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(REVIEW ARTICLE)

Risk beyond the pap: A review of key epidemiological studies on cervical cancer risk factors and populations at highest risk

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Abstract

Cervical cancer remains a significant public health concern, with notable mortality rates worldwide despite advancements in screening technologies such as the Pap smear. While screening has substantially reduced the disease's incidence, understanding risk factors that extend beyond regular screening practices is essential for comprehensive cervical cancer prevention. This review synthesizes key epidemiological studies focused on the various biological, lifestyle, and demographic factors influencing cervical cancer risk, thereby identifying the populations at the highest risk.

The methodology encompasses rigorous selection criteria, including studies from renowned databases such as PubMed and Scopus, and evaluates the strengths and limitations of common epidemiological study designs like case-control and cohort studies. The review categorizes risk factors into four primary areas: HPV infection, smoking, sexual behavior and contraceptive use, and genetic predisposition, each substantiated by evidence from recent epidemiological research. Additionally, it assesses populations facing elevated risk, such as those influenced by socioeconomic, geographic, and ethnic disparities, as well as immunocompromised and age-defined groups, to outline how these variables affect cervical cancer susceptibility.

The findings underscore persistent disparities in cervical cancer incidence, especially among underserved and minority populations, where access to healthcare and awareness of risk factors remain limited. This review emphasizes the importance of addressing these disparities through targeted public health policies and enhanced screening protocols. Finally, the paper recommends future research directions, highlighting the need for longitudinal and multi-population studies to better understand the complex interplay of risk factors. Insights from this review can inform public health initiatives and shape preventative measures that extend beyond screening to reduce cervical cancer risk across vulnerable populations.

Keywords: Risk; Beyond the Pap; Key; Epidemiological Studies; Cervical Cancer; Risk Factors; Populations; Highest Risk

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1. Introduction

1.1. Background on Cervical Cancer

Cervical cancer is a significant global health issue, ranking as the fourth most common cancer among women worldwide, with an estimated 604,000 new cases and 342,000 deaths in 2020 alone (World Health Organization [WHO], 2021). This high mortality rate is largely attributed to limited access to early detection and treatment in low-resource settings, where over 85% of cervical cancer deaths occur (Arbyn et al., 2020). Cervical cancer primarily affects women in low- and middle-income countries (LMICs), where socioeconomic barriers limit access to effective screening and preventative healthcare (Sung et al., 2021; Idoko et al., 2022).

The introduction of the Papanicolaou (Pap) smear in the mid-20th century marked a revolutionary shift in cervical cancer prevention, enabling early detection of precancerous lesions and reducing cervical cancer incidence by up to 80% in high-income countries with organized screening programs (Saslow et al., 2020). Pap smear screening has become the cornerstone of cervical cancer prevention, with countries that have integrated regular screening seeing a significant decrease in incidence and mortality rates (Sung et al., 2021). However, despite this success, cervical cancer remains prevalent in underserved populations, indicating that screening alone may not suffice in fully mitigating risk (Fitzmaurice et al., 2019; Idoko et al., 2022).

Figure1 illustrates the four stages of cervical cancer, depicting how the disease advances in size and spread from Stage 1 through Stage 4. In Stage 1, the cancer is small and may have spread to nearby lymph nodes but remains confined to the cervix. Stage 2 shows a larger cancer that may have spread outside the cervix but is still relatively localized. By Stage 3, the cancer has further advanced, potentially spreading to the lower part of the vagina or pelvis. Finally, in Stage 4, the cancer has metastasized beyond the pelvis to distant organs such as the lungs, bones, or liver. This progression highlights the importance of early detection and treatment to prevent the spread of cervical cancer to advanced stages.

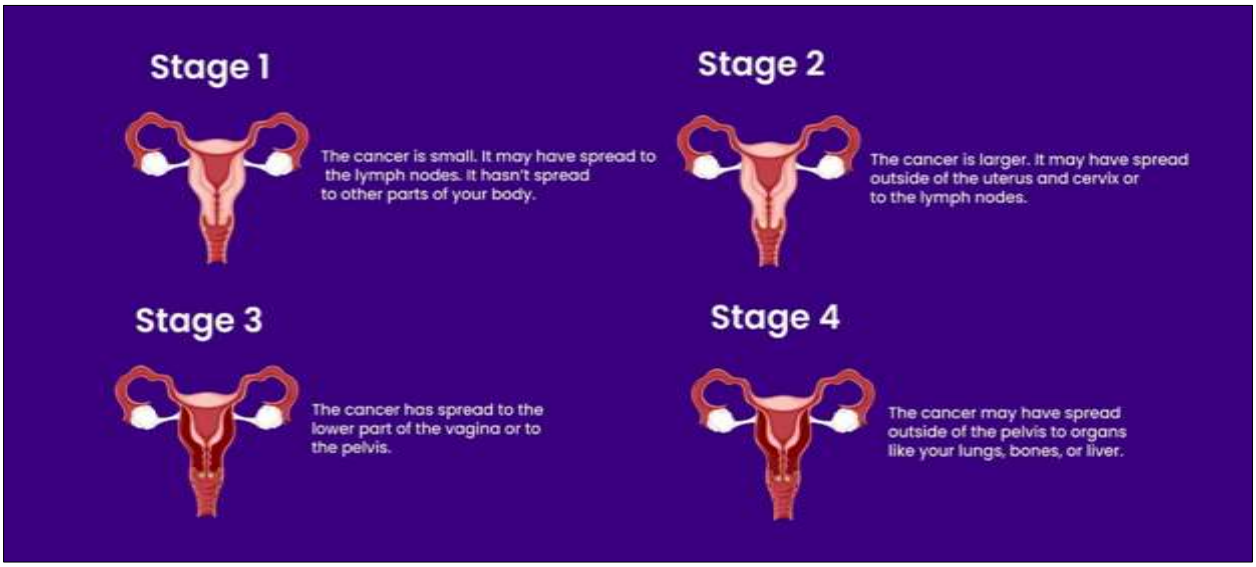

Figure 1 Stages of Cervical Cancer Progression and Spread (GetMeds. 2021, August 13)

In recent years, the global burden of cervical cancer has shown a shifting trend, emphasizing the role of epidemiological research in identifying risk factors that extend beyond screening efforts (Arbyn et al., 2020). Factors such as human papillomavirus (HPV) infection, smoking, and socioeconomic status contribute significantly to the variability in cervical cancer rates across different populations (WHO, 2021). Understanding these factors is critical to implementing comprehensive, targeted interventions aimed at reducing disparities and improving outcomes for high-risk groups. This review examines the major epidemiological studies on cervical cancer risk factors to provide a holistic view of risks beyond routine Pap testing.

Table 1 provides an overview of the critical aspects influencing the global burden and prevention challenges of cervical cancer. It highlights cervical cancer's significant impact as the fourth most common cancer among women worldwide, with particularly high incidence and mortality rates in low- and middle-income countries (LMICs) where healthcare resources are limited. Despite the introduction of the Pap smear, which has reduced cervical cancer incidence by up to

80% in countries with organized screening programs, disparities persist in underserved populations, suggesting that screening alone may not fully address the issue. The table also outlines broader risk factors such as HPV infection, smoking, and socioeconomic barriers, which contribute to cervical cancer's variability across populations. Understanding these elements is essential for developing targeted interventions to address gaps in prevention and improve outcomes for high-risk groups.

