1

INTRODUCTION

Cervical cancer (CC) is a malignancy that originates at the cellular level within the epithelium of the cervix and progresses through a series of pre-cancerous stages before becoming invasive (Singh *et al*., 2023). According to GLOBOCAN in 2022, cervical cancer is the fourth most common cancer in women around the world, with an estimated 660,000 new cases and 350,000 deaths annually (Bray *et al*., 2024). Cervical cancer represents a significant global health challenge, especially for women in low- and middle-income countries (LMICs), where the disease burden is notably higher (Sudha *et al*., 2025). This high mortality rate is particularly concerning because cervical cancer is largely preventable through screening and vaccinations. However, there is a stark contrast in outcomes between high-income countries (HICs) and LMICs, revealing an alarming disparity in cervical cancer prevention, diagnosis, and treatment options (Hull *et al*., 2020).

In high-income countries (HICs), the widespread implementation of cervical cancer screening programs, including Pap smear tests and HPV DNA testing, combined with the introduction of the HPV vaccine, has significantly decreased the incidence and mortality of cervical cancer. Countries like the United States, Canada, and Western Europe have significantly declined cervical cancer rates due to these preventive measures (Siegel *et al*., 2021). In contrast, LMICs face numerous barriers to effective cervical cancer prevention and control, leading to an overwhelming majority—nearly 90%—of cervical cancer deaths occurring in these regions (Maluf *et al*., 2022; Duncan *et al*., 2021). The lack of robust healthcare infrastructure, limited access to affordable and reliable screening programs, and insufficient availability of the HPV vaccine are significant challenges in these settings. In sub-Saharan Africa, cervical cancer is often diagnosed at advanced stages, where treatment options are scarce and survival rates are

significantly lower (Perkins *et al*., 2023). Even when screening is available, follow-up and treatment services may be inadequate, further contributing to high mortality rates.

The financial constraints of LMICs also limit the widespread implementation of HPV vaccination programs. Despite the proven efficacy of HPV vaccines in preventing infection with the high-risk HPV strains responsible for most cervical cancer cases, coverage remains low in resource-poor settings (Gültekin *et al*., 2020). The Global Vaccine Alliance (GAVI) has made efforts to subsidize HPV vaccines in LMICs. However, logistical challenges such as vaccine storage, distribution, and healthcare worker training impede large-scale vaccination efforts (Bruni *et al*., 2021).

Cultural attitudes and misinformation about vaccines in some regions have also hindered their acceptance and uptake. Socio-cultural barriers also play a significant role in hindering prevention efforts. In some communities, discussions around sexually transmitted infections and cancer prevention are taboo, and women may face stigma for seeking care related to reproductive health. Furthermore, logistical challenges, such as inadequate healthcare infrastructure, insufficient funding for national screening programs, and limited access to affordable vaccines, exacerbate these issues. Research suggests that women in these regions often cannot access preventive services due to geographical, financial, and socio-cultural barriers (Perkins *et al*., 2020).

HPV infection is one of the most prevalent sexually transmitted disease, with many individuals contracting it at some point in their lives. While the immune system clears the virus in most cases, persistent infection with high-risk HPV strains can cause pre-cancerous lesions that, if untreated, may progress to invasive cervical cancer (Zhang *et al*., 2024). The process of progression from infection to cancer can take 10-20 years, offering a long latency period during which interventions like vaccination, screening, and treatment of pre-cancerous lesions can effectively prevent the onset of cervical cancer.

In addition to HPV infection, various socio-demographic and biological factors significantly influence an individual's risk of developing cervical cancer. Sexual behavior is a major factor; early sexual initiation, multiple sexual partners, and high parity are well-established risk factors for both HPV infection and the development of cervical cancer (Sung *et al*., 2021). Co-infections with other sexually transmitted infections (STIs), such as *Chlamydia trachomatis* or HIV, also increase the risk of persistent HPV infection, thereby elevating the likelihood of cervical cancer (Mbulawa *et al*., 2022). Smoking has similarly been associated with increased risk, as tobacco use impairs immune function and can lead to DNA damage in cervical cells, further promoting carcinogenesis (Malevolti *et al*., 2023).

Despite the established causal relationship between HPV and cervical cancer, public awareness about the disease and its prevention remains alarmingly low, particularly in resource-limited settings. Awareness campaigns and health education programs have proven effective in improving knowledge about cervical cancer risk factors, the importance of screening, and the benefits of HPV vaccination (Singh *et al*., 2023). However, gaps in awareness persist, especially among women with lower levels of education, those living in rural areas, and marginalized communities. Research indicates that women who are better informed about cervical cancer and its preventive measures—such as the HPV vaccine and Pap smear screening—are more likely to adopt preventive behaviors (Williams *et al*., 2021).

