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Chapter 1

HPV And Cervical Preinvasive Lesions

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Introduction

Cervical cancer remains a major global health concern, contributing substantially to morbidity and mortality among women. It is currently the fourth most commonly diagnosed cancer in the female population worldwide (1,2). Multiple risk factors have been implicated in the development of cervical cancer, with persistent infection by human papillomavirus (HPV) identified as the predominant cause, accounting for approximately 99.7% of all cases. Additional contributing factors include tobacco use, immunosuppressive conditions, inadequate sexual health practices, and failure to participate in regular cervical cancer screening programs (3,4).

Individuals with a cervix should undergo primary screening through HPV testing. In cases where HPV is detected, reflex genotyping and cytological assessment are essential for stratifying the risk of cervical precancerous lesions and guiding the need for further diagnostic procedures such as colposcopy or therapeutic intervention. Prophylactic HPV vaccination during adolescence is projected to prevent over 90% of cervical precancers and invasive cervical cancers (5).

Epidemiology and Risk Factors of Cervical Cancer

It is estimated that the majority of sexually active individuals will acquire an HPV infection at some point during their lifetime, although the precise prevalence remains uncertain. As such, a positive HPV test should be interpreted primarily as an indicator of prior sexual exposure rather than a direct predictor of malignancy. Cervical cancer typically arises in cases where a persistent HPV infection escapes immune surveillance. Key determinants of cervical cancer risk include the presence of HPV infection, the specific genotype involved, and cytological abnormalities reflecting HPV-induced cellular transformation (1).

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The year 2022 recorded an estimated 664,000 new cases of cervical cancer and 349,000 deaths globally. Nearly 90% of cervical cancer cases occur in low- and middle-income countries, reflecting significant global disparities in access to prevention, screening, and treatment services (6).

Engagement in certain behavioral risk factors—such as having multiple sexual partners, early initiation of sexual activity, and tobacco use—has been strongly associated with an increased risk of cervical cancer. These behaviors are often more prevalent in socioeconomically disadvantaged populations, potentially contributing to higher disease incidence in these communities (1). While sexual transmission remains the primary mode of HPV dissemination, alternative routes have also been proposed. These include vertical transmission from mother to infant and potential indirect transmission via fomites such as contaminated clothing. However, the clinical significance and exact role of fomite-mediated transmission remain incompletely understood and require further investigation (1,6-8).

Moreover, individuals with immunosuppressive conditions or a history of in utero exposure to diethylstilbestrol exhibit an elevated risk for developing cervical precancerous lesions and invasive cancer (5,7).

A higher number of full-term pregnancies has been identified as a significant independent risk factor for the persistence of HPV infection and the development of cervical cancer. The proposed mechanisms underlying this association include pregnancy-related hormonal changes and a transiently suppressed immune response during gestation. In multiparous women, the transformation zone remains on the ectocervix for a prolonged period, increasing its direct exposure to HPV and other potential cofactors. However, the most widely accepted mechanism involves local tissue trauma during vaginal delivery or cellular oxidative stress, both of which may increase the likelihood of DNA damage and subsequent HPV integration (3)

HPV and Cervical Cancer Pathophysiology

Over 450 genotypes of human papillomavirus (HPV) have been characterized and classified into various genera and species based on their genetic sequences. HPVs belong to the Papillomaviridae family, comprising small, non-enveloped, double-stranded DNA viruses. They represent the most prevalent viral pathogens responsible for infections of the reproductive tract (1). HPV has undergone gradual evolutionary diversification resulting in genotypes with oncogenic potential capable of initiating cervical cancer. Analysis of over 40,000 cervical cancer specimens worldwide has demonstrated that nearly all tumors harbor at least one of thirteen high-risk carcinogenic HPV genotypes (5). Carcinogenic HPV genotypes are phylogenetically clustered within a single clade of the alpha genus. Within this genus, the alpha-9, alpha-7, alpha-5, and alpha-6 species encompass HPV genotypes classified as high-risk based on laboratory evidence of their oncogenic potential. In contrast, low-risk HPV genotypes are not linked to elevated cervical cancer risk and therefore are not included in cancer prevention protocols. Notably, nearly all high-risk HPV genotypes within the alpha-9 species group—specifically HPV-16, -31, -33, -35, -52, and -58—are recognized as carcinogenic (5).

