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Original Article

Determination of Oncogenic Human Papillomavirus (HPV) Genotypes in Anogenital Cancers in Myanmar

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Molecular and epidemiologic investigations suggest a causal role for human papillomavirus (HPV) in anogenital cancers. This study identified oncogenic HPV genotypes in anogenital cancers among men and women in a 2013 cross-sectional descriptive study in Myanmar. In total, 100 biopsy tissues of histologically confirmed anogenital cancers collected in 2008-2012 were studied, including 30 penile and 9 anal cancers from Yangon General Hospital and 61 vulvar cancers from Central Women's Hospital, Yangon. HPV-DNA testing and genotyping were performed by polymerase chain reaction-restriction fragment length polymorphism. Overall, 34% of anogenital cancers were HPV-positive. HPV was found in 44.4% of anal (4/9), 36.1% of vulvar (22/61), and 26.7% of penile (8/30) cancers. The most frequent genotypes in anal cancers were HPV 16 (75%) and 18 (25%). In vulvar cancers, HPV 33 was most common (40.9%), followed by 16 (31.8%), 31 (22.7%), and 18 (4.6%). In penile cancers, HPV 16 (62.5%) was most common, followed by 33 (25%) and 18 (12.5%). This is the first report of evidence-based oncogenic HPV genotypes in anogenital cancers among men and women in Myanmar. This research provides valuable information for understanding the burden of HPV-associated cancers of the anus, penis, and vulva and considering the effectiveness of prophylactic HPV vaccination.

Key words: human papillomavirus (HPV), ano-genital cancer, Myanmar, genotyping of HPV, cross-sectional study

Human papillomavirus (HPV) infection is a necessary cause of all cervical cancers and is etiologically related to a subset of cancers of the anus, oropharynx, penis, vagina, and vulva [1-3]. Overall, 5.2% of all cancers worldwide can be attributed to HPV infection [4]. The World Health Organization (WHO) reported that cervical cancer is the second most common cancer in women living less developed regions with an estimated 445,000 new cases in 2012 (84% of the new cases worldwide) www.who.int/mediacentre/factsheets/fs380/en/).

Anogenital HPV infection is one of the most commonly diagnosed sexually transmitted infections worldwide. Anogenital HPV types have been classified into low-risk (non-oncogenic) and high risk (oncogenic) types. Low risk types are associated with anogenital warts (condyloma acuminatum), oral and conjunctival

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papillomas, recurrent respiratory papillomatosis (in infants and young children), and mild dysplasia [5]. High-risk types are associated with high-grade dysplasia and various cancers.

Although the incidence and prevalence of HPV at sites such as the anus, penis, vagina, and vulva are at least as common as those at the cervix [6–7], the incidence of cervical cancer is much higher than that of non-cervical cancers. At non-cervical sites, the HPV-positive subset displays unique pathologic, molecular, epidemiologic, and clinical features.

The variability in HPV-attributable proportions for non-cervical cancers arises from differences in HPV detection methods across studies as well as from true geographic differences in HPV-attributable proportions. Despite this variability, 90–93% of anal cancers, 12–63% of oropharyngeal cancers, 36–40% of penile cancers, 40–64% of vaginal cancers, and 40–51% of vulvar cancers are potentially attributable to HPV infection. Notably, high proportions of cervical and non-cervical HPV-related cancers (70–76% and 63–95%, respectively) are attributable to oncogenic HPV types 16 and 18, which are targeted by currently available quadrivalent and bivalent prophylactic HPV vaccines [3].

Worldwide, there are about 97,215 cases of non-cervical cancers annually, including 50,780 cancers among men (13,485 anal cancers, 26,775 oropharyngeal cancers, and 10,520 penile cancers) and 46,435 cancers among women (14,787 anal cancers, 6,048 oropharyngeal cancers, and 25,600 vaginal/vulvar cancers) [8].

