Review

Recent Advances in Cervical Cancer Screening

Judith J. Thangaiah, MD;[1#] Frank Chen, MD, PhD, MBA[2*]

[1] *Department of Internal Medicine, Buffalo General Medical Center, Buffalo, NY*
[2] *Clinical Lab, Medina Hospital, Quest Diagnostics, Medina, NY*

Centers for Disease Control and Prevention (CDC) estimates that about 11,967 new cases of HPV-associated cervical cancer are diagnosed in the United States each year. More black and Hispanic women get cervical cancer than women of other races or ethnicities, possibly because of decreased access to Pap testing or follow-up treatment.

Based on solid evidence, cervical cancer screening and protection against HPV infection by vaccination against HPV types 16/18, use of barrier contraceptives, and sexual abstinence decreases cervical cancer incidence. Also avoidance of active and passive cigarette smoking, high parity, and long term use of contraceptives decreases the risk of cervical cancer.

In this article, we aim to review the preventative and screening methods for cervical cancer. Discussion of the latest Cervical Cancer Screening Guidelines chart given by CDC that compares recommendations from the American Cancer Society, Preventive Services Task Force, and the American College of Obstetricians and Gynecologists is done.

With the FDA approval of the first HPV test for primary cervical cancer screening on April 25th, 2014, clinicians now have 3 different first line screening options, the Pap test, co-testing with Pap and HPV tests, and HPV testing as a stand-alone test. Specifically, the Roche Cobas® HPV Test was approved for primary screening for cervical cancer as a stand-alone test.

Clinical trials that evaluate cancer-screening methods are taking place in many parts of the country. Ongoing trials on the development of Human Papillomavirus Type 16 E7- specific Human Immunologic Assays in Non-HLA2 Type Human Being, Molecular markers in Cervical Cancer Screening, and multispectral digital colposcopy are going on. These improvements in screening strategies along with therapeutic and preventive methods contribute significantly to the control and prevention of cervical cancer.

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INTRODUCTION

Cervical cancer incidence and mortality have markedly declined in the United States since the introduction of cervical cancer screening in the 1950s and 1960s. However, cervical cancer still remains an important public health issue.

The incidence of cervical cancer has declined since 1957 when cervical pap smears were introduced but this decline tapered off during 2006 to 2010, mainly among younger women. The rates were stable in women younger than 50 years of age and declined by 3.1% per year in women over 50 years. From 2006 to 2010, death rates had plateaued despite aggressive screening protocols among women younger than 50. About 12,360 cases of invasive cervical cancer were diagnosed and 4020 deaths reported in 2014 alone.

While primary prevention would be ideal in the control of cervical cancer, it has practical challenges. Although human papilloma virus (HPV) vaccination is safe and effective, there are challenges in its implementation.[1] According to teen vaccination coverage data from CDC, there is a persistent coverage gap between HPV vaccination and other vaccinations recommended for adolescents to protect adolescents from HPV-related cancers.[2]

Screening techniques include cytology, visual inspection with 3%-5% acetic acid and magnification, Lugol's iodine, colposcopy, HPV testing, and a combination of these methods. Since the implementation of Pap test, various modifications have been made to improve the sensitivity and specificity. The advent of HPV DNA testing is having a tremendous impact on the way that screening for cervical cancer is conducted. Screening strategies are constantly being revised. Recently, E6/E7 based mRNA studies and p16 immuno tests have been introduced that target the molecular alterations associated with transformation rather than simply detecting high risk HPV (hr-HPV) infections. mRNA, and p16 transformation studies are more specific than HPV DNA test.[3,4]

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***Corresponding Author:** Clinical Lab, Medina Hospital, Quest Diagnostics, Medina, NY 14103. (Email: dr.frankxchen@gmail.com)

CERVICAL CANCER SCREENING - EVOLUTION

The initial and most important step in cervical cancer screening was the introduction of Papanicolaou (Pap) testing. Implementation of Pap testing resulted in declined incidence of cervical cancer between 1955 and the mid-1980s. With the improvements in diagnostic testing and treatment protocols, the incidence of cervical cancer has further decreased.[5] The Bethesda System for reporting cervical cytology was developed at an NCI workshop in 1988, and was first used in 1991. In 2001, it was further updated to improve the utility and understandability of results.[6]

