

Screening and management of women and girls with human papillomavirus infection

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Received 24 July 2007

Abstract

In the US, reductions in cervical cancer-related mortality over the past five decades can be attributed to the implementation of screening programs. US-based guidelines recommend that screening should be initiated approximately 3 years after initiation of sexual intercourse, but no later than age 21 years and be continued at least until age 65 or 70. Annual screening is recommended by the American Cancer Society and the American College of Obstetricians and Gynecologists, although in women aged ≥ 30 years with ≥ 3 negative Pap tests, screening may be conducted every 2 to 3 years. Human papillomavirus (HPV) testing has been approved by the US Food and Drug Administration and most US guidelines say that it is reasonable to consider HPV testing, in combination with triennial cytology screening. Pharmacoeconomic analyses indicate that combined cytology and HPV testing every three years in women aged ≥ 30 years is comparable in sensitivity to annual liquid-based cytology for the detection of cervical cancer precursors and is more cost-effective. Both surgical and nonsurgical therapies are commonly employed in patients with HPV lesions although papilloma recurrence is not uncommon. Treatment should be individualized based on the extent of disease and the needs of the patient. Current treatment of cervical cancer reflects the stage of the disease and should take into account patient- and tumor-related factors to ensure optimal patient outcomes.

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Keywords: Cervix; HPV; Screening; Management; Guidelines

Screening for human papillomavirus (HPV)

In the US, there has been a 70% decrease in cervical cancer-related mortality over the past five decades [1]. This is largely attributed to the implementation of cervical cancer screening involving the Papanicolaou (Pap) test [2]. Between 2002 and 2003, US screening guidelines were published by the American Cancer Society (ACS) [3], the American College of Obstetricians and Gynecologists (ACOG) [4] and the United States Preventative Services Task Force (USPSTF) [5]. The recommendations of these guidelines are presented in Table 1.

In general, it is recommended that screening should be initiated at approximately 3 years after initiation of sexual intercourse, but no later than age 21 years. Annual screening is recommended by the ACS and ACOG, although in women aged ≥ 30 years with ≥ 3 negative Pap tests, screening may be conducted every 2 to 3 years. USPSTF and ACS also advocate

that screening can be discontinued in women aged 65 [5] or 70 years [4] who have ≥ 3 consecutive negative Pap tests and no abnormal tests in the preceding 10-year period.

The availability of sensitive molecular methods for detecting high-risk HPV strains provides an alternative approach to managing women with certain cytological abnormalities [6]. HPV DNA testing has been approved by the US Food and Drug Administration for use as an adjunct to cytology for cervical cancer screening [7]. Based on a review of the literature and expert opinion, the American Society for Colposcopy and Cervical Pathology (ASCCP) published consensus guidelines from 29 professional organizations, Federal agencies, and national and international health organizations saying that it is reasonable to consider adding HPV DNA testing to triennial cervical cytology screening in women aged ≥ 30 years [6]. In women who have negative cytology results but are high-risk HPV DNA positive, colposcopy should not be routinely performed and instead HPV DNA testing in combination with cervical cytology should be repeated at 12 months. A review of

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Table 1
US cervical cancer screening guidelines

	American Cancer Society [3]	US Preventative Services Task Force [5]	American College of Obstetricians and Gynecologists [4]
Initiation of screening	≈3 years after onset of sexual activity but no later than age 21 years	Within 3 years of onset of sexual activity or age 21 years, whichever comes first	≈3 years after onset of sexual activity but no later than age 21 years
Screening intervals			
Conventional Pap test	Annually; every 2–3 years for women aged ≥30 years with 3 negative cytology tests ^a	At least every 3 years	Annually; every 2–3 years for women aged ≥30 years with 3 negative cytology tests ^a
If liquid-based cytology used	Annually; every 2–3 years for women aged ≥30 years with 3 negative cytology tests ^a	Insufficient evidence	Annually; every 2–3 years for women aged ≥30 years with 3 negative cytology tests ^a
If HPV testing used	Every 3 years if HPV negative, cytology negative	Insufficient evidence	Every 3 years if HPV negative, cytology negative
Discontinuation of screening	Women aged ≥70 years with ≥3 recent, consecutive negative tests and no abnormal tests in prior 10 years ^a	Women aged >65 years with negative tests, who are not otherwise at high risk for cervical cancer	Inconclusive evidence to establish upper age limit
Post-total hysterectomy	Discontinue if hysterectomy was for benign reasons and no prior history of high-grade CIN ^a	Discontinue if hysterectomy was for benign reasons	Discontinue if hysterectomy was for benign reasons and no prior history of high-grade CIN ^a