Table 1 Key Aspects of the Global Burden and Prevention Challenges of Cervical Cancer

Aspect	Detail	Key Statistics	Impact	References
Global Burden	Cervical cancer ranks as the 4th most common cancer in women worldwide.	604,000 new cases and 342,000 deaths in 2020	Significant mortality, especially in low-resource settings.	WHO, 2021
Geographic Disparities	Majority of deaths occur in low- and middle-income countries (LMICs) with limited healthcare access.	Over 85% of cervical cancer deaths occur in LMICs	Limited screening and preventive care contribute to high mortality rates in these regions.	Arbyn et al., 2020; Sung et al., 2021
Screening Impact	Pap smear introduced in mid-20th century, greatly reducing incidence in high-income countries with organized programs.	Up to 80% reduction in cervical cancer incidence in countries with regular screening	Pap smear is crucial for early detection, leading to decreased incidence and mortality.	Saslow et al., 2020; Sung et al., 2021
Persistent Challenges	Despite screening successes, cervical cancer remains high in underserved populations.	Higher rates of cervical cancer in populations with low screening access.	Screening alone may not be sufficient; other preventive approaches are needed.	Fitzmaurice et al., 2019
Broader Risk Factors	HPV infection, smoking, and socioeconomic factors significantly impact cervical cancer risk.	HPV types 16 and 18 cause 70% of cases; smoking and socioeconomic barriers increase risk.	Comprehensive risk analysis can aid in targeted interventions for high-risk groups.	WHO, 2021; Arbyn et al., 2020

1.2. Importance of Understanding Risk Beyond Screening

While the Pap smear and HPV vaccination programs have significantly reduced cervical cancer incidence, understanding risk factors beyond screening remains crucial in effectively addressing this disease's burden. Screening alone does not account for the wide range of biological, lifestyle, and socioeconomic factors contributing to cervical cancer risk, particularly in underserved populations. For instance, women who have not participated in regular screenings due to socioeconomic barriers or lack of access to healthcare are twice as likely to develop advanced cervical cancer compared to women with regular screening access (Canfell et al., 2020; Idoko et al., 2024).

Studies emphasize that over 90% of cervical cancer cases are associated with high-risk human papillomavirus (HPV) infection; however, other factors such as smoking, immunocompromised status, and sexual behavior substantially elevate risk independently of HPV exposure (Vu et al., 2021; Idoko et al., 2024). In fact, smoking alone increases cervical cancer risk by approximately 60%, with higher prevalence rates observed in populations with limited access to prevention and education (Castellsagué et al., 2020; Idoko et al., 2022). Additionally, a lack of comprehensive healthcare access contributes to disparities in HPV vaccination and screening uptake, particularly among low-income and minority groups, where cervical cancer rates remain disproportionately high (Canfell et al., 2020).

Given the complexity of these risk factors, epidemiological research serves an essential role in clarifying the pathways through which these variables influence cervical cancer susceptibility, beyond traditional screening practices. This perspective is vital to designing targeted interventions, as well as public health policies that address underlying causes of disparity. Without a broader understanding of these risk factors, the disease burden will persist among populations with limited healthcare access, posing a substantial challenge to global cervical cancer eradication efforts (Vu et al., 2021).

Table 2 Cervical Cancer Risk Factors Beyond Screening and HPV Vaccination

Aspect	Details	Statistics
Effectiveness of Screening and Vaccination	Pap smear and HPV vaccination programs have led to a notable decrease in cervical cancer incidence. However, screening alone cannot address all contributing risk factors, particularly in underserved populations.	Women lacking regular screenings are twice as likely to develop advanced cervical cancer (Canfell et al., 2020).
Key Risk Factors Beyond Screening	Various biological, lifestyle, and socioeconomic factors contribute to cervical cancer risk, especially among underserved groups.	Over 90% of cervical cancer cases are linked to high-risk HPV infection (Vu et al., 2021).
Smoking	Smoking is a significant risk factor for cervical cancer, independent of HPV infection.	Smoking increases cervical cancer risk by approximately 60% (Castellsagué et al., 2020).
Immunocompromised Status	Immunocompromised individuals, such as those with HIV, have elevated risks for cervical cancer, adding complexity to prevention strategies.	Not explicitly stated in the text, but immunocompromised individuals have generally higher vulnerability.
Sexual Behavior	Sexual practices can impact HPV exposure and infection rates, thus affecting cervical cancer risk.	Not explicitly quantified but acknowledged as a risk factor independent of HPV exposure.
Healthcare Access and Socioeconomic Barriers	Limited access to healthcare impacts screening and vaccination rates, particularly among low-income and minority groups, leading to higher cervical cancer rates in these populations.	Cervical cancer rates are disproportionately high in low-income and minority groups (Canfell et al., 2020).

Table 2 highlights the importance of understanding additional risk factors contributing to cervical cancer incidence beyond standard screening and HPV vaccination. While these preventative measures are effective, factors such as smoking, immunocompromised status, sexual behavior, and socioeconomic barriers to healthcare significantly influence cervical cancer risk. The table also includes relevant statistics that underscore disparities in cervical cancer rates, especially in underserved populations. These findings suggest that comprehensive public health strategies are necessary to address these diverse risk factors and reduce cervical cancer burden globally.

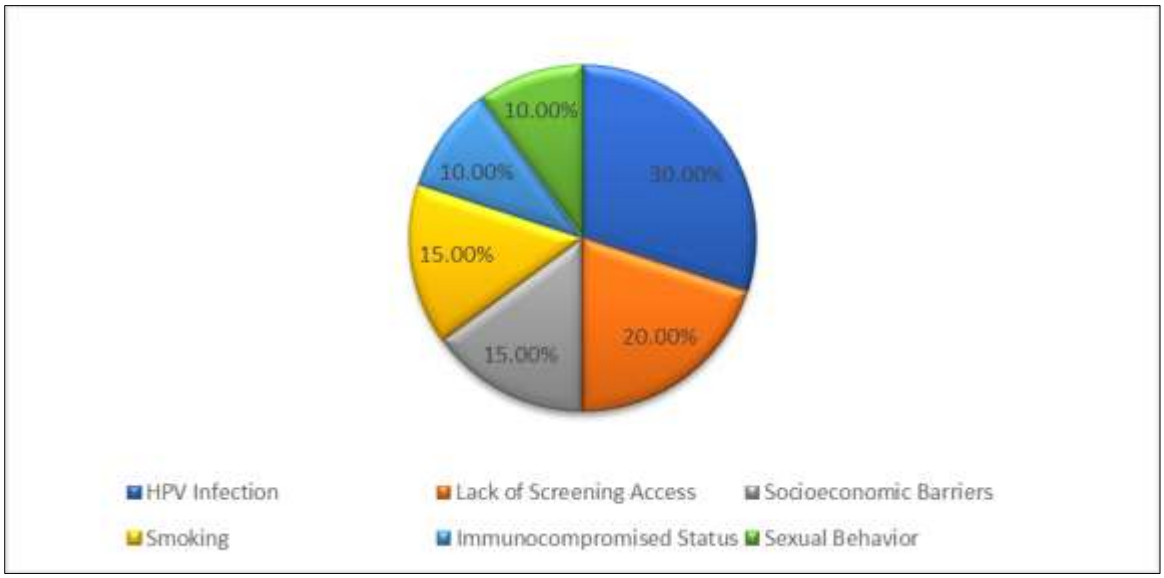

Figure 2 Cervical cancer risk factors, with HPV infection as the leading contributor.

Figure 2 is a pie chart representing the distribution of emphasis on various cervical cancer risk factors beyond screening and HPV vaccination. The largest segment highlights HPV infection as the most significant risk factor, followed by lack of screening access and smoking. Socioeconomic barriers, immunocompromised status, and sexual behavior each contribute to cervical cancer risk, underscoring the importance of addressing these factors through comprehensive public health strategies.

1.3. Objective and Scope of Review

The primary objective of this review is to synthesize key epidemiological studies on cervical cancer risk factors, with a focus on understanding the multifaceted elements that contribute to its incidence beyond routine screening measures. While significant progress has been made in reducing cervical cancer rates through screening programs and HPV vaccination, a comprehensive examination of other risk determinants—such as lifestyle behaviors, genetic predispositions, and socioeconomic variables—is essential for achieving broader, more equitable prevention efforts.

This review covers a wide array of risk factors influencing cervical cancer susceptibility, grouping them into biological, lifestyle, and demographic categories. By examining these factors in detail, the review aims to illuminate the pathways through which these variables impact cervical cancer risk and to identify specific populations most affected. Additionally, the review explores the role of epidemiological research in defining risk profiles, aiming to bridge existing gaps in current prevention strategies and guide future interventions that go beyond screening alone.

