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Review Article

Review on Uterine Cervix Cancer

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Abstract

Cervical cancer is abnormal growth of cells in the uterine cervix generally at the district of the uterus that joins the vagina. It can be spread to other organs in the human body if untreated. Previously it ranked the second cancer affecting ladies worldwide after breast cancer and second causing cancer death among women. Recently, it is the fourth-most common cancer worldwide and the fourth-most common cause of cancer death in women. The most common type of cervical cancer is squamous cell carcinoma followed by adenocarcinoma, while other type is less in number. This paper focusing on a major type; squamous cell carcinoma.

Keywords: Cervical Cancer; Cervical Intra Epithelial Neoplasia (CIN); Risk Factors; Prevention; Etiology; Treatment

Introduction

Cervical cancer is the fourth most common cancer among women globally, with an estimated 570,000 new cases in 2018. Nearly 90% of the 311,000 deaths worldwide in 2018 occurred in LMICs [1]. In 2020 an estimated 604 000 new cases and 342 000 deaths in 2020. About 90% of the new cases and deaths worldwide occurred in low- and middle-income countries [2]. According to American Cancer Society (2021) 14,480 new cases of invasive cervical cancer will be diagnosed and about 4,290 deaths will occur in the US [3].

The dissemination of cervical malignancy varies across the world, with more than 85% of deaths occurring in developing countries [4]. More than 90% of the greatest frequency paces of malignant cervical neoplasm happen in sub-Saharan Africa [5].

Squamous cell carcinoma of the cervix is proceeded by premalignant changes known as cervical intraepithelial neoplasia (CIN) or cervical dysplasia, classified into CIN I as mild dysplasia), CIN II as moderate dysplasia and CIN III as severe dysplasia and carcinoma in situ (CIS) depending on appearance of cells under microscope and area of tissue affected. Other recent classification by Bethesda System, which divides all cervical precancerous lesions into two groups: Low-grade Squamous Intraepithelial Lesion (LSIL) and High-grade Squamous Intraepithelial Lesion (HSIL). LSIL coincide CIN I, and HSIL incorporates of CIN II and CIN III. This premalignant change is curable and treated when detected early, nevertheless; if untreated can progress and develop into cancer.

Presentation

The early stages of cervical cancer may be completely asymptomatic [6]. Vaginal bleeding, contact bleeding or (rarely)

a vaginal mass may indicate the presence of malignancy. Also, moderate pain during sexual intercourse and vaginal discharge are symptoms of cervical cancer. In advanced disease, metastases may be present in the abdomen, lungs or elsewhere.

Symptoms of advanced cervical cancer may include: loss of appetite, weight loss, fatigue, pelvic pain, back pain, leg pain, single swollen leg, heavy bleeding from the vagina, leaking of urine or feces from the vagina, [7] and bone fractures.

Etiology

Human Papilloma virus (HPV) infection plays an etiological role in the development of cervical cancer, and most of cervical cancers contain HPV DNA [8].

Walboomers., *et al*. 1999: proved that Human Papilloma virus is responsible of 99.7% of all invasive carcinomas of the cervix [9] HPV is sexually transmitted [10].

The relation between HPV and cervical cancer discovered by the German scientist Dr. Harald zur Hausen. HPV DNA(HPV16) first isolated from cervical cancer biopsies by Dr. zur Hausen and his team in 1983, then after year, they detected HPV 16 and HPV 18 in patients with cervical cancer.

Not all infection with HPV can develop into cancer, although there are about 100 types of HPV, small group only recognized to be linked to CIN and invasive carcinoma. There are two main classes of HPV; high risk HPV and low risk HPV.

Regarding Burd (2003), Low-risk HPV types include types 6, 11, 42, 43, and 44. And High-risk HPV types include types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70. Also he added that included in the high-risk group are some HPV types that are less frequently found in cancers but are often found in squamous intraepithelial lesions [11]. Walboomers (1999), asserts that types 16 and 18 cause about 70% of cervical cancer cases [9]. Xi., *et al*. 2009 and Moscicki., *et al*. 2006; underline that, HPV 16 is the most cancer-causing and account for 55 to 60% of cervical malignant growths around the world. Followed by HPV 18 which account for 10 to 15% of cervical malignancy [12,13].

Infection with HPV cause alterations in the cells of the cervix and development of dysplasia, these changes is reversible and can be return back to normal cells especially in cases of mild and moderate dysplasia so the persistence of infection by HPV is necessary for progression into cancer cells.