CIN=cervical intraepithelial neoplasia.

^a Exceptions apply (e.g. women who are immunocompromised, history of prenatal exposure to DES).

the data in women aged ≥30 years who had been tested with a combination of cervical cytology and HPV DNA testing shows that the combination has a negative predictive value between 99% and 100% [7].

In 2003, the European Union recommended that cancer screening should only be offered on a population basis in organized screening programs, and that quality assurance should be conducted at all levels [8]. A recent review of cervical cancer screening programs and policies in 18 European countries indicated that there is a wide variation with regard to the adoption of these recommendations across the European Union [9]. By 2003, 16 countries either had screening programs in place or had initiated pilot screening programs. However, there were substantial differences with regard to the targeted age groups (range for initiation of screening 15 to 30 years) and the screening intervals (range 1 to 5 years). Across this region, the recommended lifetime number of Pap smears varied from 7 to 50. Six countries employed invitational screening programs and these countries

also maintained fully centralized national or regional screening registration databases [9].

Cost of screening and management of HPV infections

In the US, there is a substantial healthcare burden associated with the management of HPV infections, and this is particularly evident in the 15 to 24 age group [10]. In the year 2000, in this age group, the direct medical costs associated with HPV infection (manifest as cervical abnormalities in women and external genital warts in men and women) were second only to the costs associated with HIV infection (US\$ 2.9 vs. 3.0 billion) [10]. Following an adjustment to reflect the results of a model of the natural history and progression of HPV infection, the costs attributable to the follow-up of abnormal Pap smears and the treatment of cervical neoplasia in young women were US \$2.7 billion.

Significant costs are also associated with screening for cervical cancer [11]. A US-based observational cohort study ($n=103,476$), demonstrated that irrespective of age, cervical HPV-related disease resulted in annual healthcare costs of US\$ 26,415 per 1000 women [11]. Routine cervical cancer screening accounted for two-thirds of the annual cervical HPV-related healthcare costs; 17% of costs were attributed to the management of cervical pre-cancers and 10% to the treatment of invasive cervical cancer.

However, screening programs have been shown to effectively reduce the risk of cervical cancer. According to the results of a US-based state-transition pharmacoeconomic model, annual conventional Pap smear tests, in a cohort of women, were associated with an 89% reduction in cervical cancer risk at a mean lifetime cost of US\$ 2,457 per woman [12]. In contrast, triennial liquid-based cytology, incorporating HPV testing for women with atypical squamous cells of undetermined significance (ASC-US), reduced cervical cancer risk by 90% at a lifetime cost of US\$ 1,358 per woman. The combination of triennial liquid-based cytology plus HPV testing for all women aged ≥30 years was associated with a 90–92% risk reduction and a 30% reduction in costs relative to annual cytology.

The addition of HPV testing to triennial cytology as a screening option for cervical cancer in women aged ≥30 years appears to be more cost-effective than conventional cytology alone [12–14]. A state-transition pharmacoeconomic model that simulated the natural history of HPV infection and cervical cancer in a US cohort of women aged ≥30 years determined that the combination of HPV DNA testing and cytology costs an additional US\$ 289 per lifetime, reduces the lifetime cervical cancer risk by an additional 2% and has an incremental cost-effectiveness ratio of US\$ 228,700 per life year gained [12].

