PERIODIC HEALTH EXAMINATION, 1995 UPDATE: 1. SCREENING FOR HUMAN PAPILLOMAVIRUS INFECTION IN ASYMPTOMATIC WOMEN

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Objective: To develop recommendations for practising physicians on the advisability of screening for human papillomavirus (HPV) infection in asymptomatic women.

Options: Visual inspection, Papanicolaou testing, colposcopy or cervicography, use of HPV group-specific antigen, DNA hybridization, dot blot technique, Southern blot technique or polymerase chain reaction followed by physical or chemical therapeutic intervention.

Outcomes: Evidence for a link between HPV infection and cervical cancer, sensitivity and specificity of HPV screening techniques, effectiveness of treatments for HPV infection, and the social and economic costs incurred by screening.

Evidence: MEDLINE was searched for articles published between January 1966 to June 1993 with the use of the key words "papillomavirus," "cervix neoplasms," "mass screening," "prospective studies," "prevalence," "sensitivity," "specificity," "human" and "female."

Values: Proven cost-effective screening techniques that could lead to decreased morbidity or mortality were given a high value. The evidence-based methods and values of the Canadian Task Force on the Periodic Health Examination were used.

Benefits, harms and costs: Potential benefits are to prevent cervical cancer and eliminate HPV infection. Potential harmful effects include the creation of an unnecessary burden on the health care system and the labelling of otherwise healthy people as patients with a sexually transmitted disease for which therapy is generally ineffective. Potential costs would include expense of testing, increased use of colposcopy and treatment.

Recommendations: There is fair evidence to exclude HPV screening (beyond Papanicolaou testing for cervical cancer) in asymptomatic women (grade D recommendation).

Validation: The report was reviewed by members of the task force and three external reviewers who were selected to represent different areas of expertise.

Sponsors: These guidelines were developed and endorsed by the task force, which is funded by Health Canada and the National Health Research and Development Program. The principal author (K.J.) was supported in part by the National Health Research and Development Program through a National Health Fellowship (AIDS).

Objectif : Formuler, à l'intention des médecins praticiens, des recommandations sur l'opportunité d'effectuer des tests de dépistage d'infection au virus des papillomes humains (VPH) chez les femmes asymptomatiques.

Options : Inspection visuelle, test de Papanicolaou, colposcopie ou cervicographie, utilisation de l'antigène spécifique au groupe VPH, hybridation de l'ADN, «dot blot», technique de transfert de

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Southern ou réaction en chaîne de polymérase suivis d'interventions thérapeutiques physiques ou chimiques.

Résultats : Indication d'un lien entre une infection au VPH et le cancer du col, sensibilité et spécificité des techniques de dépistage du VPH, efficacité des traitements de l'infection au VPH et coûts socio-économiques du dépistage.

Preuves : On a effectué dans MEDLINE une recherche d'articles publiés entre janvier 1966 et juin 1993 en utilisant les mots clés «papillomavirus», «cervix neoplasms», «mass screening», «prospective studies», «prevalence», «sensitivity», «specificity», «human» et «female».

Valeurs : On a accordé une grande valeur aux techniques de dépistage rentables éprouvées qui pourraient entraîner une baisse de la morbidité ou de la mortalité. On a utilisé les méthodes et les valeurs fondées sur les preuves du Groupe d'étude canadien sur l'examen médical périodique.

Avantages, préjudices et coûts : Les avantages possibles consistent à prévenir le cancer du col et à éliminer l'infection au VPH. Les effets préjudiciables possibles comprennent l'imposition d'un fardeau inutile au système de soins de santé et la désignation de personnes autrement en bonne santé comme patients ayant une maladie transmise sexuellement dont le traitement est en général inefficace. Les coûts possibles comprendraient les frais liés aux examens, à l'utilisation accrue de la colposcopie et au traitement.

Recommandations : Il y a de bonnes indications pour exclure le dépistage du VPH (outre le test de Papanicolaou pour le dépistage du cancer du col) chez les femmes asymptomatiques (recommandation de catégorie D).

