Clinical Research

Transition of DNA-HPV over time in HPV-infected women: a 7-year cohort study

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ABSTRACT

BACKGROUND Approximately 99% of cervical cancer cases worldwide are associated with one of the high-risk human papillomavirus (HPV) types. This study aimed to determine the transition rate of DNA-HPV over time in women aged 18–69 years with HPV infection in Can Tho City, Vietnam, from 2013 to 2020.

METHODS The 2-phase cohort study was conducted on 213 women between 2013 and 2020. Phase 1 involved a retrospective cohort study (2013–2018), and phase 2 included a prospective cohort study (2018–2020). HPV testing was performed using real-time polymerase chain reaction on cervical fluid. McNemar's test was employed to compare differences in HPV transition between 2013 and 2020.

RESULTS From 2013 to 2018, the transition, clearance, and non-transition rates were 17.1%, 65.8%, and 66.2%, respectively, revealing a significant difference in the number of HPV cases during this period ($p = 0.007$). From 2018 to 2020, the transition, clearance, and non-transition rates were 9.8%, 44.9%, and 82.2%, respectively. Overall, the DNA-HPV changes from 2013 to 2020 indicated rates of 14.3% for transition, 68.5% for clearance, and 67.1% for non-transition. A significant difference in HPV cases was found between 2013 and 2020 ($p = 0.001$).

CONCLUSIONS The longer duration resulted in a more significant difference in the DNA-HPV transition among HPV-infected women.

KEYWORDS DNA, HPV infection, Vietnam, women

Cervical cancer is the third leading cause of cancer in women and the second leading cause of death in women aged 15–44 years.[1] The cervical cancer incidence is approximately 500,000 individuals diagnosed each year worldwide. In 2020, approximately 604,127 new cases of cervical cancer were reported, alongside 341,831 deaths from the disease.[1,2] In the U.S., cervical cancer incidence in 2019 was 6.7 per 100,000 individuals, and the mortality rate was 31.6%.[3] New cases of cervical cancer in the country were estimated at 13,170, with 4,250 deaths.[3] In Vietnam, according to the Cancer Information Center 2018 report, 2,420 deaths were reported among 4,177 women diagnosed with cervical cancer, with approximately seven deaths per day.[4]

Human papillomavirus (HPV) is responsible for skin papilloma in humans. Almost 99% of the patients with cervical cancer worldwide are positive for one of the high-risk HPV types.[5,6] HPV infections can resolve spontaneously without clinical symptoms,

and individuals with low-risk HPV infections often clear the virus without developing cancer. Prolonged inflammation associated with high-risk HPV types, including HPV 16, 18, and 45, can lead to lesions in cervical epithelial cells, initially at low levels, and then progress to cervical precancerous abnormalities. This progression can take several years to several decades, which is common in women aged 40–50 years.[7] However, HPV is difficult to detect by serological tests.[8] Detection of the virus is based on DNA found in the skin, oral mucosa, and genital samples.[9] Hence, this study aimed to examine variations in DNA-HPV levels across different time intervals as a foundation to assess the eradication and persistence of HPV in the uterus in women with cervical infections and develop targeted strategies for cervical cancer prevention.

METHODS

This retrospective cohort study was conducted from 2013 to 2018, while the prospective cohort study was conducted from 2018 to 2020 on female residents in nine districts of Can Tho City, Vietnam. This study used data from a cross-sectional study of 1,490 women infected with HPV in 2013. Real-time polymerase chain reaction (PCR) showed that 99 women were positive for DNA-HPV, and 1,391 were negative for DNA-HPV. In 2018, these women were selected to participate in this study using a 1:2 matching method with the same age categories and residences. Two HPV-negative controls were selected for each HPV-positive case.

The second HPV test was performed using real-time PCR of the cervical fluid of the participants. The outcomes were categorized as infection when they showed any presence of the 14 high-risk HPV types, which are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68, and non-infection when the results showed no record of these HPV types. Women infected with type 16 and 18 were examined using colposcopy and other cervical cancer tests. Participants with a history of cervical cancer or current cancer treatment were excluded from the study. Thus, 73 positive and 140 negative DNA-HPV patients were included in this study. In 2020, a third HPV test was performed, revealing 49 positive and 164 negative DNA-HPV cases.

