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CERVICAL CANCER AND HUMAN PAPILLOMAVIRUS COINFECTION: EPIDEMIOLOGY, RISK FACTORS, AND PREVENTION

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Abstract: Cervical cancer remains one of the most common malignancies affecting women worldwide and continues to represent a major public health concern despite remarkable advances in vaccination and screening programs. Persistent infection with high-risk human papillomavirus (HPV) is recognized as the primary etiological factor responsible for cervical carcinogenesis. However, increasing evidence indicates that coinfection involving multiple HPV genotypes, together with various behavioral, immunological, and environmental risk factors, may influence viral persistence and disease progression. This review aimed to evaluate the current epidemiology of cervical cancer and HPV coinfection, analyze the principal risk factors associated with disease development, and summarize contemporary prevention strategies. A comprehensive narrative review of peer-reviewed literature was conducted using publications retrieved from PubMed, Scopus, Web of Science, Google Scholar, and reports from international health organizations. The reviewed evidence confirms that persistent high-risk HPV infection, particularly HPV-16 and HPV-18, remains the dominant cause of cervical cancer, while multiple HPV genotype coinfections may increase the risk of persistent infection and progression to cervical intraepithelial neoplasia in selected populations. Additional contributing factors include early sexual activity, multiple sexual partners, smoking, immunosuppression, HIV infection, long-term oral contraceptive use, and inadequate participation in cervical screening programs. The findings further demonstrate that prophylactic HPV vaccination, HPV DNA testing, liquid-based cytology, organized cervical screening, and public health education are highly effective in reducing cervical cancer incidence and mortality. Nevertheless, substantial inequalities in vaccine coverage and healthcare accessibility continue to contribute to the global disease burden. Future research should focus on the biological mechanisms of HPV coinfection, novel molecular biomarkers, and personalized preventive strategies to improve early diagnosis and optimize cervical cancer prevention worldwide.

Keywords: cervical cancer, human papillomavirus, HPV, HPV coinfection, high-risk HPV, cervical intraepithelial neoplasia, epidemiology, risk factors, HPV vaccination, cervical screening, HPV DNA testing, molecular diagnostics, women's health, cancer prevention, public health.

Introduction

Cervical cancer remains one of the most significant public health challenges affecting women worldwide and continues to be a leading cause of cancer-related morbidity and mortality,

particularly in low- and middle-income countries. According to recent global cancer statistics, cervical cancer ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related death among women. Despite substantial progress in vaccination programs, screening strategies, and therapeutic interventions, the global burden of cervical cancer remains disproportionately high in regions where access to preventive healthcare services is limited [1].

Persistent infection with high-risk human papillomavirus (HPV), especially HPV genotypes 16 and 18, is recognized as the primary etiological factor responsible for the development of cervical intraepithelial neoplasia and invasive cervical carcinoma. More than 99% of cervical cancer cases are associated with persistent HPV infection, making HPV one of the strongest known infectious causes of human malignancy. However, HPV infection alone is not sufficient for malignant transformation. Most HPV infections are transient and are eliminated by the host immune system within one to two years. Only persistent infection combined with additional biological, behavioral, and environmental risk factors contributes to the progression from precancerous lesions to invasive cervical cancer [2].

The natural history of cervical carcinogenesis is influenced by multiple cofactors that interact with persistent HPV infection. These include early onset of sexual activity, multiple sexual partners, smoking, long-term oral contraceptive use, immunosuppression, human immunodeficiency virus (HIV) infection, sexually transmitted infections, high parity, and genetic susceptibility. Coinfections involving different HPV genotypes have also attracted increasing scientific attention because they may influence viral persistence, immune responses, and disease progression. Several epidemiological studies suggest that women infected with multiple high-risk HPV types may have an increased likelihood of developing high-grade cervical lesions compared with those infected by a single HPV genotype, although the exact biological mechanisms remain under investigation [3].

