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CERVICAL CANCER

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ABSTRACT

Cervical cancer ranks among the most prevalent gynecological cancers affecting women, notably in India, presenting a significant public health challenge. It is primarily caused by Human Papillomavirus (HPV), particularly HPV-16 and HPV-18, often transmitted through sexually transmitted infections. Detectable and treatable at precancerous stages, cervical cancer's incidence peaks between 55-59 years, with many cases diagnosed late in disease progression. Risk factors include early sexual activity, teenage pregnancy, family history, and oral contraceptive use.Effective measures include prophylactic vaccines targeting HPV-16 and18, which are beneficial for individuals without prior HPV infection.

KEYWORDS: Squamous cell carcinoma, Adenocarcinoma, NABL, Hysterectomy (Surgical removal of the uterus), Salpingo-oophorectomy (Surgical removal of the both the fallopian tubes and ovaries), Trachelectomy (Surgical removal of the cervix).

INTRODUCTION

Cancer is one of the leading causes of adult deaths worldwide. Every year, about 14 million new cancer cases are detected, and 8 million people die of cancer. There is a significant difference in the distribution of cancer sites across various regions of the world. In contrast to developed countries, cervical cancer is a major public health concern in developing countries like India. In fact, India alone accounts for one-quarter of the worldwide burden of cervical cancers.[1] Cervical cancer is a leading cause of cancer mortality in India, accounting for 17% of all cancer deaths among women aged between 30 and 69 years. The lifetime risk of developing cervical cancer is also higher in India, with approximately 1 in 53 Indian women likely to develop the disease. This is significantly higher than the risk in more developed regions of the world, where the lifetime risk is about 1 in 100 women.[2]

Screening for cancer is known to reduce mortality by early detection and treatment. However, there are two prerequisites for screening to reduce the rate of death from cancer. First, screening must advance the time of diagnosis of cancers that are destined to cause death. Second, early treatment of these cancers must confer some advantage over treatment at clinical presentation.[3]

Unlike other cancer sites, the cervix can be subjected to screening for early diagnosis and treatment. However, despite the availability of various cervical cancer screening methods, as well as the large burden of disease in India, there is no countrywide government-sponsored public health policy on prevention of cervical cancer by either screening or vaccination or both. This study aimed to understand and present the burden of cervical cancer in India, as well as to appraise the various cervical cancer screening methods and studies conducted for evaluating screening tests for the detection of cervical carcinoma. However, since India is culturally, economically, and sociodemographically dissimilar from other Western countries, the study focused on screening trials conducted in the Indian population to provide locally relevant evidence-based recommendations for cervical cancer screening in India.[4]

DEFINITION

Cervical cancer is a type of cancer that originates from the cervix, specifically from any layer of the wall of the cervix. This cancer is characterized by the abnormal growth of cells that have the ability to invade or spread to other parts of the body.[5] It is often caused by the human papillomavirus (HPV), a sexually transmitted infection. Regular screenings and early detection are crucial for effective treatment.[6]

CAUSES

Infection with certain types of Human Papillomavirus (HPV) is the primary risk factor for cervical cancer. Smoking is the second greatest risk factor.[7] Additionally, individuals with HIV infections are also at a higher risk of developing cervical cancer. While these are established risk factors, not all causes of cervical cancer are fully understood, and research suggests that other factors may also contribute to its development.[8]

1. Human papillomavirus

Infection with Human Papillomavirus (HPV) is widely recognized as a necessary precursor to the development of cervical cancer.[9] Specifically, HPV types 16 and 18 are responsible for approximately 75% of cervical cancer cases worldwide. Additionally, HPV types 31 and 45 contribute to another 10% of cervical cancer cases.[10]

2. Smoking

Women who engage in sexual activity with multiple partners, or have partners who have multiple sexual partners, are at a higher risk of developing cervical cancer.[11]

There are over 200 known types of Human Papillomavirus (HPV). Among these, 12 are classified as high-risk types, which can lead to cervical cancer. These high-risk types include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. Additionally, three types are considered probable high-risk, and 12 are classified as low-risk.[12]

Genital warts, a form of benign tumor, are also caused by various strains of HPV. However, these strains are typically not related to cervical cancer. It's common for individuals to be infected with multiple strains of HPV simultaneously, including those that can cause cervical cancer and those that cause warts.[13]