A DNA-HPV transition assessment was then performed by comparing the results between 2013 and 2018, 2018 and 2020, and 2013 and 2020 to assess changes in terms of three outcomes: (1) Non-transition, for persistent and negative results, was defined as unchanged HPV test results at the different times and calculated by the number of samples with unchanged positive and negative results divided by the total number of samples; (2) Clearance was defined as a change in HPV test from positive to negative and calculated by the number of previous positive cases that became negatives in the current test divided by the number of previous positive cases; and (3) Transition was defined as a change in the outcome of HPV test from negative to positive and calculated by the number of previous negative cases that became positives in the current test divided by the number of previous negative cases.

At each time point, women with positive HPV without abnormal cytology results were advised to improve their nutrition, adopt healthy lifestyle habits, practice safe sexual practices, and undergo regular medical examinations. Additionally, they were recommended to receive gynecological disease treatment periodically every 6 months or in the presence of unusual symptoms. Women who tested positive for HPV, exhibited abnormal Papanicolaou test results, and showed cervical lesions upon visual inspection with acetic acid, along with histopathological findings, were treated according to the standard protocol outlined by the Ministry of Health of Vietnam.

Statistical analyses were performed using the SPSS software version 18 (SPSS Inc., USA). Categorical variables were presented as frequencies and percentages. McNemar's test was used to compare differences in test results between retrospective and prospective studies.

This study was approved by the Ethics Committee in Biomedical Research at Can Tho University of Medicine and Pharmacy (No. 16/HĐĐĐ-PCT, 16th February 2018) and granted permission from the local authorities in Can Tho City.

RESULTS

In 213 women (73 HPV-positive and 140 HPV-negative), the mean (standard deviation) age was 47.4 (10.3) years, with the majority in the 46–69 years age group (Table 1). Menopausal status was observed in 38.1% of the women, whereas 10.3% of women were perimenopausal. Additionally, 4.2% reported a change

Table 1. Characteristics of the participants

Characteristics	HPV-positive, n (%) (N = 73)	HPV-negative, n (%) (N = 140)	Total, n (%) (N = 213)	*p*
Age (years)				0.48
18–35	9 (12.3)	18 (12.9)	27 (12.7)	
36–45	16 (21.9)	41 (29.3)	57 (26.8)	
46–69	48 (65.8)	81 (57.9)	129 (60.6)	
Menstruation status				0.3
Menstruating	32 (43.8)	78 (55.7)	110 (51.6)	
Perimenopausal	9 (12.3)	13 (9.3)	22 (10.3)	
Menopausal	32 (43.8)	49 (35.0)	81 (38.1)	
Partner change				0.72
Yes	2 (2.7)	7 (50.0)	9 (4.2)	
No	71 (97.3)	133 (95.0)	204 (95.8)	

Table 2. DNA-HPV transition rates after 5 years (2013–2018)

	DNA-HPV (2018)		Total, n (%)	*p*
	Positive, n (%)	Negative, n (%)		
DNA-HPV (2013)				**0.007**
Positive	25 (34.2)	48 (65.8)	73 (100.0)	
Negative	24 (17.1)	116 (82.9)	140 (100.0)	
Total	49 (23.0)	164 (77.0)	213 (100)	

Table 3. DNA-HPV transition rates after 2 years (2018–2020)

	DNA-HPV (2020)		Total, n (%)	*p*
	Positive, n (%)	Negative, n (%)		
DNA-HPV (2018)				0.42
Positive	27 (55.1)	22 (44.9)	49 (100.0)	
Negative	16 (9.8)	148 (90.2)	164 (100.0)	
Total	43 (20.2)	170 (79.8)	213 (100.0)	

Table 4. DNA-HPV transition rates after 7 years (2013–2020)

	DNA-HPV (2020)		Total, n (%)	*p*
	Positive, n (%)	Negative, n (%)		
DNA-HPV (2013)				**0.001**
Positive	23 (31.5)	50 (68.5)	73 (100.0)	
Negative	20 (14.3)	120 (85.7)	140 (100.0)	
Total	43 (20.2)	170 (79.8)	213 (100.0)	

in sexual partners. No significant differences were noted in general characteristics between the HPV-positive and HPV-negative groups.

After a 5-year follow-up period (2013–2018), the transition and clearance rates were 17.1% and 65.8%, respectively, whereas non-transition cases accounted for 66.2% (Table 2), with a statistically significant difference (p = 0.007). However, no statistically significant differences were noted in the transition and clearance rates of HPV infection during the 2-year follow-up period from 2018 to 2020 (p = 0.42). The transition and clearance rates were 9.8% and 44.9%, respectively, whereas non-transition cases accounted for 82.2% (Table 3).

