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REVIEW

Human papillomavirus-human immunodeficiency virus coinfection and host cell DNA methylation in vulvar carcinogenesis

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Vulvar cancer accounts for about 5% of all gynaecological malignancies. Previously, it was regarded as a disease of the elderly because it occurred in women over 60 years old. Its incidence is rising due to the coinfection of human papillomavirus (HPV) and human immunodeficiency virus (HIV). High-risk HPV (HR-HPV) predominantly drives both the premalignant and invasive diseases of the vulva in the young population. Women living with HIV have compromised immunity, and the synergism of HPV and HIV might be responsible for their higher predisposition to anogenital neoplasia. They are at a higher risk of infection with multiple HPV genotypes, multifocal disease, persistent infection, and reactivation of latent infections. Genomic alteration through deoxyribonucleic acid (DNA) methylation by persistent HPV infection is implicated in carcinogenesis through the E6/E7 oncogenic pathway. These epigenetic alterations progressively accumulate in HPV-infected cells and induce cancers over time. Premalignant lesions that display abnormal methylation patterns similar to those in cancerous lesions are likely to progress to malignancy within a short period. Such methylation biomarkers can be used to triage premalignant lesions to treatment or monitoring. This review describes the distribution of HPV genotypes and host cell DNA methylation patterns across vulvar premalignant and invasive lesions.

Keywords: vulvar lesions, DNA methylation, human papillomavirus, human immunodeficiency virus

Introduction

Vulvar cancer is an uncommon gynaecological malignancy. Worldwide, it accounted for over 45 000 new cases and 17 000 deaths in 2020, with an age-standardised incidence rate (ASIR) and mortality of 0.9 and 0.3, respectively.[1] It ranked second to cervical cancer as human papillomavirus (HPV)-associated female genital tract malignancies. It shares common risk factors with cervical cancer; hence, the carcinogenesis of cervical cancer is a model for other HPV-related genital cancers. Over 90% of vulvar cancer cases are accounted for by the squamous cell histological types (basaloid and warty), while the uncommon subtypes account for the remaining percentage.[2,3]

In Africa, the true prevalence of vulvar cancer is unknown because of its rarity, but it ranks fourth among gynaecological cancers.[1] The incidence is rising in South Africa, especially among younger women. The estimated ASIR in 2018 was 7.2 per 100 000 population, the highest rate in the world compared with less than 0.2–4.2 per 100 000 in developed countries.[4] This high rate has been postulated to be due to the increased prevalence of HPV infection and human immunodeficiency virus (HIV) cases, the early age of sexual intercourse initiation, and changes in sexual behaviour.[4,5] In an epidemiological study by Chikandiwa et al.,[5] the median age at vulvar cancer diagnosis decreased by 18 years (64 years in 1994 to 46 years in 2012). In the same study, the mortality rate increased by 2.6%, while the ASIR increased by 1.7% among South African women younger than 50 years.[5] This mirrors the trend in the increasing incidence of HIV among the population, with a resultant high disease burden in the population and overstretched healthcare system.

Vulvar cancer is a devastating malignancy that used to be seen in high-income countries and among elderly women aged above 60 years. However, most patients with vulvar cancer in Africa are younger than 60 years, and the majority are associated with high-risk HPV (HR-HPV) and HIV coinfection.[4,6-8] The World Health Organization (WHO) divided vulvar cancer into HPV-associated and HPV-independent types, indicating two independent aetiological pathways for the development of these cancers.[2,3,9] In areas where HIV is not endemic (HIV-negative populations), HPV drives about 20% of the vulvar malignancies, while *TP53* gene mutations or other molecular or genetic processes drive the remaining cases.[3,10,11]

Regardless of the categorisation of vulvar cancer, the treatment modality, viz surgery and/or radiotherapy, is the same. Although the HPV-independent types are associated with poor oncological outcomes, the HPV-associated types have been documented to have favourable prognoses.