In developing countries or low resource settings, cervical screening programs that use conventional cytology and necessitate multiple visits are not practical. Goldie et al. [15] utilized computer-based models to evaluate the cost-effectiveness of various screening strategies for cervical cancer in India, Kenya, Peru, Thailand and South Africa. In these five developing

countries, the most cost-effective cervical cancer screening strategies were those that incorporated visual inspection of the cervix with acetic acid or HPV testing over 1 to 2 clinic visits, as opposed to the more conventional 3-visit cytology-based screening strategies [15]. The strategies employing 1 to 2 visits at the age of 35 years were associated with a lifetime risk reduction for cervical cancer of 25–36% at a cost of <\$ 500 per life year gained (international dollars, year 2000). An increase in screening frequency was associated with greater risk reductions but a 5- to 10-fold increase in the cost-effectiveness ratio.

Management of clinically relevant HPV infections

Treatment of HPV lesions

Management approaches for the treatment of HPV lesions are detailed in Table 2. Both surgical and nonsurgical therapies are commonly employed in patients with HPV lesions although papilloma recurrence is not uncommon. Treatment should be individualized based on the extent of disease and the needs of the patient. Anogenital lesions and warts are the most frequently occurring HPV lesions, and surgical excision is often the simplest treatment approach [16]. Surgery (e.g. cryosurgery, laser ablation or electrocautery) is also the standard treatment strategy for other anogenital lesions. In patients with CIN, electrosurgical loop excision of the

transformation zone (LLETZ, LEEP) is a safe and effective treatment option and is associated with a 90% to 95% cure rate at 1 year.

There are currently no standardized recommendations for anal dysplasia and malignancies, vulval intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VAIN) and penile intraepithelial neoplasia (PIN) [16].

Respiratory papilloma recurrence is not uncommon in patients with HPV lesions and therefore adjuvant therapies (i.e. antiproliferative agents, photodynamic therapy, cryotherapy) may replace surgery. While prophylactic vaccines have been shown to be effective in the prevention of HPV infection, but they have no therapeutic benefit. Therapeutic vaccines that can target infected cells in order to control the growth of invasive tumors are currently in development [16]. To date, the results of clinical trials of these vaccines are equivocal, and studies are ongoing.

Management of women with cervical cytological abnormalities

The management of women with ASC is dependent on whether the Pap test is classified as ASC-US or ASC cannot exclude high-grade squamous intraepithelial lesion (HSIL) classified as ASC-H [6]. ASCCP consensus guidelines recommend that women with ASC-US are managed with 2 repeat cytology tests at six month intervals, immediate colposcopy or HPV DNA testing for high risk strains. Reflex HPV DNA testing (using the fluid left over after processing the liquid-based Pap smear) is the preferred approach, when liquid-based cytology is utilized. Women with ASC-H, pre-menopausal women with low-grade squamous intraepithelial lesions (LSIL) and all women with HSIL or atypical glandular cells (AGC) (except AGC favoring endometrial pathology) should be referred for immediate colposcopic evaluation. Adolescents are treated much more conservatively. HPV DNA testing is not useful in this age group and should not be used and colposcopic evaluation should be delayed in most cases and employed only if the cytological abnormality persists or is high-grade in nature (HSIL).

Management of women with cervical intraepithelial neoplasia (CIN)

Most cases of CIN grade 1 spontaneously regress without the need for treatment [17]. For women with biopsy confirmed CIN 1 preceded by ASC-US, ASC-H or LSIL cytology, the 2006 ASCCP consensus guidelines recommend follow-up with a repeat Pap test at 6 and 12 months or preferably HPV testing at 12 months (Table 3) [17]. Following 2 negative cytology results or a negative HPV test, women may recommence annual screening. Persistent CIN 1 should not be treated before 2 years and even then continued follow-up is equally acceptable and may be preferred in women wanting to retain fertility. Endocervical sampling is recommended by ASCCP prior to ablation of CIN 1.