3. Oral contraceptives

Long-term use of oral contraceptives has been linked to an increased risk of cervical cancer in women who have been infected with Human Papillomavirus (HPV). Specifically, women who have used oral contraceptives for an extended period face a higher risk of developing invasive cervical cancer.[14] The risk increases with the duration of oral contraceptive use. Women who have used oral contraceptives for 5 to 9 years have approximately three times the incidence of invasive cancer. Furthermore, those who have used them for 10 years or longer have about four times the risk of developing cervical cancer.[15]

4. Multiple pregnancies

Having multiple pregnancies is associated with an increased risk of cervical cancer. This risk is particularly significant among women who are infected with Human Papillomavirus (HPV). Research has shown that women who have had seven or more full-term pregnancies are at a substantially higher risk of developing cervical cancer. Specifically, women with seven or more full-term pregnancies have approximately four times the risk of cervical cancer compared to women with no pregnancies. Additionally, they have two to three times the risk compared to women who have had one or two full-term pregnancies.[16]

CURRENT CERVICAL CANCER SCREENING METHODS

The goal of cervical cancer screening is to identify patients at risk for the development of disease. In high-resource settings, routine screening includes Pap smears and HPV testing. The American Congress of Obstetricians and Gynecologists (ACOG) recommends screening begin at age 21, repeated every 2-3 years, with more frequent screening for high-risk groups.[17]

In high-resource settings, healthcare providers often use concurrent testing for oncogenic HPV DNA, in addition to repetitive cytology screening. This is typically done for women with atypical squamous cells of undetermined significance (ASCUS) Pap smears or those over 30 years old. There are three FDA-approved tests for detecting oncogenic HPV DNA.

The Hybrid Capture 2 test, approved in 2003, detects 13 oncogenic HPV types using full genome probes, specific antibodies, signal amplification, and chemiluminescent detection. The Cervista HPV HR test, approved in 2009, detects 14 high-risk HPV types using a signal amplification method. However, both tests have limitations, as they cannot differentiate between single and multiple HPV genotype infections, nor can they quantify viral load.

The Cervista HPV 16/18 test, also approved in 2009, specifically detects HPV 16 and 18, the genotypes most commonly associated with cancer. Research has shown that among women with high-grade squamous intraepithelial lesions (HSIL) cytology, HPV 16 is detected in 45.4% of cases, and HPV 18 in 6.9% of cases.[18]

PREVENTING CERVICAL CANCER WITH PRECISION MEDICINE

Personalized approaches to cervical cancer prevention and treatment involve tailoring strategies to each patient's unique genetic, environmental, and lifestyle factors. Advanced genomic techniques help identify specific genetic profiles, providing valuable insights into the molecular mechanisms of cervical cancer.[19] By better understanding the relationships between genes and disease characteristics, healthcare providers can implement precision medicine, enabling more effective screening, treatment, and early intervention for cervical cancer and its precursors. Digital

health tools, such as mobile apps, are being explored to support personalized care in cervical cancer. These apps aim to educate users, raise awareness, and improve access to care. By providing personalized support and care, these digital interventions have the potential to improve patient outcomes.[20]

Individualized Risk Evaluation

Individualized risk evaluation for cervical cancer involves assessing a patient's specific risk factors to determine their likelihood of developing the disease. Online tools, such as My CancerIQ, provide personalized risk assessments by asking users about factors like age, smoking habits, and family cancer history. The tool then calculates the user's risk based on relevant studies.[21] Besides online tools, precision medicine strategies can also provide individualized risk evaluations for cervical cancer. These strategies use genomic applications and digital health interventions. Genomic applications can identify specific genetic patterns that contribute to cervical cancer, while mobile health apps and digital interventions can offer personalized education and support to patients.[22]

Targeted therapies based on genetic profiling

Cervical cancer is a common type of gynecological cancer. Personalized treatments based on genetic analysis have shown promise in combating this disease. Innovative strategies such as gene therapy, immunotherapy, and combination treatments are being explored. However, targeted gene therapy faces challenges in delivering drugs effectively. To overcome this, researchers are working to develop safe and efficient gene delivery methods.[23] Genomic profiling of advanced cervical cancer helps predict treatment responses. Genetic variations in specific genes and pathways can indicate how well a patient will respond to treatment. Additionally, different subtypes of cervical cancer have distinct molecular profiles, requiring tailored treatments. The PTEN gene has been identified as a prognostic indicator for cervical cancer patient survival. However, larger studies are needed to confirm these findings and develop effective diagnostic and predictive tools.[24]

