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# Human Papillomavirus (HPV) Type Distribution in Korean Women: a Meta-Analysis

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**The aim of the present study is to estimate the overall prevalence and type distribution of human papillomavirus (HPV) in Korean women, through literature review and meta-analysis. We searched published data for the period between 1995 and 2007 using the following inclusion criteria; (1) studies using type-specific HPV tests, (2) data from Korean female, (3) with cytologic or pathologic results, (4) having more than 20 cases for each subgroup classified by cytologic results, and (5) HPV detection including types 16, 18, and at least one other type. In total, 18 studies (13,842 cases) published up to April 2007 were identified and selected. Adjusted overall HPV prevalence was 23.9% (95% CI: 23.8–24.1%) in women with normal cytology and 95.8% (95% CI: 95.4–96.2%) in women with cervical cancer. Type 16 was predominant regardless of cervical disease status, and type 58 occupied a significantly larger proportion in high-grade cervical intraepithelial lesions and cervical cancer in Korean women. HPV types 58, 33, and 52 together accounted for about 20% of infections in cervical cancer and high-grade intraepithelial lesions. After introduction of HPV prophylactic vaccines, extended protection, especially against types 58, 33, and 52, will be an important issue for cervical cancer prevention in Korea. The future dominant genotypes will require follow-up epidemiological studies with a large-scale, multicentered, and prospective design.**

**Keywords:** Human papillomavirus (HPV), polymerase chain reaction (PCR), cervical cancer, cervical intraepithelial neoplasia (CIN), prevalence

The era of a prophylactic human papillomavirus (HPV) vaccine has begun. The quadrivalent HPV vaccine protecting against cervical disease and external genital lesions caused by HPV types 6, 11, 16, and 18 was licensed for use in the United States by the Food and Drug Administration (FDA) in June 2006, and the bivalent HPV vaccine preventing cervical cancer and precancerous lesions caused by HPV types 16 and 18 was licensed for use in Australia by the Therapeutic Goods Administration in May 2007. To predict and evaluate the protective efficacy of HPV vaccines, the estimation of overall prevalence and type distribution of HPV is an important issue for every nation.

Previous meta-analyses showed a significant regional variation of overall prevalence and type distribution of HPV [2, 4–7]. According to the recent analysis of 85 studies for the HPV prevalence in cervical cancer, the overall HPV prevalence in cervical cancer was 87.6% [4]. HPV types 16 and 18 accounted for 70.7% of all cervical cancers worldwide, but the prevalence of other oncogenic types in cervical cancer varied by region. In Western countries and Africa, HPV types 45, 31, and 33 were the most prevalent genotypes after types 16 and 18. Yet in Asia, HPV types 58 and 52 were detected more frequently than types 45, 31, and 33 [2, 4].

In high-grade intraepithelial lesions (HSIL), the overall HPV prevalence was 84.2%, slightly lower than that of invasive cervical cancer [5]. The overall HPV prevalence in low-grade intraepithelial lesions (LSIL) was 71.1% [6]. HPV 16 was the most common type in both HSIL and LSIL, and the geographical variation in the prevalence of other types was more pronounced. The proportion of types 16 and 18 was inversely related to the severity of cervical lesions. However, these analyses for type-specific HPV prevalence in cervical precancerous lesions did not fully reflect the specific regional distribution. Asian data accounted for 16.7% of HSIL cases and only 3.0% of LSIL cases [5, 6].

In order to evaluate the HPV type distribution in Korean women, we carried out a pooled analysis of data from

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published studies stratified by the severity of cervical neoplastic diseases. This study also provides a comparison of HPV type distribution in Korean women with published data from other countries. In this meta-analysis, we focused on the following questions; (1) What is the overall and type-specific HPV prevalence stratified by cervical lesions of different severity ? (2) What is the prevalence of oncogenic HPV types other than types 16 and 18 in cervical precancerous or cancerous lesions ? (3) What are the characteristics of HPV infection in Korean women compared with those of other countries ?

