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Position Statement



# High-risk human papillomavirus testing as a primary screening for cervical cancer: position statement by the Korean Society of Obstetrics and Gynecology and the Korean Society of Gynecologic Oncology



**Tae-Wook Kong**,[1] **Miseon Kim**,[2] **Young-Han Kim**,[3] **Yong Beom Kim**,[4] **Jayeon Kim**,[5] **Jae-Weon Kim**,[6] **Mi Hye Park**,[7] **Joo Hyun Park**,[8] **Jeong Ho Rhee**,[9] **Myong Cheol Lim**,[10] **Joon-Seok Hong**[4]

[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Ajou University School of Medicine, Suwon, Korea
[2]Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, CHA University School of Medicine, Seoul, Korea
[3]Department of Obstetrics and Gynecology, Institute of Women's Life Medical Science, Yonsei University College of Medicine, Seoul, Korea
[4]Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam, Korea
[5]Department of Obstetrics and Gynecology, CHA Seoul Fertility Center, CHA University School of Medicine, Seoul, Korea
[6]Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Korea
[7]Department of Obstetrics and Gynecology, College of Medicine, Ewha Womans University, Seoul, Korea
[8]Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[9]Department of Obstetrics and Gynecology, Keimyung University School of Medicine, Daegu, Korea
[10]Cancer Healthcare Research Branch and Center for Uterine Cancer, Research Institute and Hospital, National Cancer Center, Goyang, Korea

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**Correspondence to**
**Miseon Kim**
Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, CHA University School of Medicine, 566 Nonhyeon-ro, Gangnam-gu, Seoul 06135, Korea.
E-mail: miseonkim@chamc.co.kr

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**ORCID iDs**
Tae-Wook Kong
https://orcid.org/0000-0002-9007-565X
Miseon Kim
https://orcid.org/0000-0002-5118-9275
Young-Han Kim
https://orcid.org/0000-0003-0645-6028

## ABSTRACT

Based on emerging data and current knowledge regarding high-risk human papillomavirus (hrHPV) testing as a primary screening for cervical cancer, the Korean Society of Obstetrics and Gynecology and the Korean Society of Gynecologic Oncology support the following scientific facts:

- Compared to cytology, hrHPV screening has higher sensitivity and detects more cases of high-grade cervical intraepithelial neoplasia.
- Qualified hrHPV testing can be considered as an alternative primary screening for cervical cancer to the current cytology method.
- The starting age of primary hrHPV screening should not be before 25 years because of possible overtreatment in this age, which has a high human papillomavirus (HPV) prevalence but rarely progresses to cancer. The screening interval should be no sooner than every 3 years and no longer than every 5 years.
- Before the introduction of hrHPV screening in Korea, research into comparative effectiveness of primary hrHPV screening for cervical cancer should be conducted to determine the appropriate HPV assay, starting age, and screening interval.

Yong Beom Kim
https://orcid.org/0000-0003-1196-369X
Jae-Weon Kim
https://orcid.org/0000-0003-1835-9436
Myong Cheol Lim
https://orcid.org/0000-0001-8964-7158

**Conflict of Interest**
No potential conflict of interest relevant to this article was reported.

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**Keywords:** Uterine Cervical Neoplasms; Cancer Screening Tests; Human Papillomavirus DNA Tests

## HIGH-RISK HUMAN PAPILLOMAVIRUS (hrHPV) INFECTION AND CARCINOGENESIS IN THE CERVIX UTERI

The human papillomaviruses (HPVs) consist of a heterogeneous group of capsid-enclosed double-stranded DNA viruses from the *Papillomaviridae* family that have a histological tropism for squamous epithelium [1]. The HPV genome is composed of the following 3 major regions: the early (E) region encoding nonstructural proteins, the late (L) region encoding the 2 capsid proteins, and the noncoding long control region that regulates viral replication and gene expression [2,3]. E5, E6, and E7 directly promote cellular transformation and alter pathways related to the immune response. The most notable activity of E6 is degradation of the tumor suppressor protein p53 via the proteasome pathway, and the E7 protein binds to the hypophosphorylated form of retinoblastoma protein and promotes its degradation via the ubiquitin-proteasome pathway.

