Iran J Public Health, Vol. 53, No.12, Dec 2024, pp.2671-2682

Review Article

Exploring the Intricacies of Cervical Intraepithelial Neoplasia and Its Connection with HPV: A Narrative Review

Parvin Karimi [1], Seyed Mohammad Reza Hosseini [2], Zahra Sadat Mousavian Hiagh [3], Sobhan Aboulhassanzadeh [4,5], Nahid Asghari [6,7], *Hamed Aghazadeh [5,8]

1. *Fars Population-Based Cancer Registry, Shiraz University of Medical Sciences, Shiraz, Iran*
2. *School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran*
3. *Laboratory of Dendrimers and Nano-Biopolymers, Faculty of Chemistry, University of Tabriz, Tabriz, Iran*
4. *School of Biotechnology Faculty of Science and Health, Dublin City University, Dublin, Ireland*
5. *Research Center for Pharmaceutical Nanotechnology (RCPN), Tabriz University of Medical Sciences, Tabriz, Iran*
6. *Department of Basic Science, Maragheh University of Medical Sciences, Maragheh, Iran*
7. *Department of Microbiology, Faculty of Basic Science, Islamic Azad University of Urmia, Urmia, Iran*
8. *School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*

***Corresponding Author:** Emails: Hamed.Aghazadeh@ut.ac.ir, Hamed.Aghazadeh860@gmail.com

(Received 12 Feb 2024; accepted 18 May 2024)

Abstract

Cervical Intraepithelial Neoplasia grade III (CIN III) represents a critical precursor to invasive cervical cancer, necessitating a comprehensive understanding of its etiology, progression, diagnosis, and preventive strategies. This review integrates an approach to synthesize current literature, conducted through a meticulous search of databases (Scopus, Web of Science, and Google Scholar) for relevant articles discussing CIN III and its association with Human Papillomavirus (HPV). The review delineates the multifaceted landscape of CIN III, elucidating the pathogenesis involving high-risk HPV types, demographic factors (age and sexual behavior), behavioral determinants (smoking and contraceptive use), and environmental influences impacting disease epidemiology. Diagnostic modalities, including Pap smears, HPV testing, and colposcopy, were assessed for their role in early detection and intervention. The results highlight the significance of HPV vaccination, screening programs, and robust public health policies in mitigating the burden of CIN III. Effective interventions, particularly excisional procedures, demonstrate efficacy in reducing the risk of progression to invasive cancer, emphasizing the importance of vigilant follow-up. A comprehensive approach integrating vaccination initiatives, early detection through screening, and equitable healthcare policies stands pivotal in combating CIN III. The review underscores the imperative of evidence-based interventions for disease prevention, reducing disparities, and enhancing public health outcomes for individuals affected by or at risk of CIN III.

Keywords: Cervical intraepithelial neoplasia; Human papillomavirus; Health policies

Introduction

Cervical Intraepithelial Neoplasia grade III (CIN III), the most severe form of cervical precancerous lesions, stands as a pivotal precursor to the development of invasive cervical cancer. This

progression from CIN III to cervical cancer underscores the urgency and significance of understanding its etiological factors, particularly its robust association with Human Papillomavirus (HPV) infection (1).

HPV, a sexually transmitted infection, has been identified as the principal etiological agent behind the development of CIN III, especially high-risk HPV genotypes such as HPV-16 and HPV-18. These high-risk types exhibit a heightened propensity to cause persistent infections, instigating the stepwise transformation of cervical epithelial cells toward neoplastic changes (2). The intricate interplay between HPV and the cervical epithelium involves viral oncoproteins, notably E6 and E7, which subvert the normal cellular regulatory mechanisms, promoting aberrant cell proliferation and genomic instability. This disruption, in turn, leads to the manifestation of CIN III lesions, characterized by severe dysplastic changes within the cervical epithelium (3).

Understanding the nuanced mechanisms underpinning the pathogenesis of CIN III and its close correlation with HPV infection is crucial for not only elucidating the disease progression but also for informing preventive strategies and targeted interventions. Addressing the multifaceted aspects of CIN III in relation with HPV infection is essential in the pursuit of effective screening, management, and prevention strategies aimed at curbing the globally burden of cervical cancer (4).

Clinical manifestations of CIN III often remain asymptomatic, emphasizing the significance of screening methods such as Pap smears and HPV testing for early detection and accurate diagnosis (5). Treatment options for CIN III range from surgical interventions like loop electrosurgical excision procedures (LEEP) and cone biopsy to medical treatments such as topical therapies, emphasizing the need for tailored approaches (6).

Pathogenesis of CIN III

CIN III development is primarily initiated by the infection of cervical epithelial cells with high-risk HPV types, notably HPV-16 and HPV-18 (7, 8). The viral infection primarily targets the basal epithelial cells of the cervical transformation zone, disrupting the normal homeostasis of the cervical epithelium (9). Upon HPV infection, the expression of viral oncoproteins, particularly E6 and E7, plays a pivotal role in modulating crucial cellular regulatory mechanisms (10). E6 and E7 proteins interact with key cellular proteins, such as tumor suppressor p53 and pRb, respectively. These interactions disrupt the normal cell cycle control mechanisms, leading to uncontrolled cell proliferation and evasion of apoptosis (11).