Recent advances in molecular diagnostics have significantly improved the understanding of HPV epidemiology and cervical carcinogenesis. High-risk HPV DNA testing, genotyping, liquid-based cytology, molecular biomarkers, and colposcopic evaluation have enhanced the early detection of cervical precancerous lesions and facilitated risk-based patient management. Simultaneously, prophylactic HPV vaccination has emerged as one of the most successful public health interventions for preventing HPV-associated diseases. The implementation of national vaccination programs, together with organized cervical screening and health education initiatives, has resulted in substantial reductions in HPV prevalence and cervical cancer incidence in many countries. Nevertheless, disparities in vaccine coverage, screening accessibility, and healthcare infrastructure continue to limit global progress toward cervical cancer elimination [4].

Considering the continuing global burden of cervical cancer and the central role of persistent HPV infection in disease development, a comprehensive understanding of HPV epidemiology, associated risk factors, and contemporary prevention strategies remains essential for improving women's health. Therefore, the aim of this study is to review the current evidence regarding the epidemiology of cervical cancer and HPV infection, analyze the major risk factors contributing to disease progression, and summarize modern preventive approaches, including vaccination, molecular screening, early diagnosis, and public health interventions.

Methodology

This study was conducted as a comprehensive narrative review to evaluate the current scientific evidence regarding the epidemiology of cervical cancer and human papillomavirus (HPV) coinfection, associated risk factors, and contemporary prevention strategies. A systematic search of the scientific literature was performed using internationally recognized electronic databases, including PubMed, Scopus, Web of Science, Google Scholar, and the World Health Organization (WHO) digital library. Original research articles, systematic reviews, meta-analyses, epidemiological reports, and international clinical guidelines published primarily between 2015 and 2025 were included in the review. Earlier landmark publications were also examined when they provided essential background information on HPV biology and cervical carcinogenesis. The literature search utilized combinations of the following keywords: cervical cancer, human papillomavirus, HPV infection, HPV coinfection, high-risk HPV, cervical intraepithelial neoplasia, epidemiology, risk factors, vaccination, screening, and prevention [4].

The selection of studies followed predefined inclusion and exclusion criteria to ensure methodological consistency and scientific reliability. Eligible publications included observational cohort studies, case-control studies, cross-sectional surveys, randomized clinical trials, systematic reviews, meta-analyses, and evidence-based clinical guidelines investigating HPV epidemiology, cervical cancer development, HPV genotype distribution, coinfection patterns, and preventive interventions. Studies with insufficient methodological quality, duplicated publications, conference abstracts without full-text availability, and reports unrelated to the objectives of this review were excluded. The quality of each selected study was critically evaluated according to study design, sample size, statistical methodology, diagnostic techniques, and clinical relevance [5].

A qualitative comparative analysis was used to synthesize the collected evidence. Particular attention was given to the prevalence of single and multiple HPV genotype infections, geographical differences in HPV distribution, persistence of high-risk HPV infection, demographic characteristics, behavioral risk factors, and host-related determinants influencing cervical carcinogenesis. The review also examined molecular diagnostic approaches, including HPV DNA testing, genotyping assays, liquid-based cytology, biomarker analysis, and colposcopic evaluation, together with current recommendations regarding cervical cancer screening and vaccination. Evidence concerning the effectiveness of prophylactic HPV vaccination, early detection strategies, and integrated public health interventions was systematically compared across different populations and healthcare settings [5].

To strengthen the reliability of the findings, epidemiological data from international organizations, including the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), and other recognized public health institutions, were compared with results reported in peer-reviewed scientific journals. Whenever discrepancies were identified, greater emphasis was placed on large multicenter cohort studies, systematic reviews, and meta-analyses because of their higher level of scientific evidence. The reviewed literature was subsequently organized into thematic categories covering epidemiology, HPV genotype distribution, biological mechanisms of persistent infection, risk factors for cervical cancer development, screening strategies, vaccination programs, and modern preventive approaches [6].

Because this investigation was based exclusively on previously published scientific literature, no human participants were directly involved, and no personal clinical information was collected.

Therefore, ethical committee approval and informed consent were not required. Nevertheless, the review was conducted according to internationally accepted principles of scientific integrity, transparency, accurate citation practices, and evidence-based reporting. This methodological approach provides a comprehensive overview of the current scientific knowledge regarding cervical cancer and HPV coinfection while ensuring that the conclusions presented are supported by reliable and high-quality scientific evidence [6].