Recently, more than 170 HPV types have been isolated and characterized [4]. Among them, the International Agency for Research on Cancer Monographs classified these hrHPV (HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, and HPV59) as group 1 carcinogens for cervical cancer [5-7]. HPV16 and HPV18 are the most common carcinogenic types within this group and are responsible for approximately 50% and 20% of cervical cancer, respectively [8]. The major steps in cervical carcinogenesis are HPV infection in cervical basal cells, progression to a precancerous lesion, and cancer invasion (**Fig. 1**).

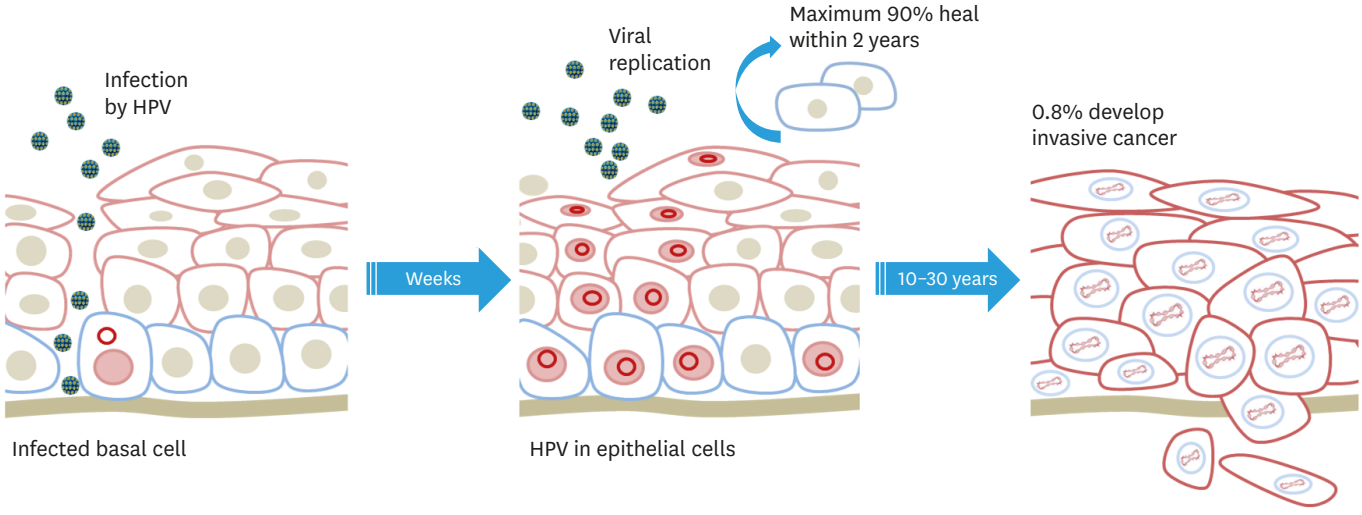


**Fig. 1.** Progression of cervical disease after human papillomaviruses infection.
HPV, human papillomavirus.


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## SCREENING STRATEGIES FOR HPV-ASSOCIATED CERVICAL DISEASE

Cervical cancer is the 4th most frequent cancer and the 4th leading cause of cancer death in women, with an estimated 570,000 cases and 311,000 deaths in 2018 worldwide [9]. In Korean women, cervical cancer is the 7th most common malignancy, and the incidence rate is still higher than that in other developed countries [10]. Based on cytology-based screening (Papanicolaou smear or liquid-based cytology) for cervical cancer, the incidence and associated mortality of cervical cancer have continued to decrease worldwide [11-13]. Since the introduction of the national cervical cancer screening program in 1999 in Korea, the incidence rate of cervical cancer has also steadily decreased from 16.3/100,000 to 9.1/100,000 in 2015 [14]. In 2015, the National Cervical Cancer Screening Guideline Development Committee, which is composed of experts from the Korean Society of Gynecologic Oncology, the Korean Society for Cytopathology, the Korean Society for Preventive Medicine, and the Korean Academy of Family Medicine, recommended a cytology-based screening for cervical cancer every 3 years in women older than 20 years old [15]. However, this cytology-based screening has a sensitivity of 51%–53% in detecting high-grade cervical intraepithelial neoplasia (CIN) [16-18].

