Journal of The Korea Convergence Society
Vol. 13. No. 1, pp. 119-129, 2022
e-ISSN 2713-6353
DOI : https://doi.org/10.15207/JKCS.2022.13.01.119

# Convergence research on cytological diagnosis of gynecological diseases and genital HPV : Based on data from the Obstetrics and Gynecology Department of a general hospital located in Suwon-si

You Hyun Joung[1], Jun Min Lee[2], Jong-Wan Kim[3], Jae Kyung Kim[4*]
[1]Student, Department of Medical Laser, Graduate School of Medicine, Dankook University
[2]Student, Department of Biomedical Laboratory Science, College of Health Sciences, Dankook University
[3]Professor, Department of Laboratory Medicine, College of Medicine, Dankook University
[4]Professor, Department of Biomedical Laboratory Science, College of Health Sciences, Dankook University

# 수원시 소재 일개 종합병원 산부인과에서 자궁경부 질환 검사의 실태조사 : HPV와 세포학적 검사의 융합연구

정유현[1], 이준민[2], 김종완[3], 김재경[4*]
[1]단국대학교 의학대학원 의학레이저 협동과정 학생, [2]단국대학교 보건과학대 임상병리학과 학생,
[3]단국대학교 의과대학 의학과 교수, [4]단국대학교 보건과학대 임상병리학과 교수

**Abstract** Cervical cytology has been widely used as a screening tool for cervical cancer. However, Human papillomavirus (HPV) detection and subtype testing are suggested to overcome the high false-negative rate associated with cytology. We aimed to investigate the clinical usefulness and infection rate in the HPV polymerase chain reaction (PCR) test performed in hospitals. HPV PCR data from 217 patients were analyzed. Analysis of variance revealed a significant difference in the infection rate among different age groups (P=0.015). The biopsy results showed that epithelial cell abnormalities and high HPV-positivity rate was observed in 1 (100%) subject aged 〈29 years, in 4 out of 5 (80%) patients in their 30s, and in 3 out of 4 (75%) patients aged ≥70 years. The prevalence of HPV infection was very high (46.1%). The highest prevalence (87.5%) was observed among patients in their 〈29, followed by those in their 30s (67.7%) and those in their 40s (31.9%).A high rate of epithelial cell abnormalities (≥ cervical intraepithelial neoplasia type 1, mild dysplasia) was observed in HPV-infected women aged〈30 years. Therefore, extensive research and prevention activities are needed in this age group. HPV PCR testing is recommended to complement cervical cytology

**Key Words :** HPV, HPV genotype, Cervical cancer, Cervical intraepithelial neoplasia, PAP, Cytology

**요 약** 자궁경부세포검사는 자궁경부암 선별검사로 널리 사용되어 왔다. 그러나, 위음성 비율이 높아 인유두종바이러스 중합효소연쇄반응 (HPV PCR) 검사로 보완이 제안되고 있다. HPV PCR 검사의 임상적 유용성을 확인하여, 자궁경부암을 예방하는 선별검사의 효과를 알아보고자 한다. 217명의 환자의 데이터를 분석하였고, 높은 HPV 감염률(46.1%)과 분산분석 결과 연령 집단간 HPV 감염률에 유의한 차이가 보였다(P=0.015). 특히, 연구기간 중 CIN3 3건 상피세포암 1건이 관찰되었는데, 고위험군 HPV(16, 33)감염이 모두 관찰되었고, 20대와 30대 상피세포 이형성증 진단 환자에서 높은 고위험군 HPV감염이 관찰되었다. 따라서 이 연령대에 대한 광범위한 연구 및 예방 활동이 필요하며, 자궁암 예방을 위한 선별검사로써 세포학적 검사와 함께 HPV PCR 검사가 유용할 것으로 판단된다.

**주제어 :** 인유두종바이러스, 자궁경부세포검사, PCR, 자궁암, 자궁경부 생검, 상피세포 이형성증

*Corresponding Author : Jae Kyung Kim(nerowolf@naver.com)
Received October 19, 2021
Revised November 16, 2021
Accepted January 20, 2022
Published January 28, 2022

## 1. Introduction

Approximately a million new cancer cases were reported worldwide in 2020. Among these, 58.3% of the cancer-related deaths are expected to occur in Asia. The most common cancers in women are breast and cervical cancers, which are the main causes of death [1]. Viral infection accounts for 15-20% of the cancer cases, and human papillomavirus (HPV) is a representative virus that causes cancer [2]. HPV is mainly transmitted by sexual contact and is involved in the carcinogenesis of cervical, skin, and vulvar cancers. Reportedly, 99.7% of the high-risk HPV DNA was found in cervical cancer samples [3]. HPV infection is mostly transient and is eliminated naturally by the host's immune response. However, if the infection persists, it can progress to cervical intraepithelial neoplasia (CIN) [4]. Particularly, if high-risk HPV infection persists for a long time, the risk of progression to cervical cancer increases [5]. Currently, approximately 200 genotypes of HPV have been discovered. Among these, approximately 40 are known to infect the human genital tract. These are classified according to the risk. Geno types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82 are classified as high-risk and genotypes 53, 66, 70, 73 are considered probable high-risk genotypes. The remaining genotypes are classified as low-risk geno types. Types 16 and 18 are known to be fatal and high-risk genotypes that cause approximately 70% of cervical cancer [6]. Vaccination and screening are recommended to prevent progression to cervical cancer due to high-risk HPV infections.