Validation : Le rapport a été examiné par les membres du groupe de travail et par trois critiques de l'extérieur choisis pour représenter divers domaines de compétence.

Commanditaires : Ces lignes directrices ont été élaborées et appuyées par le groupe d'étude, qui est financé par Santé Canada et le Programme national de recherche et de développement en matière de santé. Le principal auteur (K.J.) a été appuyé en partie par le Programme national de recherche et de développement en matière de santé dont il est boursier national (recherche sur le SIDA).

No prior recommendations from the Canadian Task Force on the Periodic Health Examination deal specifically with screening for human papillomavirus (HPV) infection, although recommendations from the task force and other groups do exist concerning screening for cervical cancer.[1-7] In the past decade or so, there has been an accumulation of evidence linking HPV infection with an increased risk for cervical cancer.[8-13] The purpose of this report was to evaluate and grade existing evidence and offer guidelines to primary care physicians for screening asymptomatic women for HPV infection. The clinical options considered were routinely screening all women, screening women at high risk (e.g., those whose sexual partners have condylomas) or no routine screening. The health outcomes considered were persistence of HPV infection, cure rates for HPV treatment, risk of cervical cancer following infection with HPV, negative consequences of a diagnosis of HPV infection ("labelling effect"), and the financial and social costs of expanded screening programs for HPV infection.

A MEDLINE search of articles published from January 1966 to June 1993 was done with the use of the terms "papillomavirus," "cervix neoplasms," "mass screening," "prospective studies," "prevalence," "sensitivity," "specificity," "human" and "female." The methods established by the task force were used for evaluating and grading the evidence.[7] Studies were selected and evaluated to determine the epidemiologic features and natural history of HPV infection, the relation between HPV infection and cervical cancer, and the effectiveness of diagnostic and therapeutic intervention. High values were assigned to articles of proven cost-effective screening techniques that could lead to decreased morbidity and mortality.

The principal author (K.J.) conducted the literature review and provided an oral and written report to the task force members. The report was critically reviewed by the task force and later by three external experts.

Burden of suffering

Despite the success of large, organized screening programs for the early detection of cervical cancer in reducing the incidence of invasive disease,[14] cervical cancer remains a significant cause of morbidity and mortality. In Canada in 1993 approximately 1300 new cases of invasive cervical cancer were diagnosed, and about 400 deaths were expected to occur from this disease.[15] In the United States an estimated 13 000 new cases of cervical cancer are diagnosed every year, with about 7000 deaths annually from prevalent disease.[16] In Canada the yearly overall cost of invasive disease and death from cervical cancer has been estimated at $180 to $270 million.[1]

Many of the epidemiologic features of HPV infection remain to be determined, and precise estimates of the incidence, prevalence and natural history of this infection are unavailable. Cases of condylomata acuminata (proliferative HPV infection) are reportable in Britain, where it is the most frequently diagnosed viral sexually transmitted disease (STD).[17] Data from STD clinics in Britain[18] and Australia[19] indicate a prevalence of 4% to 13% among clinic attendees. These data, however, are based on visible condylomata and consequently underestimate the true prevalence of HPV in-

fection, since this condition is commonly subclinical. It has been estimated that about 10% of people infected with HPV have visible lesions, 20% have lesions demonstrable with the use of colposcopy or a magnifying lens, and 70% have subclinical infection.[20] Subclinical infection can be detected only through clinical or laboratory testing, including Papanicolaou smears.

Screening for HPV infection

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 infection on cytologic examination.[21] A population-based study involving 63 115 women aged 20 to 65 years used data from a cervical cancer screening program from 1981 to 1989.[22] The overall prevalence of HPV infection detected by means of cytologic examination was 0.80%, although the annual figures increased, from 0.04% in 1981 to 1.04% in 1989. From this study a subset of 1289 women aged 22 years were found to have a prevalence of HPV infection of 3%, which increased to 7% 1 year later;[23] the estimated lifetime risk of HPV infection in this sample was calculated to be 79%. In Germany 9295 women 15 to 81 years of age who attended outpatient gynecology clinics underwent Papanicolaou testing and filter in-situ DNA hybridization;[24] 2% had specific signs of HPV infection on the Papanicolaou smears, whereas 9% were found to be HPV positive through the DNA hybridization.