Cytology depends on the morphological analysis of cervical exfoliated cells. Compared to cytology, HPV testing does not depend on morphological analysis and is commonly based on the detection of HPV DNA or mRNA. With the understanding of the causal relationship between hrHPV infection and cervical carcinogenesis, the Atypical Squamous Cells of Undetermined Significance/Low Grade Squamous Intraepithelial Lesion Triage Study showed that reflex hrHPV testing of the cytological category of "atypical squamous cells of undetermined significance" (ASCUS) resulting in a triage of colposcopy can be a feasible alternative to cytology alone [19]. The HPV triage test has been considered the preferred management for women with ASCUS on cytology since the early 2000s [20]. In 2003, the US Food and Drug Administration (US-FDA) approved the use of HPV testing as a reflex test in women over 21 years with ASCUS and as an adjunctive test in women over 30 years. Currently, the US-FDA approves the use of Cobas® HPV (Roche Diagnostics, Basel, Switzerland) and Onclarity® HPV (BD, Franklin Lakes, NJ, USA) as primary screening tests for cervical cancer. In Korea, Cobas® HPV has been approved as a primary screening test for cervical cancer. However, in 2015, the National Cervical Cancer Screening Guideline Development Committee stated that the existing evidence regarding the advantages and disadvantages of primary HPV testing is very low and the level of evidence regarding the effects of HPV/cytology co-testing is moderate [15].

## SCIENTIFIC EVIDENCE OF hrHPV TESTING AS A PRIMARY SCREENING

The first randomized controlled trial (RCT) found that HPV screening had a higher sensitivity (95%) in detecting high-grade CIN than cytology (55%) [21]. RCTs discussed in this study are summarized in **Table 1**. Four European RCTs (Swedescreen, Population-Based Screening Study Amsterdam, A Randomized Trial in Screening to Improve Cytology [ARTISTIC], and New Technologies for Cervical Cancer Screening [NTCC]) showed that earlier HPV-based screening in patients detects persistent high-grade CIN with higher sensitivity than cytology, thus the incidence of high-grade CIN was lower after HPV screening than after cytology [22-29]. Furthermore, a pooled analysis of these European RCTs found that HPV screening


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**Table 1.** Results of randomized controlled trials of high-risk human papillomavirus screening, with or without co-testing

| Study | No. of participants | Ages included (yr) | Screening interval (yr) | Arms | Criteria for immediate colposcopy | Absolute detection (%) | | Colposcopy referral rate (%) | Follow-up period (maximum, yr) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | CIN3+ | Cancer | | |
| Swedescreen [22] | 12,527 | 32–38 | 3 | Conventional cytology | ASCUS+ | 55/6,270 (0.9) | NR | NR | Mean: 4.1 |
| | | | | hrHPV with conventional cytology | ASCUS+ | 72/6,257 (1.2) | NR | NR | |
| POBASCAM [23-25] | 44,938 | 29–61 | 5 | Conventional cytology | HSIL+ | 150/20,106 (0.7) | 6/20,109 (0.03) | NR | 9.0 |
| | | | | hrHPV with conventional cytology | HSIL+ | 171/19,999 (0.9) | 12/19,999 (0.06) | NR | |
| ARTISTIC [26,27] | 24,510 | 20–64 | 3 | LBC | HSIL+ | 81/6,124 (1.3) | 4/6,124 (0.07) | 320/6,124 (5.2) | 4.5 |
| | | | | hrHPV with LBC | HSIL+ | 233/18,386 (1.3) | 5/18,386 (0.03) | 1,247/18,386 (6.8) | |
| NTCC [28,29] | 49,196 | 25–60 | 3 | Conventional cytology | ASCUS+ or LSIL+ | 33/24,535 (0.1) | NR | 679/25,435 (2.8) | 7.0 |
| | | | | hrHPV | hrHPV+ | 97/24,661 (0.4) | NR | 1,936/24,661 (7.9) | |
| HPV FOCAL [44-47] | 19,000 | 25–65 | 4 | LBC with hrHPV triage | ASCUS+ and hrHPV+ (or, for cytology only, ASC-H or LSIL+) | 41/9,408 (0.4) | NR | 290/9,408 (3.1) | 4.0 |
| | | | | hrHPV with LBC triage | hrHPV+ and ASCUS+ | 67/9,540 (0.7) | NR | 544/9,540 (5.7) | |
| FINNISH [48] | 203,425 | 25–65 | 5 | Conventional cytology | LSIL+ | 118/65,784 (0.2) | 9/65,784 (0.01) | 755/65,784 (1.1) | 5.0 |
| | | | | hrHPV with conventional cytology triage | hrHPV+ and LSIL+ | 195/66,410 (0.3) | 17/66,410 (0.03) | 796/66,410 (1.2) | |
| Compass [49] | 4,995 | 25–64 | 2.5 | LBC | ASC-H+/HSIL+ | 1/995 (0.1) | 0/995 (0) | 27/995 (2.7) | 2.5 |
| | | | 5 | hrHPV with LBC triage | HPV16/18+, other hrHPV+ with LSIL or ASC-H+ or p16/Ki-67+ | 30/4,000 (0.8) | 0/4,000 (0) | 154/4,000 (3.8) | 5.0 |
| ATHENA [31] | 40,901 | ≥25 | 3 | Cytology | ASCUS+ or hrHPV+ | 179/45,156 (0.4) | NR | 1,934/45,156 (4.3) | 3.0 |
| | | | | HPV primary | | 294/52,651 (0.6) | NR | 3,769/52,651 (7.2) | |
| | | | | Hybrid strategy* | | 240/82,994 (0.3) | NR | 3,097/82,994 (3.7) | |