In a report by Serrano B *et al.*, the prevalence of HPV DNA were 84.9%, 28.6%, 74.3%, and 90.0% for invasive cervical, vulvar, vaginal, and anal cancers, respectively. HPV 16 was the most frequent type in all lesions. Variations in the RC of HPVs 31/33/45/52/58 by cancer site were observed, ranging from 7.8% female anal cancer to 20.5% vaginal cancer. The addition of HPVs 31/33/45/52/58 to HPV types included in current vaccines (HPV 16/18) could prevent almost 90% of HPV-positive female anogenital lesions worldwide [9].

In a report by Saraiya M *et al.*, HPV DNA was detected in 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oropharyngeal, 68.8% of vulvar, 63.3% of penile, 32.0% of oral cavity, and 20.9% of laryngeal cancers, as well as in 98.8% of cervical cancers *in situ* (CCIS) [10].

HPV vaccines can potentially help to reduce HPV-related cancers. Globally, approximately 70% of cervical cancers are attributable to genotypes 16 and/or 18, which are targeted by first-generation HPV vaccines (Gardasil® and Cervarix®), and 90% to 16, 18, 31, 33, 45, 52 or 58 which are targeted by a 9-valent vaccine (Gardasil® 9) [11]. These genotypes also contribute to the majority of HPV-related vulvar [12–14] and vaginal cancers [13, 14].

The high proportion of HPV-positive non-cervical cancers that is attributable to HPV types 16 and 18 underscores the potential to prevent a majority of non-cervical HPV-related cancers among men and women through prophylactic HPV vaccination [15].

At the country level, decision-makers are likely to seek data on the local genotype-specific burden of HPV-related diseases for baseline information against which the impact of HPV vaccination can be assessed.

There are no previous studies of HPV-related anogenital cancers beyond cervical cancer in Myanmar. Determination of HPV status and genotypes in anogenital cancers may assist in patient risk stratification and prophylaxis vaccine strategy, and may ultimately guide clinicians toward the optimum treatments. The aim of this study was to determine the prevalence of HPV infection and oncogenic HPV genotypes in anogenital cancers by polymerase chain reaction and restriction fragment length of polymorphism (PCR-RFLP).

Materials and Methods

This study detected the oncogenic HPV genotypes in anogenital cancers among men and women from a cross-sectional descriptive study in 2013. A total of 100 paraffin-embedded biopsy tissues of histologically confirmed anogenital cancers collected in 2008–2012 were studied. They included 30 penile cancers and 9 anal cancers from Yangon General Hospital and 61 vulvar cancers from the Central Women's Hospital, Yangon, Myanmar. HPV DNA testing and genotyping were performed by PCR-RFLP. This research project was approved by the Ethics Review Committee on Medical Research Involving Human Subjects, Department of Medical Research (Lower Myanmar), (No. 32 Ethics 2012).

DNA extraction. DNA was isolated from sec-

tions of formalin-fixed, paraffin-embedded anogenital cancer tissues. After those tissue samples were treated with xylene and ethanol, they were suspended in 300μL of proteinase K and incubated at 56℃ overnight, then treated with Buffer AL, AW1, and AW2 according to the manufacturer's instructions (QIAamp DNA Mini Kit, Qiagen, Tokyo, Japan). Finally, DNA precipitates were eluted in 100μL buffer AE.

HPV-DNA testing. HPV-DNA testing was performed using the PCR method. Consensus sequence primer pairs within the E6 and E7 open reading frames *i.e*, forward primer (*pU-1M*): 5'-TGTCAAA AACCGTTGTGTCC-3' and reverse primer (*pU-2R*): 5'-GAGCTGTCGCTTAATTGCTC-3') (Oligo® Sigma genosys-PCR, Japan) were used to amplify HR-HPV (HPV-16, -18, -31, -33, -35, -52b, -58). The reaction mixture was formed using Taq polymerase (Applied Biosystems, Roche, MA, USA), 10Xbuffer, dNTPs, forward and reverse primers, distilled water and DNA. The reaction mixtures were subjected to 35 cycles of amplification using a thermal cycler (ASTEC, Japan). Each cycle included a denaturation at 95℃ for 1 min, annealing at 55℃ for 1 min and extension at 72℃ for 1 min. PCR products were detected by electrophoresis on 2% agarose gel, 100V, 30 min and ethidium bromide staining. Gel documentation (Bio-Rad) was then performed.