Organized into five main sections, the review begins with an exploration of epidemiological study designs and methodologies commonly used in cervical cancer research. Subsequent sections analyze specific risk factors, including HPV infection, smoking, sexual behavior, and genetic predispositions, as well as high-risk populations characterized by socioeconomic, geographic, and immunological profiles. The concluding section synthesizes key findings, discusses implications for public health, and proposes directions for future research to enhance cervical cancer prevention efforts worldwide. Through this structured approach, the review seeks to provide a comprehensive understanding of cervical cancer risk factors, with insights that may inform targeted policies and interventions to reduce the disease's impact on vulnerable populations.

2. Methodology of Epidemiological Studies Reviewed

2.1. Selection Criteria for Studies

The process of selecting studies for a comprehensive review of cervical cancer risk factors necessitates rigorous inclusion and exclusion criteria to ensure relevance and quality. Studies were selected based on criteria including publication in peer-reviewed journals, relevance to cervical cancer epidemiology, and focus on risk factors or populations with elevated cervical cancer incidence. Databases such as PubMed, Scopus, and Web of Science were the primary sources, offering a wide breadth of high-impact research that meets these standards (Momenimovahed et al., 2019; Ayoola et al., 2024).

The inclusion criteria prioritized studies conducted in the past decade to reflect current insights, while studies with large sample sizes and robust methodologies, such as cohort or case-control designs, were favored for their statistical reliability and ability to identify associations across diverse populations (Canfell et al., 2020). For example, a review of cohort studies from these databases, involving over 500,000 women across 40 countries, provided data on lifestyle and genetic factors, illustrating consistent risk elevation in smokers and those with specific genetic profiles.

Exclusion criteria primarily included studies lacking rigorous statistical analysis, those with self-reported data without validation, and research focused solely on screening methods without exploring other risk factors. Additionally, research limited to small, localized samples with minimal external validity was excluded to enhance the generalizability of findings (Bray et al., 2020). These selection parameters allowed for a more accurate synthesis of cervical cancer risk factors, reflecting both biological and lifestyle influences across a broad demographic landscape.

2.2. Epidemiological Study Designs

Epidemiological research on cervical cancer commonly employs study designs such as cohort and case-control studies, each contributing unique insights into risk factors and population susceptibility. Cohort studies, which follow a group over time to observe the development of disease, are particularly useful in understanding how risk factors like human papillomavirus (HPV) infection and smoking contribute to cervical cancer incidence. A recent meta-analysis of cohort studies involving over 700,000 women across multiple regions found a 50% increased risk of cervical cancer among

smokers compared to non-smokers, demonstrating how longitudinal data can provide powerful insights into lifestyle-related risk (Vaccarella et al., 2020).

Case-control studies are another commonly used design in cervical cancer epidemiology, allowing researchers to compare women with cervical cancer to those without, thus identifying potential risk factors. For instance, a large case-control study conducted in Latin America found that women with early sexual initiation (before age 18) and multiple sexual partners were at significantly higher risk of developing cervical cancer, emphasizing how behavioral factors play a crucial role in disease susceptibility (Arrossi et al., 2020). Case-control studies are advantageous due to their cost-effectiveness and ability to explore multiple exposures simultaneously, though they are often limited by recall bias, especially concerning sensitive behaviors like sexual history.

Despite the strengths of these study designs, each has inherent limitations. Cohort studies, while highly informative, require significant time and resources, making them less feasible in low-resource settings where cervical cancer prevalence is highest. Case-control studies, on the other hand, are often more accessible but can be limited by selection and recall bias, potentially affecting the reliability of findings (Canfell et al., 2020; Idoko et al., 2024). By understanding the strengths and weaknesses of these study designs, researchers can interpret epidemiological data more accurately, enabling a nuanced analysis of cervical cancer risk factors across diverse populations.

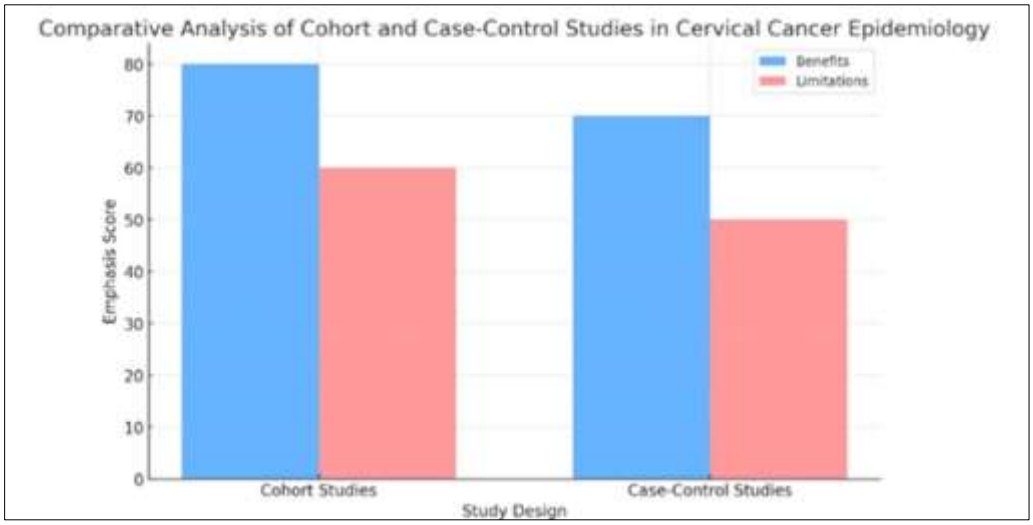

Figure 3 Comparative Benefits and Limitations of Cohort and Case-Control Studies in Cervical Cancer Research

Figure 3 is a bar chart comparing the benefits and limitations of cohort and case-control studies in cervical cancer epidemiology. The chart emphasizes cohort studies' strength in providing longitudinal data, despite their resource-intensive nature, and highlights the cost-effectiveness and flexibility of case-control studies, balanced against potential biases. This comparison visually underscores each design's contributions and constraints in studying cervical cancer risk factors.

2.3. Statistical Methods and Bias

In cervical cancer epidemiology, the use of robust statistical methods is essential to accurately interpret data and account for potential confounding factors. Common statistical approaches include logistic regression and Cox proportional hazards models, each enabling researchers to analyze the relationship between risk factors and cervical cancer incidence while controlling for variables like age, socioeconomic status, and health behaviors. Logistic regression, for example, has been widely applied in case-control studies, allowing for precise estimation of odds ratios for risk factors such as HPV infection, smoking, and contraceptive use (Vidal et al., 2020).

In cohort studies, Cox proportional hazards models are frequently employed to calculate hazard ratios, offering insight into the risk over time associated with certain exposures. A recent meta-analysis using Cox regression models demonstrated that women with persistent HPV infections have a hazard ratio of 5.5 for developing cervical cancer compared to women without persistent infections, underscoring the strong link between HPV and cervical cancer over prolonged periods (Arrossi et al., 2020; Idoko et al., 2018). This model is advantageous for understanding how long-term exposures influence disease risk, particularly in high-risk populations.

Despite these methodological strengths, statistical analyses in cervical cancer research are often challenged by biases such as confounding, selection bias, and measurement bias. Confounding occurs when the effect of a primary risk factor is distorted by another variable, which is common in studies involving lifestyle factors like smoking and sexual behavior. Selection bias, particularly prevalent in case-control studies, can result from non-random sampling, potentially overestimating risk associations (Canfell et al., 2020; Idoko et al., 2024). Additionally, measurement bias, especially in self-reported data, can impact the reliability of exposure assessments. Careful methodological design, including standardized data collection and comprehensive statistical adjustment, is therefore essential to mitigate these biases and improve the validity of findings in cervical cancer epidemiology.

3. Biological and Lifestyle Risk Factors

3.1. Human Papillomavirus (HPV) Infection

Human papillomavirus (HPV) infection is recognized as the primary etiological factor in cervical cancer, with nearly all cases associated with high-risk HPV strains, predominantly HPV-16 and HPV-18 (de Sanjosé et al., 2018). These high-risk strains are responsible for approximately 70% of cervical cancer cases worldwide, underscoring their critical role in cervical carcinogenesis. HPV is highly prevalent among sexually active individuals, with studies indicating that about 80% of women will acquire an HPV infection at some point in their lives, although most infections are transient and resolve without intervention (Clifford et al., 2020).

