pISSN 1598-2998, eISSN 2005-9256

Cancer Res Treat. 2018;50(3):813-822

https://doi.org/10.4143/crt.2017.340

Original Article

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Human Papillomavirus Genotype-Specific Persistence and Potential Risk Factors among Korean Women: Results from a 2-Year Follow-up Study

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Received July 17, 2017
Accepted August 8, 2017
Published Online August 17, 2017

Purpose

High-risk human papillomavirus (HPV) infection progression should be considered a critical factor for preventing cervical cancer, although most infections are transient and rarely persist. This study aimed to examine the specific types of HPV infections, their change patterns, and the potential risk factors among Korean women.

Materials and Methods

We included 4,588 women who visited hospitals in Busan and Suwon for cervical cancer screening, and 1,224 of these women attended a 2-year follow-up. Infection status was evaluated using HPV DNA testing (Hybrid Capture 2) and genotyping testing (Linear Array). Data regarding the potential risk factors for HPV infection were collected by trained nurses using structured questionnaires.

Results

Among the 1,224 women (mean age, 47 years), 105 women (8.6%) were HPV-positive at baseline. HPV infections had been cleared among 92 women (87.6%) within 2 years. Only 13 infections (12.4%) were remained, and the 10 cases of them are high-risk HPV types including genotype 33, 45, 16, 35, and 52. Among women who were negative at baseline, the HPV incidence was 4.8%. The HPV incidence was marginally associated with having multiple sexual partners (odds ratio, 2.0; 95% confidence interval, 1.0 to 3.9), although it was not significantly associated with HPV persistence.

Conclusion

Most HPV infections (88%) among Korean women were cleared within 2 years, with only a small number of persistent infections. The persistent HPV genotypes were different in our study, compared to those from previous studies. Having multiple sexual partners was associated with acquiring a HPV infection, but not with persistence.

Key words
Human papillomavirus, Genotype, Persistence, Clearance, Incidence

Introduction

Human papillomavirus (HPV) infection can cause cervical cancer, and the cancer burden attributed to this infection varies according to geographical region and the genotype of people who are infected with HPV. It is most prevalent in Africa, Asia, and some European countries, compared to other regions of the world. Thirteen high-risk HPV (HR-HPV) types, which are carcinogenic or presumed to be carcinogenic in humans, are frequently detected in patients who develop cervical cancer. For example, HPV types 16 and 18 account for approximately 70% of all cervical cancer cases [1]. Several epidemiological studies have evaluated the genotype-specific prevalences of HPV, factors that influence HPV acquisition, and the risk of cervical cancer development according to HPV infection status [1-4]. Furthermore, there are various factors that influence cervical cancer development, including viral infection and host factors. Thus, the prevention of cervical cancer relies on our understanding of the progression of HR-HPV infections, which involves persistence, clearance, new infections, and other determinant factors. However, most HPV infections are transient and rarely persist [5,6]. Only a few studies in specific countries and populations have considered the HPV genotype-specific incidence, persistence, clearance, and new infections [7-17]. Furthermore, only a few studies have evaluated the natural history of HPV infections in Asian countries, where the prevalence of HPV is high. Moreover, the association with cervical cancer development has been highlighted as a major health issue among women. In Korea, the prevalence of HPV is approximately 20% among women with normal cytology, based on the Papanicolaou test (Pap test) [18]. In addition, cervical cancer is a leading cancer among Korean women, with an age-standardized incidence of 9.5/100,000 women in 2012 [19]. Despite these data, there is a lack of Korean studies regarding changes in HPV infection status and the factors that contribute to these changes. Therefore, the present study aimed to examine HPV type-specific infections, their change patterns, and the factors that were involved in these changes, based on two HPV tests that were performed 2 years apart for Korean women who visited two centers.

