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Review Article

Cervical cancer

Unravelling The Complexities of Cervical Cancer: A Comprehensive Exploration

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Abstract: Cervical cancer (CC) ranks as the second most common cause of cancer-related deaths among women aged 20-39, resulting in ten premature deaths weekly. CC affects women worldwide as the most common form of genital cancer, with approximately 500,000 new cases diagnosed annually. Besides the risk of death, CC can lead to increased morbidity, causing symptoms like pain, haemorrhage, and kidney failure. These complications pose significant challenges to treatment, particularly in areas with limited healthcare access. Immune dysregulation and chronic inflammation further contribute to CC pathogenesis, creating a pro-carcinogenic microenvironment through immune cell recruitment, cytokine release, and inflammatory responses triggered by persistent HPV infection. Moreover, understanding the socio-economic determinants influencing the prevalence of CC and promoting awareness can contribute to effective public health interventions. Research endeavours in these domains are vital to reduce the burden of CC, enhance early detection, and ultimately save lives. This review covers recent research on CC global epidemiology, intricate pathogenesis insights, protein-based HPV vaccines, and diverse treatment modalities, including recurrent cases. Molecular markers indicating prognosis and the role of artificial intelligence. The review will briefly highlight preventive strategies, offering a comprehensive overview of crucial research areas in CC.

keywords: Cervical cancer, Epidemiology, Human papillomavirus, Treatments, Vaccines

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1. INTRODUCTION

In 2020, approximately 10 million people worldwide lost their lives to cancer, making it a significant contributor to global mortality. This trend is expected to escalate significantly in low and middle-income countries (LMICs), which are currently facing substantial challenges in addressing the burden of cancer[1]. Among women globally, CC ranks fourth in prevalence, trailing behind colorectal, breast, and lung cancer, with around 580,000 new cases and 342,000 deaths reported annually. CC stands as the leading cause of cancer-related deaths in 36 countries, including regions like sub-Saharan Africa, Latin America, and India[3]. The primary cause of CC remains high-risk Human Papillomavirus (HPV) infection, a connection established over three decades ago by Harald zur Hausen's identification of HPV type 16 in CC tissue[4]. This association is particularly prominent among women under 26 years old. HIV-positive individuals experience a six-fold increase in CC incidence compared to the general population, likely due to higher HIV prevalence and increased antiretroviral therapy usage among HIV-positive women. CC ranks as the second most common cause of cancer-related deaths among women aged 21-40, resulting in ten premature deaths weekly[5]. Late-stage diagnoses and the rise of cervical adenocarcinoma, often missed by cytology, insist on the urgency of enhancing HPV vaccination rates and possibly revising pap smear and HPV co-testing protocols[6]. Despite a general decrease in CC occurrence and mortality rates, significant disparities persist in vaccination, screening, treatment, and overall mortality, especially among marginalized populations such as rural or isolated women, racial and ethnic minorities, and those facing socioeconomic barriers[7]. Early intervention through vaccination and screening is crucial in combating CC. Unlike Western developed countries, where cancer rates have declined due to advancements in screening, treatment, and lifestyle changes like smoking cessation, low-income and developing nations are witnessing a rise in cancer incidence and mortality[8]. Oncogenic viruses, including HPV, play multiple roles in carcinogenesis. HPV, a sexually transmitted double-stranded DNA virus with high-risk strains classified within the Papovaviridae family, has over forty variations identified in the genital tract, categorized into high-risk and low-risk based on their carcinogenic potential[9]. Despite advancements in understanding HPV's natural history, oncogenic potential, and preventive strategies, HPV infection rates persist, particularly in developing nations with elevated CC incidences. A deeper understanding of HPV's status and its role in cancer progression is crucial for improving patient care and preventing CC advancement in HPV-infected women. Quick hysterectomy or trachelectomy, pelvic lymphadenectomy, simultaneous radiotherapy, and chemotherapy are all feasible approaches for locally invasive or early CC (ICC)[10]. According to the International Federation of Gynecology and Obstetrics (FIGO) staging system, prognosis and treatment choices are closely tied to the stage of the disease[11]. Minimally invasive surgery (MIS) offers several benefits in treating various gynecological malignancies, including reduced postoperative complications, faster recovery, and shorter hospital stays[12].