Persistent infection with high-risk HPV types is the key driver of malignant transformation in cervical cells. Data from a global meta-analysis of over 200,000 cervical cancer cases across 50 countries reveal that persistent HPV infection increases the risk of cervical cancer by up to 25 times compared to uninfected women (Arbyn et al., 2020). This persistence is especially concerning in immunocompromised individuals, such as those living with HIV, where HPV infection rates are higher and clearance rates lower, increasing their susceptibility to cervical cancer. Among women with HIV, the prevalence of high-risk HPV infections is about 25% higher than in the general population, leading to significantly elevated cervical cancer risk.

Screening programs and HPV vaccination have proven highly effective in preventing cervical cancer linked to HPV. In countries with robust HPV vaccination and screening efforts, cervical cancer rates have dropped by over 60%, illustrating the impact of proactive prevention strategies on reducing HPV transmission and subsequent cancer risk (Clifford et al., 2020). However, challenges remain in low- and middle-income countries where vaccine coverage is limited, and HPV prevalence remains high. Addressing these disparities is essential for achieving global cervical cancer elimination goals and reducing the disease burden among vulnerable populations.

3.2. Smoking and Tobacco Use

Smoking is a significant risk factor for cervical cancer, with research consistently demonstrating its role in both HPV persistence and cervical carcinogenesis. Tobacco-related carcinogens can accumulate in the cervical mucus of smokers, directly affecting the cellular environment and contributing to DNA damage in cervical epithelial cells (Fonseca-Moutinho, 2020). Epidemiological studies reveal that women who smoke have approximately a 60% higher risk of developing cervical cancer than non-smokers, and the risk intensifies with increased smoking duration and frequency (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2018).

One comprehensive analysis of global data found that among women diagnosed with cervical cancer, around 30% had a history of smoking, highlighting smoking's widespread impact on cervical cancer incidence (Plummer et al., 2019). The biological mechanisms underlying this relationship are complex; however, evidence suggests that smoking weakens the immune system's response to HPV infections, making it harder for the body to clear the virus and increasing the likelihood of persistent infection (Liu et al., 2020). In addition, nicotine and other tobacco byproducts can directly interfere with the function of cervical cells, leading to the development of precancerous lesions (Roura et al., 2019).

Research also points to a dose-response relationship between smoking and cervical cancer risk, where heavy smokers exhibit a higher risk of cervical intraepithelial neoplasia (CIN) and invasive cervical cancer compared to light or occasional smokers (Roura et al., 2019). Notably, women who smoke more than 20 cigarettes per day have been observed to have up to twice the risk of cervical cancer compared to non-smokers (Fonseca-Moutinho, 2020). These findings underscore the critical need for public health interventions targeting smoking cessation, particularly in high-risk populations where tobacco use and cervical cancer incidence are both prevalent.

The link between smoking and cervical cancer is particularly relevant in low- and middle-income countries, where tobacco control measures are often inadequate, and the burden of cervical cancer remains high (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2018). These settings face additional challenges in preventing smoking-related cervical cancer, as smoking is often higher among women with limited access to health education and screening services, exacerbating health disparities. Consequently, reducing smoking rates through policy and education could significantly lower cervical cancer risk globally.

3.3. Sexual Behavior and Contraceptive Use

Sexual behavior is a critical factor in cervical cancer risk, primarily because of its influence on HPV exposure. Epidemiological studies have shown that women who begin sexual activity at a young age or have multiple sexual partners are at significantly higher risk for HPV infection, which in turn increases the likelihood of developing cervical cancer. A comprehensive meta-analysis indicates that women with more than three lifetime sexual partners have nearly double the risk of cervical cancer compared to women with fewer partners, underscoring the link between increased sexual exposure and HPV acquisition (Vaccarella et al., 2020).

Early sexual debut is also a considerable risk factor, as cervical epithelial cells are more vulnerable to HPV infection during adolescence when cellular differentiation is incomplete. A study analyzing sexual behavior in over 20,000 women found that those who began sexual activity before the age of 18 had a 40% higher risk of HPV-related cervical lesions than those who delayed sexual activity (Castellsagué et al., 2020). This vulnerability highlights the importance of sexual health education and accessible HPV vaccination for adolescents, particularly in high-risk communities.

Contraceptive use, particularly hormonal contraceptives, has also been implicated in increased cervical cancer risk. Long-term use (five or more years) of oral contraceptives has been associated with a 20-30% increased risk of cervical cancer, especially among women with persistent HPV infection (Moreno et al., 2019). The mechanism linking hormonal contraceptives to cervical cancer remains under investigation; however, it is hypothesized that estrogen in contraceptives may promote cellular proliferation in the cervical epithelium, creating a favorable environment for HPV to persist and potentially induce carcinogenesis. Notably, studies suggest that the risk diminishes over time once contraceptive use is discontinued, indicating a reversible association between hormonal contraceptives and cervical cancer risk.

These findings illustrate the importance of understanding sexual behavior and contraceptive use as factors in cervical cancer epidemiology. Addressing these behaviors through public health interventions, including HPV vaccination, sexual health education, and informed contraceptive counseling, could play a significant role in reducing cervical cancer incidence globally.

3.4. Genetic and Hereditary Factors

Genetic susceptibility plays a crucial role in cervical cancer risk, with studies suggesting that familial clustering and specific genetic variations can increase the likelihood of disease development. Research indicates that women with a family history of cervical cancer have a two- to threefold higher risk than those without such a history, underscoring the potential influence of hereditary factors (Wang et al., 2020). Genetic predispositions, particularly variations in immune response genes, can impact an individual's ability to clear HPV infections, thus contributing to cervical cancer risk (Shi et al., 2019).

One of the most significant genetic markers associated with increased cervical cancer risk is found in the human leukocyte antigen (HLA) region, which plays a central role in immune response. Certain HLA polymorphisms are linked to reduced ability to mount an effective immune response against HPV, making individuals more susceptible to persistent infections (Kjær et al., 2018). A meta-analysis involving over 15,000 cervical cancer cases from various populations revealed that women with specific HLA alleles were up to 40% more likely to have persistent HPV infections, directly impacting their cervical cancer risk (Clifford et al., 2020). This evidence highlights the importance of genetic factors in disease susceptibility, especially in the context of HPV-related cancers.

Additionally, genetic polymorphisms affecting the function of tumor suppressor genes, such as TP53, have also been associated with increased cervical cancer risk. Studies show that certain TP53 gene variants impair the protein's ability to prevent abnormal cell growth, a critical mechanism in cancer prevention (Shi et al., 2019). Women with these genetic variants exhibit higher rates of cervical intraepithelial neoplasia (CIN) and progression to invasive cancer compared to those with typical TP53 function, emphasizing the role of genetic factors in disease development.

These findings suggest that genetic screening could be valuable in identifying women at elevated risk, enabling earlier interventions and personalized prevention strategies. By incorporating genetic risk profiling into cervical cancer prevention programs, particularly in high-risk populations, public health initiatives could better address the genetic component of cervical cancer risk.