Consequently, the dysregulation of cell cycle checkpoints by HPV oncoproteins leads to the accumulation of genetic mutations and alterations within the cervical epithelial cells, driving the progression from low-grade lesions to the severe dysplastic changes of CIN III (12). Furthermore, the viral integration into the host genome, observed in advanced CIN III lesions, can induce genomic instability and chromosomal aberrations (13). This integration event is associated with a higher risk of malignant transformation and progression to invasive cervical cancer.

The microenvironment within the cervical epithelium also contributes to CIN III pathogenesis. Inflammatory responses, immunological factors, and interactions with stromal cells influence the persistence and progression of HPV infection (14). Moreover, additional risk factors, such as hormonal influences, smoking, and co-infections, may further exacerbate the molecular alterations initiated by HPV infection, contributing to the development and progression of CIN III (15).

HPV Types and Subtypes

Several studies have extensively investigated the prevalence and impact of different HPV types on the development of CIN III (16, 17). High-risk HPV types, prominently HPV-16 and HPV-18, are widely recognized for their strong association with CIN III and subsequent progression to invasive cervical cancer (7). These HPV types exhibit a higher oncogenic potential and are frequently detected in severe dysplastic lesions of CIN III (18). Furthermore, studies have highlighted the role of other high-risk HPV types, such as HPV-31, HPV-33, HPV-45, and HPV-52, in contributing to CIN III development, albe-

it with varying prevalence rates across populations (19). Although these high-risk types are less frequent than HPV-16 and HPV-18, they have substantial oncogenicity and are often found in conjunction with other HPV types in CIN III lesions (20).

Co-infections of high-risk and low-risk HPV types have been reported, suggesting a potential role of low-risk HPV types in contributing to the persistence of CIN III lesions (21). Geographical variations in the prevalence of specific HPV types have also been documented, highlighting regional differences in HPV distribution and their association with CIN III (22). For instance, certain HPV types may exhibit higher prevalence rates in specific populations, influencing the epidemiology and clinical course of CIN III in different geographic regions.

Moreover, studies exploring the genetic diversity and genomic variations among HPV types and subtypes have provided insights into their differential oncogenic potentials and impacts on CIN III progression (23).

Risk Factors and Epidemiology of CIN III

The development of CIN III is influenced by a myriad of demographic, behavioral, and environmental factors. Studies have extensively explored these factors and their contribution to the epidemiology and global prevalence of CIN III (24, 25).

Demographic factors

Age is a pivotal determinant in the epidemiology of CIN III, with various age-related factors influencing the risk and occurrence of the condition. Studies consistently underscore a higher susceptibility to HPV infection and subsequent CIN III among younger individuals, particularly those with an early age at sexual initiation, especially before the establishment of immune responses that confer protection against viral acquisition (26). Furthermore, while CIN III can occur at any age, epidemiological data indicates a notable peak in its incidence among women of reproductive age, typically between 25 and 35 yr old (27). In this age range, there are higher sexual activity, greater HPV exposure, and an increased likelihood of persistent infections, contributing to the elevated occurrence of CIN III within this demographic group.

Behavioral factors such as the number of sexual partners and engagement in high-risk sexual activities contribute significantly to HPV acquisition and subsequent development of CIN III (28). Moreover, studies have highlighted the association between high-risk sexual behavior, including unprotected intercourse or inconsistent condom use, and an elevated incidence of CIN III (29).

Behavioral factors

Smoking stands out as a prominent behavioral factor associated with an increased risk of CIN III. Extensive research has elucidated the link between tobacco use and the development of CIN III, emphasizing the carcinogenic effects of tobacco constituents on cervical epithelial cells (30). Components of tobacco smoke, particularly carcinogens such as polycyclic aromatic hydrocarbons and nitrosamines, have been implicated in disrupting cellular functions and promoting malignant transformation within the cervical epithelium. Smoking has been shown to compromise the immune response against HPV, potentially facilitating viral persistence and the progression of HPV-related lesions to CIN III (31). Additionally, the detrimental effects of smoking on cervical cell DNA repair mechanisms contribute to genetic instability unaugment the risk of CIN III development.

Long-term oral contraceptive use has also emerged as another behavioral factor associated with an increased incidence of CIN III (32). Hormonal influences stemming from oral contraceptives are proposed to affect the natural history of HPV infections and the progression to CIN III. The hormonal alterations induced by contraceptives may modulate the immune response, potentially affecting the persistence and clearance of HPV infections. Furthermore, hormonal fluctuations associated with oral contraceptive use may promote cellular changes within the cervical epithelium, creating a conducive en-

vironment for the progression of HPV-related lesions to severe dysplasia (33). While the precise mechanisms remain under investigation, hormonal factors appear to contribute to the multifaceted pathogenesis of CIN III, warranting further exploration.

Environmental Factors

Disparities in healthcare access, often influenced by socioeconomic factors, contribute significantly to variations in CIN III prevalence. Limited access to healthcare services impedes timely screening, detection, and management of precancerous lesions, leading to delayed diagnoses and increased disease burden among underserved populations (34). Individuals from marginalized communities, with restricted access to preventive care, face higher barriers to early detection of CIN III, subsequently affecting their clinical outcomes. Furthermore, variations in screening uptake and adherence to screening programs contribute to differences in CIN III detection rates among populations. Low screening participation rates, often observed in regions with limited healthcare resources, result in missed opportunities for early identification and intervention, and further exacerbating the burden of CIN III (35).