1.1 Epidemiology of CC

CC affects women worldwide as the most common form of genital cancer, with approximately 500,000 new cases diagnosed annually (GLOBOCAN, 2012)[13]. Mortality rates from CC vary significantly across different regions. The disease typically affects women aged 30 to 40, a crucial period when they are often responsible for their families' financial and familial stability. Besides the risk of death, CC can lead to increased morbidity, causing symptoms like pain, haemorrhage, and kidney failure[14]. These complications pose significant challenges to treatment, particularly in areas with limited healthcare access. Linking cancer screening programs with cancer registries is vital for evaluating the effectiveness of vaccines and understanding the epidemiology of precancerous lesions and cancers over decades, as seen in practices in Nordic cancer registries. Over the past two decades, CC has become more prevalent among women, with India reporting its highest incidence among those aged 55 to 59. Recent data from the National Cancer Registry Program (NCRP) show that breast and CCs are the most common types among women[15]. Adenocarcinoma is more common in the endocervix, while squamous cell carcinoma predominates in the ectocervix[16]. Population-based cancer registries offer a precise overview of the issue, while hospital-based registries shed light on the relationship between disease incidence and healthcare-seeking behavior. The incidence of HPV infection, linked to cervical and penile cancers, is a significant factor, especially in areas with a high prevalence of human immunodeficiency virus.

1.2 Pathogenesis of CC

CC primarily arises from chronic infection with high-risk variants of the HPV, resulting from a complex interplay of various factors. HPV invades cervical cells through sexual contact, integrating its genetic material into host DNA upon successful infection. Viral oncoproteins E6 and E7, produced by HPV, play a crucial role in CC development by promoting uncontrolled cell division and inhibiting programmed cell death, disrupting cellular proliferation and apoptosis regulation[17,18]. These oncoproteins also interfere with tumor suppressor proteins like pRb and p53, which are critical for preventing abnormal cell growth and maintaining genomic integrity. Immune dysregulation and chronic inflammation further contribute to CC pathogenesis, creating a pro-carcinogenic microenvironment through immune cell recruitment, cytokine release, and inflammatory responses triggered by persistent HPV infection[19]. HPV also undermines the host immune response against infected cells through immune evasion mechanisms, including antigen presentation inhibition and major histocompatibility complex (MHC) downregulation[20]. Epigenetic modifications such as DNA methylation, histone modifications, and altered noncoding RNA expression play a role in CC development by controlling gene expression patterns related to apoptosis, DNA repair, and cell cycle regulation. These modifications occur in host and viral DNA, contributing to dysregulated cellular pathways and malignant phenotype emergence. Overall, CC has a multifaceted pathogenesis involving viral factors, host immune responses, and epigenetic modifications, collectively driving the malignant transformation of cervical cells. Understanding these mechanisms is crucial for developing effective prevention strategies and targeted therapies for CC. The Pap smear test, vital for cervical cancer (CC) screening, aims to detect abnormalities in cervical cells, including cervical intraepithelial neoplasia (CIN) stages 1, 2, and 3. Through this non-invasive procedure, a healthcare provider collects cells from the cervix to examine for any precancerous or cancerous changes. CIN 1 indicates mild dysplasia, while CIN 2 and CIN 3 signify moderate to severe dysplasia, respectively, with increasing potential for progression to invasive cancer if

left untreated. Early detection through Pap smears enables timely interventions, such as further testing or treatments, enhancing the chances of successful management and prevention of cervical cancer.

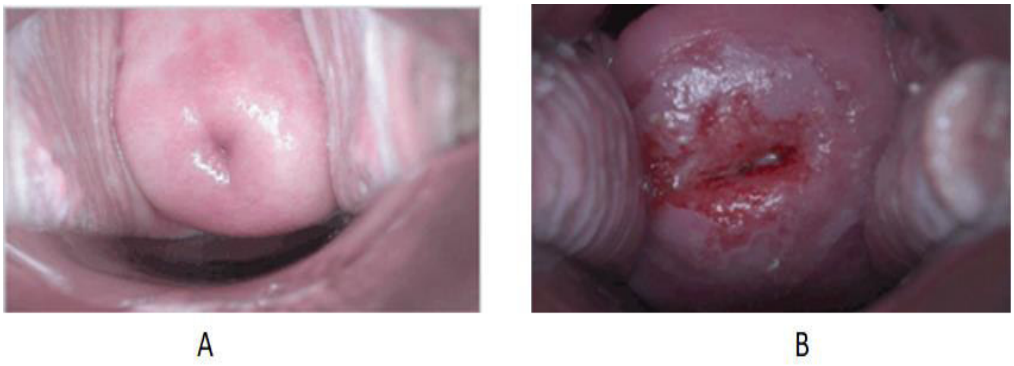

Fig 1: The cervix showed no abnormalities upon visual inspection with acetic acid (A), while a positive result indicating Cervical Intraepithelial Neoplasia Grade 1 (CIN-1) was observed during visual inspection with acetic acid. (B)