HPV genotyping. In PCR-positive cases, HPV genotyping was analyzed by PCR-RFLP method. HR-HPV genotypes were decided by agarose gel electrophoresis and ethidium bromide staining of the digest of the PCR product with restriction enzyme(s), *Ava* II (HPV 16, HPV 18 and HPV 33), *Rsa* I (HPV 31), *Bgl* II (HPV 52b), *Acc* I (HPV 58), and *Ava* I (HPV 35) (Wako, Osaka, Japan). The enzymes were digested under the conditions recommended by the manufacturer [16].

Statistical analysis. Data analysis was performed by using Microsoft Office Excel 2007 and the Statistical Package for Social Sciences (SPSS-165), *i.e.*, the SPSS full version free download (http://en.softonic.com/s/spss-16-full-version-free-download/) accessed December, 2013.

Results

A total of 100 paraffin-embedded biopsy tissue samples of anogenital cancer cases collected in 2008–2012 were studied. They included 30 penile cancers and 9 anal cancers from Yangon General Hospital and 61 vulvar cancers from the Central Women's Hospital, Yangon, Myanmar. Most vulvar cancer patients were aged 50–59 years and 60–69 years (24.6% each) followed by 40–49 years (23%), ≧70 years (19.7%), and 30–39 years (8.2%). The most common age group of penile cancer patients was 40–49 years (26.7%) followed by 30–39 years (23.3%), 60–69 years (20%), 50–59 years (16.7%), and ≧70 years (13.3%). In anal cancers, the most common age group was 60–69 years (33.3%) (Table 1). Among the 9 cases of anal cancers, 7 (77.8%) were women and 2 (22.2%) cases were men.

Histopathological diagnosis. Histopathologically, all cases of vulvar cancers and penile cancers were squamous cell carcinomas (SCC). Among women who had anal cancers, 5 cases (71.4%) were SCC and 2 (28.6%) were adenocarcinoma. All men who had anal cancers were diagnosed as adenocarcinoma.

HPV DNA testing. Overall, 34% of anogenital

Table 1 Proportions of vulvar, penile, and anal cancers by age group

Cancers	Age groups (Years)					Total
	30–39	40–49	50–59	60–69	≧70	
Vulva Cancer	5 (8.2%)	14 (23.0%)	15 (24.6%)	15 (24.6%)	12 (19.7%)	61 (100.0%)
Penile Cancer	7 (23.3%)	8 (26.7%)	5 (16.7%)	6 (20.0%)	4 (13.3%)	30 (100.0%)
Anal Cancer	2 (22.2%)	2 (22.2%)	2 (22.2%)	3 (33.3%)	0 (0%)	9 (100.0%)
Total (Count)	14	24	22	24	16	100
(% within Anogenital Cancer)	(14.0%)	(24.0%)	(22.0%)	(24.0%)	(16.0%)	(100.0%)

cancer cases were positive for HPV. Of those, 64.7% were vulvar cancers, 23.5% penile cancers, and 11.8% anal cancers. Analysis of each anogenital cancer revealed HPV in 44.4% of anal cancers (4/9), 36.1% of vulvar cancers (22/61), and 26.7% of penile cancers (8/30) (Fig. 1) (Table 2). Among the 4 cases of HPV positive anal cancers, 75% were women diagnosed as squamous cell carcinoma and 25% were men diagnosed as adenocarcinoma. The proportions of HPV in different histopathological grades of squamous cell cancers were (21%) in well-differentiated, (27%) moderately differentiated, and (52%) poorly differentiated cases (Fig. 2). Anogenital cancer patients infected with oncogenic HPV were aged 60–69 years (29.4%) followed by ≧70 years and 50–59 years (23.5% each), 40–49 years (14.7%), and 30–39 years (8.8%) (Fig. 3).