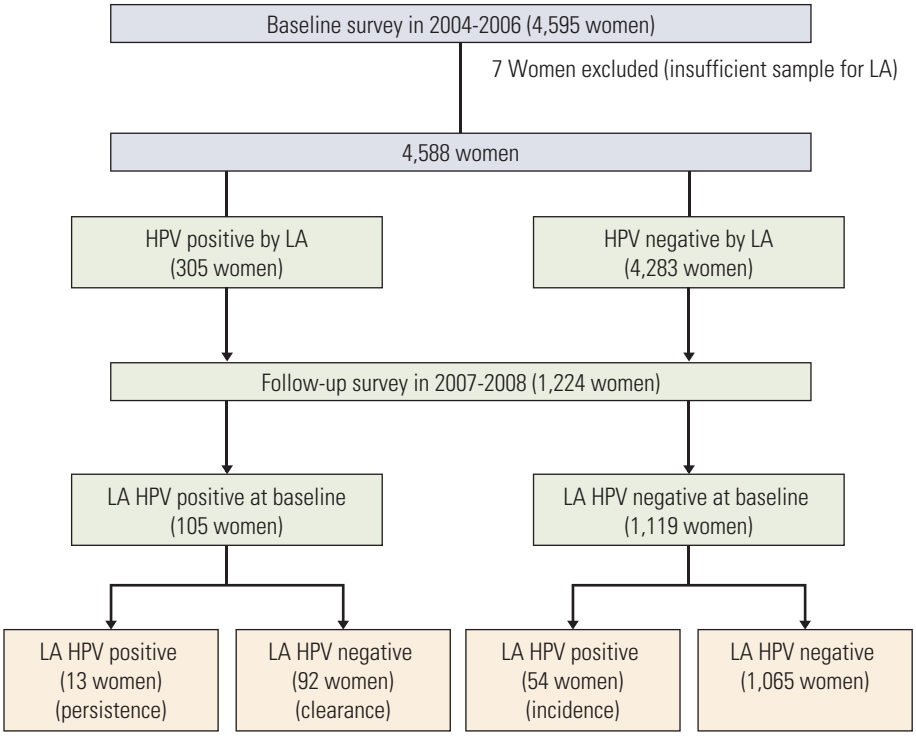

Fig. 1. Participants in baseline and follow-up survey and their classification by the status of human papillomavirus (HPV) infection. LA, linear array.

Materials and Methods

1. Study population

This retrospective study evaluated prospectively collected data from a baseline test and a test at the 2-year follow-up. A total of 4,595 women visited government-affiliated hospitals in Busan and Suwon (Korea) for baseline testing between November 2004 and December 2006, as part of the National Cervical Cancer Screening Program. Among these women, 1,224 women subsequently attended the follow-up testing during 2007 and 2008. The details of the baseline testing have been described elsewhere [5], and Fig. 1 shows the inclusion and exclusion criteria for the present study.

2. Data collection

Data regarding the potential risk factors for HPV infection were obtained using questionnaires at the baseline test. A trained research nurse interviewed each participant and completed the structured questionnaire regarding their socio-demographic characteristics (age, marital status, educational level, and age at marriage), lifestyle behaviors (smoking, alcohol drinking, and number of sexual partners), obstetrical and reproductive history (parity, age of women at first childbirth, oral contraceptive use, intrauterine device use, and hormone therapy), and clinical characteristics (sexually transmitted disease histories for the participant and their partner, family and individual cancer history, and cervical screening history).

The outcome variable was based on the results from two HPV tests at the baseline and follow-up testing. The results were categorized according to the HPV infection change status: (1) type-specific persistence (positivity for the same HPV DNA type in both tests), (2) type-specific HPV clearance (a negative result for a specific HPV type after a previously positive result), and (3) incident HPV infection (a change from HPV DNA negativity at baseline to HPV DNA positivity at the follow-up test). The HPV testing was performed using the Hybrid Capture 2 system (HC2; Digene, Gaithersburg, MA), and HPV genotyping was performed on HC2-positive samples using a Linear Array assay (LA; Roche Molecular Systems, Branchburg, NJ) [20].

