Received: 11 May 2024 | Accepted: 23 May 2024

DOI: 10.1111/jog.15995

INVITED ARTICLE

Impact of human papillomavirus types on uterine cervical neoplasia

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Funding information
Japan Agency for Medical Research and Development, Grant/Award Number: 23wm0325057h0001

Abstract

Human papillomavirus (HPV) is a major cause of cervical cancer. As the natural history of HPV-associated cervical lesions is HPV genotype-dependent, it is important to understand the characteristics of these genotypes and to manage them accordingly. Among high-risk HPVs, HPV16 and 18 are particularly aggressive, together accounting for 70% of HPV genotypes detected in cervical cancer. Other than HPV16 and 18, HPV31, 33, 35, 45, 52, and 58 are also at a high risk of progression to cervical intraepithelial neoplasia (CIN)3 or higher. Recent studies have shown that the natural history of HPV16, 18, 52, and 58, which are frequently detected in Japan, depends on the HPV genotype. For example, HPV16 tends to progress in a stepwise fashion from CIN1 to CIN3, while HPV52 and 58 are more likely to persist in the CIN1 to CIN2 state. Among the high-risk HPVs, HPV18 has some peculiar characteristics different from those of other high-risk HPV types; the detection rate in precancerous lesions is much lower than those of other high-risk HPVs, and it is frequently detected in highly malignant adenocarcinoma and small cell carcinoma. Recent findings demonstrate that HPV18 may be characterized by latent infection and carcinogenesis in stem cell-like cells. In this context, this review outlines the natural history of HPV-infected cervical lesions and the characteristics of each HPV genotype.

KEYWORDS
cervical cancer, cervical intraepithelial neoplasia, genotype, human papillomavirus, stem cell

INTRODUCTION

Human papillomavirus (HPV) is a primary cause of cervical cancer and the second most common pathogen-driven cancer following *Helicobacter pylori*.[1] Approximately 95% of cervical cancers are caused by HPV infection.[2] Despite the recent introduction of an HPV vaccination, cervical cancer remains the fourth most commonly diagnosed cancer among women worldwide and the fourth leading cause of cancer-related deaths.[3] Approximately 10 000 patients were newly diagnosed with cervical cancer in 2019 in Japan, and this number is slightly increasing.[4]

As cervical cancer is caused by HPV infection, the vaccine is expected to be effective in preventing this disease. In Sweden and Denmark, where HPV vaccines were introduced early on, their effectiveness in preventing cervical cancer development has been confirmed using real-world data.[5,6] In Japan, a national vaccination program began in 2013 but was suspended shortly thereafter until 2021. This suspension has delayed the coverage of the HPV vaccine in Japan, and it is expected to take even longer to eradicate cervical cancer.

In addition, most HPV-associated cervical cancers develop via cervical intraepithelial neoplasia (CIN), making screening highly effective in reducing cervical cancer incidence. As HPV-based screening is expected to increase in the future, it is important to understand the characteristics of HPV genotypes to manage cervical lesions. This review outlines the natural history of

HPV-associated cervical lesions as well as the characteristics of each HPV genotype.

HPV INFECTION AND CERVICAL CANCER DEVELOPMENT

HPV is a small virus with a double-stranded circular DNA genome of approximately 8 kbp. HPV consists of early genes (E6, E7, E1, E2, E4, E5, and E8) involved in viral gene replication, late genes (L1,2) encoding capsid proteins that wrap the circular DNA, and a long control region (LCR). Early genes have distinctive functions, and the expression of these genes is usually altered along with the epithelial differentiation.[7] Oncoproteins, E6 and E7, have transforming properties and immortalize HPV-infected cells by suppressing p53 and pRB, respectively.[8,9] E1 encodes a virus-specific DNA helicase which is necessary for viral replication. E2 is also necessary for viral replication, and it regulates transcriptional levels of the oncogenes E6 and E7 by binding to E2 binding sites (E2BS) in the HPV genome. E4 plays a role in virus escape from the epithelial surface by disrupting the keratin network.

High-risk HPV infection is the first step toward cervical cancer development. P53 is inactivated by E6, and the cells become apoptosis-resistant. E7 inactivates pRb, thereby providing the cells with the ability to proliferate without control. In addition, E6 can also induce chromosomal instability and increase telomerase activity[10,11] thereby contributing to cell immortalization and carcinogenesis. Recently, it was further shown that HPV16 E6 can cause chromosomal instability by degrading CENP-E through E6-associated ubiquitin-protein ligase E6AP/UBE3A.[12]