Biological factors, including family history of cancer, genetic predispositions, and co-existing health conditions, also play a critical role in determining an individual's risk of developing cervical cancer. For instance, women with HIV are at a much higher risk of developing cervical cancer due to immunosuppression, which increases the likelihood of persistent HPV infection (Moodley *et al*., 2021). Understanding these factors enables researchers to identify gaps in healthcare delivery and opportunities for intervention. For instance, targeted screening programs that prioritize high-risk groups, such as women with HIV or those with a history of multiple sexual partners, can significantly improve early detection and reduce cervical cancer mortality (World Health Organization, 2021).

Targeted therapy offers a more precise approach for treating cervical cancer by specifically attacking cancer cells while minimizing damage to healthy tissues, which helps to limit the side effects commonly seen with traditional therapies. The advent of next-generation sequencing (NGS) technologies has further enhanced the potential of targeted therapies by enabling the identification of genetic variants that drive cancer development and progression. Among these technologies, whole exome sequencing (WES) stands out as a transformative tool for uncovering the genetic underpinnings of cervical cancer. By analyzing all protein-coding regions of the genome—collectively known as the exome, which constitutes about 1% of the human genome but harbors the majority of disease-causing mutations (Evans and Matulonis, 2016)—WES has significantly advanced our understanding of this disease. When tumor suppressor pathways are disrupted, cells lose their ability to regulate division and repair genetic damage, leading to unchecked proliferation, genetic mutations, and genomic instability—key hallmarks of cancer development. These changes gradually drive the progression from pre-cancerous lesions to invasive cervical cancer (Doorbar *et al*., 2012).

Several studies have highlighted genetic mutations in genes related to DNA repair, cell cycle regulation, and immune response pathways, which are linked to an elevated risk of developing cervical cancer (Wang *et al*., 2020). For instance, mutations in genes such as *TP53*, which plays a critical role in regulating the cell cycle and maintaining genomic stability, have been frequently observed in cervical cancer patients (Miyamoto *et al*., 2021). These alterations can lead to the loss of p53 function, resulting in unregulated cell proliferation and tumorigenesis. Similarly, mutations in *PTEN* and *PIK3CA*, which are involved in the phosphoinositide 3-kinase (PI3K) signaling pathway, have been linked to cervical cancer progression, emphasizing the importance of cell signaling in this malignancy (Kris *et al*., 2020).

Sanger sequencing, often considered the gold standard for DNA sequencing, provides highly accurate results and is commonly used to confirm the presence of specific genetic mutations discovered through high-throughput methods like WES. This step is essential for ensuring that the identified variants are genuinely associated with cervical cancer and not the result of sequencing errors or

population-specific genetic variations (Wang *et al*., 2023). Moreover, integrating Sanger sequencing into the workflow of cervical cancer research strengthens the clinical applicability of the findings. In clinical settings, decisions regarding personalized treatment options, such as targeted therapies, depend heavily on the accuracy and reliability of genetic data. Therefore, validating variants with Sanger sequencing reinforces confidence in their association with cervical cancer and lays a solid foundation for further research into functional studies and therapeutic target development (Shendure and Akey, 2015).

In addition to confirming the presence of genetic variants, researchers must evaluate the pathogenicity of these variants to determine their role in cervical cancer development. This evaluation is crucial because not all genetic variants are harmful; some may be benign or have inconsequential effects on cellular functions. Bioinformatics tools play a pivotal role in this assessment, allowing researchers to predict the potential impact of mutations on protein structure and function. Tools like SIFT, LRT, PolyPhen2, FATHMM, MutationTaster, RadialSVM, and LR assess the impact of amino acid changes on protein function, helping to determine whether a variant could be pathogenic (Garcia *et al*., 2022).

Furthermore, multidisciplinary collaborations among oncologists, geneticists, and public health professionals can lead to innovative interventions, such as developing combination therapies that target genetic and environmental risk factors. These collaborative efforts can also facilitate the sharing of knowledge and resources, ultimately advancing our understanding of cervical cancer and fostering new strategies to combat it. By leveraging insights from each discipline, we can develop more holistic approaches that improve prevention, enhance treatment strategies, and ultimately reduce the global burden of this preventable disease.

With this background, this study aims to seek knowledge and awareness on cervical cancer and its preventive measures. It will also go further to explore the socio-demographic characteristics and known biological risk factors of patients with cervical cancer. A major objective is to identify the most prevalent histological type of cervical cancer seen in the study population. The study will also focus on

identifying novel genetic variants associated with the most common histological type of cervical cancer in this cohort.

Null Hypothesis

There is no significant relationship between socio-demographic factors, biological risk factors, and genetic variants in cervical cancer patient population

Alternate Hypothesis

There is a significant association between socio-demographic factors, biological risk factors, and genetic variants in cervical cancer patient population

The objectives set for the present investigation are to

- Assess cervical cancer awareness, knowledge, and preventive behaviours among women via online surveys.
- Investigate cervical cancer patient's socio-demographic profile and causative biological factors through a hospital-based cohort study.
- Identify genetic variants by Whole Exome Sequencing and evaluate their pathogenicity and associated pathways in cervical cancer patient samples.
- Validate the identified novel variants using Sanger sequencing.

A brief review of literature is presented in the next chapter.