3. Statistical analysis

The proportions of HPV type-specific persistence and clearance were calculated among the 105 women who were HPV-positive, based on their baseline LA results. The incidences of new HPV type-specific infections were calculated among the 1,119 women who were HPV-negative, based on their baseline LA results. Pearson's chi-square test and Fischer exact test was used to assess the frequency distributions of potential risk factors for changing HPV infection status. Logistic regression analyses were also used to evaluate the role of potential risk factors in the changes in HPV infection status. Associations were reported as odds ratios (ORs) and 95% confidence intervals (CIs). All tests were two-sided, and a p-value of < 0.05 was considered statistically significant. All analyses were performed using STATA software ver. 13 (StataCorp LP, College Station, TX).

4. Ethical statement

The study protocol was approved by the Institutional Review Board of the National Cancer Center, and all participants provided written informed consent at the baseline test.

Results

Among the 4,588 women who participated in the baseline survey, only 1,224 women were followed-up and included in the present analysis. When we compared the participants from the baseline and follow-up testing, we did not observe any noticeably differences in their socio-demographic, behavioral, and reproductive characteristics, or in their HPV infection rates (S1 Table). The mean patient age at baseline was 47 years (range, 21 to 66 years), most participants were married or cohabitating, 17% of the participants had ≥ 2 sexual partners during their lifetime, and the prevalence of HPV infections was 8.6%. At the 2-year follow-up, the prevalence of HPV infection decreased to 6.0%. All participants and the high-risk group for HPV infection were most likely to live in Busan, have ≥ 2 sexual partners during their lifetime, have a family history of cancer, and have a history of HPV infection at baseline (Table 1).

Among the 105 HPV infections from the baseline, only 13 infections (12.4%) were remained, and the 10 cases of them are HR-HPV types including genotype 33, 45, 16, 35, and 52. Among the 1,119 women who tested negative at the baseline, 54 women (5%) exhibited new HPV infections at the follow-up. The most frequent HPV genotypes found in new infection cases were genotypes 39, 52, 16, 51, and 58 (Table 2).

Persistent HPV infections were relatively common among unmarried women, women with ≥ 2 more sexual partners during their lifetime, and women with a family history of cancer. Cleared and new infections were relatively common among women with a history of a sexually transmitted disease or *Chlamydia* infection. Persistent and new infections were more common in Busan, compared to Suwon (Table 3).

Table 1. General characteristics of 1,224 study participants at the follow up by HPV infection status