HPV infection is very common among young women. However, it usually subsides on its own. Neutralizing antibodies to the HPV L1 antigen are detected in approximately 70% of infected women. These neutralizing antibodies can prevent HPV from penetrating the cervical basal cells. However, since most of the antibodies produced by natural infection have very low titers, they do not consistently prevent repeated infection with HPV of the same subtype [4]. Vaccination is recommended to prevent HPV infection. The commercially available quadrivalent vaccine has been reported to be highly effective in preventing the progression of CIN or adenocarcinoma in situ caused by high-risk genotypes 16 and 18 [7]. Therefore, the World Health Organization recommends two doses of vaccination, and vaccination is most effective for women (9-26 years of age) before the first sexual contact [8]. However, there are no official data on HPV vaccination rates in Korean adult women. According to a previous study, the rate of vaccination was low (6.1~19%) in married women, and more efforts are needed to prevent cervical cancer [9].

In addition to HPV vaccination, early detection of cervical cancer is important. Cervical cancer develops after a long period of precancerous stages such as dysplasia and carcinoma in situ. Diagnosis and treatment through appropriate screening tests at these precancerous stages can reduce the incidence and mortality of cancer. Cervical cytology has been widely used as a screening test [10]. However, due to the high false-negative rate, various auxiliary tests have been attempted. HPV DNA detection and subtype testing have been suggested as alternative screening tests [11]. In a study comparing HPV DNA testing and cytology testing for cervical cancer incidence in India, Among 131,749 women, the HPV group had a significant reduction in the number of advanced cervical and cervical cancers. In addition, there was no reduction in death from advanced cervical cancer or cervical cancer when compared to the cytological group [12]. This study aimed to investigate the clinical usefulness

and infection rate in the HPV PCR test currently performed in hospitals. We compared the diagnosis obtained via uterine cytology and punch biopsy with that obtained via screening tests from the national cancer-screening program. Data from the pathology department of a general hospital in Suwon were analyzed and reviewed.

## 2. Materials and methods

### 2.1 Data collection

This study analyzed 217 HPV tests from outpatients and inpatients of the obstetrics and gynecology department at a general hospital in Suwon, Gyeonggi-do between January 2017 and May 2021. HPV infection and genotype were confirmed by reviewing the patients' medical records. Additionally, the availability and results of cytology and punch biopsy were investigated, and 67 patients were subjected to biopsy. To protect the personal information of the research patients, random numbers were assigned without collecting personally identifiable information. This study was exempted from deliberation by the Dankook University Institutional Review Board (approval number: DKU 2021-10-041).

### 2.2 HPV analyses and Clinical examination

For HPV infection and genotype testing, samples were collected from the patients' cervices using a dedicated brush. Each sample was placed in a dedicated container with phosphate-buffered saline (PBS), and the test was performed by EONE Laboratories. The bead microarray method was used. HPV genotypes included 15 high-risk [16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82], 4 probable high-risk [26, 53, 66, 69), and 21 low-risk types [6, 11, 30, 32, 40, 42, 43, 44, 54, 55, 61, 62, 67, 70, 71, 72, 74, 81, 83, 84, 87). Thus, 40 genotypes were examined; subtypes not included among these were classified as "other types."For cytologic examination, cervical samples were stained with Papanicolaou stain using Thinprep (Cytyc Corp Boxborough, MA, USA), which is a piece of liquid cytology equipment. The results were analyzed by a pathologist and reported according to the 2014 Bethesda System. In addition, results of punch biopsy were investigated by reviewing the medical records.

### 2.3 Variable Description

WNL: Within normal limits

Non-neoplastic findings: Benign proliferative or reactive lesion (Atropy, Inflammation, Organisms)

ASC-US: atypical squamous cells of undermined significance

LSIL: low-grade squamous intraepithelial lesion

HSIL: high-grade squamous intraepithelial lesion

### 2.4 Statistical analyses

IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses, and the data are expressed as percentages (%). Initially, HPV infection was investigated by dividing the patients into different age groups, and the infection rate within each group was determined. Subsequently, the infection rate was compared among different groups using analysis of variance (ANOVA). A P-value $<0.05$ was considered statistically significant. In addition, low-risk and high-risk HPV infections were investigated according to the age groups. Cytological examinations were cross-analyzed with normal lesions in one group and lesions with low-grade or higher dysplasia in another group.