Disparities in vaccination coverage across regions and populations influence the dynamics of HPV infections and subsequent CIN III incidence. Areas with high vaccination coverage witness a reduction in the prevalence of high-risk HPV types targeted by the vaccines, consequently lowering the incidence of CIN III lesions associated with these HPV strains (36). Disparities in vaccine access, coverage, and implementation strategies significantly influence the distribution of HPV infections and subsequent CIN III incidence among diverse populations.

Global Prevalence and Genotype Distribution

Regions with limited resources, particularly in low- and middle-income countries, face challenges in establishing comprehensive screening programs and providing access to preventive healthcare services (37). Consequently, these areas often exhibit higher incidence rates of CIN III due to delayed diagnoses, missed opportunities for early intervention, and inadequate healthcare infrastructure. HPV prevalence varies significantly among different geographical regions and populations, contributing to diverse patterns of CIN III epidemiology. Disparities in HPV prevalence, influenced by factors such as sexual behaviors, cultural practices, and access to vaccination, significantly impact the incidence and distribution of CIN III (38). Regions with a higher prevalence of high-risk HPV types often experience a heightened burden of CIN III and cervical cancer-related complications. The complexity of CIN III epidemiology across diverse populations underscores the importance of region-specific approaches to disease prevention and management. Tailoring interventions and healthcare strategies based on epidemiological profiles, healthcare infrastructure, cultural practices, and socioeconomic factors are essential in effectively addressing the burden of CIN III (39). Addressing these multifaceted demographic, behavioral, and environmental factors through targeted interventions, including comprehensive screening programs, vaccination initiatives, and behavioral modifications, is essential in reducing the global burden of CIN III and its associated sequelae.

HPV-16, HPV-18, and HPV-31 were consistently 1st, 2nd, and 3rd most frequent genotypes, respectively (40). However, the genotype HPV-52 is the most dominant strain of some Asian countries (41, 42). Moreover, the distribution of high risk-HPV types varied in asymptomatic men of Croatia (39%) (43), Poland (14.3%) (44), Mexico (8.7%) (45), Lithuania (20%) (46), and Iran (9.5%) (47). In a systematic review, the estimated global prevalence of high-risk HPV in men was 20%-30% (48).

Clinical Presentation and Diagnosis

The clinical presentation and accurate diagnosis of CIN III are crucial for timely intervention and preventive measures. Understanding the clinical manifestations and diagnostic methods, supported by references, is essential in recognizing and managing this precancerous condition (49).

Clinical Manifestations of CIN III

CIN III often manifests asymptomatically in its early stages, which poses challenges for early detection. However, as the lesion progresses, clinical manifestations may include abnormal vaginal bleeding (especially postcoital or intermenstrual bleeding), unusual vaginal discharge, or, in rare cases, pelvic pain. These symptoms, when present, might indicate an advanced stage of the lesion and necessitate further investigation (50).

Diagnosis and treatment of CIN III

Pap Smears (Cytology): Pap smears serve as a primary screening tool for detecting cervical abnormalities, including CIN III. This method involves collecting cervical cells to examine cellular changes indicative of precancerous or cancerous lesions. However, Pap smears may have limitations in lower sensitivity and specificity, occasionally leading to false-negative or false-positive results (51).

HPV molecular Testing: HPV testing, particularly for high-risk HPV types (e.g., HPV-16 and HPV-18), has become integral in screening for CIN III. This method detects the presence of HPV DNA in cervical samples and aids in identifying individuals at higher risk of developing CIN III. Combining HPV testing with cytology (co-testing) has shown improved sensitivity in detecting high-grade lesions, enhancing early identification and intervention (52).

Colposcopy and Biopsy: Colposcopy, a procedure involving the magnified examination of the cervix using a colposcope, is employed when abnormalities are detected via Pap smears or HPV testing. Colposcopy allows for detailed visualization of suspicious areas, facilitating targeted biopsies for histological confirmation of CIN III (53). Detecting and treating CIN III lesions at an early stage significantly reduce the risk of malignant transformation and subsequent development of invasive cancer (5). Timely identification through effective screening methods like Pap smears, HPV testing, and colposcopy enables prompt intervention, especially by involving conservative treatments such as LEEP, or cone biopsies. Indeed, cervical conization as an excisional surgery, used to both diagnose and treat cervical dysplasia by removing a cervix portion that is cone-shaped (transformational and suspicious cervical lesions) as a sample biopsy for histopathological analysis (54). Modalities like loop excision of the transformation zone (LLETZ), LEEP, laser conization, or cold knife cone (CKC) can be used for cervical conization (54). However, female patients with high-Grade squamous intraepithelial lesion had higher risk of recurrent lesions than general population although they underwent conization or LEEP for removing cervical lesions (55). Beyond these excisional surgeries, there are some ablative therapies like cryotherapy, thermal ablation, laser therapy, photodynamic therapy, and focused ultrasound that are recently suggested for lesion ablation (56). Early detection of CIN III not only improves clinical outcomes but also reduces the need for more invasive treatments and minimizes the physical and psychological burden on affected individuals. Regular screening and prompt follow-up for abnormal findings remain fundamental in achieving early detection and ensuring timely management of CIN III lesions.

