Human Papilloma Virus Testing Improves Detection of Early Cervical Cancer

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Recently, testing for human papilloma virus (HPV) was added to the Papanicolaou (Pap) test in the guideline recommendations for cervical cancer screening. Alan G. Waxman, MD, MPH, of the University of New Mexico, Albuquerque, New Mexico, USA, discussed the recent addition of HPV testing to cervical cancer screening recommendations.

The current American Cancer Society–American Society for Colposcopy and Cervical Pathology–American Society of Clinical Pathology guidelines [Saslow D et al. *CA Cancer J Clin* 2012] and the American College of Obstetrics and Gynecology (ACOG) guidelines [ACOG. *Obstet Gynecol* 2012] for the screening of cervical cancer recommend that women aged 21 to 29 years be screened by cytology every 3 years, whereas the US Preventative Services Task Force recommends that women aged 21 to 65 be screened by cytology every 3 years [Moyer VA et al. *Ann Intern Med* 2012]. In addition, these institutions now recommend that women aged 30 to 65 years also receive testing for HPV in addition to the Pap test (co-testing). If both cytology and high-risk HPV testing are performed and both are negative, they should be repeated in 5 years. Prof. Waxman pointed out that only US Food and Drug Administration (FDA)–approved and clinically validated HPV tests should be used for cervical cancer screening.

The benefits of co-testing with cytology and HPV are that it has greater sensitivity and negative predictive value than cytology alone, and thus, it can lead to earlier diagnosis of cervical cancer. The Population Based Screening Study Amsterdam study randomly assigned almost 45,000 women to 2 rounds of cervical cancer screening with co-testing or cytology alone during a 4- to 6-year period [Rijkaart DC et al. *Lancet Oncol* 2012]. In the first round of testing, co-testing detected twice as many cancers as cytology alone, although this difference was not statistically significant. By the second round, however, there were significantly fewer cancers in the group tested with co-testing (p=0.031). Similarly, premalignant changes, defined as cervical intraepithelial neoplasia (CIN) 2, were detected more frequently by co-testing (p=0.015) in the first round of testing, and the incidence of CIN 3+ decreased in the second round (p=0.023). A systematic review that pooled this study with other randomized, controlled trials conducted in Europe showed that HPV-based screening resulted in a decrease in invasive cervical cancer at 3.5 and 5.5 years [Ronco G et al. *Lancet* 2014]. Furthermore, a study of almost 332,000 women demonstrated that adenocarcinoma *in situ* (AIS) and adenocarcinoma of the cervix were diagnosed more frequently in women who were screened with HPV testing or co-testing compared with cytology alone (p<0.0001; Table 1) [Katki HA et al. *Lancet Oncol* 2011].

Table 1. Cancer Diagnosis by Cervical Cancer Screening Method

	AIS	Adenocarcinoma
Total	70	27
Pap−	42 (60%)	23 (85%)
Pap+	28 (40%)	4 (15%)
HPV+	56 (80%)	21 (78%)
Pap− and HPV+	31 (44%)	17 (63%)
Pap+ and HPV−	3 (4%)	0

AIS=adenocarcinoma in situ; HPV=human papilloma virus; Pap=Papanicolaou test aka cytology.

Peer-Reviewed Highlights From the

American College of Obestricians and Gynecologists Annual Clinical Meeting 2014

April 26-30 Chicago

Table 2. Risk of CIN 3+ in Young Women at 5 Years After Cervical Screening

	Age Range		
	21–24 Years (n=133,947)	25–29 Years (n=135,382)	30–64 Years (n=165,360)
LSIL	3.0*		5.2**
ASC-US HPV+	4.4*		
ASC-US/HPV–	0.57	0.59	0.43
Negative	0.2	0.36	0.26

*Significant difference from 25 to 29 years or from 30 to 64 years; **5.2 is the colposcopy threshold. LSIL=low-grade squamous intraepithelial lesion; ASC-US=atypical squamous cells of undetermined significance; HPV=human papilloma virus.

Recently, an FDA panel recommended an expanded indication for the Cobas HPV test that permits cytology to be replaced by a specific HPV test in women aged 25 and younger using a limited, defined protocol. Patients with a negative Cobas HPV test can continue to be followed as recommended by their provider, whereas patients who test positive for the HPV 16 or HPV 18 strain should undergo colposcopy. Patients who test positive for other high-risk HPV strains should be tested by cytology to determine if a colposcopy is needed.

In 3.4% to 8.2% of patients who are co-tested, the HPV test is positive, and cytology is negative [Saslow et al. *Ca Cancer J Clin* 2012]. In these cases, immediate colposcopy is not warranted because the 5-year risk of CIN 3+ in these women is 4.5%, which is lower than the threshold level for colposcopy [Katki HA et al. *J Lower Genital Tract Dis* 2013]. Instead, for women older than 30 years, repeat co-testing at 1 year is recommended, although HPV DNA typing is an acceptable alternative. If repeat co-testing is performed and both tests are negative, then repeat co-testing should be performed again at 3 years. If, however, on repeat testing, the patient remains HPV-positive, or if cytology is atypical squamous cells of undetermined significance (ASC-US) or worse, then colposcopy should be performed. Patients who undergo HPV DNA typing that is negative for strains 16 or 18 should undergo repeat co-testing at 1 year.

Screening with an HPV test, if negative, allows for longer intervals between testing. In a cohort of more than 24,000 women, the rate of CIN 3+ detected at 3 years was 0.51% with negative cytology and 0.12% with negative HPV tests, and at 6 years, it was 0.97% and 0.27% with negative cytology or HPV testing, respectively [Dillner J et al. *BMJ* 2008]. Similarly, in a cohort of 1.4 million women, the 5-year risk of developing CIN 3+ after negative cytology or co-testing was 0.26% and 0.08%, respectively [Katki HA et al. *J Lower Genital Tract Dis* 2013].

A recent meta-analysis suggests that a negative Pap test with or without a transformation zone (TZ) component has good specificity and negative predictive value [Elumir-Tanner L et al. *CMAJ* 2011]. If a woman aged 21 to 29 years has a negative Pap test without endocervical cells (EC) or the TZ, routine screening should be continued. If a patient older than 30 years has a negative Pap without EC–TZ and the HPV status is unknown, however, then testing for HPV infection is preferred; however, repeat cytology in 3 years is acceptable. If the patient is HPV-positive, then HPV DNA typing, or co-testing in 1 year, should be performed.

Cervical cancer is rare in adolescents and young women, but HPV infection is common. In addition, low-grade cytological abnormalities are common and typically regress spontaneously. In addition, the 5-year risk of CIN 3+ is lower than the recommended threshold for colposcopy (Table 2) [Katki HA et al. *J Lower Genital Tract Dis* 2013]. Therefore, colposcopy is not recommended in women aged 21 to 24 years following a cytology result of ASC-US or low-grade squamous intraepithelial lesion (LSIL). Women in this age group who have ASC-US or LSIL, and who are HPV-positive or whose HPV status is unknown, should undergo repeat cytology at 12 months. Those who are HPV-negative can return to routine screening (i.e., cytology in 3 years). If the repeat cytology finds ASC with possible high-grade squamous intraepithelial lesion (HSIL; ASC-H), atypical glandular cells, or HSIL, referral to colposcopy is indicated; if negative, LSIL, or ASC-US, cytology should be repeated another 12 months later. If these results are ASC-US or worse, colposcopy should be performed.

The addition of HPV testing to cytology testing for the screening of cervical cancer has resulted in the need for fewer screening cycles in women who co-test negative, while enabling the earlier diagnosis of cervical cancer.