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Review Article

Human Papillomavirus and Precancerous Conditions of the Cervix- A Review

Alemnju Venceslas Tarnju

Bachelors Medical Lab Science (B.MLS), Faculty of Health Science, Buea, Cameroon 2nd Year Medical student All Saints University School of Medicine, Roseau, Dominica.

Corresponding Author: Alemnju Venceslas Tarnju, Bachelors Medical Lab Science (B.MLS), Faculty of Health Science, Buea, Cameroon 2nd Year Medical student All Saints University School of Medicine, Roseau, Dominica.

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Abstract

Human papillomavirus (HPV) is present in precancerous conditions of the cervix. This review attempts to elucidate our understanding of precancerous cervical cancer, with particular emphasis on the central aetiologic function of persistent human papillomavirus (HPV) infection.

The review dwells on recent studies that focused on detecting precancerous cervical lesions using visual inspection with acetic acid (VIA), convection cytology (Pap smear testing), and Schiller test. Anomalies in staining the exocervical epithelium and intraepithelial lesions upon detection with polymerize chain reaction indicated HPV infection. The stages in the evolution of cervical cancer have been widely studied and understood, resulting in successful cancer etiology and prevention.

Keywords: hpv; pap smear; schiller test; via; cin

Introduction

Human papillomavirus (HPV) has caused severe infections worldwide. Breast cancer is the number one cause of mortality in women, which is preceded by HPV. It has caused malignancy and mortality in women across the world [1]. HPV infections have been estimated to reach 500,000 a year, with an estimated 80 percent being recorded in the third world. Female mortality is recorded at 250,000 [1].

Early screening and treatment reduce this cancer rate significantly, preventing the formation of late-stage cancer. HPV predisposition is seen in the early onset of sexual intercourse, multiple sexual partners, HPV genome, women on oral contraceptive pills, immune-deficient individuals, or smoking lifestyle, to name a few. Lack of adequate health care systems leading to inadequate screening has precipitated an increase in advanced cancer that is no longer manageable or treated. Half of the female population who are sexually active and are not immunized will come down with HPV during their adult lives [2].

The Human papillomavirus belongs to the Papilloma viridae family; double-stranded circular

DNA virus, protected by an Icosahedral protein capsid [2], which is none enveloped. Because there is no host genome integration of viral DNA, HPV types 6,11,42, and 44 cause infection of lesser severity. Malignant HPV occurs when the P53 suppressor gene and retinoblastoma gene are inactivated due to the presence of oncoproteins E6 and E7. Several types (40, classified in the Alpha papillomavirus genus) are seen to infect mucosal tissue in the anogenital area [3], and each has connections with cancer. Low grade cervical intraepithelial lesions (LSIL), condylomas, and respiratory papilloma are seen in low-grade HPV. The high-risk types can cause squamous and granular high-grade intraepithelial lesions and oropharyngeal cancer. The immune response is responsible for removing most of the HPV from the system. Types HPV16 and HPV18 have vaccines currently in use worldwide. HPV16 and 18 have cancerous lesions of the cervix in 70% of cases [3].

It is crucial to find out the genomic types as the information can lead to knowledge of the spread, location and geographic areas of HPV infection. High-risk HPV types research has changed into lineages and sub-lineages (1.5–10% and 0.5–1.4% of nucleotide divergence, respectively) with various carcinogenicity [3].

Different subsets of HPV16 and HPV18 have their specific geographic locations and specific ethnic groups that they predominate, whereas, in other types such as HPV 58, these parameters are not so exact. The time lag from the time of infection to the actual HPV disease or cervical cancer development takes a long time, approximately 10 to 20 years. In this research, however, we will be reviewing articles and determining the relationship between HPV and precancerous cervical lesions.

Methods

The purpose of this review is to explain the understanding of precancerous cervical cancer, focusing on the central aetiologic function of persistent human papillomavirus (HPV) infection

The literature of scholarly articles was found using various accepted search engines such as google scholar, ScienceDirect, PubMed, Embase, and Scopus. Key search terms or phrases included human papillomavirus, precancerous lesion, cervical cancer, and HPV cancer.

Based on the research aim, the criteria for selecting the articles were based on whether the papers are about HPV related cancer and their methodology should be approved by the appropriate authorities or recognized method worldwide, which meets the necessary ethical guidelines. We considered any HPV detected in the study, even if it was only HPV16 and HPV18, or broad- spectrum HPV detection [1].

Most of the studies in the reviewed articles sought approval from patients before the researchers conducted the screening. The different tests used for the detection of HPV included schiller test, visual inspection with acetic acid (VIA), convection cytology (Pap smear testing), and polymerase chain reaction (PCR).

Schiller test

The cervix and vagina were examined using a Graves speculum and applying Lugol's iodine to the exo- cervical epithelium. This procedure is known as the Schiller test. Bright yellow areas with no iodine uptake close to the cervix's external area were considered positive [1].

Visual Inspection with Acetic Acid (VIA)

VIA is a fast-screening test for detecting early cervical or precancerous lesion with a moderate specificity and sensitivity. It is easy to handle and requires less specialized skilled personal with equal or greater specificity as Pap smear. Some studies used a 3-5% acetic acid for the VIA and considered positive when there is a distinct, well defined, dense acetowhite area [1].