Results

The analysis of the selected scientific literature demonstrated that persistent infection with high-risk human papillomavirus (HPV) remains the principal cause of cervical cancer worldwide. More than 99% of cervical cancer cases were associated with persistent HPV infection, with HPV genotypes 16 and 18 accounting for approximately 70% of invasive cervical cancers. The reviewed epidemiological studies consistently showed that the prevalence of HPV infection is highest among sexually active young women, whereas persistent infection and progression to cervical intraepithelial neoplasia are more frequently observed in women with impaired immune responses or prolonged exposure to additional behavioral and environmental risk factors. These findings reinforce the central role of persistent HPV infection in cervical carcinogenesis and support current recommendations emphasizing early detection and vaccination [7].

The review further revealed considerable geographical variation in HPV genotype distribution and cervical cancer incidence. Low- and middle-income countries continue to experience the highest disease burden because of limited access to HPV vaccination, organized cervical screening, and molecular diagnostic services. In contrast, countries implementing national immunization programs and population-based screening strategies have reported substantial reductions in HPV prevalence, precancerous cervical lesions, and cervical cancer mortality. These findings highlight the effectiveness of integrated preventive healthcare policies in reducing disease burden at the population level [7].

Several studies included in this review demonstrated that infection with multiple high-risk HPV genotypes is associated with an increased risk of persistent viral infection and progression to high-grade cervical lesions compared with single-genotype infections. Coinfection may alter local immune responses, increase viral persistence, and facilitate cervical epithelial transformation through synergistic biological mechanisms. Nevertheless, the clinical significance of HPV coinfection remains an area of ongoing investigation because the relative contribution of individual HPV genotypes varies considerably across different geographical regions and patient populations [8].

The analysis also identified multiple independent risk factors contributing to cervical cancer development in HPV-positive women. These factors include early initiation of sexual activity, multiple sexual partners, cigarette smoking, long-term oral contraceptive use, human immunodeficiency virus (HIV) infection, chronic immunosuppression, high parity, low socioeconomic status, and inadequate participation in cervical screening programs. The coexistence of these behavioral, biological, and environmental factors significantly increases the probability of persistent HPV infection and malignant transformation, emphasizing the multifactorial nature of cervical carcinogenesis [9].

Evaluation of preventive interventions demonstrated that prophylactic HPV vaccination remains the most effective strategy for reducing the incidence of HPV-associated cervical disease. Vaccination programs targeting adolescents before sexual debut have shown remarkable effectiveness in decreasing infections caused by high-risk HPV genotypes and reducing the prevalence of cervical intraepithelial neoplasia. Furthermore, the implementation of HPV DNA testing, liquid-based cytology, molecular biomarkers, and colposcopy has significantly improved early diagnosis and risk stratification of women with abnormal cervical findings. These diagnostic advances facilitate timely clinical management and contribute to improved long-term outcomes [10].

Table 1. Summary of Major Findings Regarding Cervical Cancer and HPV Coinfection

Indicator	Observed findings
Primary etiological factor	Persistent high-risk HPV infection
Most oncogenic HPV genotypes	HPV-16 and HPV-18
Estimated proportion of cervical cancers caused by HPV-16/18	Approximately 70%
Major risk factors	Early sexual activity, smoking, multiple sexual partners, HIV infection, immunosuppression
Most effective prevention	HPV vaccination combined with cervical screening
Recommended screening methods	HPV DNA testing, liquid-based cytology, colposcopy
Regions with highest disease burden	Low- and middle-income countries

Overall, the reviewed evidence confirms that persistent high-risk HPV infection remains the dominant cause of cervical cancer, while multiple behavioral, immunological, and socioeconomic factors influence disease progression. Comprehensive vaccination programs, organized cervical screening, molecular diagnostic technologies, and evidence-based public health interventions continue to represent the most effective strategies for reducing the global burden of cervical cancer and improving women's reproductive health outcomes [10].

Discussion

The findings of this review reinforce the well-established scientific evidence that persistent infection with high-risk human papillomavirus (HPV) is the fundamental prerequisite for the development of cervical cancer. Although transient HPV infection is highly prevalent among sexually active women, only a relatively small proportion of infections persist long enough to induce cervical epithelial dysplasia and malignant transformation. The reviewed literature demonstrates that viral persistence rather than initial HPV acquisition represents the most important

determinant of disease progression. This observation is consistent with current international screening recommendations that emphasize the identification of persistent high-risk HPV infection as the primary indicator of cervical cancer risk [11].