Table 3 Comparison of Biological and Lifestyle Risk Factors for Cervical Cancer

Risk Factor	Description	Mechanism	Impact on Risk	Relevant Populations
HPV Infection	Primary cause of cervical cancer; persistent infections raise risk.	HPV infects cervical cells, leading to transformation and cancer.	Increases risk up to 25x in persistent cases, especially in HIV+ individuals.	Sexually active, higher in HIV+ women and areas with low vaccination coverage.
Smoking/Tobacco Use	Worsens HPV infections, contributing to cancer via DNA damage and immune suppression.	Tobacco carcinogens accumulate in cervical mucus, damaging DNA.	Raises risk by ~60%, up to 2x for heavy smokers.	Higher in women with limited healthcare access, especially in low-income regions.
Sexual Behavior	Early sexual activity and multiple partners raise HPV exposure.	Increased HPV exposure, especially in adolescents.	~2x higher risk for early debut or multiple partners.	Common in younger women and high-risk regions.
Contraceptive Use	Long-term hormonal contraceptives linked to higher cancer risk.	Estrogen promotes cell proliferation, aiding HPV persistence.	Raises risk by 20-30% for long-term users; reduces after stopping use.	Relevant to reproductive-age women, especially with HPV or multiple partners.
Genetic/Hereditary Factors	Genetic predispositions, like family history, heighten HPV infection risk and cancer susceptibility.	Variants in immune/tumor suppressor genes impair HPV response.	Family history/markers (HLA, TP53) raise risk up to 40%.	Relevant to women with family history or specific genetic traits.
Genetic and Hereditary Factors	Certain genetic predispositions, such as a family history of cervical cancer and specific gene variants, increase susceptibility to HPV infection and cervical carcinogenesis.	Genetic variations, especially in immune response genes (e.g., HLA polymorphisms) and tumor suppressor genes (e.g., TP53), impair immune response to HPV and increase the risk of cancer.	Family history and genetic markers (HLA, TP53) increase risk by up to 40%, particularly with persistent HPV infections.	Particularly relevant to women with a family history of cervical cancer or known genetic mutations, regardless of HPV status.

Table 3 provides a comparative overview of the key biological and lifestyle risk factors associated with cervical cancer, highlighting their descriptions, mechanisms of action, impact on cancer risk, and relevance to specific populations.

HPV Infection is the leading cause of cervical cancer, with high-risk strains (particularly HPV-16 and HPV-18) responsible for the majority of cases. Persistent HPV infection significantly increases cancer risk, particularly in immunocompromised individuals, such as those living with HIV.

Smoking is another major risk factor, as tobacco carcinogens accumulate in the cervix, impairing the immune system's ability to clear HPV and leading to DNA damage. Smokers have a considerably higher risk of developing cervical cancer, especially with prolonged tobacco use.

Sexual Behavior plays a role through increased exposure to HPV, particularly among women who begin sexual activity at an early age or have multiple sexual partners. The risk of cervical cancer rises with the number of sexual partners and early sexual debut, as this increases the likelihood of HPV acquisition.

Contraceptive Use, particularly long-term use of hormonal contraceptives, has been linked to a slightly higher risk of cervical cancer. This is believed to be due to the role of estrogen in promoting cellular changes in the cervix that may facilitate the persistence of HPV infections.

Genetic and Hereditary Factors can increase susceptibility to cervical cancer, particularly in women with a family history of the disease or certain genetic markers. Variations in immune response genes (e.g., HLA polymorphisms) or tumor suppressor genes (e.g., TP53) can impair the body's ability to fight off HPV infections, leading to a higher risk of cancer development.

In summary, the table outlines how these factors—HPV infection, smoking, sexual behavior, contraceptive use, and genetic predisposition—contribute to the risk of cervical cancer, with an emphasis on the biological mechanisms behind each factor and the populations most affected. Addressing these risk factors through prevention, education, and screening could significantly reduce the global burden of cervical cancer.

4. Populations at highest risk

4.1. Socioeconomic and Demographic Factors

Socioeconomic and demographic factors significantly impact cervical cancer risk, with evidence indicating that women from lower socioeconomic backgrounds face higher incidence rates and poorer outcomes. Limited access to healthcare services, including HPV vaccination and routine screening, is a primary barrier for low-income populations, particularly in low- and middle-income countries (LMICs), where over 80% of cervical cancer cases and deaths occur (Bray et al., 2018; Onuh et al., 2024). Within these populations, cervical cancer screening rates are often lower than 20%, compared to over 70% in high-income countries, highlighting the disparities that drive the global burden of this disease (Canfell et al., 2020).

Education level is another key demographic factor associated with cervical cancer risk. Women with lower levels of education are less likely to be informed about preventive measures and the importance of regular screening, further exacerbating disparities in cervical cancer incidence (Vu et al., 2021). A study examining educational disparities in cervical cancer outcomes found that women with less than a high school education had nearly twice the mortality rate compared to those with college-level education, emphasizing the need for targeted educational initiatives to raise awareness about cervical cancer prevention and early detection (Bray et al., 2018).

Furthermore, geographic disparities contribute significantly to the uneven distribution of cervical cancer cases worldwide. In many rural areas, particularly in LMICs, healthcare infrastructure is insufficient to support widespread screening and treatment efforts, leaving women in these regions at greater risk. For example, cervical cancer mortality rates in sub-Saharan Africa are up to five times higher than in North America, largely due to inadequate access to preventive healthcare and early treatment options (Canfell et al., 2020). Addressing these socioeconomic and demographic barriers is essential for reducing global disparities in cervical cancer outcomes, as targeted public health interventions and improved healthcare access can play a pivotal role in reaching high-risk populations.

Table 4 Impact of Socioeconomic and Demographic Factors on Cervical Cancer Risk

Risk Factor	Description	Impact on Cervical Cancer Risk	Populations Most Affected
Socioeconomic Status	Lower socioeconomic status is linked to reduced access to healthcare, including HPV vaccination and cervical cancer screening.	Limited access to healthcare services increases cervical cancer risk due to delayed detection and lack of prevention.	Women in low- and middle-income countries (LMICs) and underserved populations in high-income countries.
Healthcare Access	Women with limited access to screening and vaccination are at higher risk due to undetected HPV infections and delayed treatment.	Lack of screening and vaccination increases incidence and mortality rates, as early detection is critical.	Rural and remote areas, particularly in LMICs where healthcare infrastructure is insufficient.
Education Level	Women with lower education levels are less informed about preventive measures like regular screening.	Lower education correlates with higher cervical cancer mortality due to reduced awareness and screening rates.	Women with less than a high school education, particularly in underserved or rural regions.
Geographic Location	Geographic disparities, such as rural areas and LMICs, contribute to insufficient healthcare infrastructure and screening programs.	Inadequate healthcare access and lack of prevention programs result in higher cancer incidence and mortality.	Women in rural regions, particularly in sub-Saharan Africa, Asia, and parts of Latin America.

Table 4 emphasizes how socioeconomic and demographic factors—such as income, education, geographic location, and healthcare access—are directly tied to the risk of cervical cancer. Populations in low-income countries, rural areas, and those with limited education face greater challenges in accessing preventive healthcare, which contributes to higher rates of cervical cancer incidence and mortality. Addressing these disparities through targeted interventions, such as improving access to screening and HPV vaccination, education, and healthcare infrastructure, is crucial for reducing the global burden of cervical cancer.

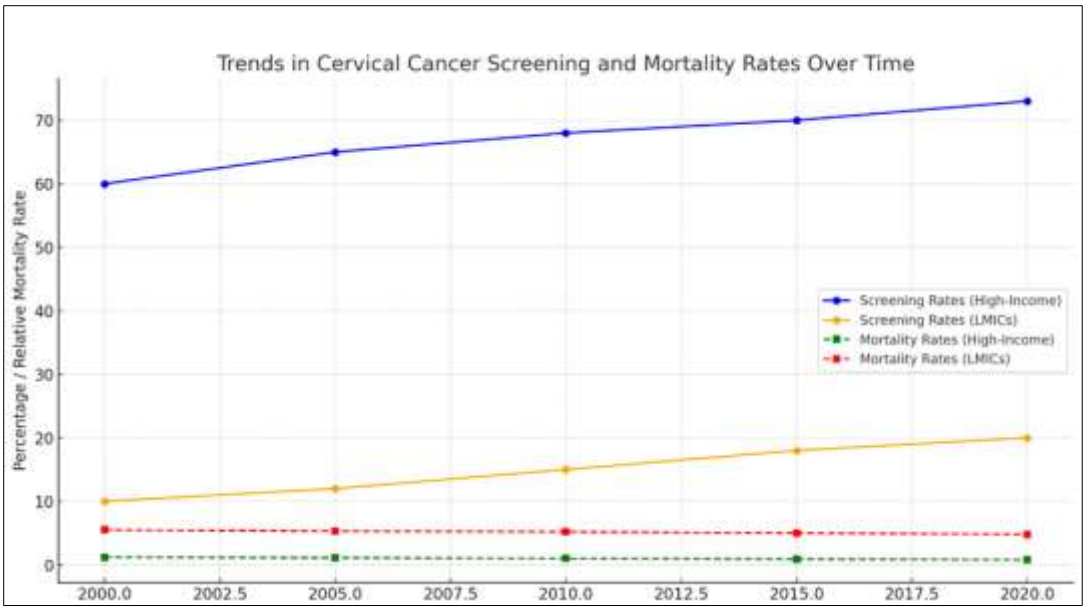

Figure 4 Trends in Cervical Cancer Screening and Mortality Rates: A Comparative Analysis of High-Income and Low- and Middle-Income Countries (2000-2020)

- Cervical Cancer Screening Rates: Showing an increase for both high-income countries and LMICs, with a more significant rise in high-income countries.
- Cervical Cancer Mortality Rates: Depicting a decrease over time for both groups, with a sharper decline in high-income countries compared to LMICs.