For women with biopsy confirmed CIN 2 or 3 and a satisfactory colposcopy, either excision and ablation are ASCCP

Table 2
Suggested treatment approaches for the management of HPV lesions

Strategy	Treatment	Clinical efficacy
Surgery	Large loop excision transformation zone	Intraepithelial neoplasia
	Scalpel, curette, scissors	Warts
	Electrosurgical techniques	Warts
	Laser therapy	RRP
Destructive therapies	Cryotherapy	External warts, Intraepithelial neoplasia
	Photodynamic therapy	RRP
	Salicylic acid, trichloroacetic acid	External warts
Antiproliferative agents	Podophyllin/podophyllotoxin	Warts
	Bleomycin	Plantar warts
Antiviral agents	Cidofovir	Anogenital warts, verruca vulgaris, RRP, intraepithelial neoplasia
Immunotherapies	Interferon	RRP
	Imiquimod	Anogenital warts
	Duct tape occlusion therapy	Verruca vulgaris
Miscellaneous	Therapeutic vaccines	Intraepithelial neoplasia, RRP, anogenital warts
	Indole-3-carbinol	RRP, CIN
	Human α -lactalbumin made lethal to tumor cells (HAMLET)	Warts

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CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; RRP = recurrent respiratory papillomatosis.

Table 3
American Society for Colposcopy and Cervical Pathology treatment recommendations for cervical intraepithelial neoplasia

Stage		Recommendation
Biopsy confirmed CIN-preceded by ASC-US, ASC-H or LSIL cytology	Follow-up without treatment	Repeat Pap test at 6 and 12 months or HPV testing at 12 months. Women with regression during follow-up should have repeat cytology at 12 months. If CIN 1 persists for at least 2 years, either continued follow-up or treatment is acceptable.
Biopsy confirmed CIN-preceded by HSIL or AGC-NOS Cytology	Treatment	Satisfactory colposcopy: Either excision or observation (only if the ECC is negative) with colposcopy and cytology at 6 month intervals for 1 year; with persistent HSIL after 1 year of observation, excision is recommended. Unsatisfactory colposcopy: excision is recommended. If CIN 1 persists for at least 2 years, either continued follow-up or treatment is acceptable using ablative or excisional treatment if the colposcopy is satisfactory or excisional treatment if the colposcopy is unsatisfactory as determined by the treating physician. Endocervical sampling should be conducted prior to ablation. Excisional modalities are preferred for recurrent CIN 1 occurring after ablative therapy.
Biopsy confirmed CIN 2,3	Treatment	Satisfactory colposcopy: excision and ablation; excisional modalities are preferred in patients with recurrent CIN 2,3. Adolescents who have CIN 2 or CIN 2,3 either treatment or observation for up to 24 months using both colposcopy and cytology at 6 month intervals is acceptable. Treatment is recommended for Adolescents who have CIN 3 or if CIN 2,3 persists for 24 months. Unsatisfactory colposcopy: diagnostic excisional procedures.
	Follow-up	HPV DNA testing at 6 to 12 months or cytology or combination of cytology and colposcopy at 6-month intervals (until ≥ 2 negative cytologic results), then annual follow-up. Following identification of high-risk HPV, colposcopy is recommended. In HPV negative women, annual cytology is recommended for at least 20 years.

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CIN=cervical intraepithelial neoplasia; LEEP=loop electrosurgical excisional procedure.

recommended treatment approaches (Table 3) [17]. In those women with an unsatisfactory colposcopy, diagnostic excisional procedures are advocated. Following 2 negative cytology results, women may resume annual cytology screening. A colposcopy is recommended if high risk HPV types are identified in post-treatment followup; following negative HPV

testing, annual cytology follow-up is recommended. In adolescents who have CIN 2 or CIN 2,3 either treatment or observation for up to 24 months using both colposcopy and cytology at 6-month intervals is acceptable. Treatment is recommended for Adolescents who have CIN 3 or if CIN 2,3 persists for 24 months.