The clinical performance of the cytology-based screening technology has limitations. The sensitivity of the conventional Pap test for the detection of high-grade lesions has a wide range from 30% to 87%.[7] To overcome this limitation, liquid based cytology (LBC) was developed. In LBC, the sampling technique involves use of a cytobrush which is rotated by 360 degrees five times around the cervix and the exfoliated cells in the cytobrush are stirred in a proprietary solution. This sampling method reduces specimen inadequacy by 80% and the specimen can be used for HPV, chlamydia and gonorrhea testing in addition to cytological examination. The ThinPrep Pap test was approved by FDA in 1996 and three years later, SurePath Pap test was also approved. Women now benefit from a lower inadequacy rate of cervical samples since the switch from conventional methods to LBC method. According to some studies, the clinical sensitivity of LBC in the detection of high-grade lesions has increased from 88% to 93% compared to conventional tests.[8,9] Other advantages of LBC include improvement in sample adequacy, reproducibility, and ability to support HPV co-testing.[10,11]

Automation of manual screening of cytology slides is another advancement that occurred over the past 20 years. This method screens the slide automatically and presents a number of fields that are reviewed by the cytotechnologist, thereby reducing screening errors and increase productivity. Two automated screening systems have been developed, which are the BD FocalPoint GS Imaging System and the ThinPrep Imaging System. The BD FocalPoint system uses SurePath liquid-based cytology and the ThinPrep imager uses ThinPrep liquid-based cytology. FDA approval of these two imaging systems for primary cervical screening is based on evidence that they are capable of detecting an equivalent or higher percentage of high-grade dysplasia than manual screening.[12]

Molecular and epidemiologic studies have demonstrated strong association between high-risk strains of HPV and cervical carcinoma.[13-15] Tests for high-risk HPV DNA have been developed for use on cervical samples. Studies show that the high-risk HPV tests can improve the sensitivity of the Pap test to greater than 95%.[16,17] These improvements in cytologic screening techniques as well as the introduction of HPV DNA testing has greatly facilitated the identification of women at high risk for cervical cancer and the revision of screening strategies.

Of recent, several biomarkers that play an important role in the cervical cancer development are being studied. There markers include p16INK4a (CDKN2A), survivin (BIRC5), metalloproteinase 9 (MMP9), topoisomerase 2 alpha (TOP2A), minichromosome maintenance 5 (MCM5), and MKi67 proteins (MKI67).[18-21]

HPV TESTS

Large randomized trials conducted in many parts of the world suggest the use of HPV tests as a primary screening tool.[22,23] There are validation guidelines and laboratory guidelines suggested for HPV testing. The sensitivity of the candidate test for ≥ CIN2 should be at least 90% of the sensitivity of the reference assay which is Hybrid Capture 2 HPV DNA test. The specificity of the candidate test for ≥ CIN 2 should be at least 98% of the specificity of the reference assay.[24]

Evidence shows that HPV testing generally has a higher sensitivity but lower specificity than does cytology in the detection of CIN2 and CIN3.[23,25-30] Among women older than 30 years, cytology had a specificity of 97% compared with 94% for HPV testing.[23,31] The specificity of HPV DNA testing would be even lower among women younger than 30 years, who have more transient HPV infections. To improve specificity and minimize over-treatment with HPV DNA testing, the suggested approaches are (1) triage HPV-positive results with cytology[32] or another more specific molecular assay[33] and (2) further workup pursued only after two sequential positive HPV tests.[34,35] The reason for the lesser sensitivity of HPV testing for invasive cervical cancers is explained. The invasive cells have major molecular rearrangements and the viral DNA load is lower.[36] Many countries are considering HPV testing as a primary screening tool followed by triage with Pap test.[16,23] FDA approved HPV tests are compared below in **Table 1**.

CLINICAL UTILITY AND SCOPE OF HPV DNA TESTING

There is variation in interpretation of ASCUS Pap smears among cytopathologists.[40] 2.5 million ASCUS Pap results are reported every year in the United States.[41] HPV DNA testing is utilized in this scenario to avoid unnecessary colposcopy procedures. Patients with ASCUS who turn out to be positive for high-risk HPV DNA go for colposcopy and those who are negative have repeat Pap tests at 6 months and 12 months. If the repeat Pap tests are also negative, patients revert back to the routine screening guidelines.