This visualization emphasizes the progress in screening and treatment over the years while highlighting persistent disparities.

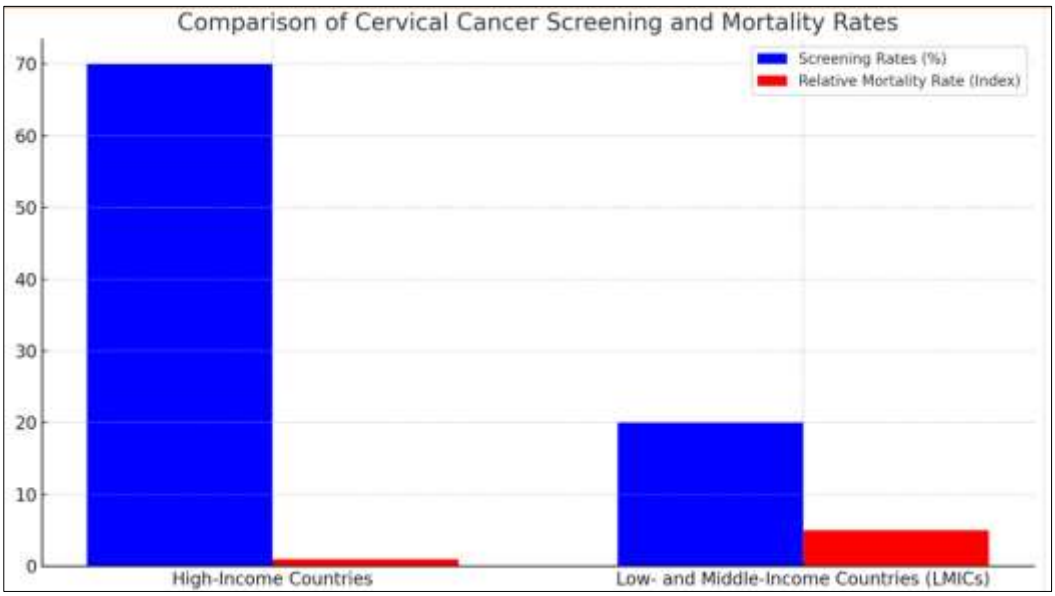

Figure 5 Disparities in Cervical Cancer Screening and Mortality Rates

The combined bar chart compares cervical cancer screening rates and relative mortality rates between high-income countries and low- and middle-income countries (LMICs).

- Screening Rates: High-income countries have a significantly higher screening rate (over 70%), whereas LMICs exhibit much lower rates (around 20%). This discrepancy indicates limited access to preventive healthcare services in LMICs.
- Mortality Rates: The chart shows that the relative mortality rate for cervical cancer in LMICs is up to five times higher than in high-income countries, highlighting severe healthcare disparities.

These differences underscore the urgent need for improved access to screening and healthcare services in LMICs to reduce the global burden of cervical cancer and enhance early detection and treatment.

4.2. Geographic and Ethnic Variations

Geographic and ethnic variations play a significant role in cervical cancer incidence, with certain regions and ethnic groups experiencing notably higher rates of the disease. For instance, women in sub-Saharan Africa, Latin America, and South Asia face disproportionately high cervical cancer rates, largely due to limited access to preventive healthcare and HPV vaccination (Bruni et al., 2019). In sub-Saharan Africa alone, cervical cancer accounts for over 20% of all female cancers, a staggering statistic when compared to less than 3% in North America, where screening programs are more widely accessible (Arbyn et al., 2020; Ezeami et al., 2024). These disparities underscore the critical need for targeted interventions in regions with limited resources.

Ethnic disparities in cervical cancer rates are also evident within countries, particularly in nations with ethnically diverse populations. In the United States, for example, Hispanic and Black women have significantly higher cervical cancer incidence and mortality rates than their White counterparts. Hispanic women experience a 32% higher incidence rate, while Black women have a mortality rate that is nearly twice that of White women (Benard et al., 2021; Ezeami et al., 2024). These differences are often attributed to socioeconomic factors, cultural barriers, and unequal access to healthcare, including lower screening rates and delayed treatment among minority groups.

Cultural factors further influence cervical cancer risk, as attitudes toward sexual health, HPV vaccination, and screening can vary significantly across ethnic groups. Studies suggest that cultural beliefs and stigmas surrounding HPV and cervical cancer may discourage women from seeking screening or vaccination, especially in communities where there is limited awareness or acceptance of preventive healthcare (Bruni et al., 2019). Addressing these geographic and ethnic disparities requires culturally sensitive health education, policy initiatives to improve access to preventive services, and a global commitment to reducing inequalities in cervical cancer outcomes.

Table 5 Geographic and Ethnic Disparities in Cervical Cancer Incidence: Key Findings and Contributing Factors

S/N	Aspect	Key Points	Primary Factors	Sources
1	Geographic Variation in Cervical Cancer Rates	Regions like sub-Saharan Africa, Latin America, and South Asia have disproportionately high rates.	Limited access to preventive healthcare and HPV vaccination	Bruni et al., 2019
2	Comparison Between Regions	Cervical cancer accounts for over 20% of all female cancers in sub-Saharan Africa compared to less than 3% in North America.	Availability of screening programs	Arbyn et al., 2020
3	Ethnic Disparities in the United States	Hispanic women have a 32% higher incidence rate; Black women have nearly double the mortality rate compared to White women.	Socioeconomic factors, cultural barriers, and unequal access to healthcare	Benard et al., 2021
4	Cultural Influence on Cervical Cancer Risk	Cultural beliefs and stigmas can discourage screening and vaccination, leading to higher risks in certain communities.	Limited awareness or acceptance of preventive healthcare	Bruni et al., 2019

Table 5 summarizes key findings on geographic and ethnic variations in cervical cancer incidence. It highlights the disparities across different regions and ethnic groups, the underlying causes, and references to support each point. Here's a breakdown of the table's content:

- Geographic Variation in Cervical Cancer Rates: This section points out that regions like sub-Saharan Africa, Latin America, and South Asia exhibit disproportionately high cervical cancer rates due to limited access to preventive healthcare and HPV vaccination. The source cited for this observation is Bruni et al. (2019).
- Comparison Between Regions: The table details how cervical cancer represents over 20% of all female cancers in sub-Saharan Africa, contrasting sharply with less than 3% in North America, where screening programs are more readily available. This comparison underscores the influence of healthcare infrastructure on disease outcomes, with reference to Arbyn et al. (2020).
- Ethnic Disparities in the United States: This section highlights that Hispanic women have a 32% higher incidence rate, and Black women experience nearly double the mortality rate compared to White women. These disparities are often linked to socioeconomic factors, cultural barriers, and unequal access to healthcare, with Benard et al. (2021) cited as the source.
- Cultural Influence on Cervical Cancer Risk: The table discusses how cultural beliefs and stigmas related to sexual health, HPV vaccination, and screening can deter women from seeking preventive care. This is particularly impactful in communities with limited awareness or acceptance of healthcare practices. Bruni et al. (2019) is again cited for this point.