HPV genotyping. HPV genotyping was analyzed by the RFLP method. The most prevalent HPV genotypes in anogenital cancers were HPV 16 (44.1%), HPV 33 (32.4%), HPV 31 (14.7%), and HPV 18 (8.8%). Among anal cancers, the only genotypes were HPV 16 (75%) and HPV 18 (25%). In vulvar cancers, HPV 33 was the most common genotype (40.9%) followed by HPV 16 (31.8%), HPV 31 (22.7%), and HPV 18 (4.6%). In penile cancers, HPV 16 (62.5%) was the most common genotype followed by HPV 33 (25%) and HPV 18 (12.5%) (Fig. 4) (Table 3).

Discussion

The prevalence of HPV is significantly greater in cancers of the genital organs than in those of other organs. The acquisition rate of genital HPV infections

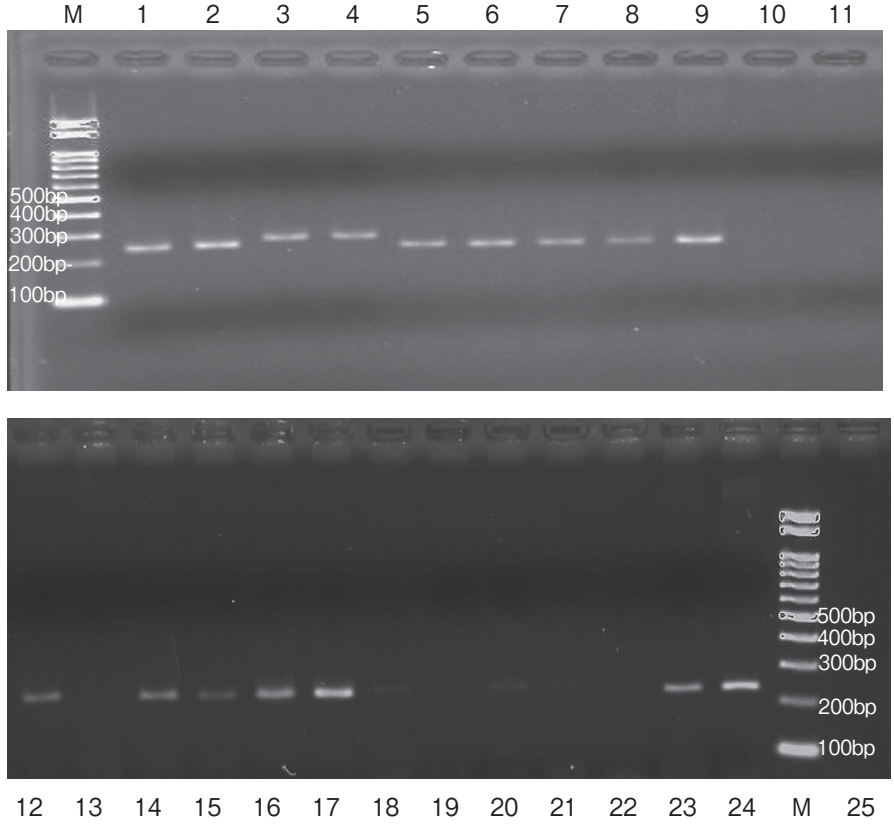

Fig. 1 Amplification of HPV using *pU1M/pU2R* primers showing lane M, molecular marker: 100 bp ladder, lane 1–positive control, lane 11–negative control, lanes 2 to 9, 12, 14 to 18, 20, 23, 24–positive for HPV DNA, lanes 10, 13, 19 to 21, and 22–negative for HPV DNA by 2% agarose gel electrophoresis with ethidium bromide staining, gel documentation (Bio-Rad). Lanes 1, 2, 5 to 9, 12, 14 to 18, 20, 23, and 24 about 240 bp each, and lanes 3 and 4 are each about 270 bp. Histopathological diagnosis of lanes 2 to 10 is vulvar cancer, that of lanes 12 to 14 is anal cancer, and that of lanes 15 to 24 is penile cancer.