## 3. Results

Altogether, 217 patients underwent cervical cytology and HPV testing during the study period(Table 1). The highest number of HPV-positive cases were observed among patients in their 60s (64 cases, 29.5%), followed by patients in their 50s (55 cases, 25.3%) and 40s (47 cases, 21.7%). The lowest number of HPV-positive cases were observed among patients aged <20 years (8 cases, 3.7%). However, the highest HPV-positivity rate (87.5%) was observed among patients in their 20s. In addition, patients in their 30s also exhibited a higher positivity rate (66.7%) than those aged >40 years, indicating that younger females exhibited a higher HPV infection rate (Fig. 1). ANOVA revealed a significant difference in the infection rate among different age groups (P=0.015). According to the results of cervical cytology by age group, women in their 30s exhibited the highest rate of abnormal diagnosis (atypical squamous cells of undermined significance [ASC-US]: 6 [28.6%], low-grade squamous intraepithelial lesion [LSIL]: 1 [4.8%], high-grade squamous intraepithelial lesion [HSIL]: 1 [4.8%]). The abnormal diagnoses among women in their 60s were ASC-US: 18 (28.1%), LSIL: 1 (1.6%), and HSIL: 1 (1.6%). No increasing or decreasing trend due to age was observed.

**Table 1. Cytological diagnoses and prevalence of human papillomavirus (HPV) infection by age group**

| | | Gynecological cytology diagnosis results | | | | | HPV | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age group | Number of tests | WNL | Non-neoplastic findings | ASC-US | LSIL | HSIL | Negative | Positive | F | P |
| Under 29 | 8 (3.7) | 1 (12.5) | 6 (75.0) | 0 | 1 (12.5) | 0 | 1 (12.5) | 7 (87.5) | | |
| 30s | 21 (9.7) | 1 (4.8) | 12 (57.1) | 6 (28.6) | 1 (4.8) | 1 (4.8) | 7 (33.3) | 14 (66.7) | | |
| 40s | 47 (21.7) | 9 (19.1) | 26 (55.3) | 10 (21.3) | 1 (2.1) | 1 (2.1) | 32(68.1) | 15 (31.9) | 2.910 | 0.015 |
| 50s | 55 (25.3) | 4 (7.3) | 40 (72.7) | 8 (14.5) | 2 (3.6) | 1 (1.8) | 32 (58.2) | 23 (41.8) | | |
| 60s | 64 (29.5) | 2 (3.1) | 42 (65.6) | 18 (28.1) | 1 (1.6) | 1 (1.6) | 33 (51.6) | 31 (48.4) | | |
| 70+ | 22 (10.1) | 0 | 17 (77.3) | 3 (13.6) | 2 (9.1) | 0 | 11 (50.0) | 11 (50.0) | | |
| Total | 217 (100) | 17 (7.8) | 143 (65.9) | 45 (20.7) | 8 (3.7) | 4 (1.8) | 117 (53.9) | 100 (46.1) | | |

Data are presented as number (percentage).

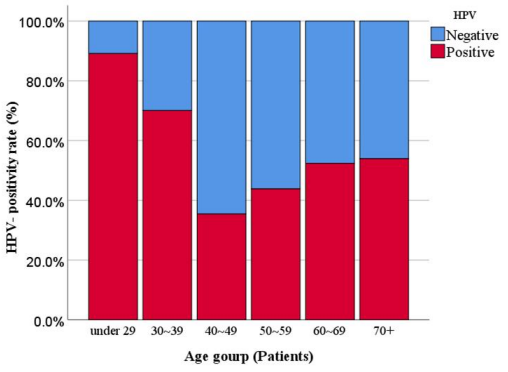


**Fig. 1. Human papillomavirus (HPV) infection patterns by age group**

To analyze the risk of HPV infection by age group, HPV genotypes were classified into risk groups. Among the infected patients, 74 (50%) were in the high-risk group, 16 (10.8%) in the probable high-risk group, and 58 (39.2%) in the low-risk group. The high-risk group comprised five patients in their 20s (62.5%), 14 patients in their 30s (63.6%), 12 patients in their 40s (63.2%), 17 patients in their 50s (50.0%), and 20 patients in their 60s (37.0%). The HPV genotype with the highest frequency of infection was type 52 (16 cases, 10.7%) followed by type 16 (10 cases, 6.7%), type 51 (10 cases, 6.7%),type 81 (10 cases,

6.7%), and type 58 (9 cases, 6.0%). However, 25 cases of multiple infections were included, with one patient infected with up to nine genotypes. After correcting for this factor, the high-risk group consisted of 5/7 (71.4%) patients in their 20s, 14/14 (100%) patients in their 30s, 12/15 (80.0%) patients in their 40s, 17 patients in their 50s, 20/31 (64.5%) patients in their 60s, and 6/11 (54.6%) patients aged ≥70 years. High-risk group genotypes exceeded 50% in all age groups, and patients in their 30s exhibited a high rate of high-risk infection (100%) (Table 2).

Among the patients who underwent cervical biopsy, HPV PCR test results were confirmed in 67 patients(negative in 30 patients [44.8%] and positive in 37 patients [55.2%]). In addition, the rates of mild or higher grade of cervical epithelial dysplasia were 35.8% (24 cases) and 40.3% (27 cases) in the HPV-negative group and HPV-positive group, respectively. The biopsy results showed that epithelial cell abnormalities and high HPV-positivity rate were observed in 1 (100%) patient aged below 29 years, in 4 out of 5 (80%) patients in their 30s, and in 3 out of 4 (75%) patients aged ≥70 years.