Overall, the table underscores the complex interplay between geographic location, ethnicity, socioeconomic status, and cultural factors in influencing cervical cancer incidence and outcomes. It emphasizes the need for targeted interventions, policy changes, and culturally sensitive health education to address these disparities.

4.3. Immunocompromised Populations

Immunocompromised individuals are at a markedly higher risk for cervical cancer, as weakened immune systems are less able to clear human papillomavirus (HPV) infections, leading to increased rates of persistent infections and subsequent cancer development. Among women living with HIV, cervical cancer incidence is significantly elevated; studies indicate that HIV-positive women are five to six times more likely to develop cervical cancer than HIV-negative women, with some reports showing an incidence rate of up to 40 per 100,000 in this population (Serraino & Zucchetto,

2019; Aladetan et al., 2024; Jenča et al., 2024). This increased risk is due to the immunosuppressive effects of HIV, which inhibit the body's ability to combat HPV, the primary etiological agent in cervical carcinogenesis.

Organ transplant recipients also face a higher cervical cancer risk due to the long-term immunosuppressive therapy required to prevent organ rejection. Research reveals that transplant recipients are approximately two to three times more likely to develop cervical cancer compared to the general population (Engels et al., 2020; Forood et al., 2024). The immunosuppressive medications in these individuals hinder the immune system's effectiveness in clearing HPV infections, thereby elevating the risk of progression from infection to malignancy. Given that persistent HPV infection is a primary factor in cervical cancer, the impact of these medications places immunocompromised individuals in a particularly vulnerable category (Forood et al., 2024).

The role of immunosuppression in cervical cancer risk extends to other conditions requiring immunosuppressive treatments, such as autoimmune diseases. For instance, women undergoing immunosuppressive therapies for conditions like lupus or rheumatoid arthritis exhibit a higher prevalence of HPV infection and subsequent cervical dysplasia, with a reported increase in cervical intraepithelial neoplasia (CIN) by 30% compared to women not undergoing such treatments (D'Souza et al., 2020). These findings highlight the necessity for enhanced cervical cancer screening protocols tailored to immunocompromised populations, ensuring timely detection and intervention to reduce disease progression in these high-risk groups.

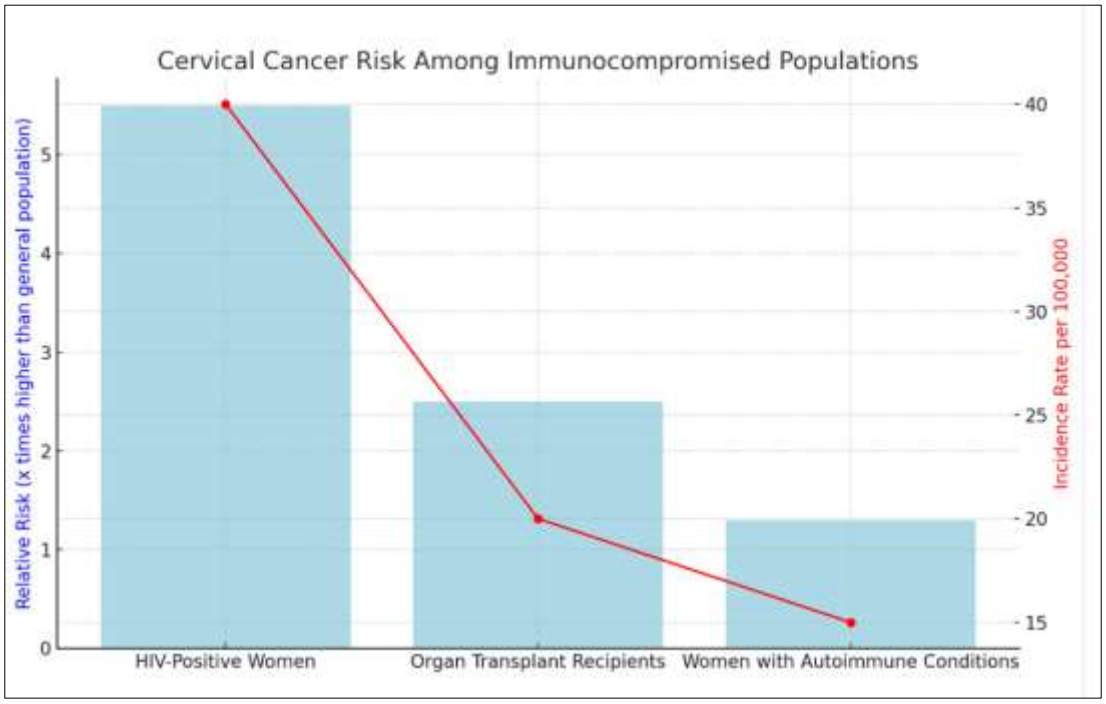

Figure 6 Elevated Cervical Cancer Risk and Incidence Among Immunocompromised Populations

Figure 6 highlights the increased risk and incidence of cervical cancer among different immunocompromised populations:

- HIV-Positive Women have the highest relative risk, being 5.5 times more likely to develop cervical cancer than the general population, with an incidence rate of approximately 40 per 100,000.
- Organ Transplant Recipients face a 2.5 times higher risk, with an incidence rate around 20 per 100,000, due to long-term immunosuppressive therapy.
- Women with Autoimmune Conditions undergoing immunosuppressive treatment show a moderately increased risk (1.3 times higher), with an incidence rate of about 15 per 100,000. This summary underscores the necessity for enhanced cervical cancer screening and preventive protocols tailored to these high-risk groups to facilitate timely detection and intervention.

4.4. Age-Related Risk Variations

Age is a significant factor in cervical cancer risk, with particular age groups exhibiting heightened vulnerability due to physiological and behavioral differences. Epidemiological studies reveal that women aged 35-44 years experience the highest incidence of cervical cancer, accounting for approximately 30% of cases globally, as this age group is more likely to have persistent human papillomavirus (HPV) infections acquired during younger years (Bray et al., 2018). Persistent HPV infections, especially with high-risk strains, often require years to progress from infection to precancerous lesions and ultimately invasive cancer, which aligns with increased diagnoses in this middle-aged demographic.

Young women, especially those under 25, are also vulnerable to HPV infection due to early sexual activity and a still-developing cervical transformation zone, which is more susceptible to HPV entry and infection (Vaccarella et al., 2019). However, cervical cancer incidence in this age group remains relatively low, as many infections are transient and are typically cleared by the immune system. In contrast, cervical cancer rates increase significantly with age among those who do not clear the infection, particularly in women over 65. Although the incidence rate decreases after age 65, mortality rates are disproportionately high in this group, largely due to lower screening rates and delayed diagnosis (Canfell et al., 2020).

The trend of reduced screening in older age groups is concerning, as studies indicate that about 20% of cervical cancer cases occur in women aged 65 and older, with the mortality rate in this group being nearly twice as high as in younger populations (Bray et al., 2018). This disparity underscores the importance of continuing screening efforts beyond typical age cutoffs to ensure early detection in older women, who may otherwise be overlooked in preventive healthcare. Targeted interventions and screening policies that address age-specific risks are crucial for reducing the burden of cervical cancer across all age groups.