HPV-16 is the most oncogenic genotype, implicated in over 60% of cervical squamous cell carcinomas and adenocarcinomas, as well as a significant proportion of oropharyngeal and other anogenital malignancies. Other genotypes within the alpha-9 species—namely HPV-31, -33, -35, -52, and -58—are considered intermediate-risk and collectively account for approximately 2% to 4% of cervical cancer cases each (1,5). There is notable regional and ethnic variation in the distribution

of HPV genotypes linked to cervical cancer. For instance, HPV-35 has been associated with a higher incidence of cervical cancer among individuals of African descent compared to those from other racial backgrounds (9). Within the alpha-7 species group, HPV-18 and HPV-45 are linked to the development of both squamous cell carcinomas and adenocarcinomas, collectively accounting for approximately 20% of cervical cancer cases. The less oncogenic genotypes within the alpha-7 species HPV-39, HPV-59, and HPV-68 as well as HPV-51 from the alpha-5 species and HPV-56 from the alpha-6 species, are classified as lower-risk carcinogens, each contributing to less than 2% of cervical cancer cases (5).

The squamocolumnar junction of the cervix is especially vulnerable to HPV-driven carcinogenesis, with cellular alterations that precede cervical cancer frequently originating in this region. Recent studies have identified “reserve cells” as key targets for malignant transformation and potential reservoirs for latent HPV infection. These cells reside above the basement membrane, are dispersed throughout the area, and extend proximally beneath the glandular epithelium of the endocervical canal, adjacent to the visible squamocolumnar junction (10).

Active and Latent Infections

A newly acquired HPV infection, irrespective of genotype, is defined as an active infection characterized by the production of new viral particles. Active HPV infections may be clinically silent, without cytological or visible cervical abnormalities, or present with equivocal or low-grade cellular changes. However, the development of precancerous lesions in the context of new infection is uncommon. Even when cellular abnormalities such as low-grade squamous intraepithelial lesions (LSIL) arise, the majority of infections resolve spontaneously within 12 to 24 months, either due to diminished viral fitness or effective immune-mediated clearance by the host. Although immunological protection against reinfection has been documented, naturally acquired immunity remains incomplete and is not yet fully clarified (5).

HPV infections can persist in the basal epithelial cells of the cervix, undergoing a phase of slow viral replication known as latent infection. During this latent phase, cervicovaginal HPV tests typically yield negative results, no overt cytological abnormalities are observed, and the associated cancer risk remains minimal. Reactivation of latent HPV infections can occur intermittently throughout an individual’s life, with recurrence rates reported to be as high as 15% within five years. Consequently, a newly positive HPV test may represent either a recent acquisition or reactivation of a previous infection; however, current clinical assays are unable to differentiate between these scenarios. The risk of progression to cervical precancer within five years is approximately 3% for both new and reactivated infections, indicating that this distinction has limited clinical significance (11,12).

Persistence and Progression to Precancer

Persistent infection with carcinogenic HPV genotypes may lead to the neoplastic transformation of infected cervical epithelial cells. The term "precancer" denotes the transition from active viral replication to clonal expansion of transformed cells. While replicating HPV infections complete the viral life cycle, resulting in production and release of virions, precancerous lesions are characterized by the expression of HPV oncoproteins that dysregulate the host cell cycle and inhibit apoptosis. This suppression of programmed cell death disrupts normal epithelial renewal processes, thereby facilitating neoplastic progression. Precancerous lesions maintain several normal cellular characteristics, including contact inhibition, whereby cells cease proliferation upon contact with the

basement membrane. The epithelial growth occurs outward from the basement membrane, facilitating early detection of abnormal cellular proliferation. These precancerous cells may occasionally undergo spontaneous regression and, when they do progress, typically expand laterally within the epithelium for extended periods without invasion. This prolonged phase of intraepithelial growth underpins the effectiveness of cervical cancer screening programs (5).