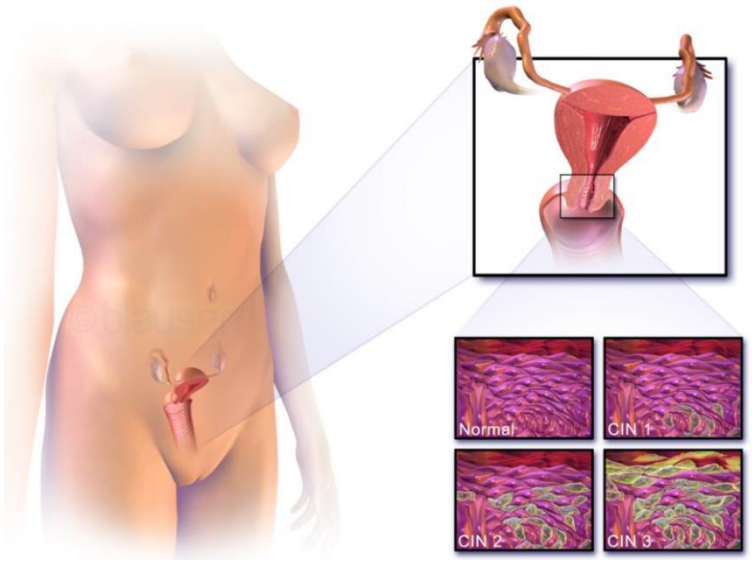

Fig 2: Cervical cancer site and illustration of typical versus irregular cell characteristics.

1.3 HPV vaccine

Emerging as a potentially effective method for combating CC, HPV antigen-specific immunotherapy targets metastases while minimizing damage to healthy cells. Patients with precancerous lesions associated with gynaecological malignancies have shown significant clinical responses when synthetic long peptide vaccines derived from HPV16 E6 and E7 antigens were administered[22]. However, the complexity of Human leukocyte antigen serotype (HLA) molecules and genetic diversity among populations pose challenges in establishing a universally efficacious immunogenic epitope. Researchers are exploring the potential application of lengthy peptides containing numerous overlapping HPV E6 and E7 epitopes to address this challenge. This approach broadens the immune response and improves vaccine effectiveness across various genetic compositions. Additionally, incorporating adjuvant interventions may enhance the immunogenicity of these vaccines, which currently exhibit suboptimal efficacy. Therapeutic vaccination using long peptides of HPV E6 and E7 shows promise in managing site-specific infections and newly infected areas despite current challenges. Efforts to enhance vaccine effectiveness persist due to the need to overcome constraints on immunogenicity. Research into adjuvant and fusion protein strategies is crucial to leveraging the therapeutic potential of HPV antigen-specific immunotherapy in the fight against CC[23].

1.4 Treatment of CC

Treatment options for CC, including surgery, radiation therapy, or chemotherapy, are tailored to the clinical stage of the disease. The primary goals of treatment selection are to achieve local and systemic disease control. Appropriately initiating local therapy is crucial for optimal outcomes since CC is often detected while localized in the pelvic area. Patients identified with metastasis to nearby tissues during surgical exploration, such as the vaginal cuff or pelvic lymph nodes, are classified as high-risk[24]. In specific cases, intravaginal irradiation with either a low dose rate (LDR) or a high dose rate (HiDR) may be recommended[25]. Adjuvant chemoradiotherapy is considered for high-risk patients to

improve survival rates. Intensity-modulated radiotherapy (ItMRT) during pelvic radiotherapy (PRT) offers the advantage of reducing radiation exposure to critical anatomical structures like the bladder, rectum, small intestine, and pelvic bones, thereby minimizing treatment interruptions due to adverse effects such as diarrhea and bone marrow toxicity[26].