The combination of the high sensitivity of HPV DNA testing and the high specificity of cytology can increase the screening interval in women tested negative with cytology and HPV DNA tests. Such a combined test was approved by the FDA in 2003 for primary screening of low risk women aged ≥ 30 years every 3 years. Large-scale studies have provided solid evidence for the existence of HPV-negative cervical cancers. Co-testing with cervical Pap cytology and FDA-approved hrHPV tests will maximize the detection of cervical cancers.[42,43]

Table 1. FDA approved assays for detecting HPV.[37-39]

FDA approved HPV assays	Clinical Indications	Detection method	HPV typed detected	Collection and processing of specimens	Limitations	Advantages
Hybrid Capture 2 HPV DNA test	1.Reflex testing of patients with ASC-US, to determine the need for referral to colposcopy 2. In conjunction with routine Pap testing of women over age 30 to adjunctively screen for the presence or absence of high-risk HPV types	Qualitative detection using In vitro nucleic acid hybridization assay with signal amplification using microplate chemiluminescence	13 high-risk HPV types 6, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	The HC2 DNA Collection Device or HC Cervical Sampler (cervical broom) with samples deposited in either Digene Transport Medium or a Cytyc PreservCyt vial	Cross-reactivity of its probe cocktail with untargeted HPV types resulting in inaccurate results. Lack of an internal control to evaluate specimen adequacy or the presence of potentially interfering substances.	Most frequently used diagnostic HPV test worldwide. The recommended reference assay.
Cervista HPV HR Test	Same as HC2	Qualitative detection using invader chemistry. It is a signal amplification method for detecting specific nucleic acid sequences utilizing isothermal reactions.	14 high-risk HPV types -16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	Collected in PreservCyt solution of the ThinPrep Pap Test preservation system, using a broom-type device or endocervical brush/spatula.	Potential cross-reactivity with HPV types 67 and 70, which give positive results	Can be used with cervical specimens collected in ThinPrep PreservCyt solution.
Cervista HPV 16/18 Test	Same as HC2	Same as HPV HR Test- Invader chemistry	Qualitative detection of DNA from HPV types 16 and 18	Same as those for HPV HR.	Cross-reactivity to high levels of HPV high-risk type 31. Very low levels of infection or sampling error may cause a false-negative result.	Same as HPV HR test
Cobas 4800 HPV test	1.To triage ASC-US positive women who are ≥ 21 years, to screen women ≥ 30 years for high-risk HPV genotypes 16 and 18 along with cytology, 2.Primary HPV screening for cervical cancer in women 25 and older in the United States	Polymerase Chain Reaction (PCR) and nucleic acid hybridization methods for the detection of 14 high-risk (HR) HPV types in a single analysis.	The test specifically identifies HPV types 16 and 18 while concurrently detecting the 12 remaining high-risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) at clinically relevant infection levels	Cervical specimens collected in Cobas PCR Cell Collection Media (Roche) or ThinPrep PreservCyt solution.	Limited literature on the analytical and clinical validation of the Cobas 4800 HPV test.	The Cobas HPV test has high quality, is automated. Approved for primary screening for cervical cancer as a stand-alone test.
Aptima HPV assay	Same as HC2	Transcription mediated amplification-based assay.	Detection of E6/E7 mRNA transcripts of 14 high-risk HPV types -16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	Collected in ThinPrep Pap test vials containing PreservCyt solution or the Aptima Cervical Specimen Collection and Transport Kit.	No discrimination between the 14 high risk HPV types.	No cross-reactivity with any tested high-risk HPV types or with normal flora and opportunistic organisms that may be found in cervical samples. At the CIN3+ end point, the assay is equally sensitive (95 percent) as HC2 but more specific than HC2