A battle of two endemic infections in sub-Saharan Africa

Globally, HPV is the most common sexually transmitted infection. It is also linked to a greater proportion of lower anogenital tract squamous cell dysplasia and malignancies. HPV is mainly contacted through close skin-to-skin and mucosa-to-mucosa contact. Most of the infections acquired within the first year of sexual contact clear before the age of 30. However, people with compromised immunity tend to have impaired clearance, which leads to persistent infections. The odds of HPV-associated anogenital dysplasia and cancers are higher in women living

with HIV, and they have about a ten-fold increased risk of developing squamous-type anogenital cancers than the general population.[12]

HPV can infect and become persistent in the epithelial lining of the lower genital tract, anus, and the oropharyngeal sites. It causes multifocal infection in these areas through the field cancerisation effect. It is well-documented that HR-HPV is responsible for almost all cervical cancers. However, its association with vulvar cancer is variable due to the two distinct pathways to its carcinogenesis and geographical variation. The most extensive worldwide data collected by de Sanjosé et al.[13] over 30 years reported a prevalence of 28% for HPV positivity in vulvar cancer. This falls within the range of 15–100% quoted in many studies across a worldwide geographical distribution, HPV testing methods, and test kit sensitivity.[14-17]

The prevalence variability of HPV-associated vulvar squamous cell carcinoma (SCC) also reflects the prevalence of HPV in a particular geographical location. A South African study quoted the prevalence of HPV among young South African women to be as high as 66%, and they were more likely to have multiple strains of the virus.[18] Hence, HPV-associated vulvar lesions are lower in the developed world compared to low-resource settings, which have a high burden of HPV-related vulvar cancers.

A systematic review of 162 studies showed that HPV was prevalent in 76% of vulvar high-grade squamous intraepithelial lesions (vHSIL) and 39% of vulvar cancer.[17] Among South African studies, the pathological evidence of HPV in vulvar cancer ranged between 78% and 82%.[6,19] Immunohistochemical staining for the upregulation of $p16^{INK4\alpha}$ is a valuable surrogate marker for the evidence of HPV-associated dysplasia.[20] In Zambia, a prevalence of 88.9% and 100% was reported by Maate et al.[21] for vulvar cancer and high-grade intraepithelial lesions, respectively. Mpunga et al.[16] also reported a 77% prevalence of HPV-associated vulvar cancer in Rwanda. Most other published data were from developed countries where the prevalence ranged between 20% and 50%.[8,22] In a meta-analysis by Faber et al.,[14] the pooled prevalence of HPV-associated vulvar cancer was 40%, while 76% of vulvar intraepithelial neoplasias (VIN) were associated with HPV. This underscores the variability of HPV's causal relationship with vulvar lesions, unlike cervical squamous pathology, where the causality is almost invariable.

The synergism of HPV and HIV has been well explained in the literature. However, the intricacy of the interaction in the causality of vulvar dysplasia and cancer has not been widely documented. The presence of HPV significantly impacts the acquisition of HIV, and HIV enhances viral integration, persistence, acquisition of new variants and rapid progression of cellular dysplasia to severe disease or malignancy.[22] Consequently, there is a higher prevalence of HPV among people living with HIV.[23]

Although the life expectancy of people living with HIV has improved since the adoption of highly active antiretroviral therapy (HAART), there is a rising trend in the incidence of anogenital cancers. Studies have reported significant increases in the occurrence of HPV-related anal cancers among men living with HIV who have sex with men.[24,25] While Konopnicki et al.[23,26,27] found a significant decrease in the risk of persistent cervical HPV infection among women with prolonged HIV viral suppression and a $CD4^+$ count above 500 cells/µl, other literature did not find a significant impact of HAART on the incidence of HPV-related anogenital lesions among females living with HIV. It was also reported that HPV type 16 (HPV16), among other serotypes, appeared to be refractory to clearance in the cervix despite compliance with effective antiretroviral drugs.[28] Mbulawa et al.[29] reported that people living with HIV have more than double the risk of acquiring new HPV infections than their negative cohort.

