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Updates of the current screening guidelines for the early detection of cervical cancer

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Recently, consensus guideline for the early detection of cervical cancer in Korea has been developed and published. It was developed based on preexisting guidelines, including 2006 American Society for Colposcopy and Cervical Pathology (ASCCP) consensus guidelines. However, some consensus guidelines have recently revised and updated in line with the issuance of our guidelines, such as ASCCP, American Cancer Society guidelines. Unfortunately, these updated contents were not reflected in our guidelines. In addition, Cochrane Gynaecological Cancer Group published their meta-analyses data on human papillomavirus testing versus repeat cytology for triage of atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesion cytology. Therefore, in the following context, we will discuss on the updated contents, differences from our guidelines, and future research recommendations.

Keywords: Cytology, Guideline, Human papillomavirus

Recently, practice guideline for the early detection of cervical cancer in Korea has been released in this journal [1]. It was developed based on preexisting guidelines generated by the American Society for Colposcopy and Cervical Pathology (ASCCP) [2], the National Comprehensive Cancer Network [3], the United States Preventive Services Task Force [4], and the Institute for Clinical Systems Improvement [5]. Coincidentally, updated versions of ASCCP guideline [6] and American Cancer Society (ACS) guideline [7] have been issued around the same time. Therefore, the updated contents of the above-mentioned guidelines are not reflected in ours. The essential changes of the 2012 ASCCP guidelines from prior 2006 version are as follows [6]: 1) cytology reported as negative but lacking endocervical cells can be managed without any repeat, 2) cytology reported as unsatisfactory requires repeat even if human papillomavirus (HPV) is negative, 3) For atypical squamous cells of undetermined significance (ASC-US) cytology, immediate colposcopy is not an option. The serial cytology option for ASC-US incorporates cytology at 12 months, and then if negative, cytology every 3 years, 4) ASC-US and HPV-negative results should be followed with co-testing at 3 years rather than 5 years, 5) ASC-US and HPV-negative results are insufficient to allow exit from screening at age 65 years, 6) women aged 21–24 years are managed conservatively.

Recently reported rates of cytology results reported as negative but lacking endocervical cells have ranged from 10% to 20% [8]. Prior guidelines recommended early repeat cytology [9]. A recent meta-analysis found that negative cytology had favorable specificity and negative predictive value despite absent endocervical cell component [10]. Given that most cytology is performed using liquid-based media, unsatisfactory cytology results arise mainly from insufficient squamous cells [11]. The 2012 ASCCP guidelines recommended repeat cytology in 2 to 4 months for women with an unsatisfactory cytology result. Those two issues regarding specimen adequacy were not included in our guidelines.

The management of women with ASC-US has also been

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revised in 2012 ASCCP guidelines. Immediate colposcopy recommended by prior guidelines is no longer an acceptable option. HPV testing is preferred, but repeat cytology in 1 year is also acceptable. If HPV is positive, colposcopy is recommended, same as the management of women with low-grade squamous intraepithelial lesion (LSIL). If HPV is negative, women can return to routine screening in 3 years, which is also supported by the updated ACS guidelines. Of note, interval of repeat cytology was extended from 6 months to 1 year. ASC-US-LSIL Triage Study (ALTS) was performed before the 2001 Bethesda system update, which separate ASC-H cytology from the ASC-US category. For this reason, the observed 3% 5-year risk of cervical intraepithelial neoplasia (CIN) 3+ after ASC-US among women aged 30 years and older was lower than the 2-year risk seen in ALTS. As a matter of fact, risk was low enough to justify annual rather than semiannual cytology as sufficiently sensitive to identify women with CIN 3+ [12]. Data from published studies have shown that the risk of precancerous lesions following an ASC-US, HPV-negative result is very low, and not qualitatively different from a negative co-test. The updated ACS guidelines recommend a 3-year interval for cytology screening of women aged 21–29 years or 30–65 years, and a 5-year interval for co-testing of women aged 30–65 years. Recently, Cochrane Gynaecological Cancer Group published their meta-analyses data on HPV testing versus repeat cytology for triage of ASC-US and LSIL cytology [13]. Of 2,938 references identified, 39 different studies were identified, allowing computation of the accuracy of hybrid capture 2 (HC 2) triage in women with ASC-US, and 24 studies were used to evaluate the accuracy of HC 2 in triage of LSIL women. For HC 2 triage in ASC-US cases, the pooled sensitivity and specificity for detection of CIN 2+ was 90.9% and 60.7%, respectively. For cytology triage in ASC-US cases, the pooled sensitivity with the test threshold was ASC-US+ was 71.5% (95% confidence interval [CI], 62.9 to 78.8). The pooled specificity of repeat cytology with test threshold was ASC-US+ was 68.4% (95% CI, 59.9 to 75.8). Triage of ASC-US cases with HC 2 was 27% more sensitive than repeat cytology at the cytological cut-off ASC-US+ for detecting CIN 2+ ($p<0.001$). The specificity of a repeat cytology at the cut-off ASC-US+ was nearly identical to the specificity of HC 2 for the detection of CIN 2+. They concluded that HC 2 is a more accurate method than repeat cytology to triage women with ASC-US. We think that the updates regarding triage of ASC-US should be included in the next version of our guidelines.