ARTISTIC, A Randomized Trial in Screening to Improve Cytology; ASCUS, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ATHENA, Addressing THE Need for Advanced HPV Diagnostics; CIN, cervical intraepithelial neoplasia; hrHPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; HPV, human papillomavirus; HPV FOCAL, Human Papillomavirus for Cervical Cancer Screening; LBC, liquid-based cytology; LSIL, low-grade squamous intraepithelial lesion; NR, not reported; NTCC, New Technologies for Cervical Cancer Screening; POBASCAM, Population-Based Screening Study Amsterdam.
*A hybrid strategy uses the cytology strategy for women 25–29 years old and co-testing with both cytology and HPV (pooled 14 genotypes) in women ≥30 years.

provides 60%–70% greater protection against cervical cancers than cytology [30]. In the USA, the Addressing THE Need for Advanced HPV Diagnostics (ATHENA) trial showed higher sensitivity in detecting CIN3+ (CIN3 and cervical cancer) in the HPV primary strategy group than in the cytology strategy group (76.1% vs. 47.8%) in 2015 [31]. Women in the HPV primary strategy group underwent colposcopy if they were found positive for HPV16 or HPV18 (or underwent reflex cytology if other types of HPV were positive) in the ATHENA trial.

Three-year risks for CIN3+ following a negative result in hrHPV screening or HPV/cytology co-testing were significantly lower than those of cytology alone in the ATHENA trial and Gage's study [31,32]. A US Preventive Services Task Force (US-PSTF) systematic review also found that hrHPV screening detected CIN3+ with a higher rate than cytology. However, HPV/cytology co-testing did not increase the detection rate of CIN3+ [33]. Instead, hrHPV screening and HPV/cytology co-testing both increased the number of diagnostic colposcopies [33].

Randomized trials for primary HPV screening have not yet been published in Korea. In 2016, Choi et al. [34] retrospectively compared the clinical performance of primary HPV screening, HPV/cytology co-testing, and cytology alone using 1,000 cervical samples. The sensitivity was calculated using CIN2+ with colposcopy biopsy as the gold standard, and the sensitivities of primary HPV screening, HPV/cytology co-testing, and cytology alone were 71.7%, 72.5%, and 63.8%, respectively.


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## OTHER CURRENT RECOMMENDATIONS: STARTING AGE AND SCREENING INTERVAL

Guidelines for cervical cancer screening in several countries are summarized in **Table 2**. The National Institute for Public Health and the Environment in the Netherlands revealed that the HPV screening for women aged 30–60 years every 5 years was the primary screening method in their national cervical cancer screening program [35]. Moreover, in Australia, the Papanicolaou test performed biannually for women aged 18–69 years has been replaced by HPV screening performed once in 5 years for women aged 25–74 years [36]. However, the ideal starting age and screening interval of primary HPV screening are still under investigation. The Society for Gynecologic Oncology and the American Society for Colposcopy and Cervical Pathology issued interim guidelines recommending primary HPV screening as an acceptable approach in women 25–65 years old based on the ATHENA trial [37]. Although disease detection increases, there are concerns about potential disadvantages, such as unwarranted diagnostic colposcopies, of primary hrHPV screening before the age of 25 years. Several diseases detected in this age group can be safely treated up until the age of 30 years [38-40]. Therefore, general guidelines have recommended less aggressive management for cervical abnormalities in these age groups, and most RCTs enrolled their study populations based on this evidence [41].