## MATERIALS AND METHODS

### Study Selection and Data Abstraction

We searched the electronic bibliographic databases (*Pubmed* and *Medline* for international journals, *KMbase* and *KoreaMed* for publications written in Korean) and selected the source materials from identified articles published from 1995 to April 2007. The references cited in identified articles were selected by manual search. We used the following keywords in the *MeSH* database search: "human papillomavirus (HPV)", "papillomavirus infection", "cervical cancer", "cervical intraepithelial neoplasia (CIN)", "polymerase chain reaction (PCR)", "DNA probes, HPV", "human", and "female".

We selected studies for this meta-analysis using these inclusion criteria; (1) studies using type-specific HPV tests (PCR or HPV DNA chip), (2) data from Korean female, (3) including cervical cytologic or pathologic results, (4) including more than 20 cases for each subgroup classified by cytologic results; and (5) HPV detection including types 16, 18, and at least one other type. If data or data subsets were used in more than one article, then only the article with the largest sample size was included.

For each selected study, the following key variables were extracted; (1) sample size, (2) year of publication, (3) type of cervical specimen (biopsy, cytology, or combination), (4) method of HPV DNA detection, (5) results of cervical cytology or pathology, and (6) overall and type-specific HPV prevalence stratified by disease severity. The majority of these articles did not include detailed information on the region or age of the subjects, and most data for cervical cancers did not include detailed histopathologic information (cell origin, such as squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, *etc.*), so we did not include age, region, and further histopathologic classification of cervical cancers as key variables.

### Estimation of HPV Type Distribution

HPV genotype prevalence was expressed as a percentage of all cases tested for HPV and consisted of data from single or multiple infections. Data of multiple infections were not provided in some studies. All studies provided the information on HPV types 16 and 18.

For the HPV detection and genotyping, the most frequently used method was the HPV DNA Chip (Mygene Co., Seoul, South Korea), a PCR-based DNA microarray system [1, 3, 9, 11, 13, 15–17, 20–23, 26]. The HPV DNA chip contains 22 type-specific probes that consist of 15 high-risk groups (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 69). The genotyping experiment, including the preparation and testing of specimens, was performed using a procedure outlined in the manufacturer's protocol. Briefly, DNA was isolated from cervical specimens using a DNA isolation kit (Intron Biotech. Inc., Seoul, South Korea), and target HPV DNA was amplified by PCR with consensus GPd5+/d6+ primers (GP5d+, 5'-tttkttachgtkgtdgatacyac-3'; GP6d+, 5'-gaaahataaaytgyaadtcataytc-3'; k, g/t; h, t/a/c; d, a/t/g; y, t/c). β-Globin was amplified using PCR with PC03/PC04 primers (PC03, 5'-acacaactgtgttcactagc-3'; PC04, 5'-caacttcatccacgttcacc-3') as internal controls. Amplified DNA was labeled by indocarbocyanine-dUTP (NEM Life Science Products, Inc., Boston, MA, U.S.A.). The PCR product was hybridized onto the chip at 40°C for 2 h, and washed with 3×SSPE and with 1×SSPE for 2 min each. Hybridized signals were visualized with a DNA Chip Scanner (GSI Lumonics, Scanarray Lite, Ottawa, Canada). The HPV DNA chip can identify HPV infection in a type-specific manner as well as a multiple HPV infection (Fig. 1).

In two studies [8, 24], HPV DNA was tested using the oligoprobe cocktail, in the GP5+/6+ primer-mediated PCR-enzyme immunoassay (EIA) method described by Jacobs *et al.* [12] to detect the following 36 HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 6, 11, 26, 34, 40, 42, 43, 44, 53, 54, 55, 57, 61, 70, 71 (equivalent to CP8061), 72, 73, 81 (equivalent to CP8304), 82/IS39, 83 (equivalent to MM7), 84 (equivalent to MM8), and CP 6108.