Risk factors

The infection with high-risk HPV is the main factor for developing cervical cancer, however there are other factors can aid to cancer progress. These factor as listed by Kumar., *et al*. (2013), include; early age at first intercourse, multiple sexual partners and male partner with multiple previous sexual partners, immune and hormonal status, or co-infection with other sexually transmitted agents and persistent of infection by high-risk strains of papillomavirus [14]. Many researches approved that that tobacco smoking is connected to a raise the risk of cervical intraepithelial neoplasia and cervical cancer, moreover Nagelhout., *et al*. (2021) in their metanalysis study confirmed this positive correlation between smoking and development of CIN and cervical cancer [15]. Furthermore, risk factors such as immunocompromised state, or HIV infection likely led to persistence of HPV infection and an increased risk for the development of CIN [6,12]. Addition risk factors noted by Sanjay., *et al*. 2015 include: dietary habits that diet lacking fruits and vegetable as well as being in excess as weight greater than before increase the risk; multiple pregnancies that women with three or more pregnancies cause hormonal change and immune system is weak during the period of pregnancies; as well as oral contraceptives, some studies recommended that, the use of oral contraceptives for birth control may increase the risk of cervical cancer [16]. Further the exposure to diethylstilbestrol (DES) in utero [17].

More recently, somatically acquired mutations in the tumor suppressor gene LKB1 were identified in more than 20% of cervical cancers [14].

Pathophysiology

The HPV genome is composed of six early (E1, E2, E3, E4, E6 and E7) and two late (L1 and L2) proteins [18]. Two viral proteins, E6 and E7, alter cell cycle control and are the main arbitrators of HPV-induced oncogenesis HPV-infected squamous the viral proteins E6 and E7 are expressed and uncouple cell growth arrest and differentiation primarily through the inactivation of p53 and pRb, respectively. At the core of these events are the facts that inactivation of pRb by E7 forces infected cells to remain in a

proliferative state and escape cell cycle exit, while abrogation of p53 by E6 ensures cell survival by preventing apoptosis triggered by this aberrant growth signal. HPV is basic mechanisms of pathogenesis and oncogenicity [19,20].

More recently, somatically acquired mutations in the tumor suppressor gene LKB1 were identified in more than 20% of cervical cancers. LKB1 was first identified as the gene mutated in Peutz-Jeghers syndrome, an autosomal dominant condition characterized by hamartomatous polyps of the GI tract and a significantly elevated risk of epithelial malignancies at a variety of anatomic sites including the cervix [14].

Epidemiology

According to The American Cancer Society's estimates for cervical cancer in the United States for 2021 are: 14,480 new cases of invasive cervical cancer will be diagnosed and about 4,290 women will die from cervical cancer [3].

Arbyn., *et al*. (2020) who had studied worldwide analysis, they utilized data of cancer estimates from 185 countries from the Global Cancer Observatory 2018 database. They found that around 570 000 cases of cervical malignant growth and 311 000 women died from the disease. Cervical cancer was the fourth most common malignant growth in ladies, positioning after breast cancer (2·1 million cases), colorectal cancer (0·8 million) and lung cancer (0·7 million). The assessed age-standardised incidence of cervical cancer was 13·1 per 100 000 ladies internationally and shifted generally among nations, with rates ranging from less than 2 to 75 per 100 000 women. Cervical cancer was the leading cause of cancer-related death in women in eastern, western, middle, and southern Africa. The most elevated occurrence was assessed in Eswatini, with around 6·5% of ladies developing cervical malignant growth before age 75 years. China and India together presented in excess of 33% the worldwide cervical cancer weight, with 106 000 cases in China and 97 000 cases in India, and 48 000 deaths in China and 60 000 deaths in India. Worldwide, the average age at determination of cervical cancer was 53 years, going from 44 years (Vanuatu) to 68 years (Singapore). The worldwide typical age at death from cervical malignant growth was 59 years, going from 45 years (Vanuatu) to 76 years (Martinique). Cervical cancer positioned in the top three malignant tumors affecting women youthful than 45 years in 146 (79%) of 185 nations surveyed [21].

Prevention

Cervical neoplasm can be viably controlled through primary and secondary prevention, for example, cervical screening and prophylactic HPV inoculation [22].

