Mapping HPV infections: from usual locations to rare manifestations

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Abstract

Human papillomaviruses (HPVs) are responsible for approximately 5% of all cancers, with high-risk types causing nearly all cervical cancer cases. While cervical cancer is the most recognized outcome of HPV infection, the virus also contributes to vulvar, vaginal, penile, anal, and head and neck cancers. HPV types 16 and 18 are the primary culprits in these malignancies. HPVs exhibit strict host specificity and encompass over 100 types, some linked to benign conditions like genital warts. The viral oncoproteins E6 and E7 play a crucial role in cancer development by inhibiting tumor suppressor genes. HPV-related diseases manifest in various ways, from common conditions like anogenital and plantar warts to rare presentations such as recurrent respiratory papillomatosis, conjunctival papillomas, and middle ear carcinomas. The clinicians must recognize this diversity to ensure the accurate diagnosis and management. Preventive measures, particularly large-scale vaccination, are essential to reduce the incidence and complications of HPV-related diseases.

Keywords: *human papillomavirus, HPV-related cancers, cervical cancer, atypical localizations*

Rezumat

Virusurile papilomatozei umane (HPV) sunt responsabile pentru aproximativ 5% dintre toate cancerele, tulpinile cu risc înalt cauzând aproape toate cazurile de cancer de col uterin. Deși cancerul de col uterin este cel mai cunoscut rezultat al infecției cu HPV, virusul contribuie și la apariția cancerelor vulvare, vaginale, peniene, anale și ale capului și gâtului. Tipurile de HPV 16 și 18 sunt responsabile de apariția acestor malignități. Infecția cu HPV prezintă o specificitate strictă față de gazdă, existând peste 100 de tulpini, unele legate de condiții benigne, precum verucile genitale. Oncoproteinele virale E6 și E7 joacă un rol crucial în dezvoltarea cancerului, prin inhibarea genelor supresoare tumorale. Afecțiunile asociate HPV se manifestă în diverse moduri, de la condiții comune precum verucile anogenitale și plantare până la prezentări rare, cum ar fi papilomatoza respiratorie recurentă, papiloamele conjunctivale și carcinoamele urechii medii. Clinicienii trebuie să recunoască această diversitate, pentru a asigura un diagnostic corect și o gestionare adecvată. Măsurile preventive, în special vaccinarea pe scară largă, sunt esențiale pentru a reduce incidența și complicațiile bolilor legate de HPV.

Cuvinte-cheie: *virusul papilomatozei umane, cancere asociate HPV, cancer de col uterin, localizări atipice*

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Introduction

Human papillomaviruses (HPVs) are small, circular DNA viruses with double-stranded genomes that belong to the *Papillomaviridae* family, and they exhibit strict host specificity, based on genotype. Around 5% of all cancers are associated with HPV infections. Significantly, almost all cervical cancer cases are caused by infections with high-risk HPV (hrHPV) types[1]. Human papillomaviruses represent a large and diverse group of viruses. Over 100 types have been described, using the study of their complete genome, although, as supported by the detection of subgenomic amplicons, it is believed there are even more HPV types out there that have yet to be fully isolated[2]. HPV subtypes are classified as low-risk or high-risk, based on their association with benign or malignant lesions, respectively. HPV 6 and 11 are the most commonly identified in benign lesions; these subtypes are linked to up to 90% of genital warts[3]. Out of the 15 high-risk genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82), the ones most commonly associated with malignancy are genotypes 16, 18, 31, 33, 35, 45, 52 and 58, of which 16 and 18 are the most important[4]. The viral oncoproteins E6 and E7 are key contributors to malignant transformation. Traditionally, they are known for their strong inhibitory effects on the tumor suppressor genes *Tp53* and *RB*. These oncoproteins engage in a variety of complex and interrelated activities that eventually result in cell immortalization and the development of malignancy[5]. Among a species, individual viruses exhibit a preference for either cutaneous or mucosal surfaces[6]. HPV is the root cause for many malignant processes which in turn cause a huge burden on health systems, particularly in low-income countries. In an analysis performed in 2012, it came to light that approximately 4.5% of new cases of cancer (640,000 new cases) were believed to be caused by the HPV infection[7]. About 29.5% of infection-related cancers were linked to HPV, and more than half of infection-associated cancers in women were caused by HPV[8]. This article aims to review the most common localizations of HPV infection, as well as some rare atypical presentations.