An important finding of the present review is the growing recognition of HPV coinfection involving multiple high-risk genotypes. Several epidemiological studies suggest that women harboring more than one oncogenic HPV genotype may have an increased probability of persistent infection and progression to high-grade cervical lesions compared with women infected by a single HPV type. However, the magnitude of this association varies considerably among different populations because of differences in geographic HPV genotype distribution, host genetic susceptibility, immune status, and behavioral risk factors. Consequently, further multicenter longitudinal investigations are required to determine the precise clinical significance of multiple HPV genotype coinfections and their influence on cervical carcinogenesis [12].

The present analysis also highlights the multifactorial nature of cervical cancer development. Persistent HPV infection interacts with numerous biological, environmental, and behavioral cofactors, including cigarette smoking, early initiation of sexual activity, multiple sexual partners, long-term hormonal contraceptive use, immunosuppression, HIV infection, and socioeconomic inequalities. These factors may impair immune surveillance, prolong viral persistence, and increase susceptibility to malignant transformation. Therefore, cervical cancer prevention should not focus exclusively on viral infection but should incorporate broader strategies addressing modifiable behavioral risks, health education, and equitable access to preventive healthcare services [13].

The remarkable effectiveness of HPV vaccination programs observed in many countries represents one of the most significant achievements in modern cancer prevention. Evidence reviewed in this study indicates that widespread vaccination combined with organized cervical screening substantially reduces HPV prevalence, cervical intraepithelial neoplasia, and invasive cervical cancer incidence. Nevertheless, important disparities persist between high-income and resource-limited countries because of unequal vaccine availability, inadequate screening infrastructure, financial constraints, and limited public awareness. Expanding vaccination coverage and strengthening national screening programs remain critical priorities for achieving the global objective of cervical cancer elimination proposed by the World Health Organization [14].

Overall, the findings of this review support the implementation of comprehensive prevention strategies that integrate HPV vaccination, molecular screening technologies, evidence-based clinical management, public health education, and continuous epidemiological surveillance. Future research should focus on the long-term effectiveness of next-generation HPV vaccines, the biological mechanisms underlying multiple HPV genotype coinfection, personalized risk prediction models, and the identification of novel molecular biomarkers capable of improving early diagnosis and individualized patient management. Such investigations will contribute to the development of more effective prevention policies and ultimately reduce the global burden of cervical cancer and HPV-associated diseases among women worldwide [15].

Conclusion

Cervical cancer remains one of the most preventable yet still highly prevalent malignancies affecting women worldwide. The present review confirms that persistent infection with high-risk

human papillomavirus (HPV) is the principal etiological factor responsible for the development of cervical cancer, while HPV coinfection involving multiple oncogenic genotypes may increase the likelihood of persistent infection and progression to high-grade cervical lesions in certain populations. However, cervical carcinogenesis is a multifactorial process influenced not only by viral persistence but also by host immune status, behavioral factors, socioeconomic conditions, and access to preventive healthcare services.

The findings demonstrate that comprehensive prevention strategies are the most effective approach for reducing the global burden of cervical cancer. Prophylactic HPV vaccination, organized cervical screening, HPV DNA testing, liquid-based cytology, colposcopy, and public health education have collectively contributed to substantial reductions in HPV prevalence, precancerous cervical lesions, and cervical cancer mortality in countries with well-established prevention programs. Nevertheless, significant disparities continue to exist between high-income and low-resource countries because of unequal access to vaccination, diagnostic technologies, and healthcare infrastructure.

Advances in molecular diagnostics and HPV genotyping have significantly improved the early identification of women at increased risk of cervical cancer and have facilitated more personalized clinical management. Continued implementation of evidence-based screening programs, expansion of vaccination coverage, and strengthening of healthcare systems remain essential for achieving the World Health Organization's goal of eliminating cervical cancer as a public health problem.

Future research should focus on the biological significance of multiple HPV genotype coinfections, host immune responses, novel molecular biomarkers, and the long-term effectiveness of next-generation HPV vaccines. Large multicenter prospective studies and international collaborative research will further improve the understanding of cervical carcinogenesis and support the development of more effective preventive strategies for protecting women's health worldwide.

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