Primary prevention

- **Vaccination:** Primary prevention through vaccination against human papillomavirus (HPV) which is the main etiological factor of CC, has been introduced into immunization programs in most of the European countries [23].
- Prophylactic HPV immunizations have become a set up and crucial technique for primary prevention of cervical malignancy [24]. HPV vaccination is targeted at girls 9-13 years of age [25]. Gardasil quadrivalent HPV 6/11/16/18 vaccine created by Merck (Whitehouse Station, New Jersey, United States) and Cervarix bivalent HPV 16/18 vaccine by GlaxoSmithKline (Brentford, London, United Kingdom) are generally accessible in more than 100 nations through local or public inoculation programs. They had been brought into public vaccination programs in something like 40 nations by the beginning of 2012 [26]. The adequacy and safety of these have been set up in clinical trials and post-market observation in populaces [27,28]. A deliberate survey of HPV immunization clinical trials shows that viability is 50–90% in preventing intraepithelial neoplasm grade 2+ (CIN 2+) related with HPV 16 and 18 [29].
- **Condoms:** Condoms offer some protection against cervical cancer [30].
- **Smoking avoidance:** As well as may other types of cancer, carcinogens from tobacco can increase the risk of CIN and cervical cancer. Regarding to American Cancer Society (2020), Women who smoke are about twice as likely as non-smokers to get cervical cancer [31].
- **Nutrition:** Eating fruits and vegetables, studied showed that, higher levels of vegetable consumption were associated with a 54% decrease risk of HPV persistence [32]. As well as vitamin A [33], vitamin B12, vitamin C, vitamin E, and beta-Carotene which associated with low risk [34].
- Avoid many sexual partners during sex.
- Avoiding other risk factors such as early marriage and child bearing [35].

Secondary prevention

The screening tests is effective in reduction and limitation of cervical cancer mortality as high grade (grade 2 and 3) cervical intraepithelial neoplasia can be treated by excisional techniques.

The incidence of and mortality from cervical cancer have declined markedly in the United States since the mid-20th century, largely because of widespread screening practices that were initiated in the 1950s [36]. Dr Georges Papanicolaou's screening method (the Pap smear) started in the US in the 1940s. It was widely used in the UK a decade later and a national programme of cervical screening was established in 1988.

As more outcome data has become available, screening, and treatment guidelines for cervical intraepithelial neoplasia (CIN) have evolved. Detection of the disease in a precancerous state, close monitoring, and treatment are paramount in the prevention of cervical cancer [37].

Lately, there has been overpowering proof that HPV testing is more successful than cytology for CC screening, giving expanded consolation and permitting longer screening spans to be taken on [38]. However highly sensitive tests have been created and are at present used to trade cervical cytology for primary screening [39].

Visual inspection investigation with 3%-5% acetic acid (VIA) as well as Lugol's iodine (VILI) are simple, cost-effective with practical effortlessly and have all the earmarks of being a good alternate screening way to cytology [40]. Several studies of cross-sectional and randomized controlled studies proved that the accuracy and efficacy of Visual inspection with acetic acid (VIA) in reducing cervical cancer mortality in low- and medium-income countries [41]. Also, it has been shown to decrease mortality in developing countries [42,43]. Jeronimo (2014) and his colleges added that the Visual inspection with acetic acid (VIA) or Lugol's iodine (VILI), and HPV DNA-based testing are also utilized for screening purposes in developing countries [44].

WHO (2013) assert that At a minimum, screening is recommended for every woman 30-49 years of age at least once in a life time [45].

In 2016 and 2017 quality assurance of the program was restricted to on location reviews of the facilities where Pap spreads are gathered, of the cytological labs and colposcopy focuses [46].

Diagnosis

Papanicolaou (Pap) test: Liquid-based monolayer cytology can be used to reduce the number of false-negative results related to Conventional Cytology.

Biopsy: Confirmation of the diagnosis of cervical malignant or premalignant requires a biopsy of the cervix. This is usually done through colposcopy, an amplified visual inspection of the cervix supported by utilizing a dilute acetic acid (e.g. vinegar) solution to highlight abnormal cells on the surface of the cervix [6,47].

Imaging: Such as ultrasound, CT scan, and MRI have been used to look for alternating disease, spread of the tumor, and effect on adjacent structures [48].

Stages

Stage of cancer describes the size of a tumor, and is it localized or spread to other part of the body which can be detected by physical exam, imaging scans, and biopsies. Stage descriptions that used for cervical cancer is according staging system developed by International Federation of Obstetrics and Gynecology (Federation Internationale de Gynecologie et d'Obstetrique, or FIGO).

Stage I

Cancer only in the uterus, but has spread from the cervix lining into the deeper tissue. There is no distant spread.