Results from 10 recent surveys of HPV prevalence in various populations are presented in Table 1. The overall prevalence rates varied from 0.8%[22] to 88%[32] depending on the groups studied. As expected, since HPV infection is known to be an STD, rates among patients in STD clinics, sexually active adolescents and sexual contacts of women with HPV infection were higher than rates in other groups. Generally, although there were some exceptions,[26] the number of lifetime sexual partners has been a major factor in determining the risk of HPV infection. When it was possible to examine the effect of age, it was found that young women (adolescents and women in their 20s) were at significantly greater risk for HPV infection than older women.

Evidence linking HPV infection to cervical cancer

The primary issue of concern is the possible link between HPV infection and cervical cancer. Although there have been discussions on the links between HPV infection and squamous cell carcinomas of the larynx, nasal cavity and paranasal sinuses, lung and esophagus[33] these links have not been extensively studied; in this article we will concentrate on the possible association with cervical cancer.

The association between HPV infection and cervical cancer has been supported by evidence from animal studies,[34,35] molecular biology,[36–38] clinical case reports[39,40] and epidemiologic studies.[9–11,41–44] The earliest direct link between a papillomavirus infection and malignant transformation was reported in 1935, in rabbits with infectious papillomatosis (Shope papilloma).[34] A second example from animal studies is the malignant transformation of bovine papillomas under the influence of environmental factors in cattle.[35]

The development of DNA hybridization techniques in the late 1970s has allowed the identification of HPV DNA and the classification of these viruses into different types. Over 60 separate types of HPV have been identified to date, a new type having a genome homology of less than 50% in comparison with other known types.[45] Studies of HPV DNA in a variety of genital lesions have characterized the types of HPV that are most closely associated with risk for genital cancer.[36–38,46–48] The most important types in this regard are HPV types 16 and 18. In 1984 Gissmann and associates[36] reported finding one or both of these HPV types in 57.4% of cases of invasive cervical cancer. In a study from Scotland involving 30 women with different genital cancers HPV-16 DNA was found in 84% of the tumours and HPV-18 DNA in 8%.[37] Koutsky, Galloway and Holmes[20] combined and analysed the results of four studies[38,46–48] meeting predetermined criteria to examine the association between cancer and HPV types 16 and 18 relative to types 6 and 11 (usually considered to be associated with condylomata and low-grade cervical intraepithelial neoplasia [grade 1 CIN]). The latter two types of HPV had an inverse relation to increasing severity of histologically defined cervical lesions, whereas HPV-16 or HPV-18 was found in 20% of the patients with grade 1 CIN lesions, 51% of those with grade 2 or 3 CIN lesions and 63% of those with invasive cervical cancer which showed a strong positive association.

Epidemiologic studies, with or without viral typing, have confirmed the connection between HPV infection and cervical cancer.8 Table 2 summarizes the findings of 11 such studies within the past decade that have demonstrated an association between HPV infection and cervical cancer, as well as the correlation between the presence of HPV infection and increasing grade of disease. Meisels and Morin[21] found evidence of HPV infection (koilocytosis) on Papanicolaou smears in 1.69% of over 234 000 women screened in Quebec and in 25.6% of those whose Papanicolaou smears showed signs of either dysplasia or neoplasia. The study by de Villiers and collaborators[24] involving 9295 women showed a prevalence of HPV infection of 5% to 10% among women whose Papanicolaou smears showed no abnormalities but one of 35% to 40% among those whose smears showed any degree of cytologic abnormality. A cohort of 241 women attending an STD clinic in the United States was followed prospectively for a mean of 25 months.[9] The outcome of interest was the time from a first positive HPV DNA test result (dot-blot hybridization) to the development of grade 2 or 3 CIN. The 2-year cumulative incidence of grade 2 or 3 CIN was 28% among women with a positive test result, as compared with 3% among

those with a negative test result. Compared with women free of HPV infection, those with cervical HPV infection had a higher relative risk (RR = 11; attributable risk 78%) of having grade 2 or 3 CIN.