Common sites of HPV infection

During the late 1990s and 2000s, prospective epidemiologic research delineated the temporal link between exposure to high-risk (HR) human papillomavirus and the subsequent onset of cervical intraepithelial neoplasia (CIN) and cervical cancer. These findings, bolstered by robust biological plausibility drawn from fundamental scientific studies, resulted in the recognition of HR-HPV as a crucial – though not sole – factor in nearly all cases of cervical cancer[9]. The primary contributors are HPV 16, detected in 50-70% of instances, and HPV 18, detected in 7-20% of instances[10,11]. HPV infections are typically contracted through sexual encounters, with newly sexually active adolescents and young adults facing the highest risk[12]. During active HPV infection, minor cervical abnormalities, such as low-grade squamous intraepithelial lesions (LSIL) or CIN grade 1 (CIN1), may be identifiable during screening, yet they usually resolve spontaneously, within one or two years, without intervention[13]. Around 90% of newly acquired HPV infections also tend to become undetectable within one-two years[13], a process commonly termed "viral clearance". However, this could also indicate immune suppression below detectable levels or viral latency[14]. Approximately 60% of cases trigger a detectable immune response[15], marked by the presence of serum antibodies specific to the HPV type responsible for the infection, although their effectiveness in preventing reinfection remains uncertain[16]. A small fraction of HPV infections persist beyond 12 months, elevating the risk of progressing to cervical pre-cancer (high-grade squamous intraepithelial lesions – HSIL, or CIN grade 2 or 3 – CIN2/3), and potentially cancer, if left untreated[13].

HPV not only acts as a carcinogen in cervical cancer, but also contributes to a portion of vulval, vaginal, penile, anal, and head and neck cancers due to high-risk HPV infection, with HPV 16 being the predominant factor[17]. Although vaginal cancer is not as commonly encountered in clinical practice as cervical cancer, it remains an important issue in women's health worldwide, as it is closely related to HPV infection and, therefore, preventive interventions have the potential to be highly effective[18]. In a study that gathered data from over 500 cases of vaginal cancer from 31 countries, HPV DNA was found in 74% of cases of invasive cancers and in 96% of vaginal intraepithelial neoplasia grade 2/3 cases[19]. The most common type detected for either vaginal intraepithelial neoplasia or invasive cancers was HPV 16 (59% of cases), and in the case of vaginal intraepithelial neoplasia, it was followed by HPV 18 (6%), HPV 52 (6%) and HPV 73 (5%), while for invasive cancers types, HPV 18 (5%), HPV 31 (5%) and HPV 33 (5%) were detected. It is also proven that HPV-associated vaginal cancers tend to manifest earlier in life[19].

Regarding vulvar cancers, HPV is still a top risk factor, even though not as prominent as with cervical cancer, as shown in a meta-analysis published in 2023; for vulvar invasive carcinoma and intraepithelial vulvar neoplasia, HPV was found in 39.1% of cases and 76.1% of cases, respectively. In both instances, types 16 and 33 were most commonly detected[20]. The slight silver lining – if one can call it that – is that HPV-related vulvar squamous carcinoma has a better prognosis regardless of age or stage at diagnosis, although it is of note that, as with most HPV-associated malignant tumors, they tend to appear at younger ages[21].

Similarly, with an estimated 27,000 new cases in 2018 worldwide, a female-to-male ratio of almost 5:1 and with the diagnostic rates among women being on the rise, anal cancer is becoming an increasingly more relevant topic in women's health[22]. HPV is a major risk factor for epidermoid anal cancer, and the HPV strains incriminated are strikingly similar to those responsible for the aforementioned cancers. A Danish team tested over 300 specimens of anal cancers for HPV using PCR, and the results showed that 88% tested positive, most notably for type 16 (73%), followed by types 18, 33 and 31[22]. It is of note that women are significantly more likely to have HPV-positive anal cancer (93%) compared to men (69%)[10]. The risk factors for HPV-associated anal cancer are similar to any HPV-related disease: a large number of sexual partners, promiscuous sexual behavior, a history of venereal diseases, and smoking[23].