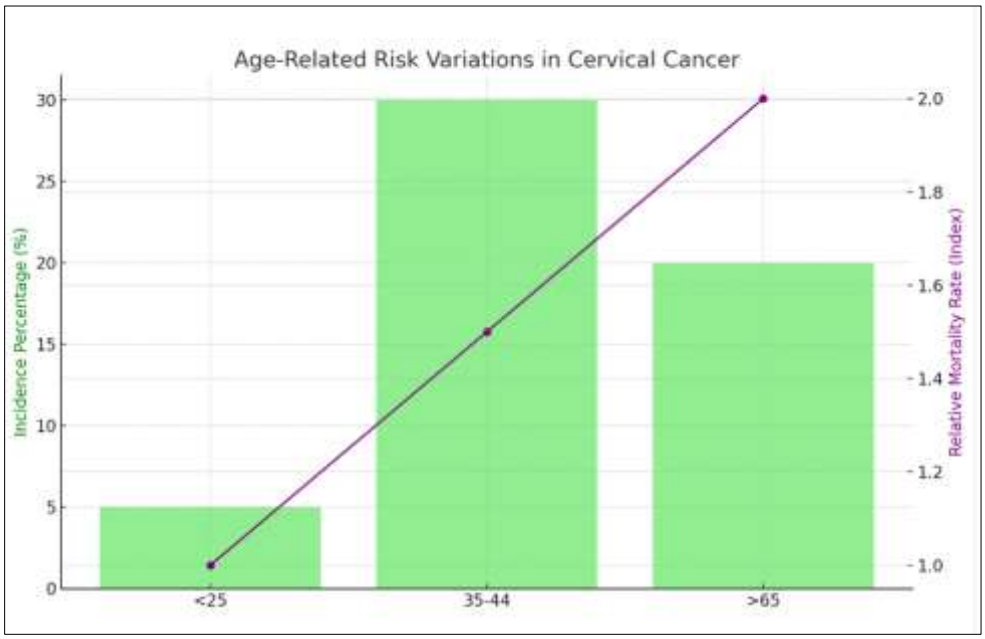

Figure 7 Age-Related Incidence and Mortality Variations in Cervical Cancer

The chart in figure 7 depicts the variation in cervical cancer incidence and relative mortality rates across different age groups:

- Incidence Rates: Women aged 35-44 have the highest incidence, making up about 30% of global cases due to the progression of persistent HPV infections acquired earlier in life. Women over 65 represent 20% of cases, while those under 25 have a low incidence (approximately 5%).
- Mortality Rates: Women over 65 face significantly higher mortality rates, nearly twice as high as younger age groups, due to reduced screening and late diagnoses. The 35-44 age group shows a moderate increase in mortality, while the youngest group (<25) has the lowest mortality rate.

This emphasizes the need for targeted screening and preventive measures tailored to specific age groups to reduce both incidence and mortality.

5. Discussion and Future Directions

5.1. Synthesis of Findings

This review has synthesized key epidemiological studies on cervical cancer risk factors, underscoring the complexity of influences beyond mere HPV infection. While HPV remains the predominant cause of cervical cancer, additional biological, lifestyle, demographic, and genetic factors play crucial roles in modulating risk across diverse populations. The data reveal that smoking, early sexual debut, and multiple sexual partners significantly elevate the risk of persistent HPV infection, particularly among women with limited access to preventive healthcare services. Furthermore, the interaction between socioeconomic status and health behavior contributes to stark disparities in cervical cancer incidence and mortality, with low-income, rural, and ethnically marginalized groups disproportionately affected. These findings emphasize that cervical cancer is not solely a biological challenge but also a deeply entrenched socio-economic issue that requires multi-dimensional solutions.

Geographically and demographically, the burden of cervical cancer is most pronounced in low- and middle-income countries, where healthcare infrastructure and public health education are often limited. Age-related data demonstrate that women aged 35-44 represent a critical demographic for early intervention, given the increased incidence in this age group, likely due to the time-lagged progression of persistent HPV infections acquired in younger years. Similarly, older women, especially those over 65, are at significant risk due to reduced screening rates, which contributes to later-stage diagnoses and higher mortality. The impact of immunocompromised status, particularly among HIV-positive women and organ transplant recipients, further illustrates the vulnerabilities within specific populations that necessitate tailored preventive strategies.

This synthesis of findings highlights the urgency of integrated prevention approaches that account for both medical and socio-economic risk factors. Screening programs, while vital, must be supported by broader initiatives that improve healthcare accessibility, encourage behavioral health education, and address socio-economic barriers to preventive care. Comprehensive prevention efforts that incorporate these multi-dimensional insights can better address the underlying causes of cervical cancer disparities and pave the way for more equitable health outcomes across populations at highest risk.

5.2. Implications for Public Health and Policy

The synthesis of cervical cancer risk factors presents clear implications for public health strategies and policy development. Given the complex interplay of biological, lifestyle, socioeconomic, and demographic factors, it is evident that a one-size-fits-all approach to cervical cancer prevention is insufficient. Public health frameworks must prioritize equitable access to HPV vaccination and cervical cancer screening, especially for underserved populations in low- and middle-income countries and marginalized communities in high-income nations. Expanding vaccination programs to cover a broader demographic range and ensuring vaccination affordability and accessibility could profoundly reduce HPV-related cancer risk, particularly among populations with historically low immunization rates.

Effective public health policy must also address the behavioral and lifestyle risk factors contributing to cervical cancer. Integrating smoking cessation programs with cervical cancer prevention initiatives, for instance, could mitigate one of the most significant modifiable risk factors associated with HPV persistence and progression to malignancy. Policies promoting comprehensive sexual health education, especially targeting young women, can help reduce the risk associated with early sexual debut and multiple sexual partners. This education should emphasize HPV prevention, safe sexual practices, and the importance of early screening, providing young people with the tools and knowledge to make informed health decisions.

Furthermore, the socio-economic barriers that restrict healthcare access for low-income, rural, and ethnically diverse populations require targeted policy responses. Financial support for screening services, transportation aid for rural residents, and culturally sensitive health education campaigns can improve early detection and reduce advanced cervical cancer cases in high-risk communities. Policies promoting routine screening beyond the conventional age limits—especially for women over 65—are essential, as data reveal a significant number of cases in this age group due to decreased screening rates.

Incorporating genetic risk assessment into cervical cancer prevention programs could also enhance targeted screening and intervention strategies, identifying individuals with a heightened genetic susceptibility. Policymakers and healthcare providers should consider genetic screening as part of an integrated prevention strategy, offering

personalized care options for those with genetic predispositions to persistent HPV infections or cervical cancer progression.

Ultimately, the path forward demands a coordinated, multi-faceted policy approach that aligns preventive healthcare services with educational, social, and economic support systems. By addressing the underlying factors that drive cervical cancer disparities, public health policy can create a robust framework for prevention that is responsive to the diverse needs of at-risk populations and committed to reducing the global burden of cervical cancer.

5.3. Recommendations for Future Research

The comprehensive analysis of cervical cancer risk factors reveals several critical gaps in current knowledge, pointing to essential avenues for future research. First, there is a pressing need for longitudinal studies that examine the long-term interactions between genetic susceptibility, HPV persistence, and lifestyle factors such as smoking and contraceptive use. While current studies highlight correlations, in-depth research into the causal pathways and mechanisms underlying these risk factors could deepen our understanding of cervical carcinogenesis and guide more precise intervention strategies.

Future research must also prioritize multi-population studies that explore the impact of socio-economic and cultural variables on cervical cancer outcomes. Expanding research across diverse geographic regions and demographic groups, particularly in low- and middle-income countries, is crucial for capturing the nuanced social and economic barriers to effective prevention. Studies that investigate the efficacy of culturally tailored education programs and the impact of economic support for screening and vaccination on high-risk populations would provide invaluable data to inform public health policy and interventions.

Additionally, there is an urgent need for research focusing on age-specific risk profiles and screening efficacy among older women. With significant evidence showing higher mortality rates due to late diagnoses in women over 65, future studies should evaluate the potential benefits of extending regular screening beyond traditional age limits and assess the most effective screening intervals for older age groups. This could pave the way for revised guidelines that reflect the evolving understanding of age-related cervical cancer risk.

Exploratory research on integrating genetic risk assessment into cervical cancer prevention programs is another promising area. Identifying genetic biomarkers linked to HPV persistence and cancer progression could support the development of personalized screening and vaccination protocols, making prevention efforts more targeted and effective. Research should focus on the feasibility, cost-effectiveness, and ethical considerations of incorporating genetic screening within public health frameworks, particularly in resource-limited settings.

6. Conclusion

In summary, a future-oriented research agenda must be both comprehensive and inclusive, addressing the diverse factors that contribute to cervical cancer risk across populations. By advancing research in these targeted areas, the scientific community can support the development of a more equitable, efficient, and precise approach to cervical cancer prevention and control, ultimately working toward the goal of global cervical cancer eradication.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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