Gage et al. [32] compared the 3- and 5-year risks of cervical cancer in women with negative hrHPV screening and negative HPV/cytology co-testing. The 3-year risk in women with a hrHPV-negative result was lower than the 5-year risk in women with a cytology-negative/

**Table 2.** Guidelines for cervical cancer screening in different countries

| Country | Screening ages (yr) | Primary screening test and interval | Use of hrHPV screening |
|---|---|---|---|
| Australia [36] | 25–69 | hrHPV screening with partial HPV genotyping and reflex LBC triage every 5 yr | - |
| Canada [50,51] | 25–69 | Cytology every 3 yr | With regional variation and rollout of primary HPV screening in pilot studies |
| England [52,53] | 25–49 | hrHPV screening every 3 yr | - |
| | 50–64 | hrHPV screening every 5 yr | - |
| Germany [52,54] | ≥20 | Cytology annually | HPV primary testing in implementation, HPV triage testing [55] |
| Netherlands [35] | 30–64 | hrHPV screening every 5 yr | - |
| Singapore [56] | 25–29 | Cytology every 3 yr | - |
| | 30–69 | hrHPV screening every 5 yr | - |
| Sweden [52] | 23–50 | hrHPV screening every 3 yr | - |
| | 51–60 | hrHPV screening every 5 yr | - |
| USA | | | |
| ACS/ASCCP/ASCP (2012) [57] | 21–29 | Cytology every 3 yr | - |
| | 30–65 | Co-testing every 5 yr (preferred)<br>Cytology every 3 yr | - |
| Interim guidance (2015) [58] | ≥25 | - | hrHPV screening with genotyping |
| US-PSTF (2018) [42] | 21–29 | Cytology every 3 yr | - |
| | 30–65 | Cytology every 3 yr (preferred)<br>hrHPV screening every 5 yr (preferred)<br>Co-testing every 5 yr | - |

ACS, American Cancer Society; ASCP, American Society for Clinical Pathology; ASCCP, American Society for Colposcopy and Cervical Pathology; hrHPV, high-risk human papillomavirus; HPV, human papillomavirus; LBC, liquid-based cytology; US-PSTF, US Preventive Services Task Force.


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hrHPV-negative co-testing result (0.011% vs. 0.014%, p=0.21). These results show that hrHPV screening with a 3-year interval is at least as effective as a 5-year interval co-testing. The guidelines issued in September 2018 by the US-PSTF confirmed a similar protocol, recommending HPV screening or HPV/cytology co-testing every 5 years for women aged 30–65 years [42]. In the US-PSTF systematic review, a microsimulation model suggested similar life-years achieved by HPV screening with 3- and 5-year intervals, but in a 3-year interval, several tests and procedures were required [43]. A pooled analysis of European RCTs also showed that 5-year intervals for HPV screening were safer than 3-year intervals for cytology [30]. However, 3 (Swedescreen, ARTISTIC, NTCC) of the 4 European RCTs utilized 3-year screening intervals and follow-up data based on the ATHENA trial [22,27,29,31].

## CONCLUSION

For almost 2 decades, scientific evidence from large-scale epidemiological studies has established the diagnostic and preventive value of primary hrHPV screening for high-grade CIN and cervical cancer. However, there are still several challenges in the introduction of hrHPV screening in Korea. First, direct cost-effectiveness comparisons among primary hrHPV screening, cytology, and HPV/cytology co-testing are required. Comparative effectiveness studies that consider the starting age, screening interval, and follow-up visits for primary hrHPV screening are also necessary. These studies may be time-consuming and will likely require significant effort. Nevertheless, the scientific evidence for hrHPV screening should be strongly considered, and we should consider integrating hrHPV screening with published screening and treatment guidelines and comprehensively discuss this new strategy to healthcare providers and patients.

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