Progression to Invasive Cervical Cancer

CIN III represents a significant precursor to invasive cervical cancer but all CIN III lesions do not progress to malignancy. Studies have indicated that a proportion of untreated CIN III lesions have the potential to progress to invasive cancer over an extended period, particularly if it has been left unmonitored or managed inadequately (57). However, the rate of progression from CIN III to invasive cervical cancer is not unique and varies among individuals. Factors influencing progression to invasive cervical cancer include the extent of cervical involvement, the persistence of high-risk HPV infections, immune responses, and the presence of cofactors such as smoking or immunosuppression (58). The efficacy of these interventions in preventing invasive cancer is supported by long-term follow-up studies showing a substantial decrease in the incidence of invasive cancer following adequate treatment of CIN III lesions.

Monitoring and Follow-up of CIN III

Regular monitoring and follow-up after treatment for CIN III are critical for assessing treatment efficacy, detecting potential recurrences, and ensuring long-term surveillance to prevent disease progression. Close surveillance allows for the identification and management of persistent or recurrent lesions, minimizing the risk of invasive cancer development (59). While interventions are effective in reducing the risk of invasive cancer, long-term outcomes also depend on factors such as HPV persistence, immunological responses, and lifestyle factors. Persistent HPV infections, particularly high-risk types, may contribute to residual or recurrent disease post-treatment, necessitating vigilant follow-up and management (60). Long-term surveillance and close follow-up are crucial components in managing CIN III, minimizing the potential for progression, and ensuring favorable long-term outcomes for affected individuals.

Preventive Measures and Public Health Implications

HPV vaccination represents a cornerstone in primary prevention against CIN III and cervical cancer. Vaccines targeting high-risk HPV types, notably HPV-16 and HPV-18, have demonstrated its efficacy in preventing persistent infections and subsequent development of CIN III lesions associated with these strains (61). Vaccination programs aimed at adolescents and young adults before HPV exposure have shown substantial promise in reducing the incidence of HPV infections and precancerous lesions. The prophylactic FDA-approved vaccines include Gardasil (Tetravalent: protects against HPV-6, 11, 16, and 18), Gardasil 9 (Nonavalant: protects against HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58) and bivalent HPV vaccine Cervarix™ (Bivalent: protects against HPV-16 and 18) and they are three recombinant L1 protein virus-like particles (VLP) and could prevent from cervical cancer (62-64). These existing vaccines could be more effective with novel recombinant approaches like using peptide-based vaccines to overcome the anti-vector immunity (65). Moreover, it is necessary to investigate whether these vaccines could be beneficial for HPV positive women as an adjuvant or accelerated treatment of CIN II/III lesions or not (65). On the other hand, several clinical trials investigated the application of other new different vaccines among patients with CIN II/III or CIN III. In a randomized double blind, placebo-controlled phase II trial by Harper et al, the Tipapkinogen Sovacivec (TS) vaccine could be safe for at least 30 months and histologically clear CIN II/III high-risk HPV type in one third of patients (66). Another randomized phase II clinical trial, DNA vaccine GX-188E was able to induce CIN III regression of HPV type 16/18 lesions (67). In another phase 1/2a clinical trial study by Park et al, oral BLS-M07 vaccine could increase producing serum HPV16 E7 antibody among CIN III patients that induced protective humoral immunity in a safe non-surgical way (68). Another phase II clinical trial by García-Hernández, MVA E2 stimulated the immune system against HPV and could regress high-grade cervical lesions of CIN II or CIN III (69). Detailed information of completed studies are included in Table 1.

Screening programs, particularly cervical cytology (Pap smears) and HPV testing, are pivotal in early detection and secondary prevention of CIN III. Routine screening enables the identification of precancerous lesions, allowing for timely intervention and treatment, thereby reducing the risk of progression to invasive cancer (24). Co-testing with Pap smears and HPV testing has shown enhanced sensitivity in detecting high-grade lesions, improving the effectiveness of screening strategies (70).

Effective public health policies are indispensable in promoting vaccination coverage, implementing screening programs, and ensuring access to preventive healthcare services. Comprehensive policies advocating for HPV vaccination as a part of routine immunization schedules, promoting the awareness about the importance of screening, and facilitating access to healthcare for underserved populations are imperative (71). Policy-making that emphasizes equity in healthcare ac-

cess and coverage is vital in reducing disparities in CIN III incidence and cervical cancer burden. Emphasizing the importance of these preventive measures through education, advocacy, and policy implementation not only reduces disease incidence but also contributes to improved public health outcomes, reduced healthcare costs, and better quality of life for individuals affected by or at risk of CIN III and cervical cancer. Table 1 show completed clinical trials of HPV vaccines for CIN II/III or CIN III prevention.