The first, and currently only FDA approved test for primary HPV screening for cervical cancer in women 25 and older in the United States is the Cobas® HPV Test, which is manufactured by Roche Molecular Systems, Incorporated, Pleasanton, California.[38] As with any laboratory test, the sensitivity of HPV testing is not 100%. A subset of squamous and glandular carcinomas such as gastric type adenocarcinoma may not be detected by HPV testing.[44] A recent United States cancer registry study found that 9.4% of cervical cancers were HPV negative and an additional 3.2%

contained rare HPV subtypes. Quality assurance of HPV testing and evidence based algorithms for the follow up of HPV testing should be developed more thoroughly.[45]

CURRENT GUIDELINES FOR SCREENING

Table 2 is a comparative table with cervical cancer screening guidelines for average-risk women by American Cancer Society (ACS), American Society, for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP), American College of Obstetricians and Gynecologists (ACOG) and US Preventive Services Task Force (USPSTF) released in 2012.

Table 2. Cervical Cancer Screening Guidelines for Average-Risk Women.

Cervical Cancer Guidelines		American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP)[46] 2012	U.S. Preventive Services Task Force (USPSTF) 2012	American College of Obstetricians and Gynecologists (ACOG)[47] 2012
When to start screening[48]		Age 21.	Age 21.	Age 21 regardless of the age of onset of sexual activity.
Cytology (conventional or liquid based)	21-29 yrs.	Every 3 years.	Every 3 years.	Every 3 years.
	30-65 yrs.	Every 3 years.	Every 3 years.	Every 3 years.
HPV co-test (cytology + HPV test administered together)	21-29 yrs.	Not recommended.	Not Recommended.	Not recommended.
	30-65 yrs.	Every 5 years.	Every 5 years.	Every 5 years.
Primary HPV testing		For women aged 30-65 years, screening by HPV testing alone is not recommended in most clinical settings.	Recommend against screening for cervical cancer with HPV testing (alone or in combination with cytology) in women aged <30 years	Not addressed.
When to stop screening		Aged >65 years with adequate screening history*	Aged >65 years with adequate screening history.	Aged >65 years with adequate screening history.
Screening post-hysterectomy		Total hysterectomy- stop screening.	Stop screening.	Stop screening.
		Supra-cervical hysterectomy -continue screening according to guidelines.		
Need for a bimanual pelvic exam		Not addressed in 2012 guidelines but was addressed in 2002 ACS guidelines.[49]	Addressed in USPSTF ovarian cancer screening recommendations.	Addressed in 2012 well-woman visit recommendations.[47] Aged <21 years- "external-only" genital examination is acceptable. Aged ≥21 years- complete pelvic examination is a shared decision between the patient and her health care provider. Annual examination of the external genitalia should be continued
Screening among those immunized against HPV 16/18		Routine Screening according to the age.	Routine Screening.	Routine Screening.

*Adequate screening is defined as three consecutive negative cytology results or two consecutive negative co-tests within 10 years before stopping the screening, with the most recent test/co-test performed within 5 years. Women aged >65 years who have a history of CIN2, CIN3, or AIS should continue screening for at least 20 years after regression or adequate management.

These guidelines do not apply to women who have had high-grade precancerous cervical lesion (CIN 2 or 3) or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised, or are HIV positive. These recommendations apply to women who have a cervix, regardless of sexual history. No distinction should be made in screening guidelines or management whether conventional cytology or liquid-based cytology is used.

CURRENT GUIDELINES FOR SCREENING

With better molecular insights into alterations induced by HPV E6 and E7 oncogenes, biomarkers can be used as effective triage tools. Since the altered expression of these biomarkers result in cellular neoplastic transformation, they have improved specificity over high-risk HPV testing. Studies show that p16/Ki-67 dual staining on suspicious cervical cells has improved validity in the identification of

high-grade cervical cancer precursors compared to hr-HPV tests. It results in 50% reduction in colposcopy referral for ASCUS and LSIL patients compared with hr-HPV triage.[4,50-53]

A recent study by Bierkens et al[54] shows that methylation levels of two genes CADM1 and MAL increases with the grade of dysplasia and are highest in carcinomas. Also, the methylation levels increased with the duration of hr-HPV infections.