Table 2 Proportion of oncogenic human papillomavirus in vulvar, penile, and anal cancers

HPV DNA	Vulva cancer	Penile cancer	Anal cancer	Total
HPV Positive	22 (36.1%)	8 (26.7%)	4 (44.4%)	34 (34%)
HPV Negative	39 (63.9%)	22 (73.3%)	5 (55.6%)	66 (66%)
Total	61 (100%)	30 (100%)	9 (100%)	100 (100%)

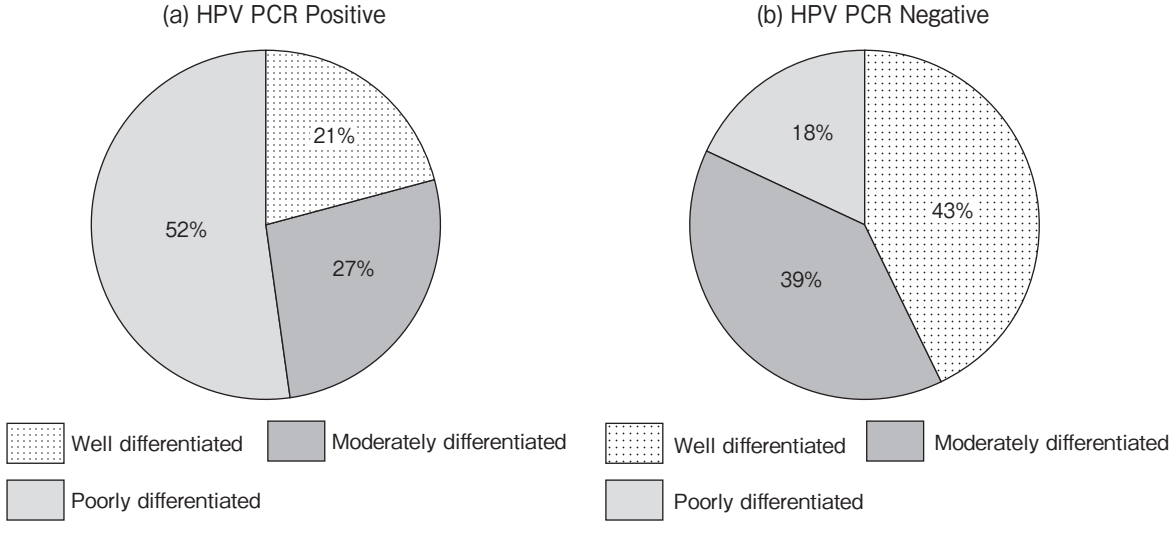

Fig. 2 Proportions of oncogenic HPV in different histopathological grades of squamous cell cancers.

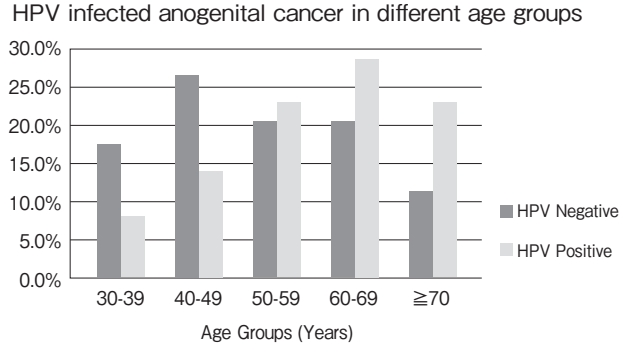

Fig. 3 Proportion of oncogenic human papillomavirus in anogenital cancers by age groups.

clearly correlates with the number of lifetime sexual partners [17]. Based on molecular and epidemiologic evidence, it is currently accepted that all cervical cancers and sizeable proportions of cancers of the anus, oropharynx, penis, vagina, and vulva are etiologically related to HPV infection. Recently, the incidence of HPV-related cancers such as cancers of the anus, penile, and vulva has increased substantially [18].