Table 1: Completed clinical trials of HPV vaccines for CIN II/III or CIN III prevention

NO.	*NCT Number*	*Interventions*	*Age*	*Phases*	*Enrollment*	*Location(s)*
1	NCT01653249	Vaccine consisting of 4 HPV-16 E6 peptides+ Candin	Adult	Phase I	52	USA
2	NCT02733068	HPV-16/18 vaccine	Adult	Phase III	12000	
3	NCT01304524	VGX 3100	Adult	Phase II	167	USA
4	NCT00543543	V503	Child Adult	Phase III	14840	
5	NCT02139267	GX-188E	Adult	Phase II	72	Korea
6	NCT03763565	Bivalent or Quadrivalent HPV vaccines	Adult		993	Thiland
7	NCT00779766	HPV GSK 580299 vaccine	Adult	Phase III	6081	China
8	NCT04425291	Quadrivalent or 9-valent HPV Vaccine	Adult	Phase III	1680	China
9	NCT05372016	9-valent Human Papillomavirus	Child Adult	Phase III	1200	China
10	NCT03676101	9-valent HPV Recombinant Vaccine	Child Adult	Phase I	90	China
11	NCT00929526	GSK 580299	Adult	Phase III	752	Japan
12	NCT03105856	CERVARIX	Adult	Phase IV	3000	Mexico
13	NCT00518336	Cervarix				
14	NCT01077856	Gardasil	Adult		54516	
15	NCT00122681	Cervarix, GSK	Child Adult	Phase III	18729	USA/Australia/Belgium/Brazil/Canada/Finland/Germany/Italy/Philippines/Spain/Taiwan/Thailand/UK
16	NCT00316693	Cervarix	Adult	Phase II	1046	Japan
17	NCT00541970	Cervarix	Child Adult	Phase I	961	Canada/Germany/Germany
18	NCT04607850	ChAdOx1-HPV	Adult	Phase I	99	Belgium/Estonia/

Table 1: Continued …

				Phase II		UK
19	NCT03629886	Bivalent HPV-16 and 18 Vaccine	Adult Older Adult	Phase IV	6051	China
20	NCT01634503	GX-188E	Adult	Phase I	9	Korea
21	NCT00091130	HspE7	Adult	Phase II	139	USA
22	NCT00365378	HPV 16 L1 Vaccine	Child Adult	Phase II	2409	
23	NCT00294047	Cervarix	Adult Older Adult	Phase III	5752	USA/UK
24	NCT00988559	DNA vaccination	Adult Older Adult	Phase I	132	USA
25	NCT00121173	pNGVL4a-Sig/E7(detox)/HSP70 DNA vaccine	Adult Older Adult	Phase I Phase II	16	USA
26	NCT00054041	HspE7	Child Adult Older Adult	Phase II	84	USA
27	NCT00667563	Quadrivalent HPV-6, 11, 16, 18 recombinant vaccine	Adult Older Adult	Phase I	150	India
28	NCT00788164	pNGVL4a-Sig/E7(detox)/HSP70 DNA vaccine	Adult Older Adult	Phase I	75	USA
29	NCT00128661	AS04 vaccine	Adult	Phase III	7466	Costa Rica

All given data were obtained from https://clinicaltrials.gov/. CIN: Cervical Intraepithelial Neoplasia; HPV, Human Papillomavirus

Future perspective

CIN III stands as a significant precursor to invasive cervical cancer, necessitating comprehensive understanding, vigilant screening, and effective interventions. This review has illuminated various aspects crucial in comprehending the multifaceted nature of CIN III, including its pathogenesis, risk factors, diagnosis, outcomes, and preventive measures. The discussion underscored the pivotal role of HPV infection in the initiation and progression of CIN III, emphasizing the significance of high-risk HPV types, such as HPV-16 and HPV-18, in driving precancerous changes within the cervical epithelium. Demographic, behavioral, and environmental factors were highlighted as influential determinants impacting CIN III epidemiology, with age, sexual behavior, smoking, healthcare access, and vaccination coverage playing pivotal roles. Diagnostic methods such as Pap smears, HPV molecular testing, and colposcopy were reviewed for their effectiveness in detecting and monitoring CIN III lesions, underscoring the importance of early detection in mitigating disease progression. Moreover, the long-term outcomes and prognosis of CIN III, along with the effectiveness of interventions in reducing the risk of invasive cancer, were emphasized, acknowledging the pivotal role of excisional procedures and vigilant follow-up in preventing malignancy. The discussion on preventive measures highlighted the transformative impact of HPV vaccination, screening programs, and robust public health policies in reducing the burden of CIN III and cervical cancer. Vaccination programs target-

ing high-risk HPV types, alongside comprehensive screening initiatives and equitable healthcare policies, hold promise in mitigating disease incidence, reducing disparities, and improving public health outcomes.

Conclusion

A multifaceted approach encompassing robust preventive strategies, early detection, effective interventions, and equitable healthcare access is imperative in combating the burden of CIN III. Emphasizing education, awareness, and evidence-based interventions are crucial in minimizing disease progression, reducing the incidence of invasive cancer, and ultimately improving the well-being of individuals affected by or at risk of CIN III. Therefore, there is a need to combat with HPV infection via proper strategy that includes immunization, screening, treatment, and palliative care of public health system for managing and eradicating cervical cancer. It is suggested to perform additional research for timely detection and treatment of suspicious HPV patients that requires reviving the cooperation between governments, and health managers with considering limitations in the health system.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

The authors would like to present their gratitude to the Tabriz University of Medical Sciences, Tabriz, Iran for supporting this study.