Natural history of HPV infection

The natural history of untreated HPV infection is not well understood, since studies have shown different outcomes.[8,12,13,20,42,49] In a prospective study in Finland 343 women were followed for a mean of 18.7 months after identification of cervical HPV infection;[49] 25% of the lesions regressed spontaneously, 61% remained unchanged, and 14% progressed to carcinoma. In a group of 100 women followed in Britain for a minimum of 19 months spontaneous regression occurred in 11%, no change was noted in 64%, and CIN developed in 26%.[42] HPV-16 (but not HPV-6) was significantly associated with time to progression. In another study 235 women in Canada with mild to moderate cervical dysplasia and HPV infection were followed for up to 24 months without treatment.[12] Of the 163 who were not lost to follow-up, progression was evident in 9 (6%), spontaneous regression occurred in 134 (82%), and there was no change in the remaining 20 (12%).

Most of the studies of the natural history of HPV infection involved the use of diagnostic cervical biopsies or other interventions and therefore may not accurately reflect the true course of HPV infection. Although the likelihood

Table 1: Reported prevalence of human papillomavirus (HPV) infection*

Study	Type of study	Screening tests	Patient population	Results
Syrjanen et al, Finland, 1990[22]	Population-based survey	Papanicolaou smear	63 115 women aged 20 to 65 yr	HPV rate 0.8% overall; 6.1% among those 20 to 29 yr and 2.2% among those 30 to 39 yr
De Villiers et al, Germany, 1987[24]	Survey	Papanicolaou smear, filter in-situ DNA hybridization	9 295 women seen at outpatient gynecology clinics	HPV rate 10% to 13% among those 15 to 50 yr and 2% to 5% among those over 55 yr
Collins et al, Hong Kong, 1990[25]	Survey	Papanicolaou smear, in-situ DNA hybridization	215 pregnant women	HPV rate 1.5% through Papanicolaou testing and 5% through DNA hybridization
Rohan et al, Canada, 1991[26]	Survey	PCR	105 women from a student health clinic	HPV rate 18.1% overall, 2.9% for HPV-6 and -11, and 10.5% for HPV-16 and -18
Fisher et al, United States 1991[27]	Survey	Southern blot technique	107 female adolescents at a suburban adolescent health service	HPV rate 32% overall
McKinnon et al, Australia, 1991[28]	Survey	Papanicolaou smear, cervicography	245 women aged 16 to 53 yr at an STD clinic	HPV rate 41% overall (18% through Papanicolaou testing); 20.4% among those with CIN (8.2% through Papanicolaou testing)
Van den Brule et al, the Netherlands, 1991[29]	Survey	Papanicolaou smear, PCR	1 346 asymptomatic women, 593 gynecology outpatients	HPV rates for those with normal smears were 3.5% among asymptomatic women and 14% among outpatients; HPV rates for those with abnormal smears were 70% among women with mild dysplasia, 84% among those with severe dysplasia and 100% among those with CIN
Horn et al, United States, 1991[30]	Survey	Papanicolaou smear, Southern blot technique	116 women at an STD clinic	17% had visible warts, 41% had an abnormal Papanicolaou smear, and 12% had a positive Southern blot result
Mandal et al, Britain, 1991[31]	Survey	Cytologic examination, DNA hybridization	105 asymptomatic men at an STD clinic	HPV rate 40% overall, 27% by cytologic examination and 20% by DNA hybridization
Chow et al, Singapore, 1991[32]	Case series	Colposcopy	25 male partners of women with genital HPV infection or CIN	Subclinical HPV infection in 88%

*PCR = polymerase chain reaction, STD = sexually transmitted disease, CIN = cervical intraepithelial neoplasia.

of progression is most consistently associated with the presence of HPV-16 and less so with other types of HPV[8,13,20] has not been universally demonstrated.[50] It is still uncertain how useful it would be to screen for HPV-16 or other HPV types.