Table 4
Current treatment options for cervical cancer

Stage		Treatment approach
Ia1 (minimal microscopic invasion depth <3 mm × width <7 mm)	Absence of lymphovascular invasion	Conization—in women wanting to retain fertility Simple hysterectomy—if fertility is not an issue
	Presence of lymphovascular invasion	Modified radical hysterectomy with pelvic node dissection Radial trachelectomy with laparoscopic pelvic node dissection—in women wanting to retain fertility
Ia2 (depth 3–5 mm × width <7 mm)	Absence of lymphovascular invasion	Conization Extrafascial hysterectomy Radical trachelectomy/hysterectomy may be warranted
	Presence of lymphovascular invasion	Radical hysterectomy with pelvic node dissection Radial trachelectomy with laparoscopic pelvic node dissection—in women wanting to retain fertility
Ib1–IIa	Involvement of para-aortic lymph nodes	Radical hysterectomy with pelvic lymphadenectomy Surgical approach plus extended-field radiotherapy
	Ib2 (primary tumor >4 cm)	Primary surgery as for stage Ib then tailored post-operative radiation ± chemotherapy, primary radiotherapy, or neoadjuvant chemotherapy
IIb–IVa		Radical external beam radiation therapy plus brachytherapy Concurrent chemotherapy, in addition to radiotherapy, should be considered
Recurrent cervical cancer		Depends on previous treatment, site or extent of recurrence, disease-free interval and patient's performance status After surgical therapy treatment with chemoradiation is recommended, ventral pelvic relapses following primary or adjuvant radiation should undergo surgery Radical hysterectomy may be adequate for small (<2 cm) lesions, but most patients will need pelvic exenteration

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Management of cervical cancer

Current treatment of cervical cancer reflects the stage of the disease (Table 4) [18]. Micro-invasive cervical carcinoma (stage Ia) is most likely curable with non-radical treatment. The majority of patients with stage Ib–IIa cervical cancer are treated with radical surgery or radical radiotherapy. Radical surgery can preserve ovarian function and avoids any potential chronic radiation damage to surrounding tissues. Neoadjuvant chemotherapy followed by radical surgery may be considered as an alternative to conventional chemotherapy in patients with bulky Ib2–IIa cervical cancer [18]. In locally advanced cervical cancer (stage IIb–IVa), standard treatment comprises radical external beam radiation therapy plus brachytherapy. In patients with locally advanced metastatic and recurrent cervical cancer, treatment is based on previous treatment, site or extent of recurrence, disease-free interval and patient's performance status. Concurrent use of cisplatin-based chemoradiation therapy is palliative.

Summary

The introduction of cervical cancer screening has been largely responsible for the reduction in cervical cancer-related mortality. The relatively recent approval of HPV testing by the FDA for cervical cancer screening when combined with cytology in women aged ≥ 30 years has allowed for extension of the screening interval to 3 years without any reduction in sensitivity compared to annual liquid-based cytology and with improved sensitivity compared with annual conventional cytology. Pharmacoeconomic analyses from the US and from developing countries indicate that the combination of cytology and HPV DNA testing is a more cost-effective approach than conventional cytology screening for cervical cancer. US-based guidelines say that it is reasonable to consider utilizing this combined approach in triennial screening of women aged ≥ 30 years. Many cervical HPV lesions do not require therapy. True pre-cancerous abnormalities are generally effectively managed with surgical treatment while more advanced cervical cancer requires a chemoradiation-based approach.

Questions and answers

Why were the screening recommendations of the ACS and ACOG changed from screening beginning at the outset of sexual activity or age 18 to 3 years after the onset of sexual activity or age 21?