In one study by Shin *et al.* [25], HPV DNA was amplified by the use of the short polymerase chain reaction (PCR) fragment SPF10 primer set, as described by Kleter *et al.* [14]. Amplification products were first tested by probe hybridization in a microtiter-plate assay, to detect the presence of HPV DNA. SPF10 amplimers from HPV-positive samples were subsequently analyzed by reverse hybridization in an HPV line-probe assay. PCR products are hybridized at high stringency to these probes, generating a type-specific hybridization pattern. This method permits specific detection of 25 genotypes: HPV types 6, 11, 16, 18, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52,

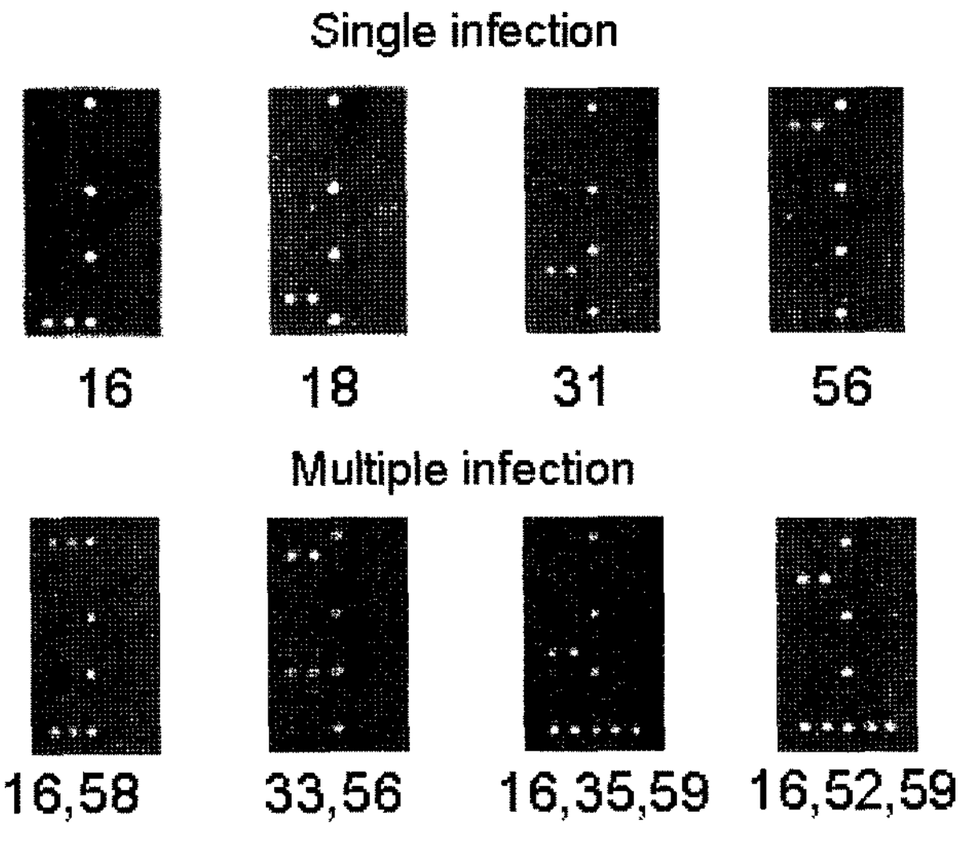



**Fig. 1.** The results of the HPV DNA Chip. For the HPV detection and genotyping, the HPV DNA chip was the most frequently used method (used in 13 studies).
The HPV DNA chip can identify a single HPV infection with more than 20 type-specific probes that consist of at least 15 high-risk groups (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 69) as well as multiple HPV infections in samples.

53, 54, 56, 58, 59, 66, 68/73, 70, and 74. Part of the β-globin gene from each sample was amplified as a positive control for DNA isolation.

HPV DNA chip and PCR-based HPV DNA tests using GP5+/6+ or SPF10 primers can identify more than 20 HPV genotypes. Therefore, all of them are classified as HPV type-specific tests with a broad spectrum.

In two studies [10, 18], HPV DNA types were identified by analyses of restriction fragment length polymorphism (RFLP) patterns and PCR using type-specific primers. HPV DNA was amplified using consensus PCR primers (sense, 5'-TGTCAAAAACCGTTG-TGTCC-3'; antisense, 5'-GAGCTGTCGCTTAATTGCTC-3') specific for the sequences within E6 and E7 open reading frames of HPV types 16, 18, 31, 33, 35, 52, and 58, to generate about 250-bp-long PCR products. Digestion of PCR products by restriction enzymes produced characteristic DNA banding patterns for each HPV type visualized by gel electrophoresis. Five different restriction enzymes (AvaII, AfaI, AvaI, BglII, and AccI) were used to digest PCR products in the study by Hwang [10], whereas only two restriction enzymes (AvaII and AfaI) were used in the study by Oh *et al.* [18]. AvaII digestion of PCR products can identify HPV types 16, 18, and 33. Digestion with AfaI, AvaI, BglII, and AccI can identify HPV types 31, 35, 52, and 58, respectively. After analyzing RFLP patterns, confirmation of HPV types was identified with PCR using type-specific primers for HPV 16, 18, 31, 33, 35, 52, and 58. In these two studies using the PCR-RFLP method, no more than eight HPV types were identified. Thus, they were classified as studies using HPV type-specific tests with a narrow spectrum.