Numerous viral and host biomarkers associated with precancerous lesions have been identified. Notably, DNA methylation of both viral and host genomic regions increases during the transition from productive HPV infection to oncogenic transformation. This epigenetic modification is particularly evident in the viral L1 and L2 genes, which encode the viral capsid proteins in active infections (13). Methylation assays hold significant promise for detecting molecular alterations linked to cancer risk; however, these tests are not yet approved for routine clinical use (13). The p16/Ki-67 dual-stain assay (CINtec Plus), recently authorized by the U.S. Food and Drug Administration (FDA), serves as a biomarker for identifying HPV-induced cellular transformation. The protein p16 accumulates in cells where the retinoblastoma pathway is disrupted by the HPV E7 oncoprotein, while Ki-67 functions as a marker of cellular proliferation. The concurrent expression of p16 and Ki-67 is indicative of HPV-mediated neoplastic transformation. Multiple studies involving patients with positive HPV test results have demonstrated that the p16/Ki-67 dual-stain assay outperforms traditional Papanicolaou (Pap) cytology in differentiating precancerous lesions from low-grade cervical abnormalities. The p16/Ki-67 dual-stain assay is amenable to automation, and emerging research indicates that automated detection may enhance its diagnostic accuracy and overall performance (14).

Invasion: Squamous Cell Carsinomas and Adenocarcinomas

The likelihood of progression from HPV infection to precancerous and cancerous lesions is largely determined by the viral genotype. Differences in carcinogenic potential among genotypes are primarily attributed to structural variations in the E6 and E7 oncoproteins, which interfere with genomic stability and disrupt normal cell cycle regulation, thereby inhibiting apoptosis. HPV-16 confers the highest oncogenic risk. Adenocarcinomas, which originate from the glandular epithelium of the endocervix, are predominantly caused by HPV-16, -18, and -45. These adenocarcinomas exhibit distinct pathophysiological mechanisms compared to squamous cell carcinomas, which arise from the squamous epithelium of the exocervix. Importantly, precancerous adenocarcinomas are more likely to evade detection through conventional screening and colposcopy, leading to lower rates of diagnosis and treatment compared to squamous precancers. As a result, cervical cancer screening programs have historically been less effective in preventing adenocarcinomas than squamous cell carcinomas (5).

Preventions

Primary Prevention: HPV Vaccination

Current guidelines recommend initiating HPV vaccination for all children, irrespective of sex, starting at 9 years of age, with a two-dose schedule administered 6 to 12 months apart, ideally completed before the 13th birthday. For individuals aged 13 to 26 years who have not previously received the vaccine according to these guidelines, vaccination is advised; a three-dose regimen is recommended for those beginning vaccination at age 15 or older. HPV vaccines are prophylactic in nature, with maximal efficacy observed when administered prior to the onset of sexual activity.

Numerous studies have demonstrated that vaccination before age 14 yields the greatest protective benefit, with vaccine effectiveness diminishing progressively with increasing age. For individuals aged 27 to 45 years, shared decision-making is encouraged, as vaccination in this age group is generally not anticipated to be an effective or cost-efficient strategy for cervical cancer prevention at the population level (5,15).

Gardasil^{R} is a quadrivalent vaccine that provides protection against HPV types 6, 11, 16, and 18. It has been succeeded by Gardasil-9^{R}, a nonavalent vaccine which extends coverage to include HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Both Gardasil^{R} and Gardasil-9^{R} are considered interchangeable, and patients may receive a mixed vaccination schedule during the transition between these vaccines (1).

Secondary Prevention: Screening and Management

Cervical Cancer Screening

In the absence of screening, cervical cancer develops in up to 5% of the population over their lifetime. However, effective screening and timely treatment of cervical precancerous lesions can reduce this lifetime risk to below 0.5%. Routine screening of asymptomatic individuals is advised to facilitate early diagnosis and treatment of precancerous lesions, thereby preventing the development of cervical cancer. Conversely, individuals presenting with potential symptoms of cervical cancer—such as irregular vaginal bleeding, pelvic pain, or abnormal vaginal discharge—should undergo comprehensive evaluation, including a pelvic examination and cervical cytology (5).