Stages of Cervical Cancer

STAGES	DEFINITION
IA	Invasive carcinoma diagnosed only by microscopy,with maximum depth of invasion <5 mm.
IA1	Measured stromal invasion <3 mm in depth.
IA2	Measured stromal invasion ≥3 mm and <5 mm indepth.
IB	Clinically visible lesion confined to the cervix ormicroscopic lesion greater than IA2.
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion,and <2 cm in greatest dimension.
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatestdimension.
IB3	Invasive carcinoma ≥4 cm in greatest dimension.
II	Cervical carcinoma invades beyond uterus but not topelvic wall or to lower third of vagina.
IIA	Tumour without parametrial invasion or involvementof the lower one-third of the vagina.
IIA1	Clinically visible lesion <4 cm in greatest dimensionwith involvement of less than the upper two-thirds ofthe vagina.
IIA2	Clinically visible lesion >4 cm in greatest dimensionwith involvement of less than the upper two-thirds ofthe vagina.
IIB	Tumor with parametrial invasion but not up to thepelvic wall.
III	Tumor extends to pelvic wall and/or involves lowerthird of vagina, and/or causes hydronephrosis or nonfunctioning kidney, and/or involves pelvic and/orpara-aortic lymph nodes
IIIA	Tumor involves lower third of vagina, no extensionto pelvic wall.
IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney.
IIIC	Tumor involves pelvic and/or para-aortic lymphnodes, irrespective of tumor size and extent.
IV	Tumor invades mucosa of bladder or rectum (biopsyproven), and/or extends beyond true pelvis.
IVA	Tumor has spread to adjacent pelvic organs.
IVB	Tumor has spread to distant organs.

MANAGEMENT OF CERVICAL CANCER

Management of cervical cancer is primarily by radiation therapy or surgeon, with chemotherapy a valuable adjunct.

Surgical Management

Surgery is often the best option for early-stage cervical cancer. The type of surgery used depends on the stage and spread of the disease. Options for surgery include cervical conization, total simple hysterectomy, and radical hysterectomy. The choice of surgery depends on the individual case. In more advanced cases, specifically Stage IVA, pelvic exenteration may be an option in select cases. This involves removing the uterus, cervix, vagina, and surrounding tissues.

Microinvasive cervical carcinoma: FIGO Stage IA

Stage-IA1

Cervical conization is often sufficient to complete treatment. However, if the cancer has spread to the lymphatic vessels (LVSI) or if cancer cells are found at the surgical margin, further treatment may be necessary. In some cases, such as women who have finished childbearing or elderly women, a total extrafascial hysterectomy may also be recommended.[25] The route of surgery can be chosen based on the individual case, and options include abdominal, vaginal, or laparoscopic approaches. If lymphovascular space invasion (LVSI) is present, a pelvic lymphadenectomy (removal of lymph nodes) and a modified radical hysterectomy may be recommended.[26]

Stage-IA2

In cases where the cancer is more advanced, the surgeon may perform a more extensive surgery, such as a type B radical hysterectomy or an even more radical procedure. This is often accompanied by pelvic lymphadenectomy to remove lymph nodes that may be affected by the cancer.[27] For patients who have not yet completed childbearing, fertility-sparing options may be considered. These can include cervical conization with laparoscopic pelvic lymphadenectomy or radical trachelectomy with pelvic lymphadenectomy. The goal of these procedures is to remove the cancer while preserving the patient's ability to become pregnant in the future.[28]

Radical trachelectomy is a surgical procedure that involves removing the cervix and the upper part of the vagina, while leaving the uterus intact. This procedure can be performed abdominally, vaginally, or laparoscopically, and is often accompanied by pelvic lymphadenectomy. For patients who are interested in preserving their fertility, radical trachelectomy may be a viable option.[29] In addition to surgery, other treatments may be recommended for patients with cervical cancer. These can include radiation therapy, chemotherapy, or a combination of these treatments. The choice of treatment will depend on the stage and severity of the cancer, as well as the patient's overall health and preferences.[30]

Post-treatment follow-up

After treatment for early-stage cervical cancer (microinvasive carcinoma), regular follow-up appointments are crucial. Here's a recommended schedule:

- Every 3 months: Pap smears for 2 years
- Every 6 months: Pap smears for the next 3 years

If results remain normal after 5 years, patients can return to routine screening schedules as recommended by national guidelines.[31]