Type-specific HPV prevalence data were stratified by disease severity. We stratified disease severity by cytologic or pathologic results into four subgroups; (1) subgroup 1 with normal cytology, (2) subgroup 2 with low-grade cervical lesions including atypical squamous cells of unknown significance (ASCUS), LSIL, and CIN 1, (3) subgroup 3 with high-grade cervical lesions including HSIL, CIN 2, 3 and carcinoma *in situ* (CIS), and (4) subgroup 4 with invasive cervical cancer (ICC). Sample size varied among the type-specific analyses, because only studies testing for particular HPV types contribute to the analysis of that type, and multiple HPV infections were separated into each type. Thus, the sample size varied in each type-specific analysis.

### Statistical Analyses

Type-specific HPV prevalence was expressed as a crude proportion for each subgroup with different disease severity. Sources of variation in overall HPV prevalence were introduced into an unconditional multiple logistic regression analysis, and the final model included the following: year of publication, type of cervical specimen, and method of HPV DNA detection. The adjusted overall HPV prevalence and 95% confidence intervals of four subgroups stratified with disease severity were estimated by adjusting variables found to be significant in the final model. *P*-Value comparing the type-specific HPV prevalence referred to the Chi-square ($\chi^2$) test. Prevalence of the five most common HPV types was compared among subgroups by odds ratio (reference: subgroup 1) with 95% confidence intervals.

## Results

A total of 13,842 cases from 18 studies were included in this study [1, 3, 8–11, 13, 15–18, 20–26]. The study size ranged from 100 to 2,470 cases. All studies included in this analysis were cross-sectional studies, with concomitant cervical cytology and HPV testing. Detailed data of HPV type distribution are presented stratified by disease severity (Tables 1 and 2).

### Overall HPV Prevalence

The crude overall HPV prevalence was 20.4%, 63.2%, and 85.6% in normal cytology, and low- and high-grade lesions, respectively. In ICC, the crude overall prevalence of HPV infection was 88.3%. The adjusted overall prevalence of HPV infection in normal cytology was increased to 23.9% (95% CI: 23.8–24.1%). This is higher than the 15% rate in the world [19]. The adjusted overall prevalence of HPV infection in ICC was also increased to 95.8% (95% CI: 95.4–96.2%).

In the cases with invasive cervical cancer, the adjusted overall HPV prevalence ranged between 95.4% and 96.2% for the different detection methods (broad *vs.* narrow spectrum) or specimens (cytology only *vs.* biopsy only *vs.* both), although these differences were not statistically significant. In cases with high-grade lesions, the adjusted overall HPV prevalence obtained from broad-spectrum detection methods was significantly higher (86.9% *vs.* 66.8%) than that from narrow-spectrum methods ($P<0.05$).

### Type-Specific HPV Prevalence

HPV 16 was the most common type in Korean women regardless of cervical disease status (Table 2). In invasive

**Table 1.** The overall HPV prevalence of subgroups stratified by disease severity.

| Disease severity | Number of studies | Number of cases | Crude HPV prevalence (%) | Adjusted HPV prevalence (%) | 95% CI (%) |
|---|---|---|---|---|---|
| Subgroup 1 (Normal cytology) | 16 | 9,579 | 20.4 | 23.9 | 23.8–24.1 |
| Subgroup 2 (Low-grade lesions[a]) | 15 | 2,620 | 63.2 | 60.0 | 59.5–60.2 |
| Subgroup 3 (High-grade lesions[b]) | 14 | 1,027 | 85.6 | 85.8 | 85.2–86.5 |
| Subgroup 4 (Invasive cervical cancer) | 10 | 616 | 88.3 | 95.8 | 95.4–96.2 |

[a]Those including ASCUS, LSIL, and CIN1.
[b]Those including HSIL, CIN 2, 3, and CIS.
CI: confidence interval.