a) Surgery

Surgery remains a cornerstone in the treatment of early-stage cancers like CC, aiming to eradicate both primary tumors and metastatic tissue. However, traditional approaches such as laparoscopic radical hysterectomy come with potential drawbacks, including increased risks of recurrence, infertility, and urinary complications[27]. Consequently, there's a growing interest in alternative procedures such as Loop Electrosurgical Excision Procedure (LEEP), conization, and trachelectomy, which offer the possibility of preserving fertility while effectively managing the disease[28]. In addition to surgical interventions, emerging treatment modalities like immunotherapy have shown promising outcomes in CC management. Immunotherapies such as immune checkpoint inhibitors (ICI) and tumor-infiltrating lymphocytes (TIL) have effectively treated CC by harnessing the body's immune system to target cancer cells specifically[29].Furthermore, targeted therapy has emerged as a promising approach to combating CC. Targeted therapy aims to disrupt crucial pathways involved in tumor growth and progression by blocking specific proteins within cancer cells. Moreover, the role of CC stem cells (CSCs) has garnered significant attention in recent research. CSCs are believed to play a pivotal role in driving recurrence, metastasis, and resistance to conventional treatments like chemotherapy and radiotherapy. Consequently, ongoing research is dedicated to uncovering novel target genes, proteins, and signaling pathways associated with CSCs to expand the repertoire of therapeutic options available for managing CC. While surgery remains a fundamental aspect of CC treatment, the landscape of therapeutic interventions is rapidly evolving, with immunotherapies, targeted therapies, and research into CSCs offering new avenues for improving outcomes in CC patients[30].

b) Radiotherapy

Brachytherapy (Internal RT), external beam radiation therapy (EtBRT), and Intensity-modulated radiotherapy (ItMRT) are crucial components of CC treatment. Advanced diagnostic techniques such as CT scans and MRIs have greatly enhanced the assessment of the primary tumor, enabling more targeted and effective treatment planning. However, despite these advancements, radiotherapy can still lead to significant side effects, including sexual dysfunction, diarrhea, abdominal cramping, pelvic discomfort, skin toxicity, and lymphedema, implying the need for careful management and supportive care[31]. Concurrent chemoradiotherapy has emerged as a preferred approach, demonstrating superior outcomes compared to sequential methods. Intracavitary brachytherapy represents a significant advancement in minimizing radiation exposure to healthy tissues by precisely placing radioactive sources close to the tumor site, thereby maximizing therapeutic efficacy while minimizing overall damage[32].Moreover, technological advancements in EtBRT, such as ItMRT, volumetric modulated arc therapy (VMAT), and image-guided radiation therapy (IGRT), have further improved survival rates and reduced treatment-related morbidity[33]. HiDR and LoDR irradiation have shown similar survival outcomes and late toxicity, with HDR irradiation gaining popularity due to its outpatient feasibility and convenience for patients[34]. These advancements collectively represent significant progress in managing CC, offering improved outcomes and quality of life for patients undergoing radiation therapy.

c) Chemotherapy

Chemotherapy is a cornerstone in the comprehensive treatment of CC, typically administered post-surgery to mitigate the risk of cancer recurrence. The standard chemotherapy regimen often involves combining cisplatin, a platinum-based medication, with other agents such as topotecan, paclitaxel, 5-fluorouracil, and bleomycin. This combination therapy has significantly extended the average survival duration among CC patients. In instances of locally advanced CC, chemotherapy is frequently complemented with radiotherapy to enhance treatment efficacy. Moreover, palliative chemotherapy represents a crucial aspect of care for patients with advanced or metastatic CC[35.] Its primary goal is to improve the quality of life by alleviating symptoms and slowing disease progression. Recent clinical trials have shown promising outcomes from the concurrent administration of chemotherapy and radiation therapy, indicating a potential synergistic effect in managing CC. Despite these advancements, the impact of neoadjuvant chemotherapy on overall survival rates remains modest. The Gynecologic Oncology Group (GOG) has conducted randomized trials comparing platinum-based combinations with cisplatin alone[36]. While these trials have demonstrated increased response rates and prolonged survival without disease progression, they have not significantly improved overall survival outcomes. These findings implies the complexity of CC treatment and the ongoing need for refining therapeutic approaches. Future research may focus on identifying biomarkers that are predictive of treatment response, exploring novel drug combinations, and refining treatment strategies to optimize outcomes for CC patients at different stages of the disease.