Detection manoeuvre

Until fairly recently HPV infection has been diagnosed most commonly by means of visual inspection, with or without the use of a hand lens.[20] Visual inspection for proliferative lesions is a highly specific technique but, given the current understanding of latency with papillomaviruses, is not very sensitive. Application of 3% to 5% acetic acid to the area will allow visualization of some other features of HPV infection and, with the addition of colposcopy, can improve the sensitivity of clinical examination.[8,20] In general, visible proliferative lesions are more likely to represent infection with HPV type 6 or 11 than infection with type 16 or 18 or other types of HPV that are thought to imply a greater risk of cancer.[46,47,51] Papanicolaou testing has been used to identify changes related to HPV infection (mainly koilocytosis) but is only moderately sensitive in this regard. Like visual inspection and colposcopy, Papanicolaou testing is unable to distinguish different types of HPV with any acceptable degree of accuracy. A summary of available tests for HPV, with their relative sensitivities and specificities, is outlined in Table 3.

A recent study of the accuracy of Papanicolaou testing showed that among women with koilocytosis such testing had a sensitivity of only 15% in diagnosing HPV infection.[55] In a population-based screening program for cervical

Table 2: Evidence of association between HPV infection and cervical cancer

Study	Type of study	Patient population	Results
Koutsky et al, United States, 1992[9]	Prospective cohort study	241 women at an STD clinic	28% of HPV-positive women and 3% of HPV-negative women had grade 2 or 3 CIN; relative risk (RR) = 11 for HPV-positive women in relation to HPV-negative women
Reeves et al, Latin America, 1989[10]	Case–control study	759 women with invasive cervical cancer; 1467 control subjects	Odds ratio (OR) for cervical cancer was 2.9 to 9.1 according to strength of DNA hybridization reaction
Schiffman et al, United States, 1993[11]	Case–control study	500 women with CIN (grades 1 through 3); control subjects were 500 women with normal cytologic test results	76% of cases of CIN (90% and 88% of grade 2 and 3 CIN respectively) attributed to HPV infection
De Villiers et al, Germany, 1987[24]	Cross-sectional study	9295 women at outpatient gynecology clinics	HPV rate 5% to 10% among women with normal Papanicolaou smears, 35% to 40% among those with CIN or cervical cancer
Van den Brule et al, the Netherlands, 1991[29]	Prevalence survey	1346 asymptomatic women, 593 gynecologic outpatients	HPV rates for those with normal Papanicolaou smears were 3.5% among asymptomatic women and 14% among outpatients; HPV rates for those with abnormal smears were 70% among women with mild dysplasia, 84% among those with severe dysplasia and 100% among those with CIN
Ritter et al, United States, 1988[39]	Survey	191 women at hospital colposcopy clinic	OR 11.8 for CIN or cancer among HPV-positive women
Rader et al, United States, 1991[40]	Case series	30 women with atypical Papanicolaou smears, normal smears or CIN	HPV rate 17% among those with normal smears, 33% among those with atypical smears and 59% among those with CIN
Mitchell et al, Australia, 1986[41]	Cohort study	846 women with HPV infection alone on Papanicolaou smear	Cancer in situ in 3.5% of patients after 6-yr follow-up; RR = 15.6 relative to population incidence figures
Campion et al, Britain, 1986[42]	Cohort study	100 women with signs of mild atypia on Papanicolaou smear and colposcopy	HPV-16 found in 39% overall and in 85% of those showing signs of progression to grade 3 CIN
Pagano et al, Australia, 1987[43]	Cohort study	429 women with HPV infection on Papanicolaou smear	13.6% were found to have CIN initially; CIN found in additional 10% over 3 yr
Borst et al, United States, 1991[44]	Cross-sectional study with concurrent control subjects	50 women referred with atypia but not dysplasia on Papanicolaou smear	HPV rate 46% among patients with abnormal smears and among those with CIN, 11.6% among those with normal smears; HPV-16 DNA screen *not* predictive of CIN