Conflict of Interest

The authors declare that they have no competing interests.

References

1. Kalliala I, Athanasiou A, Veroniki A, et al (2020). Incidence and mortality from cervical cancer and other malignancies after treatment of cervical intraepithelial neoplasia: a systematic review and meta-analysis of the literature. *Ann Oncol,* 31 (2):213-227.
2. Pina-Sanchez P (2022). Human Papillomavirus: Challenges and opportunities for the control of cervical cancer. *Arch Med Res,* 53 (8):753-769.
3. Carrero YN, Callejas DE, Mosquera JA (2021). In situ immunopathological events in human cervical intraepithelial neoplasia and cervical cancer. *Transl Oncol,* 14 (5):101058.
4. Daponte A, Michail G, Daponte A-I, et al (2021). Urine hpv in the context of genital and cervical cancer screening-an update of current literature. *Cancers (Basel),* 13 (7):1640.
5. Stumbar SE, Stevens M, Feld Z (2019). Cervical cancer and its precursors: a preventative approach to screening, diagnosis, and management. *Prim Care,* 46 (1):117-134.
6. Gupta S, Nagtode N, Chandra V, Gomase K (2023). From Diagnosis to Treatment: Exploring the Latest Management Trends in Cervical Intraepithelial Neoplasia. *Cureus,* 15 (12):e50291.
7. Moscicki A-B, Schiffman M, Franceschi S (2020). The natural history of human papillomavirus infection in relation to cervical cancer. In: *Human papillomavirus.* Ed(s): Elsevier, pp. 149-160.
8. Kaliterna V, Barisic Z (2018). Genital human papillomavirus infections. *Front Biosci (Landmark Ed),* 23 (9):1587-1611.
9. Doorbar J, Zheng K, Aiyenuro A, et al (2021). Principles of epithelial homeostasis control during persistent human papillomavirus infection and its deregulation at the cervical transformation zone. *Curr Opin Virol,* 51:96-105.
10. Estêvão D, Costa NR, da Costa RMG, Medeiros R (2019). Hallmarks of HPV carcinogenesis: The role of E6, E7 and E5 oncoproteins in cellular malignancy. *Biochim Biophys Acta Gene Regul Mech,* 1862 (2):153-162.
11. Karimian A, Ahmadi Y, Yousefi B (2016). Multiple functions of p21 in cell cycle,

apoptosis and transcriptional regulation after DNA damage. *DNA Repair (Amst),* 42:63-71.
12. Choi P-W, Liu TL, Wong CW, et al (2022). The Dysregulation of MicroRNAs in the Development of Cervical Pre-Cancer—An Update. *Int J Mol Sci,* 23 (13):7126.
13. Bodelon C, Vinokurova S, Sampson JN, et al (2016). Chromosomal copy number alterations and HPV integration in cervical precancer and invasive cancer. *Carcinogenesis,* 37 (2):188-196.
14. Gardella B, Pasquali MF, La Verde M, et al (2022). The complex interplay between vaginal microbiota, HPV infection, and immunological microenvironment in cervical intraepithelial neoplasia: a literature review. *Int J Mol Sci,* 23 (13):7174.
15. Chambuso RS (2019). Human Immunodeficiency Virus/Human Papillomavirus co-infection and host molecular genetics of cervical carcinoma. https://hdl.handle.net/11427/31668
16. Mejía L, Munoz D, Trueba G, et al (2016). Prevalence of human papillomavirus types in cervical cancerous and precancerous lesions of Ecuadorian women. *J Med Virol,* 88 (1):144-152.
17. Heydari N, Oskouee MA, Vaezi T, et al (2018). Type-specific human papillomavirus prevalence in cervical intraepithelial neoplasia and cancer in Iran. *J Med Virol,* 90 (1):172-176.
18. Sand FL, Munk C, Frederiksen K, et al (2019). Risk of CIN3 or worse with persistence of 13 individual oncogenic HPV types. *Int J Cancer,* 144 (8):1975-1982.
19. Abbas M, de Jonge J, Bettendorf O (2023). Prevalence of High-Risk HPV Subtypes and Efficacy of the HPV Vaccine in Preventing Cervical Epithelial Lesions: Survey and Insights from a German Study. *Life (Basel),* 13 (8):1637.
20. Arbyn M, Xu L, Verdoodt F, et al (2017). Genotyping for human papillomavirus types 16 and 18 in women with minor cervical lesions: a systematic review and meta-analysis. *Ann Intern Med,* 166 (2):118-127.
21. Boda D, Docea AO, Calina D, et al (2018). Human papilloma virus: Apprehending the link with carcinogenesis and unveiling new research avenues. *Int J Oncol,* 52 (3):637-655.
22. Zhou H-L, Zhang W, Zhang C-J, et al (2018). Prevalence and distribution of human papillomavirus genotypes in Chinese women between 1991 and 2016: A systematic review. *J Infect,* 76 (6):522-528.
23. Rader JS, Tsaih SW, Fullin D, et al (2019). Genetic variations in human papillomavirus and cervical cancer outcomes. *Int J Cancer,* 144 (9):2206-2214.
24. Rizzo AE, Feldman S (2018). Update on primary HPV screening for cervical cancer prevention. *Curr Probl Cancer,* 42 (5):507-520.
25. Sabiha Nikhat N (2022) Evaluation of Human Papilloma Virus as a Risk Factor for Cervical Cancer in Human Immunodeficiency Virus Positive Women. Madras Medical College, Chennai.
26. Gravitt PE, Winer RL (2017). Natural history of HPV infection across the lifespan: role of viral latency. *Viruses,* 9 (10):267.
27. Syrjänen S (2018). Oral manifestations of human papillomavirus infections. *Eur J Oral Sci,* 126 Suppl 1(Suppl Suppl 1):49-66.
28. Taku O, Businge CB, Mdaka ML, et al (2020). Human papillomavirus prevalence and risk factors among HIV-negative and HIV-positive women residing in rural Eastern Cape, South Africa. *Int J Infect Dis,* 95:176-182.
29. Gursahaney PR, Cordes S, Ofotokun I, et al (2019). Factors associated with condom use among HIV-positive women living in Atlanta, Georgia. *PLoS One,* 14 (12):e0225406.
30. Vidrine JI, Fennell BS, Simmons VN, et al (2023). Enhancing long-term smoking abstinence among individuals with a history of cervical intraepithelial neoplasia or cervical cancer (Project ACCESS): protocol for a randomized clinical trial. *BMC Public Health,* 23 (1):1284.
31. Szymonowicz KA, Chen J (2020). Biological and clinical aspects of HPV-related cancers. *Cancer Biol Med,* 17 (4):864-878.
32. Venkatas J, Singh M (2020). Cervical cancer: A meta-analysis, therapy and future of nanomedicine. *Ecancermedicalscience,* 14:1111.
33. Adhikari I (2022). Association of Sexual Behaviour and Oral Contraceptive Use with Cervical Neoplasia. Facultyof Social Sciences, Tampere University, Finland.
34. Jabbour J, Robey T, Cunningham MJ (2018). Healthcare disparities in pediatric