Characteristic	Total (n=1,224)	Overall HPV infection[a] (n=73)		HR HPV infection[a] (n=52)	
	No. (%)	No. (%)	p-value	No. (%)	p-value
Region					
Busan	579 (47.3)	57 (9.8)	0.0001	41 (7.1)	0.001
Suwon	645 (52.7)	16 (2.5)		11 (1.7)	
Age group (yr)					
< 39	223 (18.2)	15 (6.7)	0.897	11 (5.0)	0.913
40-49	529 (43.2)	29 (5.5)		23 (4.3)	
50-59	401 (32.8)	25 (6.2)		16 (4.0)	
≥ 60	71 (5.8)	4 (5.6)		2 (2.8)	
Marital status					
Unmarried (single, divorced, and widower)	204 (16.7)	16 (7.8)	0.214	10 (4.9)	0.612
Married (married and cohabitant)	1,020 (83.3)	57 (5.6)		42 (4.1)	
Education level					
None/Elementary/Middle school	496 (40.5)	34 (6.8)	0.277	24 (4.8)	0.398
High school/University/≥ Master	728 (59.5)	39 (5.4)		28 (3.8)	
First marriage age (yr)					
< 25	402 (41.7)	26 (6.5)	0.169	19 (4.7)	0.125
≥ 25	561 (58.3)	25 (4.5)		16 (2.8)	
Smoking status					
Non smoker	1,150 (94.0)	70 (6.0)	1.000	49 (4.2)	0.474
Current smoker	73 (6.0)	3 (5.8)		3 (5.8)	
Alcohol drinking					
No	856 (69.9)	45 (5.3)	0.111	31 (3.6)	0.097
Yes	368 (30.1)	28 (7.6)		21 (5.7)	
Lifetime sexual partners					
1	1,003 (82.2)	49 (4.9)	0.001	34 (3.4)	0.003
≥ 2	217 (17.8)	23 (10.6)		17 (7.8)	
Extramarital affair					
No	1,065 (87.2)	59 (5.5)	0.283	42 (3.9)	0.486
Yes	156 (12.8)	12 (7.7)		8 (5.1)	
Parity					
1	150 (12.8)	10 (6.7)	0.331	7 (4.7)	0.873
2	719 (61.5)	38 (5.3)		29 (4.0)	
≥ 3	300 (25.7)	23 (7.7)		14 (4.7)	
Menopause					
No	506 (41.4)	35 (6.9)	0.24	22 (4.3)	0.889
Yes	717 (58.6)	38 (5.3)		30 (4.2)	
History of STD[a]					
No	1,155 (95.7)	67 (5.8)	0.231	47 (4.1)	0.274
Yes	52 (4.3)	5 (9.6)		4 (7.7)	
Family history of cancer					
No	809 (66.1)	38 (4.7)	0.009	24 (3.0)	0.002
Yes	414 (33.9)	35 (8.4)		28 (6.8)	
Cervical screening history					
No	158 (13.0)	5 (3.2)	0.147	4 (7.8)	0.392
Yes	1,058 (87.0)	67 (6.3)		47 (4.4)	
Chlamydia trachomatis at baseline					
Negative	1,151 (96.2)	67 (5.8)	0.336	48 (4.2)	0.712
Positive	45 (3.8)	4 (8.9)		2 (4.4)	

(Continued to the next page)

Table 1. Continued

Characteristic	Total (n=1,224)	Overall HPV infection[a] (n=73)		HR HPV infection[a] (n=52)	
	No. (%)	No. (%)	p-value	No. (%)	p-value
HPV status at baseline by LA					
Negative	1,119 (91.4)	54 (4.8)	< 0.001	36 (3.2)	< 0.001
Positive	105 (8.6)	19 (18.1)		16 (15.2)	

HPV, human papillomavirus; STD, sexual transmitted disease; LA, linear array. [a]Sample sizes for individual characteristics may not equal total due to missing values.

Table 2. HPV genotype distribution of 1,224 participants at the baseline and their changes at follow-up

