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REVIEW ARTICLE

A Review on Cervical Cancer and Current Preventive Measures

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ABSTRACT:
Despite cervical cancer marking its place at top after breast cancer, the knowledge regarding cervical cancer is limited in women population. The knowledge regarding major cause of cervical cancer, the signs and symptoms, the screening methods are not well known in developing countries when compared to developed countries. Women's are not aware of the various screening methods available for detecting precancerous lesions. Cervical cancer if found at earlier stages can be cured but cervical cancer has no signs and symptoms at the initial stages. Regular screening practice helps in identifying the abnormal changes in the cervix thereby preventing the distant metastasis and invasion of cancer to other organs like bladder. Though, globally Human Papilloma Virus (HPV) vaccines are made available for reducing the burden of cervical cancer in women, the proportion of people vaccinated are less. Knowledge regarding cervical cancer, various screening methods and HPV vaccination needs to be provided to women in a greater extent.

KEYWORDS: Cervical cancer, Knowledge, Signs and symptoms, Screening system, HPV vaccination.

INTRODUCTION:
In India, Cervical cancer is a leading cause of cancer-related deaths among women. It is a malignant neoplasm arising from cells originating in a woman's cervix, which is the lower, narrow part of the uterus[1]. Specific types of high-risk (HR) human papillomavirus (HPV) are prone to cause cervical cancer[2]. Although it one of the most frequent gynecological cancer, it is the only preventable cancer among female genital tract cancers if detected in early stages[2]. It turns out to be a deadly disease once, when it reaches the invasive stages.

On estimation, 570,000 new cases in 2018 representing 6.6% of all female cancers has been reported which marks it at the fourth most frequent cancer in women.[3] Approximately 90% of deaths occurred in low- and middle-income countries which depicts the low awareness and screening among women population[4]. According to a 2014 survey worldwide, Cervical cancer affects about 16/10,000 women per year and kills about 9/100,000 per year globally[4].

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RISK FACTORS:
- Infection with HPV- types 16 and 18 are considered responsible for about 75 -80% of cervical cancer and have been proved as not only the central cause of cervical cancer but also a necessary cause by studies conducted across the globe[5].
- Weakened immune system – For example: A woman's immunity is decreased in HIV patients which puts them at a higher risk ratio for HPV infection[6]. The time required to develop cervical cancer ranges between 5 to 10 years in women with weakened immune system and 15 to 20 years in women with normal immunity[7].
- Chalmydia Infection - Studies have shown a higher risk of cervical cancer in women who have showed evidence of past or current chlamydia infection[1].
- Other risk factors include Tobacco consumption, smoking, poor genital hygiene, multiple sexual partners, early age of sexual intercourse, increasing parity (multiparity), IUDs and Sexually Transmitted Diseases (STDs)[1].
- Stress: In a descriptive study, Lavanyaet.al., has found out that women with cervical cancer had 10% mild stress, 30% moderate stress and 60% severe stress[8].
- Overweight women are more likely to develop adenocarcinoma of the cervix. Long-term use of birth control pills increases the risk of cervical cancer[9].

Human Papilloma Virus:

Human Papilloma Virus (HPVs) infect cells of the skin and mucous membranes and are usually non-enveloped DNA viruses by genotype. It is a collection of virus where some leads to genital warts and some leads to cancer. There are 200 genetically different strains of human papillomavirus known so far among which, more than 30 infect the genital tract (cervix, vagina, vulva, penis, and anus)[10]. HPV Infection was found to be the cause of cutaneous warts (which include plantar warts, common warts and flat warts) on the hand and feet[10].

In 1980s, the link between genital HPV infections and Cervical cancer was displayed by Harold ZurHausen, a German Virologist which has now become well established[11]. In 1996, The World Health Association, in 1996, along with the European Research Organization on Genital Infection and Neoplasia and the National Institutes of Health Consensus Conference on Cervical Cancer, identified HPV as an important risk factor and major cause of cervical cancer[11]. HPVs can also be sorted into high risk and low-risk HPV based on their cervical cancer association[11]. Types 6, 11, 42, 43 and 44 are Low-risk HPV types and Types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 70 are High-risk HPV types[11].