The second step for cervical cancer development is continuous expression of oncogenes E6 and E7.[13,14] Dysregulation or dysfunction of E2 is indispensable for the continuous E6 and E7 expression. There are two major mechanisms underlining the continuous expression of E6 and E7: one is the methylation of the HPV genome, and the other one involves HPV genome integration into the human genome[13,14] Methylation of E2BS in the HPV LCR disables E2-mediated repression of the HPV early promoter.[15] The proportion of E2BS methylation as well as LCR regions increases along with the disease progression.[16,17] Not only the proportion of HPV genome methylation but also the frequency of HPV integration increases with the progression of cervical lesions, and HPV integration is found in 53.8% of CIN and 81.7% of cervical cancers.[18] In addition to inducing continuous expression of E6 and E7, HPV integration triggers various genetic alterations, such as oncogene amplification, chromosomal rearrangements, and chromosomal instability.[19–22] Furthermore, HPV integration and subsequent oncogene amplification increase oncogene expression near HPV integration sites.[21–23]

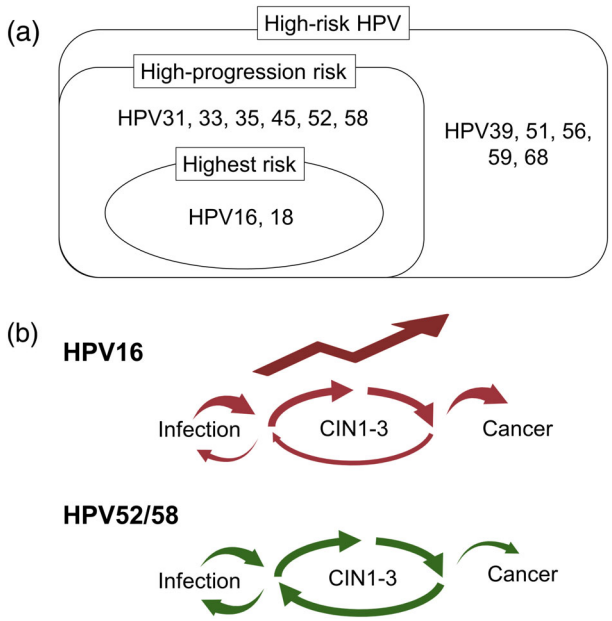

FIGURE 1 Cervical cancer risk and characteristics of HR-HPVs. (a) Risk stratification of HR-HPV genotypes. (b) Natural history of HPV16, 52, and 58. Created using Biorender.com.

The final step during cervical cancer development is the accumulation of human genome alterations in genes including *PIK3CA*, *PTEN*, and *KRAS*.[19,24–26] Recent next generation sequencing (NGS)-based studies have revealed that somatic variants are characterized by cancer histology; there are some specific variants such as recurrent E322K substitutions in the *MAPK1* gene and inactivating mutations in the *HLA-B* gene in squamous cell carcinoma and other variants such as *ELF3* and *CBFB* in adenocarcinomas.[26] Likewise, HPV-derived cervical cancer is characterized by multi-step carcinogenesis, including HPV infection, persistent expression of E6 and E7, introduction of genomic instability, and accumulation of somatic mutations.

HPV GENOTYPE

More than 200 genotypes of HPV have been reported.[27] Of these, only the mucosal type infects the cervix. The International Agency for Research on Cancer classifies HPV into four groups according to the risk of carcinogenesis[28]; Groups 1 and 2A include 13 HPV genotypes which have a high risk of carcinogenesis: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Among high-risk HPVs (HR-HPVs), HPV16 and 18 are particularly highly malignant and together account for 70% of HPV genotypes detected in cervical cancer (Figure 1a),[29] followed by HPV45. HPV39, 51, 56, 59, and 68 have a lower risk than HPV31, 33, 35, 52, and 58 and an even lower risk if CIN is not detected immediately.[30] In contrast, low-risk HPVs include HPV6 and 11, which cause condyloma acuminatum and laryngeal papillomas.[31]

It is well known that there are geographic differences in HPV type distribution. HPV16 prevalence is high worldwide, HPV31 is more common in Europe and Latin America, while HPV18 and HPV52 are more common in Asia and North America.[32] When focusing on the HPV genotypes detected in invasive cervical cancer, HPV52 and 58 are common in Japan and other East Asian countries, HPV31 and 33 are common in Europe, and the frequency of HPV18 is high in Africa.[33] The distribution of causative HPV types also differs among cancer types. HPV16 and 18 account for approximately 70% of cervical cancers, and other HR-HPVs are also causative; while HPV16 and 18 contribute to around 85% of head and neck and anal canal cancers, HPV16 accounts for a larger proportion of these cancers.[34–36]