Oropharyngeal squamous cell carcinoma includes cancer of the base of the tongue, tonsils, uvula and soft palate, and over the past 20 years, its incidence has been on the rise, in some areas even doubling, along with HPV infection rates[24,25]. The percentage of cases that can be attributed to HPV varies greatly depending on location. In a UK-based study, it was around 51.8%, with tonsil carcinoma being the most likely to be associated with HPV (61.8%) versus the least likely – carcinoma of the uvula/soft palate (9.1%)[25]. To no surprise, HPV 16 was the leading strand, found in a striking 96.3% of cases, followed by HPV 33 and HPV 18[25].

Another type of cancer potentially linked to HPV is penile cancer. A meta-analysis of global data revealed a pooled HPV prevalence of 50.8% in penile squamous cell carcinomas[26]. Current trends showing early onset (≤64 years of age) may be partly attributed to shifts in sexual practices, leading to increased exposure to sexually transmitted diseases and HPV infection prevalence[27]. HPV types 16, 18, 31 and 33 have been detected in a high proportions of penile squamous cell carcinoma cases[19,27-29]. Premalignant lesions associated with HPV infection, such as erythroplasia of Queyrat and Bowen's disease, are linked to an elevated risk of invasive penile squamous cell carcinoma. Overall, an estimated 30-50% of invasive penile squamous cell carcinomas are associated with HPV infection, with HPV 16 being particularly notable[29].

Anogenital warts (AGWs) – also known as *condylomata acuminata* or, simply, condyloma – are attributable to human papillomavirus, particularly genotypes 6 and 11. These warts manifest as clinically visible growths on the skin or mucosa in the anogenital region. They represent a significant reason for consultation across various healthcare settings, including primary care, dermatology, gynecology and urology, imposing a considerable burden on the healthcare system, due to the need for repetitive visits

for management. Additionally, they often trigger negative psychosexual reactions in affected individuals[30]. In a study conducted in sexual health clinics in Australia, prior to the implementation of the government-funded HPV vaccination program for young women and girls, the annual incidence of anogenital warts was estimated at 2.19 cases per 1000 Australians. The highest incidence was observed in women aged 20 to 24 years old, at 8.61 cases per 1000, and in men aged 25 to 29 years old, at 7.40 cases per 1000[31]. Notably, 5.6% of sexually active American adults aged 18 to 59 years old reported having ever been diagnosed with AGWs[32]. Additionally, among Nordic women aged 18 to 45 years old, the proportion was 10.6%[33].

Viral warts – also known as *verruca pedis* or plantar warts – are prevalent skin conditions observed in both pediatric and adult populations. The HPV subtypes commonly associated with plantar warts on the hands and feet include types 1, 2, 4, 27 and 57. The inoculation of keratinocytes with HPV typically requires an epidermal abrasion and a transiently impaired immune system[34]. As HPV can survive on surfaces like fomites, showers and swimming pools, areas with abrasive nonslip surfaces pose a high risk for both harboring the virus and inducing epidermal abrasions. While around thirty percent of warts may resolve on their own, those that persist often present as cosmetically undesirable, painful, and irritating for the patient[35].

Unusual HPV localizations

Recurrent respiratory papillomatosis (RRP) presents as a benign yet potentially troublesome condition triggered by human papillomaviruses, marked by the emergence of papillomatous lesions within the respiratory tract[36]. HPV types 6 and 11 account for over 90% of RRP cases[37,38]. While RRP primarily affects the larynx, it occasionally escalates, extending to the nasopharynx, tracheobronchial tree and, more rarely, the pulmonary parenchyma[39,40]. The disease's natural trajectory varies widely, being challenging to forecast, ranging from spontaneous regression to aggressive progression, potentially leading to airway obstruction or pulmonary spread, necessitating numerous surgical interventions to maintain airway patency[41]. Although infrequent, RRP is more prevalent in children than in adults. The reported incidence rates range from 0.17 to 1.34 per 100,000 in children[42,43] and from 0.18 to 0.54 per 100,000 in adults[38,44]. Notably, a maternal history of genital warts during pregnancy and delivery strongly correlates with the onset of juvenile RRP[45].