Additionally, after a 7-year follow-up (2013–2020), the transition and clearance rates were 14.3% and 68.5%, respectively. Non-transition cases accounted for 67.1%, indicating a significant difference (p = 0.001) (Table 4).

The number of HPV-positive women decreased gradually from 73 (2013) to 49 (2019) and 43 (2020). A similar trend was observed for the number of HPV types (Table 5). HPV 16, 18, 51, and 52 remained predominant in all three stages. The prevalence of HPV 52 exhibited a declining trend, decreasing from 24% (2013) to 21% (2018) and further to 19% (2020). In contrast, the prevalence of HPV 16 and 18 showed an increasing trend. HPV 16 came from 16% (2013) to 19% (2018) and 19% (2020), while HPV 18 steadily increased from 8% (2013) to 10% (2018) and 13% (2020). In addition, seven women in 2013, three in 2018, and four in 2020 reported multiple types of HPV infections.

Table 5. The prevalence of HPV types

Type of HPV	2013, n (%) (N = 80)	2018, n (%) (N = 52)	2020, n (%) (N = 47)
16	13 (16)	10 (19)	9 (19)
18	6 (8)	5 (10)	6 (13)
31	2 (3)	2 (4)	1 (2)
33	2 (3)	1 (2)	1 (2)
35	5 (6)	2 (4)	2 (4)
39	8 (10)	5 (10)	5 (11)
45	3 (4)	2 (4)	1 (2)
51	10 (13)	6 (12)	5 (11)
52	19 (24)	11 (21)	9 (19)
56	6 (8)	3 (6)	0 (0)
58	5 (6)	4 (8)	6 (13)
59	1 (1)	1 (2)	2 (4)

DISCUSSION

In the present study, women with HPV-positive and HPV-negative infections shared some common characteristics with no statistically significant difference. Approximately 50% to 80% of sexually active women have been infected with HPV at least once, and 40% of young women were infected within 3 years of being sexually active.[10] According to Bardin et al,[11] the highest rate of HPV infection (24.2%) was recorded among women aged 25–34 years and was remarkably significant for unmarried women (37.3%); the prevalence of HPV infection decreased to 8.6% by age 55. Bruni et al[12] noted that in America and Africa, the highest rate of HPV infection was observed in individuals aged <25 years, with recovery usually occurring at the age of >45. In Central and South America, the highest rate was found in those aged >40 years, whereas in West Africa, it was >55 years. Berek[13] recommended that women with sexually transmissible infections should be tested for the presence of HPV after 30 years. This is in line with the findings of the latest report by Xia et al[14] in 2021, in which the HPV infection rate in Southeast Asia was highest among women aged 30–55 years. However, in South Asia, the highest HPV infection rates vary not only between different areas but also between countries.

Having multiple sexual partners or having partners who themselves have multiple sexual partners increases the risk of HPV infection and cervical cancer.[15] According to Bardin et al,[11] the risk of HPV infection increased 3.3-fold with a 95% confidence interval ranging from 1.6 to 6.8 in women whose partners had multiple sexual partners. Having a new sexual partner per month within the last 4 months contributes to a 10-fold higher risk of contracting HPV infection.[11]

Prolonged HPV infection is a risk factor for cervical cancer, particularly among newly infected women. In more than 90% of women, HPV infection is self-resolving, and most precancerous lesions disappear on their own. Approximately 5–10% of high-risk HPV infection cases turn into prolonged HPV infection, increasing the risk of precancerous lesions that will progress to invasive cervical cancer if left untreated.[16] HPV likely persists in infected cells for a certain time, mainly in a latent state, but can also cause symptoms or disease. Approximately 70% of infected women recover within 1 year, with approximately 90% recovering after 2 years. However, 5–10% are more likely to develop pre-cancer of the cervix or subsequent invasive cancer.[17] The progression of precancerous lesions depends on HPV infection and its treatment. This aligned with our findings, which showed a significant difference in HPV cases over time. The longer the duration, the more remarkable the change in the rate of the DNA-HPV transition.