Reported rates of HPV in penile cancers have varied from 12% to 82% while HPV is also found in approximately 90% of anal cancers and 50% of vulva cancers [19, 20]. Systematic reviews of established PCR techniques have found HPV in approximately 50% of all penile SCCs [21]. Recently, the prevalence of HPV in penile cancers was found to be 60.9% in Brazil [22] and 81.5% in northern Thailand [23]. Although the published reports on penile cancers vary widely in describing the prevalence of HPV, there tends to be a higher prevalence in Africa and in Central and South America. In this study in Myanmar, the prevalence of HPV in penile cancers was 26.7%, which is relatively similar to the 31% and 42% rates reported for USA and Paraguay, respectively; moreover, HPV 16 was the most common genotype in the present study, similar to the findings of those studies [24, 25].

Vulvar cancer is rare among all gynecological cancers worldwide. It mainly affects older women, simi-

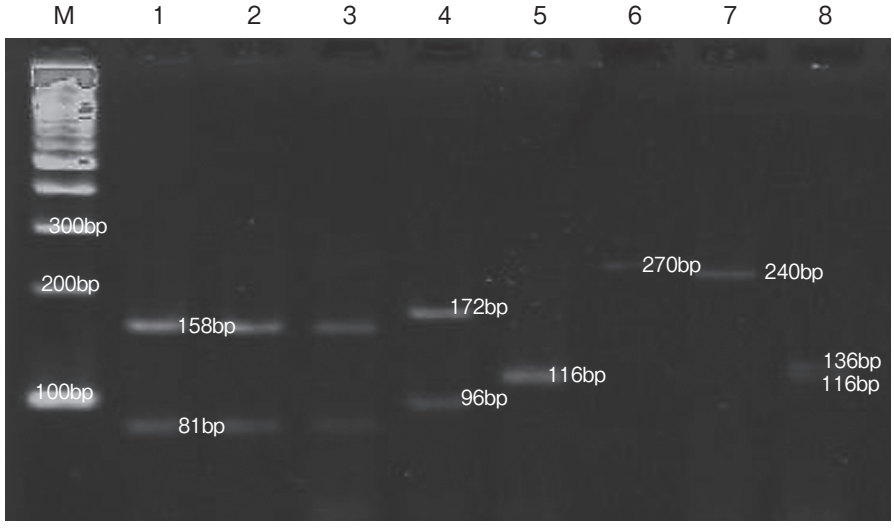

Fig. 4 Genotyping of HPV by the restriction fragment length polymorphism method showing lane M-molecular marker: 100 bp ladder, lanes 1, 2, 3-HPV 16, lane 4-HPV 18, lane 5-HPV 31, lanes 6, 7-enzyme-undigested HPV PCR-positive cases, lane 8-HPV 33, by 2% agarose gel electrophoresis (Bio-Rad) with ethidium bromide staining.

Table 3 Proportion of oncogenic human papillomavirus genotypes in vulvar, penile, and anal cancers

HPV genotypes	Vulva cancer	Penile cancer	Anal cancer	Total
HPV 16	7 (31.8%)	5 (62.5%)	3 (75.0%)	15 (44.1%)
HPV 18	1 (4.6%)	1 (12.5%)	1 (25.0%)	3 (8.8%)
HPV 31	5 (22.7%)	0 (0%)	0 (0%)	5 (14.7%)
HPV 33	9 (40.9%)	2 (25.0%)	0 (0%)	11 (32.4%)
Total	22 (100%)	8 (100%)	4 (100%)	34 (100%)