HPV type	Total	HPV positive at baseline (n=105)			HPV negative at baseline (n=1,119)
		Persistence at follow-up[a]	Clearance at follow-up[a]	Reinfection at follow-up[a]	Incidence at follow-up[a]
All[a]	105	13 (12.4)	92 (87.6)	12 (11.4)	54 (4.8)
High risk	90	10 (11.1)	80 (88.9)	9 (8.6)	47 (4.2)
HPV 16	10	2 (20.0)	8 (80.0)	0	6 (0.5)
HPV 18	5	0	5 (100)	0	3 (0.3)
HPV 31	1	0	1 (100)	0	3 (0.3)
HPV 33	3	1 (33.3)	2 (66.7)	0	0
HPV 35	5	1 (20.0)	4 (80.0)	0	0
HPV 39	10	1 (10.0)	9 (90.0)	1 (1.0)	7 (0.6)
HPV 45	4	1 (25.0)	3 (75.0)	1 (1.0)	1 (0.1)
HPV 51	11	0	11 (100)	1 (1.0)	6 (0.5)
HPV 52	15	3 (20.0)	12 (80.0)	4 (3.8)	7 (0.6)
HPV 56	12	1 (8.3)	11 (91.7)	1 (1.0)	4 (0.4)
HPV 58	6	0	6 (100)	0	6 (0.5)
HPV 59	1	0	1 (100)	0	2 (0.2)
HPV 68	7	0	7 (100)	1 (1.0)	2 (0.2)
Low risk	90	7 (7.8)	83 (92.2)	8 (7.6)	48 (4.3)
HPV 6	3	0	3 (100)	0	0
HPV 40	2	0	2 (100)	0	0
HPV 42	1	1 (100)	0	1 (1.0)	2 (0.2)
HPV 54	5	1 (20.0)	4 (80.0)	1 (1.0)	3 (0.3)
HPV 53	15	1 (6.7)	14 (94.3)	0	8 (0.7)
HPV 55	6	1 (16.7)	5 (83.3)	2 (1.9)	2 (0.2)
HPV 61	3	1 (33.3)	2 (66.7)	1 (1.0)	4 (0.4)
HPV 62	11	1 (9.1)	10 (98.9)	1 (1.0)	4 (0.4)
HPV 66	15	0	15 (100)	0	1 (0.1)
HPV 70	10	0	10 (100)	1 (1.0)	2 (0.2)
HPV 71	4	0	4 (100)	1 (1.0)	2 (0.2)
HPV 72	2	0	2 (100)	0	1 (0.1)
HPV 81	4	0	4 (100)	0	6 (0.5)
HPV 83	1	0	1 (100)	0	3 (0.3)
HPV 84	6	1 (16.7)	5 (83.3)	0	6 (0.5)
CP6108	2	0	2 (100)	0	2 (0.2)

Values are presented as number (%). [a]Same women can be counted more than once because of multiple infections.

Table 3. Factors associated with type specific HPV persistence, clearance, and incidence[a)]

Characteristic	Persistent HPV (n=13)	Overall HPV (n=92)	Incident HPV (n=54)	
	No. (%)	No. (%)	No. (%)	p-value
Region				
Busan	10 (76.9)	46 (50.0)	42 (77.8)	< 0.001
Suwon	3 (23.1)	46 (50.0)	12 (22.2)	
Age group (yr)				
< 39	2 (15.4)	24 (26.1)	10 (18.5)	0.31
40-49	2 (15.4)	35 (38.0)	25 (46.3)	
50-59	8 (61.5)	27 (29.4)	16 (29.6)	
≥ 60	1 (7.7)	6 (6.5)	3 (5.6)	
Marital status				
Unmarried	6 (46.2)	19 (20.6)	8 (14.8)	0.036
Married	7 (53.9)	73 (79.4)	46 (85.2)	
Educational level				
None/Elementary/Middle school	9 (69.2)	39 (42.4)	23 (42.6)	0.19
High school/University/≥ Master	4 (30.7)	53 (57.6)	31 (57.4)	
Smoking status				
Nonsmoker	12 (92.3)	86 (95.9)	53 (98.2)	0.352
Smoker	1 (7.7)	6 (4.1)	1 (1.8)	
Alcohol drinking				
No	8 (61.5)	58 (63.1)	34 (62.9)	0.201
Yes	5 (38.5)	34 (36.9)	20 (37.1)	
Lifetime sexual partners				
1	8 (61.5)	64 (70.3)	38 (71.7)	< 0.001
≥ 2	5 (38.5)	27 (29.7)	15 (28.3)	
Parity				
1	2 (16.6)	9 (11.1)	6 (11.3)	0.393
2	5 (41.7)	47 (58.0)	29 (54.7)	
≥ 3	5 (41.7)	25 (30.9)	18 (34.0)	
Hormone therapy use				
Never user	9 (100)	31 (81.6)	20 (83.3)	0.478
Ever user	0	7 (18.4)	4 (16.7)	
History of STD				
No	12 (100)	85 (92.4)	49 (90.7)	0.078
Yes	0	7 (7.6)	5 (9.3)	
Family history of cancer				
No	5 (38.5)	57 (62.0)	29 (53.7)	0.021
Yes	8 (61.5)	35 (38.0)	25 (46.3)	
Chlamydia trachomatis at baseline				
Negative	13 (100)	82 (90.1)	49 (94.2)	0.019
Positive	0	9 (9.9)	3 (5.8)	

HPV, human papillomavirus; STD, sexual transmitted disease. [a)]Sample sizes for individual characteristics may not equal total due to missing values.