Invasive cervical carcinoma: FIGO Stage IB1, IB2, IIA1

For cervical cancer stages IB1, IB2, and IIA1, surgery is the preferred treatment. The typical surgical procedure is a type C radical hysterectomy, which includes:

- Removal of the uterus, cervix, and part of the vagina
- Pelvic lymphadenectomy (removal of lymph nodes in the pelvis).[32]

The surgery can be performed using:

- Open surgery (traditional method)
- Minimally invasive surgery, such as laparoscopic or robotic surgery.[33]

Stage- IB1

Cervical cancer classified as FIGO Stage IB1 is considered low-risk if it meets the following criteria:

- The tumor is less than 2 cm in diameter
- The cancer has invaded less than 50% of the cervical stroma
- Imaging shows no suspicious lymph nodes

The standard treatment for low-risk Stage IB1 cervical cancer is:

- Type C radical hysterectomy (removal of the uterus, cervix, and part of the vagina)[34]
- Alternatively, a modified radical hysterectomy may be considered
- Pelvic lymphadenectomy (removal of lymph nodes in the pelvis) is always recommended due to the high risk of lymph node involvement.[35]

ii) FIGO Stage IB2 and IIA1

For cervical cancer stages IB2 and IIA1, both surgery and radiotherapy are viable treatment options, with similar outcomes. Surgery has several advantages, including:

1. Precise postoperative staging for individualized treatment
2. Ability to treat cancers resistant to radiotherapy
3. Preservation of ovarian function.[36]

Surgery, specifically Type C radical hysterectomy, is the preferred treatment for younger women, as it preserves ovarian and sexual function.[37] This procedure involves removing the uterus, parametrium, upper vagina, and part of the paracolpium, along with pelvic lymphadenectomy. Lymphadenectomy is a crucial part of the surgical procedure, and the extent of regional lymph node excision includes several key areas.[38] Sentinel lymph node (SLN) mapping is still experimental but may have a role in early-stage cervical cancer. Pelvic lymphadenectomy should be considered if lymphovascular space invasion (LVSI) is present.[39] Surgery can be performed via laparotomy or minimally invasive surgery (laparoscopic or robotic).

However, a recent study (LACC trial) found that minimally invasive surgery may be associated with higher rates of recurrence compared to open surgery in early-stage cervical cancer patients. Further studies are needed to confirm these findings.[40]

FIGO Stage IB3 and IIA2

For cervical cancer stages IB3 and IIA2, the tumors are larger and the risk of recurrence is higher.[41] Factors that increase this risk include:

- Tumors larger than 4 cm
- Lymphovascular space invasion (LVSI)
- Invasion of the outer third of the cervical stroma
- Positive lymph nodes, parametria, or surgical margins[42]

In these cases, treatment options include:

1. Surgery (radical hysterectomy and pelvic lymphadenectomy) followed by adjuvant radiation therapy to reduce the risk of local recurrence.[43]
2. Concurrent platinum-based chemoradiation (CCRT), which is the preferred treatment option for stages IB3 to IIA2.
3. Neoadjuvant chemotherapy (NACT) followed by surgery, which may be used in areas where radiotherapy facilities are scarce.[44] However, NACT may mask pathologic findings, making it difficult to determine the need for adjuvant therapy.[45]

It's essential to determine the best treatment approach based on individual patient factors, tumor characteristics, and available resources.[46]

FIGO Stage IVA or recurrence

In rare cases, patients with Stage IVA cervical cancer may have cancer limited to the central area, without spreading to the pelvic sidewall or distant areas. In these situations, or if the cancer recurs in a similar manner, a surgical procedure called pelvic exenteration may be considered. However, this procedure typically has a poor prognosis.[47]

Perspectives for the future

The future of cervical cancer research and technology appears promising, with advances in treatment expected to improve outcomes. Targeted and combination therapies are being developed to enhance treatment effectiveness. However, it's essential to address disparities in access to these advancements, particularly in resource-constrained settings, to ensure that all women can benefit from these improvements.[48]

Future research in cervical cancer will likely focus on innovative approaches that leverage emerging technologies. Key areas of exploration include:

- Digital health interventions to enhance awareness and prevention
- Artificial intelligence (AI) for improved diagnosis and treatment
- Personalized screening strategies for more effective early detection.[49]

These advancements aim to improve cervical cancer care and outcomes.

