed beforehand itself. The availability of Prophylactic HPV vaccines [53] represents the best hope for preventing most cases of cervical cancer and HPV-associated diseases [54].

Several studies have shown that the vaccine appears to prevent early-stage cervical cancer and precancerous lesions. A vaccine to prevent cervical cancer is now available named as Gardasil by U.S. Food and Drug Administration. Gardasil is the first approved vaccine targeted specifically to prevent any type of cancer. The vaccine prevents infection against two types of HPV responsible for most cervical cancer cases [55,56]. If vaccination occurs prior to wart exposure, Gardasil [57] prevents most genital warts for an average of 44 months in women and 29 months in men. Therapeutic cancer vaccines preceding conventional therapies [58] if introduced may show more promising results compared with vaccines alone.

- Practicing safe sex practices also reduces the risk of HPV and other sexually transmitted diseases. HPV infection causes genital warts. It is better to avoid sexual relationship with those infected with HPV.
- Getting regular Pap smears can help detect precancerous changes, which can be treated before they turn into cervical cancer. Pap smears effectively spot such changes, but they must be done regularly. Annual pelvic examinations, including a pap smear, should start when a woman becomes sexually active, or by the age of 20 in a nonsexual active woman. Overall, there was limited knowledge and confusion across ethnic groups about cervical cancer and its risk factors, the Pap test, and the human papilloma virus (HPV) and its association with cervical cancer [59].
- To further reduce the risk of cervical cancer, women should limit their number of sexual partners and avoid partners who participate in high-risk sexual activities.
- Women those generally smoke had to quit Cigarette smoking because it is associated with an increased risk of cervical cancer [60, 61]. Smoking is considered to be a major reason for cancer mortality [62] in many countries. An intention to quit is an important preliminary step for the behavioral change.

Nutraceuticals are alternative dietary and holistic substances that are used for the treatment or prevention of multiple forms of cancer [63]. The identification and functional verification of host proteins associated with HPV E6 and E7 oncoproteins may provide useful information for the understanding of cervical carcinogenesis and the development of cervical cancer-specific markers. There is a critical need for expedited development of biomarkers and their use to improve diagnosis and treatment for cancer. Biomarkers can be used to develop targeted therapies, predict risk for cancer, help screen for cancers, and forecast how well a person is likely to respond to a cancer treatment, or monitor the patient [64]. DNA damage is the consequence in the etiology of cancers. Oxidatively induced DNA lesions and DNA repair enzymes are potential cancer biomarkers [65]. The benefits of Nanotechnology to drug delivery in cancer chemotherapeutics are exciting, there is the potential to treat tumours and destroy cancerous cells. In future we may find the benefits of nanotechnology in treating cancers.

Conclusion

Cervical cancer, the most leading cause of death in women is caused by Human papilloma virus. It is a sexually transmitted virus and is the central etiologic factor in cervical cancer worldwide. Cancer of the cervix occurs when the cells of the cervix change in a way that leads

to abnormal growth and invasion of other tissues or organs of the body. The cancer is common in sexually active individuals, having multiple partners and also other environmental factors are the cause. Pap smears can help detect precancerous changes, which can be treated before they turn into cervical cancer. Treatment of cervical cancer relies upon on the stage of the cancer. Treatments like chemotherapy, radiotherapy are used. Radical hysterectomy and Pelvic exenteration are used in advanced stages of cervical cancer.

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