**Table 2. Prevalence of human papillomavirus (HPV) genotypes by age group**

| Risk group | Genotype | Under 29 | 30s | 40s | 50s | 60s | 70+ | Total |
|---|---|---|---|---|---|---|---|---|
| High risk | 16 | 2 (25.0) | 1 (4.5)[1] | 2 (10.5) | 4 (11.8) | 1 (1.8)[1] | 0 | 10 (6.7)[2] |
| | 18 | 0 | 0 | 1 (5.3)[1] | 0 | 0 | 0 | 1 (0.7)[1] |
| | 31 | 0 | 0 | 0 | 1 (2.9)[1] | 0 | 0 | 1 (0.7)[1] |
| | 33 | 0 | 1 (4.5) [1] | 0 | 0 | 2 (3.7)[2] | 1 (8.3)[1] | 4 (2.7)[4] |
| | 35 | 0 | 1 (4.5) [1] | 1 (5.3) | 1 (2.9)[1] | 0 | 0 | 3 (2.0)[2] |
| | 39 | 0 | 1 (4.5) | 0 | 0 | 4 (7.4)[2] | 0 | 5 (3.4)[2] |
| | 51 | 0 | 2 (9.1) | 2 (11.1) | 4 (11.8)[2] | 2 (3.7)[1] | 0 | 10 (6.7)[3] |
| | 52 | 1 (12.5) | 3 (13.6)[2] | 4 (22.2) | 1 (2.9) | 6 (11.1)[2] | 1 (8.3) | 16 (10.7)[4] |
| | 56 | 0 | 1 (4.5)[1] | 1 (5.3) | 2 (5.9)[2] | 1 (1.8)[1] | 2 (16.7) | 7 (4.7)[4] |
| | 58 | 1 (12.5) | 0 | 0 | 3 (8.8) | 3 (5.6)[1] | 2 (16.7)[1] | 9 (6.0)[2] |
| | 59 | 0 | 2 (9.1)[1] | 1 (5.3) | 0 | 1 (1.8)[1] | 0 | 4 (2.7)[2] |
| | 68 | 1 (12.5)[1] | 1 (4.5)[1] | 0 | 1 (2.9)[1] | 0 | 0 | 3 (2.0)[3] |
| | 82 | 0 | 1 (4.5)[1] | 0 | 0 | 0 | 0 | 1 (0.7)[1] |
| High-risk total | | 5 (62.5) | 14 (63.6) | 12 (63.2) | 17 (50.0) | 20 (37.0) | 6 (50.0) | 74 (49.7) |
| Probable high risk | 53 | 0 | 1 (4.5) | 0 | 2 (5.9)[2] | 8 (14.8)[6] | 2 (16.7) | 13 (8.7)[8] |
| | 66 | 1 (12.5) | 0 | 0 | 0 | 1 (1.8)[1] | 0 | 2 (1.4)[1] |
| | 69 | 0 | 0 | 0 | 0 | 1 (1.8)[1] | 0 | 1 (0.7)[1] |
| Probable high-risk total | | 1 (12.5) | 1 (4.5) | 0 | 2 (5.9) | 10 (18.5) | 2 (16.7) | 16 (10.8) |
| Low risk | 6 | 0 | 0 | 0 | 1 (2.9)[1] | 0 | 0 | 1 (0.7)[1] |
| | 30 | 0 | 0 | 0 | 1 (2.9)[1] | 1 (1.8) [1] | 0 | 2 (1.4)[2] |
| | 32 | 0 | 0 | 0 | 0 | 1 (1.8) [1] | 0 | 1 (0.7)[1] |
| | 40 | 0 | 1 (4.5)[1] | 0 | 0 | 3 (5.6) [3] | 0 | 4 (2.7)[4] |
| | 44 | 1 (12.5)[1] | 0 | 1 (5.3) | 1 (2.9)[1] | 0 | 0 | 3 (2.0)[2] |
| | 54 | 0 | 0 | 1 (5.3) [1] | 0 | 2 (3.7) [1] | 0 | 3 (2.0)[2] |
| | 55 | 0 | 0 | 1 (5.3) [1] | 0 | 0 | 0 | 1 (0.7)[1] |
| | 61 | 0 | 0 | 1 (5.3) | 2 (5.9)[2] | 2 (3.7) [2] | 0 | 5 (3.4)[4] |
| | 62 | 0 | 2 (9.1)[1] | 0 | 0 | 4 (7.4) [2] | 0 | 6 (4.1)[3] |
| | 67 | 0 | 0 | 0 | 2 (5.9)[1] | 0 | 0 | 2 (1.4)[1] |
| | 70 | 0 | 2 (9.1) | 0 | 3 (8.8)[1] | 1 (1.8) | 0 | 6 (4.1)[1] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 71 | 0 | 0 | 0 | 0 | 0 | 1 (8.3) | 1 (0.7) |
| 72 | 0 | 0 | 0 | 1 (2.9) | 1 (1.8) | 0 | 2 (1.4) |
| 74 | 1 (12.5) | 1 (4.5)[1] | 2 (10.5) | 1 (2.9) | 1 (1.8) [1] | 0 | 5 (3.4)[2] |
| 81 | 0 | 1 (4.5)[1] | 0 | 2 (5.9)[1] | 4 (7.4) [3] | 3 (25.0) | 10 (6.7)[5] |
| 83 | 0 | 0 | 0 | 0 | 1 (1.8) [1] | 0 | 1 (0.7)[1] |
| 87 | 0 | 0 | 0 | 0 | 1 (1.8) [1] | 0 | 1 (0.7)[1] |
| Other | 0 | 0 | 1 (5.3) | 1 (2.9) | 2 (3.7) | 0 | 4 (2.7) |
| Low risk total | 2 (25.0) | 7 (31.8) | 7 (36.8) | 15 (44.1) | 24 (44.4) | 4 (33.3) | 58 (38.9) |
| HPV genotype total | 8 (5.4)[1] | 22 (14.8)[5] | 19 (12.7)[1] | 34 (22.8)[7] | 54 (36.3)[10] | 12 (8.1)[1] | 149 (100) |

