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REVIEW ARTICLE

Current trends in the management and prevention of human papillomavirus (HPV) infection

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Summary

Purpose: *Herein, we critically evaluate and discuss current literature in the field of human papillomavirus (HPV) pathogenesis, treatment, and prevention.*

Methods: *Screening of the literature and selection of studies was performed until May 31st, 2019.*

Results: *HPV is considered the commonest heterosexual and homosexual sexually transmitted infection globally. Low-risk HPV subtypes are associated with genital warts, whereas persistent infection with high-risk HPV 16 and 18 subtypes is closely associated with premalignant and invasive lesions in the anogenital and oropharyngeal region. E6 and E7 genes are the main drivers of oncogenic transformation in cervix since they promote all aspects of cancer hallmarks. Importantly, the implementation of screening has reduced the HPV-associated disease burden. In this field, a shift from cytology to HPV testing is currently being observed. Furthermore, vaccination programmes have shown high effectiveness in preventing HPV infection and HPV-related lesions, whereas their future implementation on a larger scale would further enhance our primary prevention strategies.*

Conclusion: *Although HPV constitutes an evolving paradigm in cancer prevention, optimizing screening test performance, and cost-effectiveness remains debatable.*

Key words: *human papillomavirus; vaccination; Pap test; HPV testing*

Introduction

Human papillomavirus (HPV) was first described as "*human warts virus*" implicated in the pathogenesis of genital warts and laryngeal papillomatosis, whereas its possible role in carcinogenesis was suggested in the 1970s [1]. The pivotal publications of Harald zur Hausen, who isolated and studied HPV 16 and 18 from cervical carcinoma biopsies [2-4], paved the way for the subsequent studies to establish the causal relationship between HPV and several cancer subtypes. Currently, the International Agency for Research on Cancer (IARC) highlights the carcinogenic potential of HPV for cervical cancer, malignancies at other anogenital sites and carcinomas of the upper aerodigestive tract. Also, it is postulated that HPV may play a role in the pathogenesis of other cancer sites [5]. The main historical milestones in elucidating cancer potential of HPV infection and its management are reviewed by Estevao et al [6].

Epidemiology

HPV may be considered the most common sexually transmitted infection in terms of prevalence in the general population [7]. Both heterosexual and homosexual HPV transmission is pos-

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sible through penetrative or even non penetrative sexual contact. It has to be noted that the majority of infected women and men do not present with clinically significant signs or symptoms, or they may experience a transient infection [8,9]. HPV infection frequency varies according to the anatomical site; a higher prevalence is shown in the anogenital than in the oral region [10]. Although age is not associated with genital HPV prevalence among males, the rate of newly diagnosed HPV infections decreases with age among females [10].

Furthermore, the median duration of genital HPV infection is similar between the two sexes, whereas the high-risk HPV 16 subtype demonstrates the longer duration in both genders [10]. Immunocompromised patients show persistent HPV infections resulting in high-grade lesions that do not regress and usually lead to carcinogenesis [11]. The reported frequencies of low- and high-risk HPV subtypes are similar for women. However, low-risk subtypes are more frequently encountered than high-risk subtypes in men [10]. considering that almost 100% of cervical carcinoma cases can be attributable to HPV infection, women present with the highest disease burden. There is a significant geographical variation on cervical infection rates and subsequent carcinoma cases worldwide. The higher rates are noted in South America and in sub-Saharan Africa, which highlights the need for improving education and access to screening and prevention programmes in these areas [12].

HPV association with disease

HPV belongs to the family of papillomaviruses and has a circular, double-stranded DNA consisted of approximately 8kb, and it is surrounded by a proteinaceous nonenveloped coat. The virus DNA has 8 open reading frames, and it is transcribed into a single mRNA molecule that is subsequently translated into 8 proteins, including structural (L1, L2) and functional (E1, E2, E4, E5, E6, E7) ones [13].

Skin or mucosal microlesions enable the infection of normal cells in the basal epithelial layer, and HPV DNA initially remains episomal. Following infection, the early HPV genes E1, E2, E4, E5, E6, and E7 are expressed and the viral DNA replicates from episomal DNA. Although the infected cells are divided laterally, some of them may be transferred to the suprabasal cell layers, where viral DNA is actively transcripted and translated. E6 and E7 proteins are the cardinal inducers of mitosis throughout the process, whereas E1, E2, E4, and E5 are essential for viral proliferation. L1 and L2 are expressed in the upper levels of the epithelium, where the encoated HPV particles are released and may infect surrounding tissues. The integration of episomal DNA into the host DNA or epigenetic events such as hypermethylation may result in overexpression of E6 and E7 genes and the development of high-grade precancerous lesions [cervical intraepithelial neoplasia (CIN) 2 and 3] and invasive carcinoma [6, 14-16].