CONCLUSION

The Cytotechnology Education and Technology Consortium in 2014 stated that cervical cancer screening in the United States remains opportunistic, but lacks uniform test accessibility, patient compliance and an organized national program.[55]

Non-attendance is an important problem concerning the effectiveness of cervical screening programs.[56-58] Innovative programs to increase screening rates are carried out by the National Breast and Cervical Cancer Early Detection Program. Women who have no regular source of health care, women without health insurance, and women who immigrated to the United States within the past 10 years are at high risk because of the underutilization of screening methods.[59] The cervical screening methods should remain readily accessible and affordable for all women.

HPV DNA testing has a tremendous impact in both developed and developing countries considering the reproducibility and sensitivity of HPV tests. Research is going on to study if hr-HPV DNA testing can be done as primary testing method, because a negative HPV test result offers extended period of safety over negative cytology results.[60] Incorporation of hr-HPV tests in cervical screening programs can increase public awareness of the association between hr-HPV and cervical cancer, which may lead to higher utilization of prophylactic HPV vaccine.

In summary, recent advances in cervical cancer screening is one of the important multi-dimensional approach to the prevention of cervical cancer. In addition to implementation of new screening methods, evaluation of their adherence and success over time will help maximize the benefits of cervical cancer prevention strategies.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

REFERENCES

1. Block SL, Brown DR, Chatterjee A, et al. Clinical trial and post-licensure safety profile of a prophylactic human papillomavirus (types 6, 11, 16, and 18) l1 virus-like particle vaccine. Pediatr Infect Dis J. 2010;29:95-101.
2. Stokley S, Jeyarajah J, Yankey D, et al. Human papillomavirus vaccination coverage among adolescents, 2007-2013, and postlicensure vaccine safety monitoring, 2006-2014--United States. MMWR Morb Mortal Wkly Rep. 2014;63:620-624.
3. Sotlar K, Stubner A, Diemer D, et al. Detection of high-risk human papillomavirus E6 and E7 oncogene transcripts in cervical scrapes by nested RT-polymerase chain reaction. J Med Virol. 2004;74:107-116.
4. Schmidt D, Bergeron C, Denton KJ, Ridder R, European CCSG. p16/ki-67 dual-stain cytology in the triage of ASCUS and LSIL papanicolaou cytology: results from the European equivocal or mildly abnormal Papanicolaou cytology study. Cancer Cytopathol. 2011;119:158-166.
5. Sasieni P, Castanon A, Cuzick J. Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data. BMJ. 2009;339:b2968.
6. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002;287:2114-2119.
7. American College of O, Gynecologists. ACOG Practice Bulletin No. 99: management of abnormal cervical cytology and histology. Obstet Gynecol. 2008;112:1419-1444.
8. Clavel C, Masure M, Bory JP, et al. Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: a study of 7932 women. Br J Cancer. 2001;84:1616-1623.
9. Hutchinson ML, Zahniser DJ, Sherman ME, et al. Utility of liquid-based cytology for cervical carcinoma screening: results of a population-based study conducted in a region of Costa Rica with a high incidence of cervical carcinoma. Cancer. 1999;87:48-55.
10. McCrory DC, Matchar DB, Bastian L, et al. Evaluation of cervical cytology. Evidence report/technology assessment. 1999:1-6.
11. Siebers AG, Klinkhamer PJ, Grefte JM, et al. Comparison of liquid-based cytology with conventional cytology for detection of cervical cancer precursors: a randomized controlled trial. JAMA. 2009;302:1757-1764.
12. Wilbur DC, Black-Schaffer WS, Luff RD, et al. The Becton Dickinson FocalPoint GS Imaging System: clinical trials demonstrate significantly improved sensitivity for the detection of important cervical lesions. Am J Clin Pathol. 2009;132:767-775.
13. Franco EL. Cancer causes revisited: human papillomavirus and cervical neoplasia. J Natl Cancer Inst. 1995;87:779-780.
14. Harro CD, Pang YY, Roden RB, et al. Safety and immunogenicity trial in adult volunteers of a human papillomavirus 16 L1 virus-like particle vaccine. J Natl Cancer Inst. 2001;93:284-292.
15. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189:12-19.
16. Naucler P, Ryd W, Tornberg S, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med. 2007;357:1589-1597.
17. Paraskevaidis E, Arbyn M, Sotiriadis A, et al. The role of HPV DNA testing in the follow-up period after treatment for CIN: a systematic review of the literature. Cancer Treat Rev. 2004;30:205-211.
18. Barbosa LC, da Silva ID, Correa JC, Ribalta JC. Survivin and telomerase expression in the uterine cervix of women with human papillomavirus-induced lesions. Int J Gynecol Cancer. 2011;21:15-21.
19. Del Pino M, Svanholm-Barrie C, Torne A, et al. mRNA biomarker detection in liquid-based cytology: a new approach in the prevention of cervical cancer. Mod Pathol. 2015;28:312-320.
20. Santin AD, Zhan F, Bignotti E, et al. Gene expression profiles of primary HPV16- and HPV18-infected early stage cervical cancers and normal cervical epithelium: identification of novel candidate molecular markers for cervical cancer diagnosis and therapy. Virology. 2005;331:269-291.
21. Williams GH, Romanowski P, Morris L, et al. Improved cervical smear assessment using antibodies against proteins that regulate DNA replication. Proc Natl Acad Sci U S A. 1998;95:14932-14937.
22. Cuzick J, Szarewski A, Mesher D, et al. Long-term follow-up of cervical abnormalities among women screened by HPV testing and cytology-Results from the Hammersmith study. Int J Cancer. 2008;122:2294-2300.
23. Mayrand MH, Duarte-Franco E, Rodrigues I, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N Engl J Med. 2007;357(16):1579-1588.
24. Meijer CJ, Berkhof J, Castle PE, et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. International journal of cancer. Int J Cancer. 2009;124:516-520.
25. Bigras G, de Marval F. The probability for a Pap test to be abnormal is directly proportional to HPV viral load: results from a Swiss study