Data are presented as number (percentage).
Multiple genotypes causing infection were included.
Superscript numbers indicate the number of multiple infections.

However, patients in their 40s and 60s exhibited a low positivity rate (30-36.4%). The most frequently detected genotypes were type 52 (10 cases) and type 16 (7 cases), and all 7 patients infected with type 16 genotype exhibited epithelial cell abnormalities. Among them, squamous cell carcinoma in situ (SCCIS) was detected in 1 case and severe dysplasia (CIN 3) was detected in 3 cases (Table 3).

The types of HPV infection such as high-risk infection and double infection were investigated in patients with mild cervical epithelial dysplasia according to the age groups. One patient aged below29 years was infected with types 52 and 66 (high-risk genotypes and multiple infections). Among patients in their 30s, 3/4 people exhibited high-risk infection, and 2 patients exhibited multiple infections. Among patients in their 40s, 3/5 patients exhibited high-risk infection, and no patients exhibited multiple infections. Among patients in their 50s, 6/6 patients exhibited high-risk infection, and 3 patients exhibited multiple infections. Among patients in their 60s, 6/8 patients exhibited high-risk infection, and 6 patients exhibited multiple infections. Among patients aged ≥70 years, 2/3 patients exhibited high-risk infection, and no patients exhibited multiple infections (Fig. 2).

Among the patients who underwent cervical biopsy, HPV PCR test results were confirmed in 67 patients(negative in 30 patients [44.8%] and positive in 37 patients [55.2%]). In addition, the rates of mild or higher grade of cervical epithelial dysplasia were 35.8% (24 cases) and 40.3% (27 cases) in the HPV-negative group and HPV-positive group, respectively. The biopsy results showed that epithelial cell abnormalities and high HPV-positivity rate were observed in 1 (100%) patient aged below 29 years, in 4 out of 5 (80%) patients in their 30s, and in 3 out of 4 (75%) patients aged ≥70 years. However, patients in their 40s and 60s exhibited a low positivity rate (30-36.4%). The most frequently detected genotypes were type 52 (10 cases) and type 16 (7 cases), and all 7 patients infected with type 16 genotype exhibited epithelial cell abnormalities. Among them, squamous cell carcinoma in situ (SCCIS) was detected in 1 case and severe dysplasia (CIN 3) was detected in 3 cases (Table 3). The types of HPV infection such as high-risk infection and double infection were investigated in patients with mild cervical epithelial dysplasia according to the age groups. One patient aged below29 years was infected with types 52 and 66 (high-risk genotypes and multiple infections). Among patients in their 30s, 3/4 people exhibited high-risk infection, and 2 patients exhibited multiple infections.

**Table 3. Diagnosis of gynecological pathology and human papillomavirus (HPV) infection**

| Age group | Gynecological biopsy diagnostic results | HPV | | HPV risk group | | |
|---|---|---|---|---|---|---|
| | | Negative | Positive | HR | PR | LR |
| under 29 | Non-neoplastic findings | 0 | 0 | 0 | 0 | 0 |
| | Epithelial cell abnormalities | 0 | 1 (100) | 52 | 66 | |
| 30s | Non-neoplastic findings | 1 (20.0) | 0 | | | |
| | Epithelial cell abnormalities | 0 | 4 (80.0) | 16**, 33, 52, 59 | | 70 |
| 40s | Non-neoplastic findings | 2 (13.3) | 4 (26.7) | 51, $52^3$ | | 61 |
| | Epithelial cell abnormalities | 4 (26.7) | 5 (33.3) | 16*, 35, 56 | | 74, O |
| 50s | Non-neoplastic findings | 1 (5.0) | 4 (20.0) | $51^2$, 58 | | 6, O |
| | Epithelial cell abnormalities | 9 (45.0) | 6 (30.0) | $16^{4*}$, 18, 35, 51, 56, 58 | | 54, 55, 70, 74 |
| 60s | Non-neoplastic findings | 2* (9.1) | 1 (4.5) | 39 | 53 | |
| | Epithelial cell abnormalities | 11 (50.0) | 8 (36.4) | 16, $33^{2*}$, $52^2$ | $53^2$ | 30, 32, 40, 54, 61, 62, $O^3$ |
| 70+ | Non-neoplastic findings | 0 | 1 (25.0) | 52 | | |
| | Epithelial cell abnormalities | 0 | 3 (75.0) | 56, 58, 81 | | |
| Total | Non-neoplastic findings | 6 (9.0) | 10 (14.9) | 39, 51, $52^6$, 58 | 53 | 6, 61, O |
| | Epithelial cell abnormalities | 24 (35.8) | 27 (40.3) | $16^7$, 18, $33^3$, $35^2$, 51, $52^4$, $56^3$, $58^2$, 59, 81 | $53^2$, 66 | 30, 32, 40, $54^2$, 55, 61 62, $70^2$, $74^2$, $O^4$ |
| | Total | 30 (44.8) | 37 (55.2) | $52^{10}$, $16^7$ | $53^2$ | $O^4$ |