As mentioned above, among HR-HPVs, each HPV type has a different risk of malignancy, and therefore prevention and management strategies also vary depending on the HPV types. HPV16 and 18 are particularly known as HR-HPVs, and prophylactic vaccines targeting these types have been developed. Recently, the nine-valent vaccine has been introduced, and this vaccine has exhibited more than 90% efficacy in the prevention of cervical cancer.[37] Cervical cancer screening is available as a secondary prevention measure, and the need for a detailed examination has been recommended when the HPV test is positive for HPV16 or 18, even if the cytology result is negative for intraepithelial lesion or malignancy.[38]

A prospective study in Japan indicates that eight HR-HPV types, HPV16, 18, 31, 33, 35, 45, 52, and 58, have a greater than 20% risk of progression to CIN3 or higher within 5 years (Figure 1a). Therefore, careful follow-ups are required especially if infected with these HPV types and early treatment and intervention options are also being considered.[39] In addition, the multi-state Markov model, a statistical model that considers the natural history of CIN, which undergoes a bidirectional transition of repeated progression and regression, has recently been applied to more accurately predict the prognosis of CIN. This approach revealed that among HR-HPVs, the prognosis of cervical lesions varies with the HPV type. In particular, HPV16 tends to progress in a stepwise fashion from CIN1 to CIN3, while HPV52 and 58 are more likely to persist in the CIN1 to CIN2 state (Figure 1b).[40,41] Management methods that consider the characteristics of HPV types will be required in the future.

HUMAN PAPILLOMAVIRUS18

Among HR-HPVs, HPV18 has some unusual characteristics. The first such characteristic is the histological type; HPV18-associated cervical cancer is detected more frequently as adenocarcinoma and small cell carcinoma, which have a poorer prognosis than squamous cell carcinoma.[42] Second, although HPV18 has a high detection rate of more than 20% in cancers, it is only detected in 6%–7% of precancerous lesions[43,44] making secondary prevention through screening difficult. Furthermore, HPV18, like HPV16, is detected more frequently in young-onset cervical cancer[45,46]; therefore, it requires careful management along with HPV16. However, owing to the unusual characteristics of HPV18, special measures for its prevention and treatment that differ from those for HPV16 are required. Regarding virological features, it is known that viral genome integration occurs earlier in HPV18-positive cervical lesions than in HPV16-positive lesions.[47] With the advancement of next-generation sequencing, some differences between HPV16 and HPV18 have been identified. For example, HPV18 cancers have significantly higher levels of unspliced/spliced transcripts encoding active E6 oncoprotein than HPV16 cancers.[48] Another report demonstrates that HPV18-positive cervical lesions have different types of APOBEC3-related C > T trinucleotide substitution patterns compared with HPV16-positive ones.[49] However, it remains unclear how these differences relate to the uniqueness of HPV18 carcinogenesis.

Several recent studies have focused on HPV18 target cells, carcinogenesis, and histological differentiation, suggesting that HPV18 may be characterized by latent infection and carcinogenesis in stem cell-like cells.[50,51] HPV generally changes the pattern of HPV gene expression in the differentiated cervical stratified squamous epithelium. E6/E7 is usually expressed in the basal layer, E1^E4, which is involved in interaction with the keratin network, is expressed in the differentiated layer, and L1, which is involved in capsid formation, is expressed in the surface epithelium. In a paper comparing the expression of HPV-derived genes in CIN, it was reported that E1^E4 and L1 were less frequently expressed in HPV18-associated CIN.[52] This suggests a high integration rate of HPV18 as well as that of HPV18 has a viral replication method independent of epithelial differentiation. A study examining HPV18 target cells using squamocolumnar junction (SCJ) organoids[53] confirmed that HPV18 infected undifferentiated and actively dividing cells in the SCJ, and that expression of NPM3, which might be involved in chromatin remodeling and stem cell maintenance, is important for HPV18 replication in undifferentiated keratinocytes.[50] It was also found that cervical adenocarcinoma was accompanied by high expression of NPM3, drawing attention to the possibility that NPM3 may have some link not only to cervical stem cell maintenance but also to the development of cervical adenocarcinoma. Taken together, these reports suggest that HPV18 infects undifferentiated stem cell-like cells, leading to early HPV integration and latent persistent infection in stem cells independent from differentiation of stratified squamous epithelium, and therefore may have a low detection rate in precancerous lesions (Figure 2).