High-grade premalignant lesions of the vulva

There are two high-risk premalignant lesions of the vulva: high-grade squamous intraepithelial lesion (HSIL) and differentiated vulvar intraepithelial neoplasia (dVIN), as defined by the International Society for the Study of Vulvovaginal Disease in 2015.[30] They both differ in pathogenesis, risk factors, prognosis, and epidemiological distribution. HSIL, also called usual vulvar intraepithelial neoplasia (uVIN), is HPV-related and seen predominantly among younger women. The second type of premalignant vulvar lesion is HPV-independent and seen predominantly in elderly women.

HPV-associated vulvar premalignant lesions are often multifocal and can be present with intraepithelial lesions at other sites along the anogenital tract. These areas are lined by the squamous cell epithelia, in which their parabasal cells are susceptible to HPV invasion. These lesions account for the majority of high-risk VIN and are associated with HPV in over 75% of cases.[3,13,31] It is often difficult to treat because of its multifocality and high tendency for recurrence. The prevalence of vHSIL is variable, but recent literature reported upward trends in its prevalence, accounting for the more prevalent HPV-related vulvar cancers among young women.[12,13]

The uncommon dVIN has a high tendency to transform into malignancy. It is associated with chronic inflammatory dermatoses, such as lichen sclerosus and lichen simplex chronicus.[11] In a Dutch study by Bleeker et al.,[32] the risk of lichen sclerosus transforming into malignancy was 3–7% over 10–20 years. This prolonged latent interval can explain why dVIN and HPV-independent SCCs are primarily seen in the elderly. Unlike vHSIL, dVIN has a shorter interval in transforming to malignancy, hence a poorer prognosis and need for aggressive treatment once the dVIN diagnosis is made.[32]

In a study by McAlpine et al.,[33] over 80% of women with dVIN progressed to malignancy within two years, shorter than the interval for vHSIL. In another large Dutch study, Thuijs et al.[3] reported that the 10-year cumulative vulvar SCC risk from high-grade VIN was 10%, with 10% of HSIL and 50% of dVIN progressing to SCC within 10 years of follow-up. While treatment modalities other than surgery can be used to treat vHSIL, dVIN is ideally treated with surgical excision for histological evaluation because of its high risk of association with invasive disease.

Human papillomavirus genotypes

Over 200 HPV serotypes have been correctly characterised and assigned into alpha, beta and gamma papillomavirus genera,

with over 40 serotypes implicated in the cause of anogenital tract diseases in humans.[34,35] They infect the basal cells' squamous epithelium of the anogenital or head and neck regions through a breach in the mucocutaneous linings. In 2005, the International Agency for Research on Cancer (IARC) identified 12 high-risk oncogenic HPV types that have been widely implicated in cervical cancer: HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, and HPV59.[36] They belong to the *Alpha papillomavirus* genus and are clustered in the phylogenetic trees comprising Alpa-5, Alpha-6, Alpha-7, Alpha-9, and Alpha-11 species.[34,36]

Unlike cervical neoplasia, where HPV16 and HPV18 account for about 70% of the pathology, only HPV16 has been found in more than 70% of HPV-related vulvar lesions.[13,17,31,37,38] Other HPV types implicated in vulvar lesions include HPV33, HPV18, HPV31, and HPV45, respectively. Reports from multiple worldwide studies showed that HPV16 was seen in 75% of vHSIL and 50–75% of vulvar cancers, while HPV18 is seen in about 2–5% of vHSIL or cancer specimens.[13,31,37] HPV33 accounts for 6–12% of vulvar lesions, while HPV31 is implicated in less than 2% of either uVIN or cancer. HPV45 is linked to less than 4% of vulvar cancer, while it is almost non-existent in causing vHSIL.[13,31,37] In a Botswana study by Tesfalul et al.,[38] 100% of vulvar cancer specimens were positive for at least one HPV type, while about 75% of the vulvar specimens were positive for multiple strains, and the positivity was not different regarding HIV status.