Convention cytology (Pap smear testing)

Pap testing is a screening test for cervical cancer with moderate specificity. Most studies use this as the initial screening before going on with further tests.

Also, most of the studies used PCR. HPV was identified using conventional PCR, highlighting a 450-bp region of the L1 gene that encodes a viral capsid protein and allows a broad spectrum of HPV genotypes to be increased. The test is positive if the 450-bp band and the 268-bp band corresponding to the β-globin is increased and negative if only the 268-bp band is elevated [1].

Discussion/Results

The results and discussions of Human Papillomavirus and Precancerous Conditions of the Cervix based on the reviewed papers are presented below.

Detection of precancerous cervical lesions is differential by human papillomavirus (HPV) type.

Precancerous cervical lesions caused by human papillomavirus (HPV) types 18 and 45 (HPV18/45) have been underreported in comparison to cancers caused by other HPV types [4]. The study made use of ASCUS (atypical squamous cells of undetermined significance) and LSIL (low-grade intraepithelial lesion) triage (ALTS) data to examine the timeline of the diagnosis of HPV18/45 related lesions in comparison to HPV16 lesions.

Within the two years of ALTS testing, four hundred and seventy-two women (472) were diagnosed with CIN3+. For data clarity, 3.9% (18 CIN3) with missing HPV results and 8.9% (42 CIN3+) having coinfections with HPV16 and HPV18 were excluded from the analysis and interpretation. The primary analysis, therefore, utilized 412 CIN3+. The result showed positivity in 10% (42) of the patients with HPV 18/45, while 29% (121) were carcinogenic with other HPV-positive at registration [4].

The results indicated that the diagnosis depended on the risk group of the HPV. Some, e.g., HPV118/45- related CIN 3+, was diagnosed at the end of the study. HPV16-related CIN3+ was diagnosed at enrollment in comparison with other HPVs. The time of diagnosis also differs with various risk groups.

In HPV18 positive women, the time of diagnosis is delayed. This finding was compared with a previous study [4,5]. Cytology and colposcopy techniques do not adequately detect HPV18/45 lesions, leading to difficulty identifying and diagnosing HPV18/45-associated precancerous lesions [4].

Human papillomavirus (HPV) infection and the multi-stage Carcinogenesis of cervical cancer (3)

The research explains cervical cancer precursors (Table 1), reflecting different stages of persistent human papillomavirus (HPV) infection stages.

The area of metaplastic tissue between the squamous epithelium of the vagina and the glandular tissue of the cervix (susceptible to carcinogenesis) is the cervical transformation zone. Cervical cancer is virtually impossible in the absence of sexually transmitted HPV infection (6) and the lack of intermediate progression to precancer [7].

Depending on the level of cell dysplasia, the stages in cervical carcinogenesis include HPV infection, persistence, precancer, and invasion.

CIN stage	Dysplasia nomenclature
CIN I	Negative
CIN II	Squamous atypical
CIN III	Mild dysplasia
CIN IV	Moderate dysplasia
CIN IV	Carcinoma

Table 1: Stages of Human Papillomavirus (HPV) Infection [7].

Association of HPV16 and 18 genomic copies with histological grades of cervical lesions.

The research was to identify genomic copies of HPV 16 and 18 and determine the relationship between genomic copies and the various grades of lesions.

HPV infection is the leading cause of cervical intraepithelial neoplasia [8].

Patients with persistent oncogenic HPV infection showed cervical lesion progression from low to high grade and people with higher genomic copies [9,10].

This study showed a significant association between HPV 16 and cervical lesion progression for low-grade intraepithelial lesion (LSIL) to squamous cell carcinoma (SCC) ($p<0.001$). Also, HPV16 genomic copies were significantly higher in HSIL (CIN II and III) than LSIL (CINI) ($P = 0.02$). Wu et al. [11] found a strong correlation between HPV16 genomic copies and disease severity. On the other hand, HPV 18 had no such relationship between genomic copies and grade of lesion ($p=0.5$). The reason behind this was not apparent. HPV16 and HPV18 manifest in 90% of cervical lesions in patients.

Conclusion

HPV cancers are estimated to be about 100 types of HPV, with many of them being transmitted sexually. In populations where screening was paramount, HPV infections account for 5% of cytologic results [7]. The most carcinogenic forms are HPV types 16, 18, 31, and 35, among others. The HPV 16 is the primary type indicated in 20% of HPV infections but which causes 40% of the high grade squamous intraepithelial lesion. HPV 18 is a close second and is implicated in the formation of adenocarcinomas [7].

The reviewed articles aimed to determine aetiology and preventative model of cancer, providing information on the stages of HPV cancer, the pathway of HPV disease, impact of screening on development of cervical cancers, efficacy of pap smears in precancerous detection, the role of cervical intraepithelial neoplasia (cervical neoplasia) caused by certain HPV types that could potentially lead to cancer, comparing HPV infections in indigenous women in remote locations [1], determining if other HPV types are not given enough significance in cross HPV infections (e.g., HPV 45) [4]. The research also determines that low-grade squamous intraepithelial lesion (LSIL) transition to the high-grade intraepithelial lesion (HSIL) is seen in HPV 16 higher genomic copies. HPV and cervical squamous cell carcinoma development have been established in the high-risk strain [12].

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