cancer the sensitivity of cytologic examination for HPV infection was estimated at 19%, the denominator being the expected number of cases of HPV infection taken from population estimates.[57] A small study (involving 21 women) in the United States attempted to determine the sensitivity and specificity of cytologic examination and colposcopy relative to DNA hybridization techniques in diagnosing HPV infection;[53] the sensitivity of Papanicolaou smears was 57% when equivocal smears were negative for HPV, with a specificity of 50%, but the sensitivity was 100% when equivocal smears were considered positive for HPV. Colposcopy had a sensitivity of 100% but a specificity of only 10% to 20%. Reid and colleagues[54] performed a prospective survey of 1012 women from either an STD clinic or private gynecologists' offices to assess cervical cytologic examination, cervicography and DNA hybridization for HPV as screening techniques for cervical cancer. Papanicolaou testing had a sensitivity of 52.2%. No single technique succeeded in identifying all of the abnormalities, but the best sensitivity (96%) was achieved through the retesting of only women with an initial high-grade cytologic abnormality or positive cervicography result. In the prospective cohort study of Koutsky and coworkers[9] 27 of the 28 women in whom grade 2 or 3 CIN developed had cytologic evidence of grade 2 or 3 CIN as well as a positive HPV DNA hybridization test result; the other woman had grade 1 CIN on cytologic examination before biopsy.

One major limitation of laboratory testing for HPV infection is the inability to grow these viruses in vitro in a laboratory setting. HPV group-specific antigen can be detected by means of immunohistochemical staining of cell or tissue samples; however, this method shows a lack of specificity, an inability to differentiate between HPV types and a poor correlation between presence of antigen and clinical outcome.[20,57]

Other laboratory approaches for diagnosing HPV infection rely on the identification of HPV DNA through hybridization techniques that use a known nucleic acid probe. These tests are in-situ hybridization, filter in-situ hybridization, the Southern blot technique and the dot blot technique.[11,20,53,58] In-situ hybridization involves the detection of HPV DNA in fixed or frozen tissue sections and is relatively less sensitive than the other techniques. The filter in-situ method involves hybridization against specific DNA probes after transfer of exfoliated cells to a filter; this technique has the advantages of being easy to perform and not requiring a biopsy specimen but may have a higher incidence of false-positive reactions. The Southern blot and dot blot techniques were designed to use biopsy material (although they may now be performed with material collected from "noninvasive" cervical or vaginal scrapes); they involve the identification of viral DNA separated from cellular DNA through gel electrophoresis.

Most research settings tend to use the Southern blot technique as their gold standard, but it is not well-suited as a widespread screening technique because it is time consuming, labour intensive and, consequently, expensive. The hybridization assays are relatively new methods for detecting HPV and are limited by as-yet poorly defined sensitivity and specificity and problems of interpretation, at least in part because of the adequacy of the sampling technique.

Table 3: Characteristics of tests available for diagnosing HPV infection

Test	Sensitivity/specificity	Advantages	Disadvantages
Visual inspection[20]	Low/high	Easy to perform, rapid	Identifies only visible proliferative lesions; cannot type HPV
Papanicolaou testing[1,52]	Low/high	Inexpensive	Low sensitivity; cannot type HPV
Colposcopy or cervicography[53,54]	Moderate/low	More sensitive than Papanicolaou testing	Low specificity; cannot type HPV
Group-sepcific antigen[53,55,56]	Moderate/low	More sensitive than Papanicolaou testing	Cannot type HPV
In-situ DNA hybridization[53,55,56]	Moderate/high	Can localize HPV DNA in tissue; good sensitivity and specificity; can type HPV	Time and labour intensive
Dot blot technique[53,55,56]	Moderate/high	Easy to perform, rapid, relatively inexpensive; can type HPV	Relatively less sensitive; cannot localize HPV in tissue
Southern blot technique[53,55,56]	High/high	High sensitivity and specificity; good ability to distinguish HPV types	Labour intensive, expensive, requires expertise; cannot localize HPV DNA in tissue
PCR[54,56]	High/high	Extremely high sensitivity; uses fresh or fixed tissue samples; can type HPV	Risk of false-positive results; extreme care needed in handling specimens

The polymerase chain reaction is a recently developed technique in which target DNA sequences are amplified in vitro to levels that greatly enhance their detection by conventional techniques of dot blot hybridization. This procedure is extremely sensitive but may have a significant false-positive rate. It is yet unclear how useful this method may be in screening for HPV infection.