otolaryngology: a systematic review. *Laryngoscope,* 128 (7):1699-1713.
35. Gupta S, Palmer C, Bik EM, et al (2018). Self-sampling for human papillomavirus testing: increased cervical cancer screening participation and incorporation in international screening programs. *Front Public Health,* 6:77.
36. Benard VB, Castle PE, Jenison SA, et al (2017). Population-based incidence rates of cervical intraepithelial neoplasia in the human papillomavirus vaccine era. *JAMA Oncol,* 3 (6):833-837.
37. Watson M, Soman A, Flagg EW, et al (2017). Surveillance of high-grade cervical cancer precursors (CIN III/AIS) in four population-based cancer registries, United States, 2009–2012. *Prev Med,* 103:60-65.
38. Karuri AR, Kashyap VK, Yallapu MM, et al (2017). Disparity in rates of HPV infection and cervical cancer in underserved US populations. *Front Biosci (Schol Ed),* 9(2):254-269.
39. Roger VL, Sidney S, Fairchild AL, et al (2020). Recommendations for cardiovascular health and disease surveillance for 2030 and beyond: a policy statement from the American Heart Association. *Circulation,* 141 (9):e104-e119.
40. de Sanjosé S, Diaz M, Castellsagué X, et al (2007). Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infect Dis,* 7 (7):453-9.
41. Liu J, Ma S, Qin C, et al (2020). Prevalence and genotype distribution of human papillomavirus in Zhengzhou, China, in 2016. *Arch Virol,* 165 (3):731-736.
42. Rahmat F, Kuan JY, Hajiman Z, et al (2021). Human Papillomavirus (HPV) Prevalence and Type Distribution in Urban Areas of Malaysia. *Asian Pac J Cancer Prev,* 22 (9):2969-2976.
43. Bosnjak Z, Perić M, Krizan IR, et al (2013). Prevalence and genotype distribution of high-risk human papillomavirus (HR HPV) in male genital samples of Osijek-Baranja County. *Coll Antropol,* 37 (4):1203-8.
44. Walczak L, Dutkiewicz S, Marszałek A (2013). Incidence and prevalence of multiple types of genital human papillomavirus (HPV) infection in men: a study in Poland. *Ginekol Pol,* 84 (2):112-5.
45. Parada R, Morales R, Giuliano AR, et al (2010). Prevalence, concordance and determinants of human papillomavirus infection among heterosexual partners in a rural region in central Mexico. *BMC Infect Dis,* 10:223.
46. Jeršovienė V, Gudlevičienė Ž, Rimienė J, et al (2019). Human Papillomavirus and Infertility. *Medicina (Kaunas),* 55 (7): 377.
47. Salehi-Vaziri M, Sadeghi F, Bokharaei-Salim F, et al (2015). The Prevalence and Genotype Distribution of Human Papillomavirus in the Genital Tract of Males in Iran. *Jundishapur J Microbiol,* 8 (12):e21912.
48. Bruni L, Albero G, Rowley J, et al (2023). Global and regional estimates of genital human papillomavirus prevalence among men: a systematic review and meta-analysis. *Lancet Glob Health,* 11 (9):e1345-e1362.
49. Luyten A, Buttmann-Schweiger N, Luyten K, et al (2014). Early detection of CIN3 and cervical cancer during long-term follow-up using HPV/Pap smear co-testing and risk-adapted follow-up in a locally organised screening programme. *Int J Cancer,* 135 (6):1408-16.
50. Shiraz A, Crawford R, Egawa N, et al (2020). The early detection of cervical cancer. The current and changing landscape of cervical disease detection. *Cytopathology,* 31 (4):258-270.
51. Mitteldorf CAT (2016). Cervical cancer screening: from Pap smear to future strategies. *J Bras Patol Med Lab,* 52:238-245.
52. Reynolds SH (2020) HPV Primary Screening Pilot Study: molecular testing of potential triage strategies for HPV-positive women. https://secure.key4events.com/key4register/AbstractList.aspx?e=612&preview=1&aig=-1&ai=15475
53. Gandi SR, Vishwekar PS (2017). A study on correlation of Pap smear, colposcopy and colposcopic directed biopsy in women with unhealthy cervix. *J Evolution Med Dent Sci,* 6 (7):515-518.
54. Perkins RB, Guido RS, Castle PE, et al (2020). 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. *J Low Genit Tract Dis,* 24 (2):102-131.