**Table 2.** The type-specific HPV prevalence stratified by disease severity.

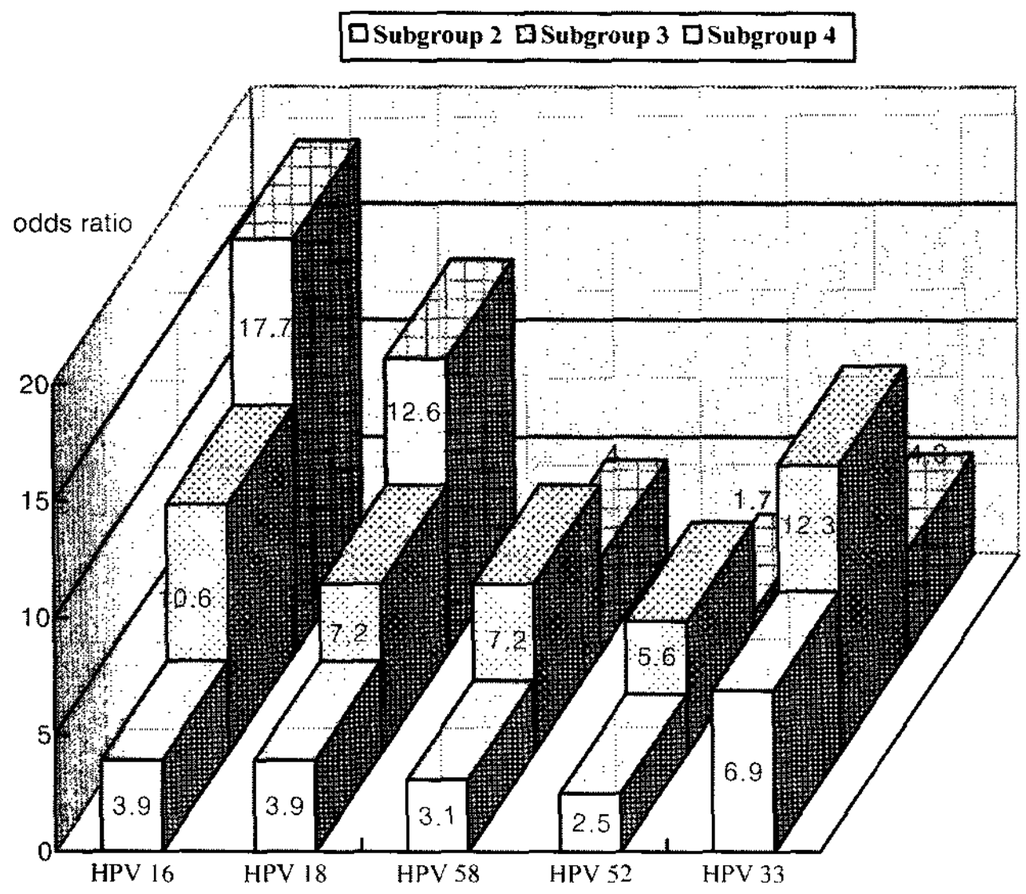
| | Number of cases (%) | | | |
|---|---|---|---|---|
| | Subgroup 4[a] (n=616) | Subgroup 3[b] (n=1027) | Subgroup 2[c] (n=2620) | Subgroup 1[d] (n=9579) |
| HPV any | 88.3% | 85.6% | 63.2% | 20.4% |
| High-risk HPV | 84.6% | 83.7% | 56.3% | 16.7% |
| HPV 16 | 53.2% | 40.6% | 20.0% | 6.0% |
| HPV 18 | 11.9% | 7.2% | 4.0% | 1.0% |
| HPV 58 | 8.6% | 14.1% | 7.4% | 2.3% |
| HPV 33 | 3.7% | 4.9% | 2.7% | 0.4% |
| HPV 52 | 3.4% | 5.0% | 4.1% | 0.9% |
| HPV 35 | 3.1% | 4.1% | 2.2% | 0.4% |
| HPV 31 | 1.9% | 3.0% | 1.7% | 0.4% |
| HPV 45 | 1.7% | 1.2% | 0.6% | 0.2% |
| HPV 56 | 1.6% | 2.7% | 2.5% | 0.9% |
| HPV 59 | 1.2% | 0.6% | 0.3% | 0.2% |
| Low-risk HPV | 4.1% | 5.4% | 7.5% | 3.8% |