comparing HPV testing and liquid-based cytology to detect cervical cancer precursors in 13,842 women. Br J Cancer. 2005;93:575-581.
26. Cardenas-Turanzas M, Nogueras-Gonzalez GM, Scheurer ME, et al. The performance of human papillomavirus high-risk DNA testing in the screening and diagnostic settings. Cancer Epidemiol Biomarkers Prev. 2008;17:2865-2871.
27. Coste J, Cochand-Priollet B, de Cremoux P, et al. Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. BMJ. 2003;326(7392):733.
28. Kulasingam SL, Hughes JP, Kiviat NB, et al. Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: comparison of sensitivity, specificity, and frequency of referral. JAMA. 2002;288:1749-1757.
29. Petry KU, Menton S, Menton M, et al. Inclusion of HPV testing in routine cervical cancer screening for women above 29 years in Germany: results for 8466 patients. Br J Cancer. 2003;88:1570-1577.
30. Whitlock EP, Vesco KK, Eder M, Lin JS, Senger CA, Burda BU. Liquid-based cytology and human papillomavirus testing to screen for cervical cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;155:687-697, W214-685.
31. Arbyn M, Ronco G, Anttila A, et al. Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. Vaccine. 2012;30 Suppl 5:F88-99.
32. Cuzick J, Clavel C, Petry KU, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. Int J Cancer. 2006;119:1095-1101.
33. Carozzi F, Confortini M, Dalla Palma P, et al. Use of p16-INK4A overexpression to increase the specificity of human papillomavirus testing: a nested substudy of the NTCC randomised controlled trial. Lancet Oncol. 2008;9:937-945.
34. Castle PE. Invited commentary: is monitoring of human papillomavirus infection for viral persistence ready for use in cervical cancer screening? Am J Epidemiol. 2008;168:138-144; discussion 145-138.
35. Koshiol J, Lindsay L, Pimenta JM, Poole C, Jenkins D, Smith JS. Persistent human papillomavirus infection and cervical neoplasia: a systematic review and meta-analysis. Am J Epidemiol. 2008;168:123-137.
36. Sundstrom K, Ploner A, Dahlstrom LA, et al. Prospective study of HPV16 viral load and risk of in situ and invasive squamous cervical cancer. Cancer Epidemiol Biomarkers Prev. 2013;22:150-158.
37. Castle PE, Stoler MH, Wright TC, Jr., Sharma A, Wright TL, Behrens CM. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. Lancet Oncol. 2011;12:880-890.
38. Stoler MH, Wright TC, Jr., Sharma A, et al. High-risk human papillomavirus testing in women with ASC-US cytology: results from the ATHENA HPV study. Am J Clin Pathol. 2011;135: 468-475.
39. Wright TC, Jr., Stoler MH, Sharma A, et al. Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV+ cytology-negative results. Am J Clin Pathol. 2011;136:578-586.
40. Sherman ME, Schiffman MH, Lorincz AT, et al. Toward objective quality assurance in cervical cytopathology. Correlation of cytopathologic diagnoses with detection of high-risk human papillomavirus types. Am J Clin Pathol. 1994;102:182-187.
41. Kurman RJ, Henson DE, Herbst AL, Noller KL, Schiffman MH. Interim guidelines for management of abnormal cervical cytology. The 1992 National Cancer Institute Workshop. JAMA. 1994;271:1866-1869.