After adjusting for all potential factors, having ≥ 2 sexual partners exhibited a marginally significant association with new HPV infections (OR, 2.0; 95% CI, 1.0 to 3.9). No factors were significantly associated with HPV persistence and clearance (Table 4).

Table 4. ORs and 95% CI of potential factors associated with HPV persistence, and incidence

Characteristic	HPV positive at baseline			HPV negative at baseline		
	Total HPV[a] (n=105)	Persistent HPV (n=13)	Adjusted OR	Total HPV[a] (n=1,119)	Incident HPV[a] (n= 54)	Adjusted OR
		No. (%)	OR (95% CI)		No. (%)	OR (95% CI)
Age group (yr)						
< 39	26	2 (7.7)	Ref	197	10 (5.1)	Ref
40-49	37	2 (5.4)	1.0 (0.1-8.8)	492	25 (5.1)	1.2 (0.5-3.9)
50-59	35	8 (22.7)	4.6 (0.7-29.0)	366	16 (4.4)	1.0 (0.4-2.4)
≥ 60	7	1 (14.3)	3.4 (0.3-60.1)	64	3 (4.7)	1.1 (0.3-4.2)
Smoking status						
Non-smoker	98	12 (12.2)	Ref	1,074	53 (4.9)	Ref
Current smoker	7	1 (14.3)	1.7 (0.1-21.7)	44	1 (2.3)	0.3 (0.1-2.4)
Lifetime sexual partners						
1	72	8 (11.6)	Ref	931	38 (4.1)	Ref
≥ 2	32	5 (15.6)	1.6 (0.4-7.0)	185	15 (8.1)	2.0 (1.0-3.9)
Family history of cancer						
No	62	5 (8.1)	Ref	747	29 (3.9)	Ref
Yes	43	8 (18.6)	4.0 (0.9-17.2)	371	25 (6.7)	1.7 (0.9-3.1)
History of STD						
No	97	12 (13.4)	Ref	1,058	49 (4.6)	Ref
Yes	7	0	-	45	5 (11.1)	2.3 (0.8-6.2)
Chlamydia trachomatis at baseline						
Negative	95	13 (13.7)	Ref	1,056	49 (4.6)	Ref
Positive	9	0	-	36	3 (8.3)	1.3 (0.3-5.5)

Adjustment was done using all variable presented in this table except region. OR, odds ratio; CI, confidence interval; HPV, human papillomavirus; STD, sexually transmitted diseases. [a]Sample sizes for individual characteristics may not equal to total due to missing values.

Discussion

The present study provided information regarding HPV genotype-specific infections and their change patterns among Korean women. These data are important, because relevant data are sparse in this population, despite the prevalence of HPV infection and incidence of cervical cancer. Furthermore, ours is the first report regarding the natural history of HPV infection among Korean women who visited clinics or hospitals for routine health examinations (e.g., cervical cancer screening), rather than for the diagnosis or treatment of gynecological symptoms. Moreover, we performed both HPV LA and HPV genotyping to confirm the HPV type-specific changes that occurred during the course of the patients' infections.