1.5 Specific Treatment for Recurrent CC

Progression, invasion, and spread of cancer heavily depend on angiogenesis, a complex process regulated by the increased expression of proangiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF)[37]. These factors are pivotal in promoting the formation of new blood vessels, essential for the migration and sustenance of tumors within the body. In CC patients, elevated levels of VEGF have been identified as a significant prognostic indicator for poor outcomes, making it a prime target for anti-angiogenic therapy aimed at inhibiting tumor growth and metastasis. Furthermore, recent research presented at the 2019 SGO (Society of Gynaecologic Oncology) annual meeting shed light on the role of poly (ADP-ribose) polymerase (PARP) in DNA repair processes within cancer cells, particularly in the context of CC[38,39]. Despite considerable advancements in PARP inhibitor therapies, there remains a subset of patients who derive limited benefits from PARP-1 therapy, especially in highly mutated cancer environments. It underscores the need for a deeper understanding of the mechanisms underlying resistance to such treatments. Moreover, there is a growing emphasis on unraveling the interplay between the

immune system and cancer progression, particularly in CC, where information on immune checkpoint inhibitors (ICI) is still evolving. Monoclonal antibody therapy, which targets immunosuppression pathways, holds promise in augmenting the immune response against cancer cells. Ongoing research endeavors seek to evaluate the efficacy of this approach in recurrent or metastatic CC patients who exhibit disease progression despite conventional chemotherapy regimens. Additionally, therapeutic vaccines targeting HPV infection, a major etiological factor in cervical malignancies, have demonstrated encouraging results when administered in combination with cisplatin, yielding moderate responses in patients with unfavorable prognoses[40]. Further exploration in targeted therapy directed at specific tumor antigens is warranted, given its potential to elicit durable responses in CC patients while maintaining excellent tolerability profiles.