SYMPTOMS OF CERVICAL CANCER:

At early stages, Cervical cancer may be completely asymptomatic. When metastasis occur, cervical cancer may spread within the pelvis, to the lymph nodes and other parts which become part of advanced cervical cancer. Symptoms of Advanced cervical cancer include:

- Persistent pelvic pain
- Unexplained weight loss
- Bleeding between periods
- Unusual vaginal bleeding
- Pain after sexual intercourse
- Leakage of urine or faeces from the vagina
- Leg pain or swelling
- Bone fractures

Stages Of Cervical Cancer:

FIGO system is the most common way to stage cervical cancer. It is a 4-stage system[12].

1. **Stage 0**: It is not included in the FIGO System and is a precancerous condition of the cervix, also known as Carcinoma in situ[12].
2. **Stage 1**: Tumour in the cervix which can be seen in the microscope. Tumour size- not more than 5mm deep and not more than 7mm wide[12].
   Stage 1A1 – The tumour is not more than 3 mm deep and not more than 7 mm wide[12].
   Stage 1A2 – The tumour is more than 3 mm, but not more than 5 mm deep and not more than 7 mm wide[12].
   Stage 1B1 – The tumour is less than 4 cm at its widest part[12].
   Stage 1B2 – The tumour is more than 4 cm at its widest part[12].
3. **Stage 2:** Tumour has grown outside of the cervix and the uterus but hasn't grown into the walls of the pelvis or to the lower part of the vagina[12].
   Stage 2A1 – The tumour is less than 4 cm at its widest part[12].
   Stage 2A2 – The tumour is more than 4 cm at its widest part[12].
4. **Stage 3:** Cancerous cells grows and are present in the lower part of the vagina. It may block the ureters. May or may not affect the nearby lymph nodes[12].
   Stage 3A – Involvement of lower third of vagina[12].
   Stage 3B – Extension to pelvic side[12].
5. **Stage 4:** It affects the bladder or rectum and starts growing out of the pelvis. May or may not affect the lymph nodes. In later stages, it spreads and affect the distant organs including the bones, liver, lungs[11].
   Stage 4A – Extension to adjacent organs[12].
   Stage 4B – Distant metastasis[12].

Progression to cervical cancer can be thus prevented by early detection and treatment of precancerous lesions.

Table1: Stages of cervical cancer [13].

Stages		Invasive Carcinoma	5-year survival rate
0		Abnormal cells in the innermost lining of cervix	100%
I (Limited to cervix)	IA1	Microscopic lesions: Stromal invasion <3mm, Lateral spread <7mm	
	IA2	Microscopic lesions: Stromal invasion <3mm and >5mm, Lateral spread <7mm	
	IB1	Macroscopic lesions: <4cm in dimension	
	IB2	Macroscopic lesions: >4cm in dimension	80% - 93%
II (Extension to Uterus/ Parametrial Vagina	IIA1	Involvement of upper 2/3rd of vagina without parametrial invasion, <4cm in diameter	
	IIA2	Involvement of upper 2/3rd of vagina without parametrial invasion, >4cm in diameter	
	IIB1	Involvement of upper 2/3rd of vagina with parametrial invasion, <4cm in diameter	58% - 65%
III (Extension to pelvic side)	IIIA	Involvement of lower third of vagina	
	IIIB	Extension to pelvic side wall and/or hydronephrosis	32% - 35%
IV (Extension to adjacent organs)	IVA	Extension to adjacent organs Example: Bladder and bowel	
	IVB	Distant metastasis	<16%

Screening for Cervical Cancer:

Screening aims to identify high-grade precancerous cervical lesions which is useful in preventing the development of cervical cancer[14]. It is the principal preventive measure used to reduce cervical cancer burden[14]. Identification of early stage invasive cancer is the main purpose for cervical cancer screening[14]. Bimanual pelvic examination, HPV test, Visual inspection with acetic acid (VIA) and Papanicolaou (Pap) smear test are various screening methods used to detect cervical cancer.