Data are presented as number (percentage).
Epithelial cell abnormality: ≥cervical intraepithelial neoplasia (CIN) grade 1, mild dysplasia
O: other type, *: CIN 3, **: squamous cell carcinoma in situ, HR: high-risk, PR: probable high-risk, LR: low-risk
Superscript numbers indicate the number of multiple infections.

Among patients in their 40s, 3/5 patients exhibited high-risk infection, and no patients exhibited multiple infections. Among patients in their 50s, 6/6 patients exhibited high-risk infection, and 3 patients exhibited multiple infections. Among patients in their 60s, 6/8 patients exhibited high-risk infection, and 6 patients exhibited multiple infections. Among patients aged ≥70 years, 2/3 patients exhibited high-risk infection, and no patients exhibited multiple infections (Fig. 2).

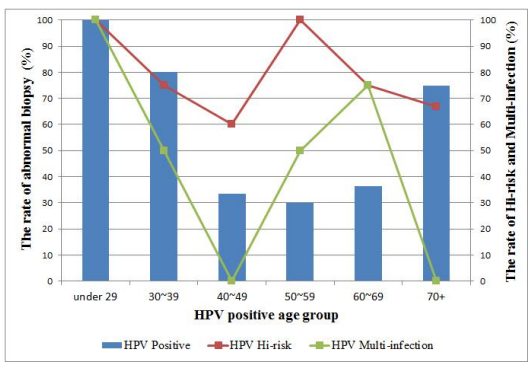


Fig. 2. High-risk genotypes and multiple human papillomavirus (HPV) infections by age in patients with epithelial cell abnormalities

## 4. DISCUSSION

The prevalence of HPV infection observed in this study was very high (46.1%). This result was significantly different from the estimate in a previous study (13%) investigating the prevalence of HPV infection among women in Busan [13] and from that (15.5%) in a study based on data from the Health Promotion Center at a hospital in Seoul [14]. This discrepancy might be attributed to the small number of patients in the present study and to the fact that the present results were based on hospital data. Thus, the high prevalence might be due to selection bias, since a greater number of patients were likely to be detected with HPV infection through health checkup and screening tests at a primary medical institution. This indicates the potential limitations of the small sample size and the sampling method used in this study. Similarly, most of the previous studies conducted in Korea failed to use a large-scale random sampling method due to the specificity of gynecological examinations (rejection of the examinee while sampling thecervix, the age at which the test is recommended, and the presence or absence of sexual experience) and the limitations related to the cost of the HPV PCR test. Therefore, it is reasonable to consider the HPV prevalence rate of 46.1% in this study as the observation result in a cervical cancer risk group.

Women infected with HPV for 1-2years or longer are at an increased risk of cervical cancer [15]. Moreover, women aged 〉30 years are more likely to have a persistent HPV infection, which increases the risk of developing high-grade cervical intraepithelial tumors (CIN 2/3) or cervical cancer [16]. Hence, HPV testing is recommended as a screening tool for women aged 〉30 years, as it has been reported to significantly reduce the overall incidence of cervical cancer when compared with conventional cytological screening [17]. In the present study, the highest prevalence of HPV infection was observed among patients in their 20s (87.5%), and the lowest prevalence (67.7%) was observed among patients in their 30s. The prevalence was 31.9% among patients in their 40s. The prevalence increased again among patients in their 50s, reaching 50.0% among patients aged ≥70 years (Fig. 1). Similarly, previous studies conducted in Korea have also shown that the prevalence of HPV was highest among patients aged 20~30 years. Younger patients are more likely to be exposed to HPV infection due to a more active sex life [13-15]. In a study on HPV infection among university students, the group with sexual experience (38.8%) exhibited an odds ratio of 12.7 when compared with the group without sexual experience (4.7%) [18]. The lowest prevalence of HPV infection was observed among patients in their 40s and showed an increasing pattern with subsequent increase in age. This finding is consistent with the results of several previous studies. HPV infection at a younger age is suppressed by the body's immunity. However, HPV is reactivated with aging due to weakened immunity and reduced hormonal levels [19,20].