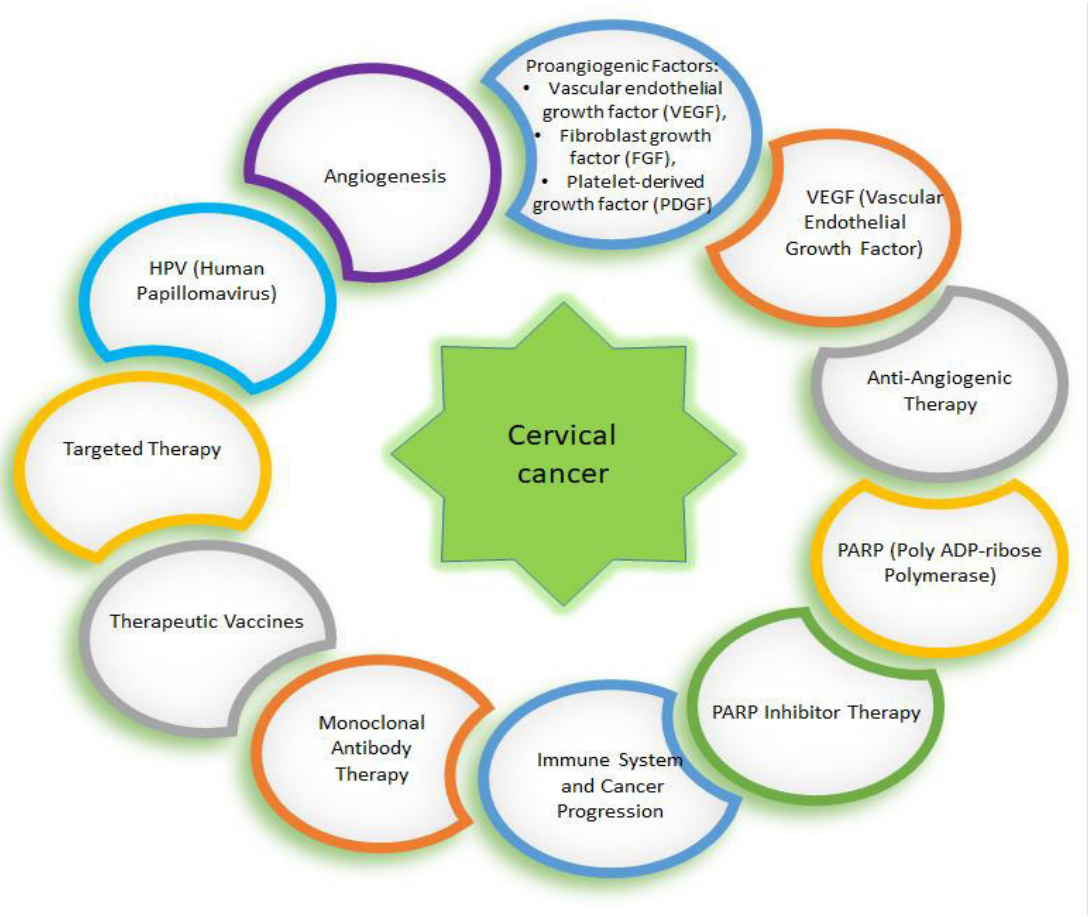

Fig 3: Factors influencing the treatment of recurrent CC

1.6 Molecular markers

In cancer management, particularly in CC surgery, evaluating various factors is imperative for forecasting the likelihood of cancer recurrence. Physicians meticulously assess tumor size, the extent of metastasis to adjacent tissues, lymphovascular space invasion (LVSI), lymph node metastasis, parametrical tissue invasion, and postoperative margin positivity. These factors are crucial in determining the prognosis and treatment course for patients undergoing CC surgery[41]. However, the landscape of cancer diagnosis and prognosis is continuously evolving with advancements in technology and research. Scientists are exploring novel methods to detect cancer cells and molecules in the bloodstream, which could revolutionize CC diagnosis and management. Circulating tumor cells (CTCs), circulating cell-free DNA (CcfDNA), circulating HPV DNA, and microRNA (miRNA) are among the promising avenues being investigated in this regard[42]. These innovative diagnostic tools hold significant promise in various aspects of CC management. They not only aid in the diagnosis of CC but also offer valuable insights into the prognosis of the disease and the progression of the tumor. Studies have shown that the presence of CTCs in the bloodstream is associated with reduced progression-free survival (PFS) in CC patients. Conversely, a decrease in the number of CTCs is correlated with a reduced risk of mortality, highlighting the prognostic significance of these circulating biomarkers. Moreover, the ability to detect and monitor these biomarkers in real time opens up possibilities for personalized treatment strategies in CC. By precisely forecasting treatment responses and survival odds based on individual patients' biomarker profiles, physicians can tailor treatment regimens to optimize outcomes and enhance patient welfare[43]. This personalized approach holds immense potential in improving survival rates and overall quality of life for CC patients undergoing surgery[44]. Incorporating these sophisticated diagnostic procedures into clinical practice represents a paradigm shift in CC management, offering new avenues for optimizing patient care and outcomes. As research advances, integrating novel biomarkers into routine clinical practice holds promise for further enhancing the efficacy of CC treatment strategies.

1.7 AI in the diagnosis of CC

AI has emerged as a powerful tool in the medical field, offering automated diagnostic capabilities with great potential for addressing various healthcare challenges. In recent years, there has been a notable expansion in its use, particularly in

medical imaging and diagnosis. AI algorithms are now utilized to assist in diagnosing a wide range of medical conditions, including gynecologic cancers, skin malignancies, tumor imaging, and retinal disorders. One of the key strengths of AI is its ability to recognize images and organize data, enabling AI systems to detect and analyze medical images accurately and identify important features and patterns that a mere human onlooker might not promptly discern[45]. In CC detection, AI has shown promise, particularly in identifying cervical epithelial dysplasia and segmenting cytoplasm, both crucial tasks for early cancer detection and screening[46]. Integrating AI technology into CC diagnosis can significantly improve diagnostic accuracy, especially in environments with limited access to specialized medical expertise. By utilizing AI algorithms, healthcare professionals can enhance their ability to identify precancerous lesions and diagnose CC in its early stages, facilitating timely intervention and treatment. In conclusion, AI technologies offer valuable support in improving the precision of CC and precancerous lesion detection. Through AI-assisted diagnostic systems, healthcare providers can enhance their capabilities in detecting and managing CC, ultimately leading to improved patient outcomes and reduced disease burden [47].