1. Bimanual pelvic exam is where the doctor physically examines the cervix, uterus, vagina, ovaries and other nearby organs for unusual changes. Physical examination of the external and internal female pelvic organs is broadly known as pelvic examination[15]. It is called "bimanual exam" when two hands are used[16]. Two fingers are inserted into the vagina and the other hand is used to gently press from outside for Identifying the cervix[16]. In a bimanual pelvic examination, the position, shape, consistency, regularity, mobility and tenderness of the cervix is determined by the doctor[17].
2. HPV test is done from cells obtained from the cervix and the sample is tested for the strains of HPV. A plastic spatula is used for collecting cells from the cervix[18]. HPV test is used for determining the presence of HPV[18]. If negative/ normal result is obtained, screening after 5 years is recommended depending on their age[18]. In case of positive results (Presence of high risk HPV- type 16 and 18), colposcopy or cervical biopsy is recommended to monitor and diagnose the condition[18]. HPV-DNA test has a sensitivity of 66- 95% for detecting precancerous lesions[19].
3. VIA Test is carried out with dilute vinegar[20]. *Vinegar* typically contains 5–20% acetic acid by volume. When vinegar is applied to the cervix, the abnormal cells in the cervix turns white which is visualised with naked eye[20]. Absence of Aceto-white lesions marks a negative/ normal result and further screening after 5 years is recommended depending on their age[20]. In case of positive results, colposcopy or cervical biopsy is recommended to monitor and diagnose the condition[20]. Attractive features of VIA include low cost, simple administration, immediate result and high specificity and sensitivity[21].
4. VILI test is carried out after VIA test with Lugol's iodine, which reacts with glycogen resulting in black or brown colouration[20]. In case of precancerous cells, the glycogen content is less or no glycogen is present in the cells, thus resulting in yellow coloration after Lugol's application[20]. It magnifies the lesion 4x along with illumination which supports the accuracy of test results in assessing the early stages of cervical cancer[22].
5. Pap test is an important screening safeguard method against cervical cancer, which involves examination of the cells from the cervix during the vaginal speculum screening[23]. Pap test is an advantageous than HPV test as HPV test only detects the presence of High Risk HPV types whereas Pap test detects abnormal growth of cervical cells[23].

Studies reveal that in developed countries, Pap smear test is dramatically reducing the number of cases of cervical cancer. The steady decline in the prevalence, incidence and mortality of cervical cancer is also largely attributed to widespread pap test screening through the world. Unfortunately, more than 95% of women in India have never been screened, despite the availability of various screening methods for prevention of cervical cancer. As per ACS guidelines, women at the age of 21 should start screening for cervical cancer. Cytology screening should be done every 3 years and co-testing (HPV testing combined with cytology) should be done every 5 years in women 30 to 65 years. Cervical cancer screening can be stopped at the age of 65 when they have adequate negative prior screening results[24].

Barriers to Cervical Cancer Screening:

In countries like India, the barriers to cervical cancer screening uptake by women is identified to be:

- In-adequacy or inexistence of a National screening system, poorly developed health services. In a population based survey, Gakidouet.al., found out coverage of cervical cancer screening system among developing countries were very low (1%) when compared among cervical cancer screening system among developed countries (75% - 80%)[25].
- Low access of the impoverished population to health care.
- Lack of technical and laboratory expertise.
- Low level of awareness and knowledge of risk factors, early signs and symptoms of disease. In a study conducted in Sangali district of Maharashtra, India, only 16.37% of women were aware about the signs and symptoms of cervix, breast and oral cancer[26].
- Stigma and misconception about female cancer and gynaecological diseases.
- Self-neglecting attitude.
- Poor infrastructure and socioeconomic limitations.
- Lack of communication between healthcare workers and community people regarding availability and benefits of the screening[27].

Cervical Cancer Vaccines:

Vaccines has been one of the most effective public health intervention for combatting infectious diseases. HPV vaccination was introduced in 2006, targeting

females in the age of 9-14 years with an objective to prevent several type of HPV that cause precancerous lesions and cancer[14]. HPV Vaccination tends to be low in developing countries when compared to developed countries.