In the genotype analysis of HPV-infected patients, women aged below 50 years exhibited a high infection rate with high-risk genotypes, with one of the patients infected with two or more HPV genotypes. The rate of high-risk infection was 71.4% among patients in their 20s, 100% among patients in their 30s, 80.0% among patients in their 40s, and 73.9% among patients in their 50s. In addition, more than 70% of the patients from ll age groups exhibited a high rate of high-risk infection (Table 2). A previous study with a design similar to that of the present study has reported consistent results, showing that 636 patients (54.9%) out of 1,158 who underwent

genotype analysis were in the high-risk group [21]. However, in a study of general health examiners, an HPV infection rate of 17.3% was observed. Among these patients, 9.0% were infected with high-risk HPV genotypes [22]. These results suggest that the HPV infection rate and the proportion of patients with high-risk infection (patients with subjective symptoms or patients receiving gynecological care through screening tests such as medical examinations) are higher in the cervical cancer risk group than in the general population.

In the investigation of the relationship between HPV infection and cervical epithelial dysplasia through cervical biopsy, a high proportion of HPV-infected women aged <30 years exhibited epithelial cell abnormalities (≥CIN 1, mild dysplasia). Particularly, three cases of severe dysplasia (CIN 3) and one case of SCCIS were detected. Severe cervical dysplasia was associated with type 16 HPV infection except in one case of CIN 3 (a woman in her 60s) (Table 3). Type 16 has been reported as a high-risk genotype associated with cervical cancer in several studies. Types 16, 18, and 19 cause approximately 70% of the cervical cancers worldwide [23]. Moreover, a previous study suggested that HPV 16 and HPV 18 vaccination was expected to reduce the lifetime risk of cancer by approximately 43% in 70% of the girls aged 9-12 years and assuming 70% coverage, three cervical screenings per lifetime between 35 and 45 years of age were expected to reduce the lifetime risk of cancer by approximately 53% [24].

The present study has some limitations. The study group did not have representativeness of the group compared to the random sampling study, since it was a general hospital outpatient study. A greater proportion of study patients were likely to be detected with HPV infection, since they underwent health checkup and screening tests at a primary medical institution. This may have led to selection bias. Statistical analysis was limited by the small number of patients and various cytological diagnoses and HPV genotypes. However, the results of the present study were consistent withthose of previous studies. Particularly, the relationship between HPV infection and cervical epithelial dysplasia was significant among women aged <30 years despite the small number of patients. Active cervical cytology and HPV testing for young women will be of great help in preventing cervical cancer, and follow-up studies targeting this age group should be conducted.

## 5. Conclusions

In this study targeting the high-risk group of patients (obstetrics and gynecology outpatientsand inpatients), we observed high rates of HPV-positivity and high-risk infection in all age groups. Particularly, these rates were higher among women aged <30 years. However, the number of young patients tested in this study was small, and very few studies have included this age group. Therefore, extensive research involving this age group is required. In addition, it is necessary to conduct vaccination and screening programs in an active manner to prevent cervical cancer. HPV PCR test is recommended to supplement cervical cytology, which is currently being performed as a national cancer-screening test.

## REFERENCES

[1] H. Sung et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a Cancer Journal for Clinicians 71(3),* 209-249.
DOI : 10.3322/caac.21660

[2] M. E. McLaughlin-Drubin & K. Munger. (2008). Viruses associated with human cancer. *Biochimica et Biophysica Acta 1782(3),* 127-150. DOI : 10.1016/j.bbadis.2007.12.005

[3] J. M. M. Walboomers et al. (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *The Journal of Pathology 189(1),* 12-19. DOI : 10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F

[4] B. G. Kim. (2015). Update of human papillomavirus vaccination. *Journal of the Korean Medical Association 58(4),* 313-318. DOI : 10.5124/jkma.2015.58.4.313

[5] A. Asiaf et al. (2014). Review of the current knowledge on the epidemiology, pathogenesis, and prevention of human papillomavirus infection. *European Journal of Cancer Prevention 23(3),* 206-224. DOI : 10.1097/CEJ.0b013e328364f273

[6] R. Reid et al. (1982). Genital warts and cervical cancer. I. Evidence of an association between subclinical papillomavirus infection and cervical malignancy. *Cancer 50(2),* 377-387. DOI : 10.1002/1097-0142(19820715)50:2<377::AID-CNCR2820500236>3.0.CO;2-A

[7] Future II Study Group. (2007). Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *New England Journal of Medicine 356(19),* 1915-1927. DOI : 10.1056/NEJMoa061741

[8] World Health Organization. (2017). Human papillomavirus vaccines: WHO position paper, May 2017 *Wkly Epidemiol Rec. 2217;92(19),* 241-68.