55. Han L, Zhang B (2023). Can prophylactic HPV vaccination reduce the recurrence of cervical lesions after surgery? Review and prospect. *Infect Agent Cancer,* 18 (1):66.
56. Xu L, Jiang Y, Zhao R (2023). Advances in ablative treatment for human papillomavirus related cervical pre-cancer lesions. *Gynecology and Obstetrics Clinical Medicine,* 3 (4):213-219.
57. Loopik DL, Bentley HA, Eijgenraam MN, et al (2021). The natural history of cervical intraepithelial neoplasia grades 1, 2, and 3: a systematic review and meta-analysis. *J Low Genit Tract Dis,* 25 (3):221-231.
58. Kelly H (2017) The epidemiology of Human Papillomavirus (HPV) infection and epigenetic factors associated with the development of cervical cancer precursor lesions in women living with HIV in Africa. London School of Hygiene & Tropical Medicine.
59. Desravines N, Miele K, Carlson R, et al (2020). Topical therapies for the treatment of cervical intraepithelial neoplasia (CIN) 2–3: A narrative review. *Gynecol Oncol Rep,* 33:100608.
60. Hoffman SR, Le T, Lockhart A, et al (2017). Patterns of persistent HPV infection after treatment for cervical intraepithelial neoplasia (CIN): A systematic review. *Int J Cancer,* 141 (1):8-23.
61. Zarankiewicz N, Zielinska M, Kosz K, et al (2020). High-risk HPV test in cervical cancer prevention-present and future. *J Pre Clin Clin Res,* 14 (3):80-84.
62. White MD (2014). Pros, cons, and ethics of HPV vaccine in teens-Why such controversy? *Transl Androl Urol,* 3 (4):429-34.
63. Toh ZQ, Kosasih J, Russell FM, et al (2019). Recombinant human papillomavirus nonavalent vaccine in the prevention of cancers caused by human papillomavirus. *Infect Drug Resist,* 12:1951-1967.
64. de Sanjose S, Quint WG, Alemany L, et al (2010). Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol,* 11 (11):1048-56.
65. Smalley Rumfield C, Roller N, Pellom ST, et al (2020). Therapeutic Vaccines for HPV-Associated Malignancies. *Immunotargets Ther,* 9:167-200.
66. Harper DM, Nieminen P, Donders G, et al (2019). The efficacy and safety of Tipapkinogen Sovacivec therapeutic HPV vaccine in cervical intraepithelial neoplasia grades 2 and 3: Randomized controlled phase II trial with 2.5 years of follow-up. *Gynecol Oncol,* 153 (3):521-529.
67. Choi YJ, Hur SY, Kim TJ, et al (2020). A Phase II, Prospective, Randomized, Multicenter, Open-Label Study of GX-188E, an HPV DNA Vaccine, in Patients with Cervical Intraepithelial Neoplasia 3. *Clin Cancer Res,* 26 (7):1616-1623.
68. Park YC, Ouh YT, Sung MH, et al (2019). A phase 1/2a, dose-escalation, safety and preliminary efficacy study of oral therapeutic vaccine in subjects with cervical intraepithelial neoplasia 3. *J Gynecol Oncol,* 30 (6):e88.
69. García-Hernández E, González-Sánchez JL, Andrade-Manzano A, et al (2006). Regression of papilloma high-grade lesions (CIN 2 and CIN 3) is stimulated by therapeutic vaccination with MVA E2 recombinant vaccine. *Cancer Gene Ther,* 13 (6):592-7.
70. Felix JC, Lacey MJ, Miller JD, et al (2016). The Clinical and Economic Benefits of Co-Testing Versus Primary HPV Testing for Cervical Cancer Screening: A Modeling Analysis. *J Womens Health (Larchmt),* 25 (6):606-16.
71. Cartmell KB, Young-Pierce J, McGue S, et al (2018). Barriers, facilitators, and potential strategies for increasing HPV vaccination: a statewide assessment to inform action. *Papillomavirus Res,* 5:21-31.