Methylation markers as predictors of severe disease

Epigenetic processes like silencing, deoxyribonucleic acid (DNA) methylation, acetylation, and histone modifications, both virally or non-virally induced, have been described and implicated in carcinogenesis.[39] Both host cells and the HPV genome can undergo methylation. Viruses cause these changes by inducing cellular enzymes, such as DNA methyltransferase (DNMT), histone deacetylase, histone acetyltransferase, histone methyltransferase, and histone demethylase, which cause alteration in host signalling pathways.[40]

DNA methylation occurs when there is a covalent reaction of a methyl group to the carbon 5-position of cytosine next to a guanine base (CpG) aggregated in CpG islands. The process is catalysed by DNMT, resulting in altered gene expression.[39,40] Generally, HPV induces epigenetic changes like DNA methylation and histone modification through its E6/E7 pathways. In infected cells, the E7 oncoprotein causes stimulation of DNMT activity, while the E6 causes upregulation of the enzymes through the p53 and Rb pathways, respectively.[39,40] The increased expression of the oncoproteins and consequent increased activities and expression of the DNMT seen in HPV-related tumours also translate to increased methylation levels. Hence, methylation activity in the tumour suppressor genes suppresses or silences their expression and functions.

Not only does transforming HPV infection have carcinogenic effects on cells through inhibiting Rb and p53 by E6/E7 proteins, but it also causes epigenetic alterations in cells and eventual induction of carcinogenesis. The progressive accumulation of genetic and molecular alterations in cells by HPV-induced epigenetic changes results in the transformation of infected cells into cancers over time. There is a strong association between DNA hypermethylation, a long period of HPV infection persistence, and the risk of invasive carcinoma.[41] Premalignant lesions that display methylation patterns similar to the cancerous patterns are likely to progress to malignancy within a short period.[42] Similarly, hypermethylation of HPV L1, L2, and E2/4 CpG genome indicates a transforming virus and an increased risk of severe intraepithelial neoplasia.[41,43]

A large body of knowledge reports that methylation levels increase with the severity and duration of cervical lesions.[42-45] In a large meta-analysis by Bowden et al.,[43] the mean methylation level was significantly higher in high-grade cervical intraepithelial neoplasia (CIN) than in low-grade CIN lesions. In another meta-analysis to determine the performance of DNA methylation for detecting severe cervical dysplasia, Kelly et al.[46] noted that methylation levels increase with the increasing severity of the intraepithelial neoplasia and are generally high in invasive diseases.

The DNA methylation test is a quantitative multiplex methylation-specific polymerase chain reaction (PCR) analysis (qMSP). However, the QIAsure FAM19A4/miR124-2 DNA methylation test (QIAGEN, Hilden, Germany), also a quantitative methylation-specific PCR, can detect small amounts of two methylated biomarkers. In the Netherlands, Steenbergen and co-workers have done remarkable work on DNA methylation in anogenital neoplasms, both as screening and triage tests.[47-52] Their studies have validated DNA methylation tests for cervical cancer screening and triage of CIN lesions for treatment or follow-up. The test can detect nearly all cervical cancers and all CIN lesions, with a 77.2% sensitivity and a 78.3% specificity for CIN grade 3, and a 95.0% sensitivity for cervical cancer.[47-51] Bonde et al.[51] reported that the negative predictive values of HR-HPV-positive, methylation-negative outcomes were 99.9% for cervical cancer, 96.9% for CIN grade 3, and 93.0% for CIN grade 2. The multiplex qMSP is not readily available in Africa, and the QIAsure test is only available in some private laboratories in Africa due to the high cost of equipment and analysis.