lar to the present study. Gargano JW *et al.* reported that HPV was detected in 68.8% of cases of invasive vulvar cancer (IVC) and in 97.1% of cases of vulvar intraepithelial neoplasia (VIN3). Patients with IVC and VIN3 differed by median age (70 vs 55 years). HPV 16 was found in 48.6% of IVC and 80.9% of VIN3 cases [26]. De Sanjose S *et al.* reported on worldwide HPV genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva from 39 countries, with HPV detected in 86.7% of VIN and 28.6% of IVC cases. HPV 16 was the commonest type (72.5%) followed by HPV 33 (6.5%) and HPV 18 (4.6%) [27]. Ngamkham J *et al.* showed that 44% of vulva cancer cases were HPV positive and the most common genotypes were HPV 16 followed by 35, 33, 18, and 58 [28]. In the present study, the prevalence of HPV in vulvar cancers was 36.1%, relatively similar to the above studies. The most common genotypes in vulvar cancers were HPV 33 (40.9%) and HPV 16 (31.8%), unlike the above studies.

A higher rate of HPV detection in vulvar/vaginal samples than in cervical samples has been reported [29]. Recently, one study of indigenous women in Australia found that a 39% prevalence of vulvar/vaginal/perianal (VVP) HR-HPV, which was significantly higher than the 26% cervical HR-HPV prevalence. HPV 16 was the most common genotype detected in both sites (VVP 11%, cervical 6%) [30]. The large discrepancy in HPV prevalence among anogenital sites may represent more persistent infection at the vulva.

Anal cancer accounts for only 1.5% of gastrointestinal malignancies. Anal cancer is more common in women than in men, yet little is known about the natural history of HPV in women. However, this disease has now shown a steady increase in incidence, particularly in HIV-positive males. Skamperle M *et al.* pointed out that the prevalence of HPV in anal cancers was 90.7% and that HPV 16 was detected in 86% of anal

cancers [31]. Ouhoummane N *et al.* showed that HPV was detected in 92% of anal cancers. HPV 16 (90%) was the most common genotype; 60% of cases were women and the median age at diagnosis was 63 years [32]. In the present study, most of the anogenital cancer patients infected with oncogenic HPV were in the older age groups (> 50 years), which may represent persistent infection. The prevalence of HPV in anal cancers was 44.4%, which is less than in other studies, although the most common genotype and age group were HPV 16 (75%) and 60–69 years, similar to the above studies. However, our previous study found that the prevalence of HR-HPV in different age groups (especially 30–39, 40–49, and 50–59 years) having cervical neoplasia especially did not differ significantly ($X^2 = 1.16$, $p = 0.28$). A previous study detected the oncogenic HPV genotypes −16, −31, −18, and −58 in the majority of cervical intraepithelial neoplasias and cervical cancers in Myanmar [33]. HPV genotype 16 was the most common genotype in cervical neoplasias in Myanmar [33–34].

Regarding the HPV PCR-positive anogenital cancer cases, HPV was identified mostly in poorly differentiated squamous cell carcinoma (SCC) (52%) followed by moderately differentiated SCC (27%) and well-differentiated SCC (21%). Regarding the HPV PCR-negative anogenital cancer cases, HPV was not detected in well-differentiated SCC (43%) followed by moderately (39%) and poorly (18%) differentiated SCC. In the present study, although oncogenic HPV was associated with all histological grades of SCC of anogenital cancers, poorly differentiated grades of SCC of anogenital cancers are more commonly associated with oncogenic HPV infection. We could not find an association between histopathological grades and HPV genotypes.

The variability of HPV detection in not only anogenital but also cervical cancers may depend on the different HPV detection methods, the types of specimens used (such as fresh tissue or formalin-fixed paraffin-embedded tissue), and also the geographic variations in HPV distribution. This subject needs further investigation, including searches for possible environmental and/or genetic factors that may impair host immunity.

In conclusion, this study identified that the most prevalent genotype in anal and penile cancers was HPV 16, which is vaccine-preventable. In vulvar cancers, on the other hand, HPV 33 and HPV 16 were the most common genotypes. This is the first report of evidence-based oncogenic HPV genotypes in anogenital cancers among men and women in Myanmar. This research provides valuable information for understanding the incidenceof HPV-associated cancers of the anus, penis, and vulva and for considering the effectiveness of prophylactic HPV vaccination.

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