An effective cervical cancer screening program comprises the following key components:

(1) Evaluate all individuals for screening eligibility and perform screening procedures as clinically indicated

(2) Conduct screening primarily through HPV testing, with or without adjunctive cytology. A negative HPV test result more reliably excludes the presence of cervical precancerous lesions compared to cytology alone. The sensitivity of cytology for detecting precancer ranges from 50% to 70%, whereas HPV testing demonstrates sensitivity exceeding 90%. Moreover, the risk of cervical cancer decreases progressively with successive rounds of negative HPV screening results. Given that approximately 97% of precancerous lesions test positive for HPV, concurrent cytology and HPV testing (co-testing) offers limited incremental benefit over HPV testing alone. Cervical cancer incidence is highest among individuals who do not undergo appropriate screening (16,17).

Average risk screening

Recent guidelines from the American Cancer Society, compared to cytology, recommend primary HPV screening alone at five-year intervals for individuals aged 25 to 65 years (5).

Surveillance or High-Risk Screening

Up to 20% of individuals in the general population have a history of abnormal screening results, precancerous lesions, malignancy, or immunosuppression, and therefore require more frequent screening at intervals of 1 to 3 years (5).

Screening Cessation

Screening is not recommended for asymptomatic individuals under the age of 21; those without a cervix (e.g., following a hysterectomy) unless there is a history of cervical cancer or precancerous lesions; or individuals over the age of 65 who meet criteria for screening discontinuation. These criteria include documentation of at least three consecutive negative cytology results or two consecutive negative HPV test results within the past 10 years (with the most recent performed within the last 5 years), no abnormal findings in the preceding 10 years, no history of cervical precancer within the past 25 years, no prior diagnosis of cervical cancer, and no evidence of immunosuppression (18).

Ensuring adequate screening before discontinuation at age 65 is essential. Underscreening remains prevalent among individuals aged 45 to 65, and only approximately one-third of women between the ages of 64 and 66 meet the established criteria for screening cessation (1,5,18).

Approximately 25% of cervical cancer cases occur in individuals over the age of 65, with mortality rates nearly twice as high as those observed in younger populations. Notably, many of these cases involve individuals who did not meet the recommended criteria for screening discontinuation (5).

Management of Abnormal Screening Test Results

The 2001 revision of Bethesda System is used to describe abnormal cervical cytology employing the following categories (19):

Squamous cell:

Atypical squamous cells (ASC)

- Of undetermined significance (ASC-US)
- Cannot exclude high grade (ASC-H)

Low-grade squamous intraepithelial lesion (LSIL)

High-grade squamous intraepithelial lesion (HSIL)

Skuamous cell carsinoma

Glandular cell:

Atypical glandüler cells (AGC)

- Non-otherwise specified (AGC-NOS)
- Favor neoplasia (AGC-favor neoplasia)
- Adenocarsinoma in stu (AIS)

Adenocarsinoma

Histological abnormalities are categorized using a two-tiered classification system, in which low-grade lesions are designated as cervical intraepithelial neoplasia grade 1 (CIN1), and high-grade lesions are classified as CIN2 or CIN3.

CIN1 is typically associated with a high likelihood of spontaneous regression, whereas CIN2 and CIN3 are more likely to persist and are recognized as precursors to cervical cancer. The progression from CIN2/3 to invasive carcinoma is estimated to occur over a period of 8 to 12 years (19).

A significant minority of women are not eligible for routine screening intervals. Up to 20% report a history of at least one abnormal screening result, and cross-sectional data from cotesting populations