Most infections (87.6%) were cleared within 2 years, although 5% of women developed new HPV infections during this time. These results are consistent with findings from previous reports, which suggested that up to 90% of incident infections are cleared within 2 years [5], and that the estimated half-life of HR-HPV infections is 8-10 months [6]. However, HPV persistency varies according to country, and our results revealed a lower persistency (12.4%), compared to results from previous studies in Brazil (19.2%) [9], Italy (49.1%) [16], Denmark (31.4% [21] and 26.9% [12]), the United States (39%) [10], and the Netherlands (44.1%) [22]. These differences may be related to differences in the target populations, who may have different potential risks for persistent infection, and/or differences in the baseline and follow-up testing interval. Nevertheless, the result from a meta-analysis on the patterns of HPV persistence worldwide, the persistence rate tends to decrease with time passed after infection [23]. The association between age and HPV persistence remains controversial. A review of the natural history of HPV infection suggests that age indirectly affects HPV persistence [24], while others studies have reported that younger age is associated with an increased risk of persistence [9,21].

Our results were similar to the persistence rate among young Korean women (17-26 years), despite the differences in the study populations' ages and the higher rate of new HPV infections among young Korean women [8]. The present study also revealed that the most persistent HPV type was HPV 33, which was followed by genotypes 45, 16, 35, and 52. These results are different with the findings from previous studies, which revealed that HPV 16 and 18 were the most prevalent incident and persistent HPV types [9,16,21,23].

After adjusting for potential risk factors, we did not observe any significant associations with HPV persistence. Some studies have revealed similar findings, although other studies have revealed significant positive [11,12,16,25] or inverse [9,21] associations between age and HPV persistence, including a large retrospective study of Korean women. Another study found that smokers were likely to have persistent HPV infections [22]. In the present study, the number of sexual partners was the only factor to exhibit a marginal association with new HPV infections, and this result is similar to the findings from previous studies [26-28]. The current findings including distributions of HPV genotype-specific infections and their change patterns among Korean women may help improve our understanding of the natural history of HPV infection in the same populations, and facilitate the development of prophylactic vaccines for specific populations.

The present study has several limitations that warrant consideration. First, there is the possibility of selection bias, based on the low follow-up participation rate. However, the participants exhibited similar characteristics at the baseline and follow-up testing, although HPV positivity was slightly more common at the follow-up (10.1%), compared to the baseline (7.7%) (S1 Table). These differences are unlikely to have significantly influenced our findings. Second, the small samples of women who were followed-up and women with HPV (n=105) might have influenced the absence of significant associations between HPV persistence and the potential risk factors in the multivariate analyses. Furthermore, the number of sexual partners not during the last two years when participants followed up but during their life time was included as one of important factors involving HPV infection status and their change. It could be linked to insignificant results on the association between sexual behaviors and change of HPV infection status. Nevertheless, our results regarding HPV change patterns evaluated a large number of Korean women at the baseline (n=4,558), and lifetime sexual behavior could represent overall tendency of sexual behaviors even if it is not the specific sexual behaviors change during the time followed up. Third, detailed data regarding the natural history of HPV infection should be obtained using long-term studies with repeated measurements over shorter intervals (e.g., every 6 months or every year), and we only evaluated HPV infection status after a 2-year interval. Also, information on further diagnosis and treatment such as Pap smear, colposcopic biopsy, and laser therapy during the follow up periods, which might be important factors associated with change of HPV infection status, were not available in this study. Fourth, HPV genotyping was only performed for HPV LA-positive cases at the baseline, although there was disagreement between the test results from HPV LA (6.0%) and HPV HC2 (7.0%) (data not shown). However, the correlation of HPV LA with HR HPV positivity is higher than that with HPV HC2, and this level of disagreement is likely acceptable, based on previously reported results [29,30].

In conclusion, the present study provided information regarding changes in HPV status over a 2-year interval among Korean women. Most infections resolved spontaneously, and only small fractions of the women experienced persistent infections or new HPV infections. The predominant persistent HPV genotypes were different in our study, compared to those from previous studies. We also found a marginally significant association between sexual behavior and HPV infection, but not with HPV persistence or clearance. Further large-scale studies are needed to better understand the natural history of HPV infections and the factors that are associated with HPV type-specific change patterns.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (http://www.e-crt.org).

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

This study was supported by research grants from the National Cancer Center (No. 0410130, 0710140, 1610200), Republic of Korea.

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