HPV infection is sexually transmitted, with an estimated 50–80% of sexually active women receiving HPV once in their lifetime, and some may be reinfected.[3,16] However, only infections with high-risk types or repeated re-infections that cause neoplastic lesions in the cervical epithelium would probably progress to invasive cervical cancer. In the present study, the rate of viral clearance increased from 44.9% (after 2 years) to 65.8% (after 5 years) and 68.5% (after 7 years). Umulisa et al[18] also stated that approximately 50–80% of women became infected with HPV within 2 to 3 years after their first sexual intercourse. Most cases were transient and asymptomatic, undergoing self-remission without intervention—only a few developed cervical cancer in the presence of a combination of co-factors. Li et al[19] reported that prolonged HPV infection was more common among women aged 15–19 and ≥55 years. Although the link between HPV infection and cervical cancer is well established, only 10–20% of cases of prolonged HPV infection progress to cervical cancer. Nearly 80–90% of HPV infections are transient and self-limiting within 24 months of first detection.[20,21] This difference may be attributed to risk factors such as old age, hormone replacement therapy,

accompanying genital infections, immunodeficiency, change of sexual partner by the husband, childbirth, as well as infection with multiple types and variants of HPV, which are all associated with persistent infection or clearance of HPV.[22–25] In contrast, all women in this study were infected with high-risk HPV types, which explains the low rate of clearance compared to those infected with low-risk types. This viral clearance did not result in sustained immunity. Continuous exposure to infection sources increases the risk of contracting the virus with or without clinical manifestations.[26] The clearance of HPV depends on the type of HPV and HIV infection. Women infected with low-risk HPV types and without HIV co-infection typically experience nearly complete clearance. However, the clearance rate was approximately 94% when infected with the high-risk type. Among patients with HIV and low-risk HPV-type infections, the clearance rate was approximately 63%. In contrast, patients with HIV and high-risk HPV have only 58% of clearance rate. The clearances of HPV 16 and 18 were lower than those of low-risk types.[23]

The present study evaluated only high-risk HPV types, with high proportions of HPV 16 and 18. As other studies evaluated both high- and low-risk HPV types, this could explain the low clearance rates in this study. The long study period (2013–2020) also contributes to various confounding factors that could influence the research outcomes. Factors such as changes in sexual partners, presence of sexually transmitted diseases, pregnancy, and overall health status can significantly affect the presence of HPV.

This study identified 12 high-risk HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. In 2018, the most prevalent HPV types were 52, 16, and 51. However, by 2020, these numbers were declining, with the prevalence of type 52 decreasing to 19%, type 16 to 19%, and type 51 to 11%. Conversely, type 18 is increasing to 13%. This was similar to other studies identifying commonly transmitted HPV 16, 18, 31, 33, 45, 51, 52, 56, and 58. Nevertheless, owing to the specificity of the study site, each locality exhibits variations in prevalent HPV types. Xia et al[14] performed a meta-analysis of all studies conducted in Southeast Asian countries from 2015 to 2021, which indicated the infection rates of HPV types in descending order of 16, 18, 58, 31, 52, 45, 33, 39, 59, 35, 68, 51, and 56. In South Asia, infections occur mainly in HPV 16, 39, 58, 33, and 18, with only a few (<2 %) cases of the remaining types. The main cases of cervical cancer were type 16 and 18, accounting for approximately 70%, whereas type 31, 33, 35, 45, 52, and 58 were accountable for 20% of cases.[5] Kabir et al[27] detected 10 high-risk genotypes of HPV 16, 18, 31, 35, 45, 51, 52, 58, 59, and 73. The prevalence of HPV 16, 18, 45, 52, and 51 was 39.6%, 19.8%, 12.9%, 8.9%, and 5.0%, respectively. Similarly, a large-scale Information Center on HPV and Cancer (HPV Information Centre) study reported that 90% of HPV infections were caused by eight common HPV types, 16, 18, 45, 31, 33, 52, 58, and 35, ranked in descending order of frequency.[4] In contrast, the present study observed type 52 as the most common type, suggesting a low risk of progression to cervical cancer amongst women with HPV-positive in Can Tho City. However, the prevalence of HPV 16 and 18 tended to increase, requiring thorough monitoring of infected women, especially those with HPV 16 and 18, although infection with HPV type 52 is more common. Wu et al[28] conducted a study of 16,693 women and recorded a 16.64% HPV infection rate with 13 high-risk HPV types, namely 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Orang'o et al[29] stated a very high rate of HPV infection in 32.5% of Kenyan women, with type 16 accounting for 6%, type 52 for 5%, and type 68, 58, and 35 for 4%. HPV 52 is the most common type in developing countries. In our study, we were unable to determine the factors influencing DNA transition among women infected with HPV over the study period due to financial constraints. Therefore, future research could delve into this issue. In conclusion, women with HPV-positive infections exhibited a transition in DNA-HPV over time. The rate of HPV DNA clearance gradually increased with remarkable statistical significance.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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