Until December 2014, the USFDA (US Food and Drug Administration) has approved two prophylactic vaccines namely Quadrivalent "Gardasil® (MSD Merck and Co. Inc.,)" and bivalenst "Cervarix® (Glaxo Smith Kline Biologicals)" which provided a huge opportunity for preventing cervical cancer[04]. Cervarix (Bivalent vaccine) is effective in preventing infection against HPV types 16 and 18 whereas Gardasil (Quadrivalent vaccine) was found effective against HPV types 6, 11, 16 and 18. Low risk HPV types like type 6 and 11 do not cause cancer but causes warts on or around the genitals, anus, mouth or throat. Based on the Clinical trial results, the FDA approved the 9-valent vaccine Gardasil 9 to prevent infections against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 in 2015[28,29].

Garadasil® and Cervarix® are both a mixture of L1 proteins of HPV serotypes 16 and 18 with aluminium and AS04 as adjuvant respectively. Clinical trials with Garadasil was carried out at three different doses at 0, 2 and 6 months which showed 100% efficacy for follow up of 1.9 years and Clinical trials with Cervarix was also carried out at three different doses at 0, 1 and 6 months which showed 90% efficacy for follow up for 15 months. Cervarix was identified to provide prevention against cervical cancer and Garadasil provides prevention against both cervical cancer and genital warts[30].

Gardasil 9 vaccine is indicated in females of age 9-45 years for prevention of cancers mostly cervical, vulvar, vaginal and anal cancer and precancerous or dysplastic lesions caused by Human Papillomavirus (HPV). It is also indicated for preventing genital warts caused by HPV. Males of age 9-45 years are indicated with Gardasil 9 vaccine for prevention of anal cancer, precancerous or dysplastic lesions and genital warts caused by HPV[28].

Dosage and Administration of Gardasil 9:

It should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

1. Age 9- 14 years: It can be administered using a 2-dose or 3-dose schedule. For the 2-dose schedule, the second dose should be administered 6-12 months after the first dose. If the second dose is administered less than 5 months after the first dose, a third dose should be given at least 4 months after the second dose. For the 3-dose schedule, it should be administered at 0, 2 and 6 months[28].
2. Age 15- 45 years: It is administered using a 3-dose schedule at 0, 2 and 6 months[28].

HPV Vaccine is not yet available within free public health services, however, it can be obtained from private health institutions upon request[15]. While the vaccine has been shown to be highly effective, high vaccine uptake is essential for successful HPV vaccine program implementation[31]. High cost of vaccine, lack of knowledge about HPV vaccine, negative attitude towards the HPV vaccine and fear of side effects contribute to reduced uptake of HPV vaccine. Unsubstantiated rumours about side effects or adverse outcomes that are not casually related to the vaccine but may negatively impact public trust and leading to suspension of HPV immunization program altogether.

CONCLUSION:

Cervical cancer tops the major deadly cancer in list after Breast cancer in women. Cervical cancer can be prevented if found in early stages but in early stages cervical cancer is asymptomatic. It is caused mainly by HPV infection. The symptoms develop once the cancer invades, therefore Cervical cancer can be diagnosed at early stages by screening methods. Preventing and treating cervical cancer and reducing the burden are possible by targeting resources to the areas with high prevalence[32]. Women at the age of 25-50 are recommended to perform regular screening test. Cervical Cancer can be treated and prevented if regular screening is done in women. Another method to prevent Cervical cancer is by vaccination. Globally, there are 3 HPV vaccine available for Cervical cancer prevention which reduces the burden in women from developing malignant cervical cancer. Pap tests are still recommended for all women– even girls who have received the human papilloma virus vaccine[33]. As the line says, Prevention is better than Cure, Prevention of Cervical cancer is better than developing malignant cervical cancer. Extensive health education to the public is needed to improve their knowledge with an emphasis on the fact that both vaccination and screening are the new standards for prevention of cervical cancer[34].

ABBREVIATIONS:

HPV-Human Papillomavirus, IUD- Intra Uterine Device, FIGO- International Federation of Gynecology and Obstetrics, VIA- Visual Inspection with Acetic acid, VILI- Visual Inspection with Lugol's Iodine, ACS- American Cancer Society.

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