This stage has subdivisions to describe the cancer in more detail

- **Stage IA:** The cancer is diagnosed only by microscopically. Tumor size can be determine by Imaging tests or evaluation of tissue samples.
- **Stage IA1:** Area of cancer tissues is less than 3 millimeters (mm) in depth.
- **Stage IA2:** Area of cancer tissues is 3 mm to less than 5 mm in depth.
- **Stage IB:** The tumor is large but localize only in the cervix It has not spread to other parts of the body.
- **Stage IB1:** The tumor depth is 5 mm or more and width less than 2cm.
- **Stage IB2:** The tumor is 5 mm or more in depth and 2 cm to less than 4 cm wide.
- **Stage IB3:** The tumor is 4 cm or more in width.

Stage II

The cancer has spread past the uterus to surrounding regions, such as the vagina or tissue close to the cervix, however it is still inside the pelvic region.

The subdivisions of this stage include:

- **Stage IIA:** The cancer is restricted to the upper two-thirds of the vagina. It has not spread to the tissue close to the cervix, which is known as the parametrial region.
- **Stage IIA1:** The cancerous area is less than 4 cm wide.
- **Stage IIA2:** The cancerous area is 4 cm or more in width.
- **Stage IIB:** The cancer has spread to the parametrial area. The cancer doesn't arrive at the pelvic wall.

Stage III

The cancer includes the lower third of the vagina or potentially: has spread to the pelvic wall; causes swelling of the kidney, called hydronephrosis; prevents a kidney from working; as well and/or involves regional lymph nodes. There is no far off spread.

- **Stage IIIA:** The cancer includes the lower third of the vagina, however it has not developed into the pelvic wall.
- **Stage IIIB:** The growth has developed into the pelvic wall as well as influences a kidney.
- **Stage IIIC:** The cancer involves regional lymph nodes. This can be distinguished utilizing imaging tests or pathology. Adding a lowercase "r" shows imaging tests were were utilized to affirm lymph node contribution. A lowercase "p" shows pathology results were utilized to determine the stage.
- **Stage IIIC1:** The tumor has spread to lymph nodes in the pelvis.
- **Stage IIIC2:** The tumor has spread to para-aortic lymph nodes. Which found in the abdomen near the base of the spine and close to the aorta, a significant supply route that runs from the heart to the midsection.

Stage IV

- **Stage IVA:** The malignant growth has spread to the bladder or rectum; however, it has not spread to distant to other body part.
- **Stage IVB:** The malignant growth has spread to different parts of the body [49].

Treatment:

Invasive cervical malignancy is treated by surgery and/or radiotherapy Chemotherapy can supplement the treatment system in late stages [46].

For beginning phase illness, studies show that insignificantly intrusive medical procedure (laparoscopy) is related with more regrettable endurance than open a medical procedure. Only chemotherapy is in many cases used to treat progressed illness. Nonetheless, for ladies with metastatic, repetitive, or persevering cervical neoplasm, the expansion of designated treatment to standard chemotherapy has been displayed to work on generally speaking endurance. Immunotherapy might be one more choice for metastatic or recurrent disease

Treatment for In Situ Cervical Cancer:

CIN is curable, although the lifetime recurrence rate is 20%.

The premalignant cervical lesions may be treated with a loop electrosurgical excision procedure (LEEP), which eliminates abnormal tissue with a wire loop warmed by electric current; cryotherapy (the destruction of cells by extreme cold); laser ablation (destruction of tissue using a laser beam); or conization which is the removal of a cone-shaped piece of tissue containing the abnormal tissue [31].

According to National Guidelines (2015), the clinical guidelines for management of CIN are listed below:

- **CIN1:** Generally, not treated. In the case of post reproductive and persistent of low-grade cytology, treatment options may be discussed with the patient.
- **CIN2:** Individual assessment is required, particularly in younger women, weighing up the risks and benefit of treatment. If treatment is decided on, LLETZa is recommended.
- **CIN3:** Should always be treated. Women with high-grade cytology (moderate dyskaryosis/dysplasia or worse) and colposcopy are eligible for see-and-treat management. LLETZa recommended [50].

Conclusion

Involvement of vaccination at high-risk carcinogenic types to women younger than 15year and screening by both cytology (Pap. stain) and HPV (detection and genotypes determinant), to detect early infection and women at risk (who have abnormal pap smear or who infected by high-risk HPV genotypes) for follow up, by repeated cytology examination in those women; have important role in reducing cervical cancer.

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