1.8 Prevention of CC

The significance of preventing HPV infection to lower the risk of CC emphasizes HPV's crucial role in its development[48,49]. Prevention includes vaccination and abstaining from sexual activity. Primary prevention strategies focus on reducing risk through behavioral interventions related to healthcare-seeking and sexual activity, alongside mass immunization targeting high-risk HPV strains[50]. A comprehensive screening program necessitates reliable tests, timely diagnostics, appropriate treatment, and diligent post-treatment follow-up. Ensuring equitable access to screening is vital due to healthcare accessibility disparities among demographic groups. Research shows that high-risk HPV strains in the cervix are key in most CC cases, including its precursor, CIN /3[51]. HPV, primarily transmitted through sexual contact, is often asymptomatic and transient but can lead to CC in a small percentage of cases[52]. The profound association between cervical HPV infection and invasive cervical cancer (ICC) is unprecedented in the realm of cancer epidemiology, marking a pivotal focus in global health initiatives. In alignment with this, the World Health Organization spearheaded a comprehensive global strategy in 2020 to expedite the eradication of cervical cancer[53]. Central to this strategy is the widespread adoption of HPV testing, including the Pap test, as integral secondary measures for early detection and intervention. Additionally, advanced diagnostic procedures such as colposcopy, HPV-DNA testing, and biopsy are recommended in cases where initial results indicate positivity, enabling targeted interventions. Timely surgical interventions are critical for patients diagnosed with CIN2, ensuring effective management and subsequent surveillance to mitigate disease progression and enhance patient outcomes[54].

1.9 Vaccine Development

CC is a significant global health concern, ranking second among cancers causing death in women worldwide. Recent advancements in research, particularly utilizing genotyping assays and highly sensitive HPV immunoassays, have provided valuable insights into the effectiveness of vaccines against HPV, the primary cause of CC. These studies have confirmed the vaccine's ability to induce a robust immune response, marking a pivotal step in the fight against this disease[55]. Despite the vaccine's proven efficacy, uncertainties persist regarding the duration of its protective effects. However, its approval in numerous countries imparts its potential to substantially impact global CC rates, provided efforts are made to enhance its accessibility and uptake. Nevertheless, challenges such as high manufacturing costs and limited options hinder widespread adoption, particularly in resource-constrained settings. To address these challenges and further improve prevention strategies, ongoing research focuses on developing second-generation prophylactic HPV vaccines[56]. Vaccines based on HPV L2 are being explored as potential alternatives. However, it is crucial to note that currently licensed HPV vaccines do not confer benefits to individuals already infected with HPV or those developing HPV-related malignancies, highlighting the need for complementary therapeutic approaches. A significant hurdle in developing effective vaccines lies in understanding the complex interplay between the cancer microenvironment and HPV-induced immune evasion mechanisms[57]. Overcoming this challenge requires continued research to elucidate the nuances of immune responses to HPV infections. Anticipated advancements in this field hold promise for developing more efficacious vaccines, potentially incorporating efficient adjuvants to enhance immune responses. By leveraging these insights, researchers aim to bolster primary prevention efforts and explore avenues for therapeutic interventions targeting HPV-related diseases beyond vaccination. In conclusion, while significant progress has been made in HPV vaccination, there remain challenges to overcome in realizing its full potential in reducing the burden of CC globally[58]. Continued investment in research and collaboration across disciplines is essential for advancing our understanding of HPV pathogenesis and developing more effective prevention and treatment strategies.

2. CONCLUSION

In conclusion, integrating AI technologies in CC diagnostics is a pivotal advancement, augmenting precision and empowering healthcare providers in detection and management. Emphasizing the critical role of preventing HPV infection for reducing CC risk, vaccination, and safe sexual practices emerge as key preventive measures. With CC ranking as the second leading cause of global female cancer mortality, recent research affirming vaccine effectiveness through advanced assays offers promise. Challenges persist in comprehending the cancer microenvironment and immune evasion mechanisms, underscoring the ongoing need for innovative research to advance our understanding and improve outcomes in CC management. The paramount significance of preventing HPV infection extends beyond vaccination and abstinence, involving comprehensive awareness campaigns and accessible healthcare resources. As CC research progresses, exploring emerging biomarkers and integrating multi-omics approaches promise to unravel complexities in disease pathways, offering potential breakthroughs in targeted therapies. Despite strides in vaccine efficacy, unraveling the intricacies of immune evasion within the cancer microenvironment poses a multifaceted challenge, urging further interdisciplinary collaboration for comprehensive advancements.

3. AUTHORS CONTRIBUTION STATEMENT

Dr. Shilpa Bhargava, Dr. John Abraham wrote the initial draft. Dr. Martha Srinivas and Dr. Somenath Ghosh contributed to critical revision and supervision. All authors reviewed the manuscript.

4. CONFLICT OF INTEREST

Conflict of interest declared none.

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