[9] K. N. Lee et al. (2017). Attitudes regarding HPV vaccinations of children among mothers with adolescent daughters in Korea. *Journal of Korean Medical Science 32(1),* 130-134. DOI : 10.3346/jkms.2017.32.1.130

[10] A. M. Park & S. B. Koh. (2008). Prevalence and Distribution of Single and Multiple HPV Infections in Cervical Cancer and Precancerous Lesion From Daegu and Gyeongbuk Province. *Korean Journal of Obstetrics and Gynecology 51(10),* 1128-1136.

[11] AT. Lorincz et al. (1987). Oncogenic association of specific human papillomavirus types with cervical neoplasia. *Journal of the National Cancer Institute 79(4),* 671-677. DOI : 10.1093/jnci/79.4.671

[12] R. Sankaranarayanan et al. (2009). HPV screening for cervical cancer in rural India. *New England Journal of Medicine, 360(14),* 1385-1394. DOI : 10.1056/NEJMoa0808516

[13] H. R. Shin et al. (2003). Prevalence of human papillomavirus infection in women in Busan, South Korea. *International Journal of Cancer 103(3),* 413-421. DOI : 10.1002/ijc.10825

[14] W. D. Joo et al. (2004). Prevalence of human papillomavirus infection in Korean women: risks of abnormal pap smear and cervical neoplasia. *Korean Journal of Gynecologic Oncology and Colposcopy 15.4,* 309-316. DOI : 10.3802/kjgoc.2004.15.4.309

[15] S. K. Kjær et al. (2010). Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. *Journal of the National Cancer Institute 102.19,* 1478-1488. DOI : 10.1093/jnci/djq356

[16] K. K. Vesco et al. (2011). Risk factors and other epidemiologic considerations for cervical cancer screening: a narrative review for the US Preventive Services Task Force. *Annals of Internal Medicine 155(10),* 698-705, W216. DOI : 10.7326/0003-4819-155-10-201111150-00377

[17] G Ronco et al. (2014). Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *The Lancet 383(9916),* 524-532. DOI : 10.1016/S0140-6736(13)62218-7

[18] H. R. Shin et al. (2004). Prevalence and determinants of genital infection with papillomavirus, in female and male university students in Busan, South Korea. *Journal of Infectious Diseases 190(3),* 468-476. DOI : 10.1086/421279

[19] E. Lazcano-Ponce et al. (2001). Epidemiology of HPV infection among Mexican women with normal cervical cytology. *International Journal of Cancer 91(3),* 412-420. DOI : 10.1002/1097-0215(20010201)91:3<412::AID-IJC1071>3.0.CO;2-M

[20] R. Herrero et al. (2000). Population-based study of human papillomavirus infection and cervical neoplasia in rural Costa Rica. *Journal of the National Cancer Institute 92(6),* 464-474. DOI : 10.1093/jnci/92.6.464

[21] K. A. et al. (2016). The impact of high-risk HPV genotypes other than HPV 16/18 on the natural course of abnormal cervical cytology: a Korean HPV cohort study. *Cancer Research and Treatment 48(4),* 1313-1320.
DOI : 10.4143/crt.2016.013

[22] S. H. Kim et al. (2009). Factors related to human papilloma virus infection rate in women. *Korean Journal of Family Medicine 30(12),* 972-978.
DOI : 10.4082/kjfm.2009.30.12.972

[23] N. Muñoz et al. (2006). Chapter 1: HPV in the etiology of human cancer. *Vaccine 24 (Suppl 3),* S1-S10.
DOI : 10.1016/j.vaccine.2006.05.115

[24] S. J. Goldie et al. (2007). Cost-effectiveness of HPV 16, 18 vaccination in Brazil. *Vaccine 25(33),* 6257-6270.
DOI : 10.1016/j.vaccine.2007.05.058

**정 유 현(You Hyun Joung)** [정회원]

- 2018년 2월 : 아주대학교 보건대학원 역학과 (보건학석사)
- 1999년 4월 ~ 현재 : 동수원병원 해부병리과
- 2019년 3월 ~ 현재 : 단국대학교 임상병리과 겸임교수

- 관심분야 : 임상병리학, 조직병리학, 임상생리학, 보건통계, 융합기술학
- E-Mail : jyouhyun@naver.com

**이 준 민(Jun Min Lee)** [정회원]

- 2014년 8월 : 한국방송통신대학교 환경보건학과 (환경보건 학사)
- 2006년 6월 ~ 2015년 12월 : 동수원병원 진단검사의학과
- 2016년 1월 ~ 현재 : 장원의료재단 U2Labs 검사실장

- 관심분야 : 면역학, 분자진단
- E-Mail : minjae@naver.com

**김 종 완(Jong-Wan Kim)** [정회원]

- 1996년 2월 : 충남대학교 의학과 (의학박사)
- 1997년 3월 ~ 현재 : 단국대학교 의과대학 의학과 (교수)
- 관심분야 : 진단검사, 혈액학, 수혈학
- E-Mail : wan1818@paran.com

**김 재 경(Jae Kyung Kim)** [정회원]

- 2008년 2월 : 단국대학교 생물학과 (박사)
- 2015년 2월 ~ 현재 : 단국대학교 보건 과학대학 임상병리학과 교수
- 관심분야 : 조직병리, 진단세포학
- E-Mail : nerowolf@naver.com