[a]Those including invasive cervical cancer.
[b]Those including HSIL, CIN 2, 3, and CIS.
[c]Those including ASCUS, LSIL, and CIN 1.
[d]Those including normal cytology.

cervical cancer, types 16 and 18 accounted for 65.1% of the cases, and the five most common types (HPV 16, 18, 58, 33, and 52) accounted for 80.8% of all ICC cases.

In high-grade cervical lesions, a similar sequence pattern of HPV type-specific prevalence was found. HPV types 16, 58, 18, 52, and 33 were the five most common types in high-grade lesions, and they accounted for 71.8% of all high-grade lesion cases. Noteworthily, HPV 58 was the second most prevalent type in high-grade lesions, and HPV types 16, 58, and 18 accounted for 62.0% of the cases. In low-grade lesions, HPV types 16, 58, 18, 52, and 33 were still the five most common types. The ranking is exactly the same for high- and low-grade lesions. HPV 16 accounted for 20.0%, and the combined proportion of types 16, 58, and 18 was 31.4%. In women with normal cytology, HPV types 16, 58, 18, 51, and 52 were the five most prevalent types, with HPV 16 accounting for 6.0%.

The odds ratio and corresponding 95% confidence intervals for the prevalence of the five most common HPV types are presented in Fig. 2. HPV types 16, 18, and 58 were predominant types in cervical neoplastic lesions. Further comparison showed that HPV types 16 and 18 were significantly more common in invasive cancer, whereas types 58, 52, and 33 were more frequent in high-grade lesions.




| | Subgroup 2[a] | Subgroup 3[b] | Subgroup 4[c] |
|---|---|---|---|
| HPV 16 | 3.9 (95% CI: 3.4–4.4) | 10.6 (95% CI: 9.1–12.3) | 17.7 (95% CI: 14.8–21.1) |
| HPV 18 | 3.9 (95% CI: 2.9–5.1) | 7.2 (95% CI: 5.3–9.8) | 12.6 (95% CI: 9.2–17.2) |
| HPV 58 | 3.1 (95% CI: 2.5–3.8) | 7.2 (95% CI: 5.8–9.1) | 4.0 (95% CI: 2.9–5.5) |
| HPV 33 | 6.9 (95% CI: 4.7–10.2) | 12.3 (95% CI: 8.1–18.8) | 4.3 (95% CI: 2.2–8.5) |
| HPV 52 | 2.5 (95% CI: 1.8–3.5) | 5.6 (95% CI: 3.9–8.0) | 1.7 (95% CI: 0.9–3.4) |

[a]Those including ASCUS, LSIL, and CIN1.
[b]Those including HSIL, CIN 2, 3, and CIS.
[c]Those including invasive cervical cancer.

**Fig. 2.** Odds ratio and corresponding 95% CI for the prevalence of the five most common HPV types in cervical neoplastic lesions compared with those of normal cytology (subgroup 1).

## DISCUSSION

### Overall HPV Prevalence

This meta-analysis included data on the overall and type-specific HPV prevalence in 13,842 Korean women, notably the largest number of cases compared with those of previous reviews.

The overall HPV prevalence was 95.8% in invasive cervical cancer, but was lower compared with the almost 100% HPV prevalence identified in studies using the most sensitive HPV detection method [27]. This was probably caused by the inclusion of studies using HPV DNA detection methods of suboptimal sensitivity. The results here might be lower than the reality.

In Korean women, the overall HPV prevalence in high- and low-grade cervical intraepithelial lesions was similar to that previously reported (84.2% and 67.1%, respectively) [5, 6].

In normal cytology, the adjusted overall prevalence of HPV was 23.9%, and was much higher than that previously reported (13.3%) [7]. We assumed that most data were recruited from hospital-based subjects, and some studies using detection methods with suboptimal accuracy resulted in the underestimation of HPV prevalence in the normal population.