42. Tjalma WA, Fiander A, Reich O, et al. Differences in human papillomavirus type distribution in high-grade cervical intraepithelial neoplasia and invasive cervical cancer in Europe. Int J Cancer. 2013;132:854-867.
43. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. Obstet Gynecol. 2015;125:330-337.
44. Kusanagi Y, Kojima A, Mikami Y, et al. Absence of high-risk human papillomavirus (HPV) detection in endocervical adenocarcinoma with gastric morphology and phenotype. Am J Pathol. 2010;177:2169-2175.
45. Ronco G, Biggeri A, Confortini M, et al. Health technology assessment report: HPV DNA based primary screening for cervical cancer precursors. Epidemiol Prev. 2012;36:e1-72.
46. Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin. 2002;52:342-362.
47. Committee on Gynecologic P. Committee opinion No. 534: well-woman visit. Obstet Gynecol. 2012;120:421-424.
48. Saraiya M, Martinez G, Glaser K, Kulasingam S. Pap testing and sexual activity among young women in the United States. Obstet Gynecol. 2009;114:1213-1219.
49. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin. 2012;62:147-172.
50. Killeen JL, Dye T, Grace C, Hiraoka M. Improved abnormal Pap smear triage using cervical cancer biomarkers. J Low Genit Tract Dis. 2014;18:1-7.
51. Klaes R, Friedrich T, Spitkovsky D, et al. Overexpression of p16(INK4A) as a specific marker for dysplastic and neoplastic epithelial cells of the cervix uteri. Int J Cancer. 2001;92:276-284.
52. Petry KU, Schmidt D, Scherbring S, et al. Triaging Pap cytology negative, HPV positive cervical cancer screening results with p16/Ki-67 Dual-stained cytology. Gynecol Oncol. 2011;121:505-509.
53. Wentzensen N, Schwartz L, Zuna RE, et al. Performance of p16/Ki-67 immunostaining to detect cervical cancer precursors in a colposcopy referral population. Clin Cancer Res. 2012;18:4154-4162.
54. Bierkens M, Hesselink AT, Meijer CJ, et al. CADM1 and MAL promoter methylation levels in hrHPV-positive cervical scrapes increase proportional to degree and duration of underlying cervical disease. Int J Cancer. 2013;133:1293-1299.
55. Cytopathology Education and Technology Consortium (CETC). Letter to the FDA regarding PMA hearing for HPV primary screening,. 2014; http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Microbiology. Accessed Nov 6, 2014.
56. Bais AG, van Kemenade FJ, Berkhof J, et al. Human papillomavirus testing on self-sampled cervicovaginal brushes: an effective alternative to protect nonresponders in cervical screening programs. Int J Cancer. 2007;120:1505-1510.
57. Raab SS, Grzybicki DM, Zarbo RJ, et al. Frequency and outcome of cervical cancer prevention failures in the United States. Am J Clin Pathol. 2007;128:817-824.
58. Sasieni P, Adams J, Cuzick J. Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. Br J Cancer. 2003;89:88-93.
59. Centers for Disease Control and Prevention (CDC). Cancer screening - United States, 2010. MMWR Morb Mortal Wkly Rep. 2012;61:41-45.
60. Cohen D, Austin RM, Gilbert C, Freij R, Zhao C. Follow-up outcomes in a large cohort of patients with human papillomavirus-negative ASC-H cervical screening test results. Am J Clin Pathol. 2012;138:517-523.