The viral oncoproteins E6 and E7 are considered as the main drivers of malignant transformation and, traditionally, they are described as potent inhibitors of the tumour suppressor genes, Tp53 and RB. Interestingly, these oncoproteins have multifaceted and interrelated actions that ultimately result in cell immortalization and malignancy. E6 inhibits pro-apoptotic p53 and BAK and promotes cell proliferation by upregulating telomerase and SRC kinase. E7-mediated inhibition of RB results in the cyclin-dependent kinase inhibitor INK4A activation through the transcription factor E2F; however, E7 exerts a downregulating effect on INK4A as well. E7 favors cell proliferation by promoting cyclin A and E expression and inactivating cyclin-dependent kinase inhibitors WAF1 and KIP1. The close relationship between E6 and E7 lies in that E6 counteracts the apoptosis signal mediated by E2F expression, whereas E7 protects E6 from INK4A inhibition [14]. Currently, it has been demonstrated that the synergistic effect of E6 and E7 oncoproteins promote several cancer hallmarks including immortalization, genomic instability, deregulation of the cell cycle, evasion of apoptosis, cell invasion, deregulation of the immune response, angiogenesis switch, inflammation promotion, deregulation of cell metabolism and epigenetics [6, 17].

HPV subtypes are divided into low-risk and high-risk ones, according to their detection in benign or malignant lesions, respectively. HPV 6 and 11 are the most frequently reported in benign lesions; up to 90% of genital warts are associated with these subtypes [18]. Anogenital warts have no metastatic potential; however, they usually have a recurrent course and may affect the quality of life, whereas their treatment is more challenging among immunocompromised patients such as persons with human immunodeficiency virus (HIV) [19]. Furthermore, HPV infection may result in low[-]grade CIN 1, which regresses spontaneously in the majority of cases and has a very low risk of progression to cancer [20]. High-risk HPV 16 and 18 subtypes are associated with high-grade CIN lesions and invasive carcinoma. A significant percentage of CIN 2 and 3 lesions may regress spontaneously, but these lesions present a non-negligible increased rate of malignant transformation, reaching more than 12% for CIN 3 [20,21]. High-risk HPV 16 and 18 subtypes are also implicated in the

pathogenesis of premalignant and invasive lesions in anogenital and oral cancer [22,23]. Both HPV-related (high-risk type, viral load, virus variants) and other factors, including immunosuppression, genetic predisposition, hormonal status, exposure to mutagens and mutagenic co-infections (such as herpes simplex), history of smoking and several sexual partners, regulate the underlying molecular events that may lead to spontaneous regression or the evolution of a persistent HPV infection to high-grade dysplasia and invasive carcinoma [14].

Diagnosis and screening – the role of molecular approaches

Warts are usually a clinical diagnosis due to the characteristic macroscopic appearance, but biopsy should be performed in case of uncertainty. Patients should also be tested for HPV and other sexually transmitted infections, including HIV [7].

Detection of both pre-invasive and cancerous cervical lesions is feasible during population screening. According to the United States Preventive Services Task Force (USPSTF) guidelines published in 2018, women aged between 21 and 29 years should undergo cervical cytology (Pap testing) every 3 years, whereas women aged 30 to 65 years have 3 screening choices including cervical cytology every 3 years or high-risk HPV testing every 5 years or co-testing every 5 years (grade A recommendations). There is also a USPSTF recommendation against screening women aged less than 21 years or more than 65 or those with cervix removal who had undergone adequate prior screening and are not otherwise considered high-risk for cancer development [24]. In the United Kingdom (UK), the National Health System (NHS) Cervical Screening Programme includes a first screening invitation at 24.5 years followed by subsequent invitation every 3 years until the age of 49 and every 5 years until the age of 64 [25]. Women aged 65 or older are only screened upon previous abnormal results or if their last screening test was before becoming 50 years old. There are three cervical cancer screening strategies as follows: 1) cytology screening alone, 2) cytology screening with HPV triage, in which HPV test is applied upon borderline cytology results, 3) HPV primary screening with cytology triage, in which cytology is performed upon positive HPV test. Women with positive results are referred to colposcopy and biopsy, as indicated. There are no available guidelines regarding screening for HPV-related carcinomas in other anatomic sites, although it may be considered on a case-by-case basis for high-risk groups [11].