Recent studies have also focused on the histological differentiation of HPV18-positive cervical cancer,

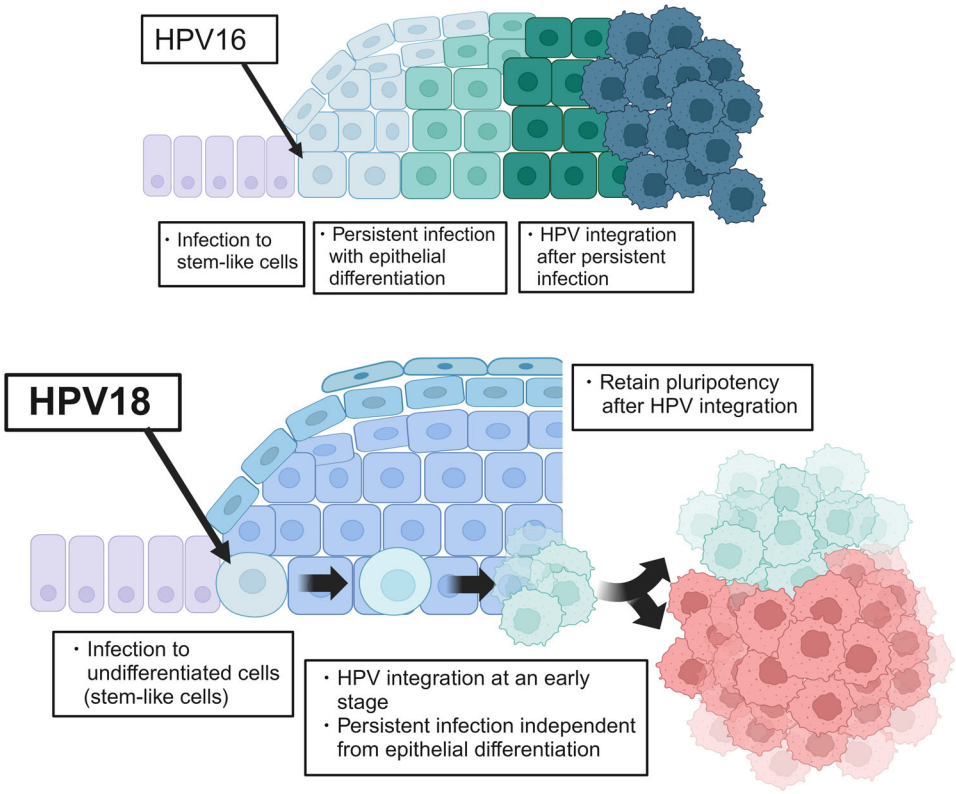

FIGURE 2 Characteristics of development of HPV18-associated cervical cancer. HPV persistently infects the uterine cervix with epithelial differentiation. HPV integration occurs after persistent infection, resulting in persistent expression of oncogenes E6 and E7 (upper panel). However, HPV18 has a viral replication strategy that is independent of epithelial differentiation, and HPV integration occurs earlier in HPV18-positive cervical lesions. HPV18-positive cells also remain pluripotent after HPV integration (lower panel). Created using Biorender.com.

revealing that HPV18-positive cells may have the pluripotency to differentiate into multiple tissue types.[23,51] A study of cervical cancers with mixed histological types revealed that these cancers share a common cellular origin regardless of the histological type and that HPV integration occurs prior to histological differentiation.[51] Interestingly, HPV18-positive cervical mixed carcinomas were also found to be associated with an undifferentiated component with low immunogenicity and high stem cell characteristics. In another study, an organoid-derived mouse model of HPV18-positive small cell carcinoma showed induced glandular differentiation, suggesting that HPV18-positive cervical carcinomas retain pluripotency (Figure 2).[23] The high prevalence of HPV18 not only in squamous cell carcinoma but also in adenocarcinoma, small cell carcinoma, and mixed carcinoma is probably because of the capacity of HPV18 to retain pluripotency even after carcinogenesis. Because HPV18-associated cervical cancer is highly malignant and difficult to prevent while it is still a precancerous lesion, there is an urgent need for the widespread use of vaccines and the establishment of biomarkers to select high-risk groups of carcinogenesis among HPV18-infected cases for early therapeutic intervention. Furthermore, HPV18-derived cancers may be less immunogenic, as they retain their stem cell characteristics. With the recent spread of immune checkpoint inhibitors, prognosis is expected to improve in many types of cancer; however, combination drugs that increase immunogenicity may be required for HPV18-associated cancers.

ACKNOWLEDGMENTS

The authors would like to thank Editage (www.editage.com) for English language editing. This work was supported by a grant to Ayumi Taguchi from AMED (grant number: 23wm0325057h0001).

CONFLICT OF INTEREST STATEMENT

Dr. Mayuyo Mori is an Editorial Board member of *The Journal of Obstetrics and Gynecology Research* and a coauthor of this article. To minimize bias, she was excluded from all editorial decision-making related to the acceptance of this article for publication. The other authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Taguchi A, Yoshimoto D, Kusakabe M, Baba S, Kawata A, Miyamoto Y, et al. Impact of human papillomavirus types on uterine cervical neoplasia. J Obstet Gynaecol Res. 2024. https://doi.org/10.1111/jog.15995