Despite the broad knowledge supporting the clinical applications of DNA methylation in cervical diseases, little is known about its significance in vulvar premalignant and invasive diseases. Thuijs et al.,[52] through the knowledge of methylation in cervical pathology, tried to establish the molecular biomarkers in vulvar premalignant and malignant neoplasia. In their first DNA methylation study on vHSIL, there were inconsistent methylation patterns across the lesions, even though most showed uniform diffuse $p16^{INK4a}$ staining. This inconsistency could be due to the heterogeneity of vulvar premalignant lesions.[52] In the same study, there was no difference in the methylation biomarker expression across the HPV genotypes when the most prevalent HPV16 was compared with other high-risk types.

In another study on a spectrum of vulvar tissues, Thuijs et al.[53] found that VIN lesions adjacent to invasive squamous cancer had high methylation patterns similar to the patterns shown by 98% of invasive vulvar cancers, while VIN lesions without adjacent invasive cancers showed mixed methylation patterns.

This suggests the increased risk of severe premalignant vulvar lesion transformation to cancer. Hence, the possible role of DNA methylation in the prediction, triaging, treatment, and prognostication of anogenital premalignant lesions. There is a high correlation between methylation levels and vulvar disease severity. The level is consistently higher in dVIN than in vHSIL, suggesting a higher risk of progression to cancer.

Several genes are implicated in the methylation process in many anogenital diseases. In this regard, Thuijs et al.[53] identified twelve genes that are silenced through methylation in vulvar premalignant and malignant diseases: *ASCL1*, *ZIC1*, *FAM19A4*, *GHSR*, *PHACTR3*, *LHX8*, *MAL*, *miR124-2*, *PRDM14*, *SST*, *CADM1*, and *ZNF582*. These genes function as tumour suppressors to prevent carcinogenesis. Other studies described other genes, such as *RASSF2A*, *RASSF1A*, *MGMT*, *WDR17*, *TWIST1*, *TEP12*, *CDKN2A*, and *TSP1*, which undergo hypermethylation in vulvar cancer.[54,55] In a large retrospective Dutch study, Voss et al.[56] validated 12 methylation biomarkers to detect vHSIL. Among the 12 biomarkers, *SST* performed the best in distinguishing vulvar high-grade lesions that required treatment.

DNA methylation has significant clinical applications in anogenital diseases. The histopathological findings often cannot determine exactly which premalignant anogenital lesions will progress to invasive diseases. This usually results in referral for definitive screening tests, like anoscopy or colposcopy, possibly leading to over-treatment and high treatment costs. The surgical treatment of vulvar premalignant lesions often leads to anatomical morbidities and psychosexual problems. Therefore, a methylation test serves either as a substitute for the usual screening test or as an additional test for triaging. Lesion methylation patterns will help identify which lesion is likely to progress, warranting treatment, and those that can be conservatively monitored. Since epigenetic changes are reversible, demethylation of transforming lesions with drugs such as DNMT inhibitor 5-Aza-2′-deoxycytidine may help reverse the HPV-induced dysphasia and cause lesion regression.

Conclusion

Unlike in cervical cancer, work on DNA methylation in vulvar tumours has been scanty. Sub-Saharan African countries carry a high burden of HPV and HIV coinfection and an increasing incidence of vulvar cancers among younger women. In contrast to cervical cancer, there is no screening modality for vulvar cancer. Most patients often present late to the healthcare system amidst other challenges. Vaccination against some HR-HPV types may effectively reduce the burdens of vulvar premalignant or invasive lesions. Therefore, adequate knowledge of the prevalence and types of HPV in premalignant vulvar lesions and vulvar cancer may assist in vaccination scale-up. DNA methylation patterns might be a valuable molecular biomarker in preventing vulvar cancer development in at-risk groups. Premalignant lesions with low methylation levels might suggest little or no intervention and regression over time. This approach will reduce the need for frequent clinical examination, as well as unnecessary treatments and costs.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

Ethical approval was obtained from the University of Pretoria, Faculty of Health Sciences Research Ethics Committee (Ref: 20/2023 — Line 2).

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