**Type-Specific HPV Prevalence**

HPV 16 was the most prevalent type in Korean women regardless of the disease status of the cervix. In invasive cervical cancer, HPV types 16 and 18 accounted for 65.1%, and HPV 58 was the third most common type. In high-grade lesions, types 16 and 18 accounted for 47.8%, and the proportion of HPV 58 was higher compared with that in invasive cancer (14.1% *vs.* 8.6%). Our results suggest that the estimated preventive effects of HPV prophylactic vaccines would be 65% in invasive cervical cancer and 48% in high-grade cervical intraepithelial disease, with the assumptions of nationwide vaccination, 100% coverage, 100% efficacy, and no cross-protection. After types 16 and 18, types 58, 33, and 52 were the most prevalent in Korean women. According to this study, the extended prevention of the future HPV vaccine including HPV types 16, 18, 58, 33, and 52 could cover about 80% of cervical cancers, 70% of high-grade cervical neoplastic lesions, and 20% of low-grade cervical neoplastic lesions.

In low-grade lesions, HPV 16 was the most common type and the proportion of types 16 and 18 was 24.0%. In previous studies with data mainly from Europe, and North and South America, HPV types 31, 51, 53, 56, 18, 66, and 58 were the prevalent types after HPV 16 in LSIL [6]. However, in this study, the fraction of HPV types 58, 18, 52, and 33 was relatively important in LSIL.

Odds ratios for infection with the five most common HPV types (types 16, 18, 58, 33, and 52) among cervical neoplastic diseases (invasive cancer, high- and low-grade neoplastic lesions) were compared with normal cytology as the reference. HPV types 16 and 18 appeared to be more important than types 58, 33, and 52 in invasive cancers, whereas the relative importance of types 58, 33, and 52 was intensified in HPV infection of high-grade lesions. HPV types 58 and 52 occupied a relatively higher portion in HPV infection of Korean women compared with those of women in other countries [4–7].

**Study Strengths and Limitations**

This meta-analysis combined type-specific HPV data from the largest number of published studies relating to Korean women, each performing HPV testing using well-validated PCR primers or the DNA chip. Our finding presents a broad overall estimate of HPV prevalence and type distribution in Korean women stratified by grade of cervical neoplasia. With the relatively large sample size and systematic literature review, the result is more likely to be representative of the Korean situation. Our understanding of the overall and type-specific HPV prevalence in Korean women is thus enhanced.

The individual HPV detection methods used by the studies included in this analysis showed different levels of accuracy, and such variation can be a potential source of bias. Since many studies tested only a subset of individual HPV types, information on multiple HPV infections was not provided. These missing data restrict our understanding of the prevalence of multiple infections in cervical disease with different grades and individual HPV types as co-factors in oncogenicity. Another weakness is the lack of standardized cytopathologic diagnostic tools across studies, resulting in the limitation associated with the cross-sectional meta-analysis of HPV distribution.

Only a small number of studies reported HPV type-specific prevalence in adenocarcinoma. Therefore, HPV type distribution, especially the fraction contributed by HPV 18, and the difference between adenocarcinoma and squamous cell carcinoma in Korean women cannot be specified. The prevalence of high-risk HPV, and the fraction of HPV 16 and HPV 18, could be higher if more sensitive HPV detection techniques are used [27].

In conclusion, our finding is a broad summary of HPV type distribution in Korean women with different grades of cervical lesions. Although the analysis confirmed the importance of HPV types 16 and 18, in comparison with previous reports from other countries, the prevalence of HPV types 58, 33, and 52 is remarkably higher in invasive cancer and high-grade cervical neoplasia in Korean women. Nationwide HPV vaccination with the soon-to-be available prophylactic vaccine can provide potential protection against 65% of invasive cervical cancer and 48% of high-grade cervical neoplasias. The preventive effect of HPV prophylactic vaccines could be increased if extended protection against HPV types 58, 33, and 52 were to be included in the future generation of HPV vaccines. Further studies with large-scale, multicentered, and prospective design will be required to fully understand the changing HPV pattern in Korean women, and to evaluate the potential efficacy of the next generation of HPV prophylactic vaccines.

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