



CHAPTER

63

*Screening
for Human
Papillomavirus
Infection*

By J. Kenneth Johnson

Screening for Human Papillomavirus Infection

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The Canadian Task Force on the Periodic Health Examination has not issued prior recommendations on screening for Human Papilloma Virus (HPV), although clear recommendations have been made for cervical cancer screening (see Chapter 73). HPV is of increasing interest because evidence linking HPV infection and increased risk for cancer of the cervix has been accumulating. This report reviews the evidence for and against HPV screening in asymptomatic women and concludes that screening should not be done since therapy is ineffective and potentially harmful.

Burden of Suffering



HPV commonly exists in a subclinical form (only about 10% of those infected have visible condylomata)

Much of the epidemiology of HPV remains to be determined, and precise estimates of incidence and prevalence are not available. Condylomata acuminata (proliferative HPV) is reportable in the United Kingdom, where it is the most frequently diagnosed viral sexually transmitted disease (STD). Data from STD clinics in the U.K. and Australia indicate a prevalence of genital warts of 4-13% in clinic attenders. These data are based on visible condylomata and considerably underestimate prevalence, since HPV commonly exists in a subclinical form (only about 10% of those infected have visible condylomata, while 20% have lesions demonstrable by colposcopy or magnifying lens). A large Canadian study of a screening program for cervical cancer in the late 1970s showed that 1.69% of 234,715 women had signs of cervical HPV on cytological examination. In a population-based study of 63,115 Finnish women aged 20-65 years, the estimated lifetime risk of infection with HPV was calculated to be 79%. HPV prevalence varies widely from 0.8% to 88% depending on the groups studied. Rates in STD clinics, for sexually active adolescents and sexual contacts of women with HPV all show higher prevalence. Those with more lifetime sexual partners and younger women (in their teens and twenties) are at significantly greater risk for HPV infection.

Over 60 separate serotypes of HPV have been identified to date. HPV-16 and HPV-18 are most closely associated with risk for genital cancers. Numerous epidemiological studies, with or without viral typing, have confirmed the connection between HPV infection and cervical cancer, as well as the correlation between the presence of

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HPV and increasing grade of disease.<1-11> A study by Meisels and Morin in Quebec found evidence of HPV (koilocytosis) on Pap smear in 1.69% of over 234,000 women screened, while HPV was found in 25.6% of Pap smears showing either dysplasia or neoplasia.<12>

In Canada in 1993 approximately 1,300 new cases of invasive carcinoma of the cervix were diagnosed, and about 400 deaths were expected to occur from this disease. The yearly overall cost of invasive disease and death in Canada from cervical cancer has been estimated at 180 to 270 million dollars.

The natural history of untreated HPV infection is not well understood, since different studies have reported different outcomes. In a Finnish prospective study, a cohort of 343 women was followed for a mean of 18.7 months. Twenty-five percent of lesions regressed spontaneously, while 61% remained unchanged and 14% progressed to carcinoma.<13> In a cohort of 100 women followed in the U.K. for a minimum of 19 months, 11 showed spontaneous regression, 64% no change, and 26% progressed to cervical intraepithelial neoplasia (CIN) type 3.<5> Two hundred and thirty-five women with mild to moderate cervical dysplasia and HPV infection were followed in Canada for up to 24 months without treatment.<14> Nine (5.5%) patients showed progression, 134 (57%) converted to normal cytology, and the rest were unchanged during follow-up. Although the likelihood of progression of HPV infection is most consistently associated with presence of HPV-16<15-17> some studies have failed to demonstrate such a relationship<18> and the importance of HPV typing in screening is therefore unclear.

Maneuver

Until recently, HPV infections have been most commonly diagnosed by simple visual inspection or with the aid of a hand lens. For proliferative lesions, this is a highly specific but very insensitive technique. Application of 3-5% acetic acid to the area allows visualization of some other features of HPV, and with the addition of colposcopy can improve the sensitivity of clinical examination. However, visible proliferative lesions are less likely to be caused by HPV types associated with a greater risk of cancer.

Pap smears have been used to identify changes related to HPV infection but are only moderately sensitive (15%).<19> Pap smears are also unable to distinguish the types of HPV with any acceptable degree of accuracy. In a population-based screening program for cervical cancer, the sensitivity of cytology for HPV infection was estimated at 19%. A small study (21 women) in the U.S. attempted to determine the sensitivity and specificity of cytology and colposcopy relative to hybridization techniques in diagnosing HPV infection.<20> Pap smear sensitivity was 57% when equivocal smears were scored as negative for HPV, with specificity of 50%, but 100% sensitive when equivocal



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smears were considered positive for HPV. Colposcopy had a sensitivity of 100% but specificity of only 10-20%. Reid *et al* compared cervical cytology, cervicography and/or DNA hybridization for HPV as screening techniques for cervical cancer among 1,012 women.<21> Pap smears had a sensitivity of 52.2%. No single technique succeeded in identifying all of the abnormalities, but the best (96%) sensitivity was achieved by retesting only those women with an initial high-grade cytologic abnormality or positive cervicography results. In the cohort study of Koutsky *et al*,<3> 27 of the 28 women who developed CIN 2/3 had cytological evidence of CIN 2/3 as well as a positive HPV DNA test, and the 28th woman had CIN 1 on cytology prior to biopsy.