Young women are especially susceptible to infection with HPV. They are more sexually active with more partners and are less likely to have developed immunity to HPV than older women. Most HPV-related lesions in young women regress within 3 years and the incidence rate of invasive cervical cancer is very low (0/100,000/year for ages 10 to 19 years according to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program—1995 to 1999). In addition, earlier onset of screening may increase anxiety, morbidity and expense from increased follow-up procedures. This is the reason that the ACS and ACOG recommended that cervical cancer screening begin approximately 3 years after initiation of sexual intercourse, but no later than age 21 years.

How do the guidelines for the management of LSIL cytology in post-menopausal women differ from the guidelines for the general population?

Both the prevalence of HPV DNA and that of CIN 2,3 are lower in older women with LSIL than in younger women. This suggests that post-menopausal women with LSIL can be managed less aggressively than pre-menopausal women. With the lower prevalence of HPV DNA positivity, HPV DNA testing becomes a useful triage tool in older women because it refers a lower proportion to colposcopy compared with younger women where 83% would be referred to colposcopy. In the 2006 guidelines, post-menopausal women with ASC-US and LSIL should be managed in the same manner as women with ASC-US in the general population.

Conflict of interest statement

MS is a consultant and serves on the Speaker's Bureau and Advisory Board for Merck.

References

- [1] Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics. 1999. *CA Cancer J Clin* 1999;48:8–31.
- [2] Solomon D, Breen N, McNeel T. Cervical cancer screening rates in the United States and the potential impact of implementation of screening guidelines. *CA Cancer J Clin* 2007;57:105–11.
- [3] Saslow D, Runowicz CD, Solomon D, Moscicki AB, Smith RA, Eyre HJ, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin* 2002;52(6):342–62.
- [4] http://www.acog.org/from_home/publications/press_releases/nr07-31-03-1.cfm.
- [5] <http://www.ahrq.gov/clinic/3rduspstf/cervcan/cervcanrr.pdf>.
- [6] Wright Jr TC, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. Consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol* 2007;197(4):346–55.
- [7] 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;119:1095–101.
- [8] The Council of the European Union. Council recommendation of 2 December 2003 on cancer screening. *Off J Eur Union* 2003;878:34–8.
- [9] Anittala A, Ronco G, Clifford G, Bray F, Hakama M, Arbyn M, et al. Cervical cancer screening programmes and policies in 18 European Countries. *Br J Cancer* 2004;91:935–41.
- [10] Chesson HW, Blandford JM, Gift TL, Tao G, Irwin KL. The estimated direct medical cost of sexually transmitted diseases among American youth, 2000. *Perspect Sex Reprod Health* 2004;36(1):11–9.
- [11] Insinga RP, Glass AG, Rush BB. The health care costs of cervical human papillomavirus-related disease. *Am J Obstet Gynecol* 2004;191(1):114–20.
- [12] Goldie SJ, Kim JJ, Wright TC. Cost-effectiveness of human papillomavirus DNA testing for cervical cancer screening in women aged 30 years or more. *Obstet Gynecol* 2004;103:619–31.
- [13] Holmes J, Hemmett L, Garfield S. The cost-effectiveness of human papillomavirus screening for cervical cancer. A review of recent modeling studies. *Eur J Health Econ* 2005;6(1):30–7.
- [14] Mandelblatt JS, Lawrence WF, Womack SM, Jacobson D, Yi B, Hwang YT, et al. Benefits and costs of using HPV testing to screen for cervical cancer. *J Am Med Assoc* 2002;287(18):2372–81.
- [15] Goldie SJ, Kim JJ, Myers E. Chapter 19: cost-effectiveness of cervical cancer screening. *Vaccine* 2006;24(Suppl 3):S164–70.
- [16] Snoeck R. Papillomavirus and treatment. *Antivir Res* 2006;71(2–3):181.
- [17] Wright Jr TC, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. Consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in-situ. *Am J Obstet Gynecol* 2007;197(4):340–5.
- [18] Kesic V. Management of cervical cancer. *Eur J Surg Oncol* 2006;32(8):832–7.