In 2006, ASCCP guidelines recommended less aggressive management for adolescents with abnormal cervical cytology, but in 2012, the updated guidelines no longer recommend screening adolescents. Instead, guidelines for management of women aged 21 to 24 years were added. Cervical cancer risk remains low through age 25 years, but it is almost 10-fold higher than risk in adolescents [14]. In these women with ASC-US or LSIL, repeat cytology in 12 months is preferred, but reflex HPV testing is also acceptable for ASC-US only. If reflex HPV testing is performed with ASC-US and the HPV result is positive, repeat cytology in 12 months is recommended. Immediate colposcopy or repeat HPV testing is not recommended. If reflex HPV testing is negative, return to routine screening with cytology alone in 3 years is recommended. The updated ACS guidelines also recommend not screening women under 21 years old. Considering high incidence of transient HPV infection, low risk of cervical cancer, and spontaneous regression of lesions, screening for adolescents should be discouraged.

Both ASCCP and ACS replenished the management of women with negative cytology and a positive HPV test. Two options exist: 1) repeat co-testing in 12 months or 2) immediate HPV genotyping test for HPV 16 alone or for HPV 16/18. If co-testing is selected, women testing positive on either test (HPV positive or ASC+ in ASCCP/LSIL+ in ACS) should be referred to colposcopy; women testing negative on both tests should return to routine screening. If immediate HPV genotyping test is chosen, women testing positive for HPV 16 or HPV 16/18 should be referred to colposcopy; women testing negative for HPV 16 or HPV 16/18 should be co-tested in 12 months.

For women aged 30 to 65 years, both ASCCP and ACS guidelines recommend either 3-year cytology intervals or 5-year co-testing intervals. Modeling studies have revealed a gradual increase in cancer risk with an increasing interval from 1 year to 3 years to 5 years [15]. They concluded that a 3-year interval for cytology provides an optimal balance of benefits and harms. When it comes to co-testing, modeling studies have shown that co-testing in 40-year-old women at a 3-year vs. a 5-year interval over a 10-year period only slightly decreases life-time cervical cancer risk while significantly increasing the number of colposcopic evaluations [15]. Our guidelines recommend shorter screening interval than above two guidelines in consideration of specific Korean situations. Nevertheless and detailed evaluations on the risks and benefits of the current screening interval should be conducted.

The updated ASCCP and ACS recommendation guidelines as well as our guidelines were developed to reflect the age- or region-specific natural history of HPV infection, cervical carcinogenesis, and expanding knowledge of different screening tests by searching evidences as much as possible. However, many important research priorities still remain.

1) How best to manage women with cytology-negative,

HPV-positive is a great concern. It should be determined the relative performances of reflex HPV testing for the most high-risk genotypes versus follow-up repeat co-testing at different intervals. Validation studies comparing many commercial HPV genotyping tests (DNA-based or RNA-based) in a screening population should be performed.

2) HPV testing as a primary screening tool should be validated. At present, HPV testing is not recommended as a primary screening strategy. Randomized controlled trials (RCTs) of HPV testing alone have demonstrated increased sensitivity for the detection of CIN 2+/ CIN 3+ after a single screening round. However, RCTs have been unsuccessful at defining the specificity of HPV testing, and hence the potential harms of primary HPV testing are poorly quantified. Nevertheless, primary screening with HPV testing alone will be promising in women aged 30 years and older. Lack of internal standard of specimen adequacy and no direct data to estimate performance of cytology in a triage setting have to be solved.

3) Prospective studies among older women are needed to define the optimal age to exit routine screening. The vast majority of cervical cancer arises from HPV infection acquired at younger age and the incidence of new infection among older women is rare. Except for women who have underwent treatment for CIN 2+, redefining the age limit before 65 years old or 70 years old might be necessary in women with consistently negative HPV.

4) Long-term follow-up studies of the effect of HPV vaccination on large cohort are needed. In addition, it should be determined whether vaccination affects the natural history or management of cytologic or histologic abnormalities. According to the results of those studies, current recommendations for vaccinated women might be changed.

CONFLICT OF INTEREST

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

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