Papillomavirus group-specific antigen can be detected by immunohistochemical staining of cell or tissue samples, but has low specificity and is unable to differentiate between HPV types. The correlation between presence of antigen and clinical outcome is poor.<15,22>

Southern blot and dot blot methods were developed using biopsy material (although they may now use 'non-invasive' cervical/vaginal scrapings) and are based on identifying viral DNA separated from cellular DNA through gel electrophoresis. The method is not well-suited to mass screening because it is time-consuming, labour-intensive, and consequently relatively expensive. Hybridization assays are relatively new methods for detection of HPV and are limited by as-yet poorly defined sensitivity and specificity and problems of interpretation, at least partly related to adequacy of sampling technique.<15,11,20,21,23,24> *In situ* hybridization is less sensitive than the other DNA identification techniques; the filter *in situ* method may have a higher incidence of false-positive reactions. The polymerase chain reaction (PCR) is extremely sensitive but may also have a significant false-positive rate.

Effectiveness of Early Detection and Treatment

There is no effective therapy for HPV infection that is specific or consistently produces long-term success. Many types of physical or chemically destructive agents (conization,<25> cryosurgery, lasers, salicylic acid, cantharidin, bi- and trichloroacetic acid), as well as chemotherapeutic agents (podophyllin, 5-fluorouracil, bleomycin) have been used for treating common warts or genital condylomata. The success rate for all of these therapies has been discouraging. For example, a randomized controlled clinical trial of patient-administered Podophyllotoxin (one of the active lignans present in podophyllin resin) showed complete clearing of penile warts in 53.3% of 34 patients, but 100% recurrence in all the patients who returned after 16 weeks for



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follow-up.<26> High recurrence rates of visible genital warts are typical of almost all studies with sufficiently long follow-up.

Two therapeutic approaches that have had somewhat better results are interferon therapy<27-29> and CO2 laser vaporization.<30-33> Although the 'cure' rates are generally better than are usually seen with the older therapies, a significant recurrence rate remains in most studies as well as a good 'cure' rate in untreated subjects, suggesting that no treatment may be a reasonable approach in many circumstances.

It should be emphasized that the goal of treatment may vary between individuals. Complete or permanent elimination of visible condylomata may not matter if the main concern is cancer detection or prevention. Older chemical treatments may be more acceptable to some patients than the newer, more invasive and expensive techniques such as laser vaporization. Currently, no therapy exists for non-visible (latent) HPV infection, and the value of detecting such latent infections through screening is unclear. Potential harmful effects include morbidity of testing and treatment, financial cost of the testing and therapeutic load and labelling of otherwise healthy individuals as STD patients.

Recommendations of Others

A Canadian workshop on cervical cancer screening held in 1989 found that there was insufficient evidence to routinely add specific tests for HPV to screening for cervical cancer.

Conclusions and Recommendations

The present screening recommendations for cervical cancer do not include specific testing for HPV infection beyond the recommendations for Pap smear screening. Current criteria for recall testing are appropriate for balancing false negative and false positive rates for Pap smears alone as a screening procedure. Addition of further diagnostic testing to the present routine would add little to the effort to reduce cervical cancer incidence. Further testing would, however, increase monetary costs considerably, stretch the existing system beyond its capacity (especially with a rapid increase in referrals for colposcopy), and likely create considerably more morbidity in terms of quality of life for many persons screened, without adding established benefit. For specific HPV screening procedures, given the prevailing imprecision of diagnostic testing for HPV, uninterpretable risk of significant disease, and generally ineffective treatments for HPV infection, there is fair evidence to exclude HPV screening from the routine periodic health examination (D Recommendation).

Unanswered Questions (Research Agenda)

The following have been identified as research priorities:

1. To refine a diagnostic method which will be sensitive and specific, non-invasive and appropriate for large-scale screening purposes to identify the type of HPV present or to predict which lesions are likely to progress.
2. To define more precisely the incidence of HPV infections in the general population.
3. To assess the risks associated with specific HPV genotypes for progression to genital cancers.
4. To identify co-factors which influence HPV transmission and which may promote carcinomatous changes in cervical lesions.
5. To develop effective methods of treating HPV infection.
6. To develop immunological therapies for HPV, especially regarding a possible vaccine.
7. To assess the efficacy of screening for HPV, including assessment of cost effectiveness of such a program.

Evidence

A literature search using MEDLINE was conducted from 1966 to June 1993, using the key words: papillomavirus, cervix neoplasms, mass screening, prospective studies, prevalence, sensitivity, specificity, human and female.

This review was initiated in January 1992 and recommendations were finalized by the Task Force in June 1992. A technical report (1993) with a full reference list is available upon request.

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Screening for Human Papillomavirus Infection

MANEUVER	EFFECTIVENESS	LEVEL OF EVIDENCE <REF>	RECOMMENDATION
<p>Human Papillomavirus (HPV) screening (added to Pap smear screening for cervical cancer*) using any of the following diagnostic tests: Visual inspection, Pap smear, Colposcopy/cervicography HPV group-specific antigen, DNA probe, Dot blot, Southern Blot or polymerase chain reaction</p>	<p>HPV is associated with increased risk and grade of cervical cancer.</p> <p>The natural history of untreated HPV infection is poorly understood and there is no effective therapy that produces long-term success.</p> <p>HPV diagnostic maneuvers have poor test characteristics or are invasive, costly or inadequately studied. Adverse effects of screening include: morbidity of testing and treatment, associated costs and labelling. Adding HPV screening to screening protocols for cervical cancer has not been studied.</p>	<p>Cohort<3-6> and case-control<8,11> studies (II-2)</p> <p>Randomized controlled trials<26-29,33> (I); cohort studies<27> (II-2); case series<24> (III) for various therapies</p> <p>Case Series<3,11,15, 19-24> (III)</p>	<p>Fair evidence to exclude from periodic health examination (D)</p>

* The Task Force recommends Pap smear screening (B Recommendation), see Chapter 73.