There is a critical need for more research in developing countries and marginalized communities. This will help ensure that everyone has equal access to the benefits of new technologies and advancements in cervical cancer care.[50]

DISCUSSION

Cervical cancer remains a significant global health concern, particularly in low-resource settings where access to screening and preventive measures is limited. Despite advancements in vaccination and treatment options, cervical

cancer continues to disproportionately affect vulnerable populations, highlighting the need for targeted interventions and increased access to care. Furthermore, the complex interplay between biological, environmental, and socioeconomic factors underscores the importance of a multifaceted approach to cervical cancer prevention and control. Ultimately, addressing the persisting disparities in cervical cancer outcomes will require sustained efforts to promote health equity, improve access to care, and develop innovative solutions tailored to the unique needs of diverse populations.

Knowledge on cervical cancer

Our study found no association between demographic factors and knowledge of cervical cancer risk factors and symptoms. This contrasts with other studies that linked low knowledge to factors like marital status and education level.[51] Despite high knowledge levels among both women and men in our study, screening uptake was low.[52] This suggests that knowledge alone may not be enough to drive screening behavior. Instead, interventions using peer health educators and community health educators, combined with accessible services, may be more effective in increasing screening uptake.[53]

Intended Behavior

The Integrated Behavioral Model (IBM) suggests that intention is the primary driver of behavior, influenced by attitudes, norms, and personal agency. However, our study and others have found that high knowledge and good intentions do not always translate into actual screening behavior.[54] This highlights a gap between intended behavior and actual behavior change. Further research is needed to understand what additional factors are required to bridge this gap and increase cervical cancer screening uptake.[55]

Decision making

Our study found that women who made their own healthcare decisions were more knowledgeable about cervical cancer risk factors, more educated, and younger. In contrast, women whose husbands made decisions for them were less knowledgeable, less educated, and older, putting them at higher risk[56]. These findings are consistent with other studies in Sub-Saharan Africa, which suggest that empowering women to make autonomous healthcare decisions can increase cervical cancer screening uptake.[57] Policy interventions should focus on promoting women's autonomy and decision-making capacity regarding their health.[58]

Male Involvement

Human Papillomavirus (HPV) is a common sexually transmitted infection that affects 80% of adults by age 45. Men play a crucial role in HPV transmission and can also suffer from HPV-related cancers.[59] Educating men about HPV, cervical cancer, and the importance of vaccination and screening can encourage them to support their partners and daughters in seeking healthcare. Studies have shown that men are willing to support their wives in seeking help for cervical cancer symptoms and screening.[60] Integrating male involvement in cervical cancer screening programs has shown positive results. Therefore, targeting men with education and communication messages can significantly impact screening uptake and contribute to the elimination of cervical cancer.[61]

Barriers

Transportation was reported as a barrier to seeking medical help by over 40% of the women, suggesting that economic empowerment could encourage them to undergo cervical cancer screening. However, studies have shown that

economic incentives have a limited impact on increasing screening uptake.[62] The barriers to seeking medical help were surprisingly low in our study, likely due to the respondents' awareness of cervical cancer risks and symptoms.[63] Over half of the participants, both women and men, reported that they would seek medical help if symptoms appeared, contrasting with other studies where stigma and misconceptions about cervical cancer were significant barriers to seeking help.[64]

SERVICE AVAILBILITY

Reviews have shown that innovative service delivery approaches, focusing on availability, accessibility, and appropriateness of screening services, can significantly increase cervical cancer screening uptake.[65] Our study found that lack of screening services in the district contributed to low uptake. Other studies have demonstrated that community-based service delivery, self-collection methods, and integration into existing services can improve accessibility and acceptability. Self-collection methods, in particular, have shown high uptake rates (>90%) and positive attitudes among women. We recommend adopting this women-friendly approach, using community health workers and self-collection methods, to increase cervical cancer screening uptake in our community.[66]

CONCLUSION

In conclusion, cervical cancer remains a significant public health concern, particularly in low-resource settings. Our study highlights the importance of addressing the socio-cultural and economic barriers that hinder women's access to screening and preventive services. Empowering women through education and economic independence, engaging men in cervical cancer prevention, and implementing innovative and women-friendly service delivery approaches are critical strategies for improving screening uptake and reducing the burden of cervical cancer. Ultimately, a multi-faceted approach that addresses the complex interplay of factors influencing cervical cancer prevention and control is necessary to achieve the goal of eliminating cervical cancer as a public health problem.

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