indicate that approximately 10% currently present with abnormal findings. Current guidelines recommend surveillance at shorter intervals typically for a minimum of 10 years, including four consecutive negative tests, following abnormal results. Consequently, within any primary care population, an estimated 10% to 20% of individuals may not meet the criteria for extended-interval screening. The 2019 ASCCP Risk-Based Management Consensus Guidelines recommend follow-up at 1-year intervals for abnormalities associated with an immediate risk of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) below 4%, but with a 5-year cumulative risk exceeding 0.55%. Surveillance at 1-year intervals is recommended for individuals with low-grade findings that do not necessitate immediate colposcopy, such as normal cytology with a positive HPV test or those undergoing follow-up after colposcopic confirmation of low-grade lesions (e.g., CIN1), as well as during the early intensive surveillance period following treatment for high-grade lesions (histologic HSIL or CIN2/CIN3). Three-year surveillance is advised for individuals with a cumulative 5-year risk of CIN3+ between 0.015% and 0.054%. In the context of long-term follow-up after resolution of most abnormalities, HPV testing or cotesting at 3-year intervals is recommended. Current evidence suggests that even after three consecutive negative HPV tests or cotests, the residual risk remains within the threshold warranting continued 3-year surveillance. Based on existing data, a return to routine screening intervals is advised in only two specific clinical scenarios:

(1) an initial finding of HPV-negative ASC-US followed by a negative HPV test or cotest,

(2) minimally abnormal screening results—such as HPV-positive negative intraepithelial lesion or malignite (NILM), HPV-positive ASC-US, or HPV-positive LSIL with low-grade disease confirmed on colposcopy (i.e., biopsy-proven CIN1 or normal histology), followed by three consecutive negative HPV tests or cotests.

Moreover, HPV genotyping enables risk stratification and guides clinical management, with colposcopic evaluation recommended when HPV types 16 or 18 are identified. When high-risk HPV genotypes other than 16 or 18 are detected, additional diagnostic information is essential to determine whether colposcopy is warranted (1,5,18).

Treatment and Prognosis

The treatment of cervical precancer typically involves excision or ablation of the entire squamocolumnar junction, along with targeted removal of lesions identified during colposcopic examination. The primary objective of treatment is to eradicate the majority of HPV-infected cells that have undergone precancerous transformation, thereby minimizing the risk of progression to invasive cervical cancer (20).

Excisional Methods

All excisional procedures are associated with an increased risk of subsequent preterm birth and premature rupture of membranes in affected women (19).

The use of electrocautery techniques—such as loop electrosurgical excision procedure (LEEP), large loop excision of the transformation zone (LLETZ), needle excision of the transformation zone (NETZ), or straight wire excision of the transformation zone (SWETZ)—can complicate the histopathological assessment of surgical margins. In certain cases, cold knife conization (CKC) may be preferred, as it facilitates more accurate evaluation of margin status. CKC is particularly recommended over electrocautery methods in instances of adenocarcinoma in situ (AIS), suspected microinvasion, inadequate colposcopic visualization, or lesions extending into the endocervical canal (19,20).

Conclusion

According to World Health Organization (WHO), due to incomplete detection and treatment, around 664000 new cases of cervical cancer are diagnosed each year, with more than 349000 deaths resulting from the disease.

Precancerous lesions—defined as abnormal cellular changes with the potential to progress to invasive cancer if untreated—include histologic high-grade squamous intraepithelial lesions (HSIL), cervical intraepithelial neoplasia grade 3 (CIN3), and adenocarcinoma in situ (AIS).

More than 90% of cervical cancer cases are attributable to infection with human papillomavirus (HPV). Although HPV vaccination has been linked to up to a 90% reduction for at least 15 years for HPV infection and cervical cancer incidence among those vaccinated during adolescence, the full protective effects will only be realized as this vaccinated cohort ages into mid to late adulthood. Consequently, cervical cancer screening remains a critical component of prevention strategies. Currently, approximately half of cervical cancer cases arise in individuals with inadequate screening and it is important to note that cases have been reported to be higher in areas of deprivation (1,5).

Programs incorporating repeated cytology (Papanicolaou test) screening, colposcopically guided biopsies, and excisional treatment of cervical precancerous lesions have led to a 60% to 80% reduction in cervical cancer incidence and mortality at the population level. However, due to inherent variability in cytological and histological classifications, integrating information on HPV infection enhances the accuracy of prevention strategies. Specifically, the risk of precancer can be more precisely estimated by identifying the HPV genotype and employing morphological and biochemical assays, such as cytology and p16/Ki-67 dual staining to differentiate between replicative infections, which are more likely benign, and abortive transforming infections, which carry a higher likelihood of precancerous transformation (5).

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