During the last decade, there is an open debate about the potential superiority of high-risk HPV testing over liquid-based cytology in terms of efficacy and cost-effectiveness. In this context, the ARTISTIC trial ("A Randomised Trial in Screening to Improve Cytology") recruited 24,510 women aged 25 to 64. Over three screening rounds approximately three years apart, the high-risk HPV testing demonstrated improved sensitivity compared to liquid-based cytology testing and provided women with longer term protection following a negative test result than a liquid-based cytology result [26]. Importantly, a pooled report of the extended follow-up of four large, European, randomized, controlled trials including 176,464 women aged 20-64 years with 1,214,415 person-years of follow-up showed that HPV-based screening conferred a 60-70% greater protection than cytology against invasive carcinoma. Interestingly, these data also suggested the initiation of screening at the age of 30 and the establishment of extended 5-year screening intervals [27]. High-risk HPV testing of self-sampling vaginal fluid may also be valuable for women who do not regularly attend screening [28].

In the era of HPV testing and its potential universal implementation as a first-line screening tool, molecular approaches are in their primetime. A comparative analysis of six HPV tests included four tests (Hybrid Capture 2, Cobas, Abbott, and Becton-Dickinson (BD)) assessing HPV DNA and two measuring RNA (APTIMA and NorChip). Apart from NorChip, all tests had a high sensitivity for revealing high-grade lesions, among which APTIMA also had the best specificity [29]. The higher specificity shown with APTIMA may be attributed to the fact that it measures the mRNA that is translated into E6 and E7 oncoproteins and, thus, it is higher expressed in more dysplastic lesions. Therefore, APTIMA may have the best sensitivity and specificity. Furthermore, next generation sequencing (NGS) technology may improve specificity [30], whereas novel approaches based on polymerase chain reaction (PCR) enrichment techniques have shown promising results in detecting and characterizing HPV variants both in oropharynx and cervix [31-33].

Treatment

Anogenital warts are managed with locoregional treatments; however, routine follow-up is essential due to the recurrence risk. Regarding CIN lesions, the treatment approach should be tailored. Taking into account the high regression rate of CIN 1 lesions, follow-up should be applied instead of invasive therapy [34]. Patients with CIN 2 and 3

lesions should undergo either conization or loop electrosurgical excision procedure or laser or cryotherapy [34]. Invasive carcinomas should be treated according to oncological principles and treatment may include surgery, chemotherapy, radiotherapy, and targeted therapies [35]. Follow-up surveillance intervals depend on the disease stage and the subsequent persistence or not of HPV infection [25].

Prevention

HPV prevention is feasible through vaccination. Currently available vaccines contain virus-like particles (VLPs) consisting of the L1 structural protein. The quadrivalent (HPV-16/18/6/11) Gardasil® and the bivalent (HPV-16/18) Cervarix® were approved in 2006 and 2007. More recently, the nonavalent (HPV-6/11/16/18/31/33/45/52/58) Gardasil9® became available. According to the American Cancer Society, vaccination of all children should be initiated at ages 11 and 12 years, whereas late vaccination for those not vaccinated at the recommended ages should be completed as soon as possible, and very-late vaccination should be offered in high-risk populations [36]. A gender[-]neutral vaccination programme has been recently recommended by the UK's Joint Committee on Vaccination and Immunisation (JCVI), as well [37]. Implementing novel vaccination strategies is currently a debatable issue in terms of cost-effectiveness in national settings. However, several European countries, including the UK and Greece, have recently adopted expanded vaccine indications aiming at whole population coverage.

Conclusion and future directions

Although HPV is a widespread infection among sexually active people worldwide, it is usually transient, and the associated lesions have a high remission rate. However, persistent HPV infection with high-risk subtypes accounts for a significant disease burden, including invasive carcinomas, especially among women and immunocompromised patients. Importantly, these lesions are potentially preventable with vaccination. The currently licensed vaccines provide protection against the most frequent HPV subtypes and related precancerous cervical and anogenital lesions. Nevertheless, a gender-neutral vaccination programme has not been implemented universally around the globe. On the one hand, public health authorities should intensify their screening and vaccination efforts on poor and high-risk populations. On the other hand, the scientific community should aim to develop cost-effective, next-generation vaccines covering all oncogenic subtypes and also targeting L2 structural protein. Furthermore, more robust HPV genotyping methods may extend screening intervals, whereas additional molecular and epigenetic markers may enhance the classification of high-risk lesions and, subsequently, our prevention strategies.

Conflict of interests

The authors declare no conflict of interests.

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