Another rare localization of HPV infection is the conjunctiva. The highest incidence of conjunctival papillomas is registered among individuals aged 20-29 years old[46]. This finding aligns with those from Dunne et al. study, which revealed the highest prevalence of cervicovaginal HPV infection among women aged 20-24 years old[47], as well as with Insinga et al. research, which indicated the highest prevalence of genital warts among women aged 20-24 years old and in men aged 25-29 years old[48]. In adults, HPV infection of the conjunctiva is commonly believed to result from autoinoculation, where the virus is transferred from contaminated fingers to the conjunctiva. Sonnex et al. have documented the presence of HPV types on the hands of patients with genital warts[49]. Additionally, conjunctival papillomas have been reported in infants, with transmission presumed to occur during birth from the infected genital tract of women to the newborn's conjunctiva[50].

Additionally, another rare location for HPV infection is the middle ear. Primary middle ear squamous cell carcinoma (MESCC) has an annual incidence of 0.8-1 per one million people, and it is the most common histological type in this area[51]. A significant number of MESCC cases have been associated with HPV infection. Although HPV's role in oncogenesis is recognized, its involvement in the pathogenesis and prognosis of MESCC remains unclear. Both alpha and beta HPV types have been found in the middle ear mucosa, but their role in carcinogenesis and their relationship with middle ear disease are not yet fully understood[52]. Alpha HPV can be found in both skin and mucosa, whereas beta HPV is commonly found on the skin and eyebrows. Notably, beta HPV was detected in 63.6% of MESCC cases in a recent case series[53].

Bowen's disease is a slow evolving precancerous dermatosis, precursor to squamous cell carcinoma, and while it was believed that only about 3-5% develop into squamous cell carcinoma, recent data reveal that the rates might be much higher, even as high as 16.3%[54-56]. High-risk mucosal types of HPV (16, 18, 31 and 33) are considered a risk factor for genital Bowen's disease, but in recent years they have also been found in extragenital lesions, highlighting once again the almost ubiquitous nature of this virus and the need for prevention[57].

Epidermodysplasia verruciformis (EV) is a rare autosomal recessive disease associated with an increased risk of non-melanoma skin cancer, mainly cutaneous squamous cell carcinoma[58]. Although the exact pathogenic mechanism in unknown, it is now accepted that it results from a combination of congenital gene mutations in the transmembrane channel TMC6/EVER1 or TMC8/EVER2 genes and HPV infection, to which they are more susceptible than the general population[59]. People with EV usually develop precancerous lesions – actinic keratosis – and in the case of about one third of patients, they later progress to invasive skin cancers, especially in areas exposed to the sun[60]. The HPV types most commonly found in skin lesions of EV patients are 5, 8, 9, 12, 14, 15, 17 and 19-25, with types 5 and 8 being the most common[61,62].

Conclusions

Human papillomavirus represents a significant cause of infection-related cancers, primarily affecting the genital and anal regions, but also contributing to malignancies in other areas, such as the oropharynx, conjunctiva, and middle ear. The most commonly found carcinogenic type is HPV 16, though numerous other types also pose substantial risks. The diverse and widespread nature of HPV-related diseases underscores the necessity for large-scale preventive measures, such as vaccination programs. Given the proven safety and efficacy of HPV vaccines,

widespread vaccination is imperative to alleviate the global healthcare burden imposed by this ubiquitous viral group. Knowing all these, one must reiterate the need for preventive measures, such as large-scale vaccination programs, given the proven safety and efficacy of vaccines.

Seeing the rise in the incidence of certain HPV-related cancers, such as anal and oropharyngeal neoplasms, it is reasonable to question whether large-scale vaccination would decrease their incidence, and not only that of cervical cancer, for which we already have proof. ■

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