Effectiveness of early detection and treatment

There is no effective therapy for HPV infection that is specific or that consistently produces long-term success.[45,59,60] Many physically or chemically destructive methods and agents (cryosurgery, laser therapy, salicylic acid, cantharidin, dichloroacetic acid and trichloroacetic acid) and chemotherapeutic agents (podophyllin, 5-fluorouracil and bleomycin) have been used to treat common warts and genital condylomata.[60,61] 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 lignins present in podophyllin resin) showed complete clearing of penile warts in 53.3% of 34 patients but a recurrence rate of 100% in the patients who returned after 16 weeks for follow-up.[59] High rates of recurrence of visible genital warts are typical of almost all studies with sufficient length of follow-up. The destructive treatments often have a good success rate in the short term, but either because of inadequacy of treatment or inability to treat nonvisible areas of HPV infection the long-term success rate is generally poor.[59–64]

Two therapeutic approaches that have had somewhat better results are interferon therapy and carbon dioxide laser vaporization.[62–69] A summary of recent trials of these treatments is presented in Table 4. The study by Carmichael and Maskens,[12] in which no treatment was given, is included for comparison. Although the "cure" rates were generally better than usually seen with the older therapies, the recurrence rate was still high in most studies (35% to 90% depending on the length of follow-up); also, the cure rate was good in the group of untreated subjects, which suggests that no treatment is a reasonable approach in many circumstances.

The goal of treatment may vary. Complete or permanent elimination of visible condylomata is one goal. Cancer de-

Table 4: Trials of treatment of HPV infection

Study	Type of study	Intervention	Subjects	Results
Carmichael et al, Canada, 1989[12]	Cohort study	No treatment	235 women with mild to moderate dysplasia and HPV infection	2-yr follow-up: signs of progression in 10%, no change in 60% and regression in 30%
Ferenczy et al, Canada, 1985[62]	Case series	Carbon dioxide (CO_2) laser therapy	20 patients with genital warts or CIN	6-mo follow-up: recurrrence in 35% overall; recurrence in 67% with HPV infection and in 9% without HPV infection
Riva et al, United States, 1989[63]	Case series	CO_2 laser therapy	16 women with vulvar papillomatosis	Cure in 19%, relapse in 81%; mean time 4.6 mo
Shafi et al, Britain, 1990[64]	Case series	CO_2 laser therapy	25 women with HPV lesions	High morbidity; persistent subclinical HPV infection in 88%
Eron et al, United States, 1986[65]	Randomized controlled trial	Intralesional α-2b interferon (IFN) therapy	296 patients with genital warts	Reduced wart size with IFN at 13 wk; cure rate 13% with IFN and 17% with placebo; no long-term follow-up
Yliskoski et al, Finland, 1990[66]	Randomized controlled trial	IFN cream v. placebo for 1 yr	19 women with CIN and infection with HPV-16	No difference clinically: remission in 44% (4/9) of women given IFN and in 70% (7/10) of those given placebo; 33% (3/9) in IFN group and 70% (7/10) in placebo group remained HPV positive
Dunham et al, Britain, 1990[67]	Randomized controlled trial	Perilesional injections of IFN v. no treatment	14 women with CIN	Clinical improvement in 86% (6/7) of women given IFN and in 43 (3/7) of control subjects
Yliskoski et al, Finland, 1991[68]	Cohort study	Conization	116 women with HPV infection and grade 2 or 3 CIN	HPV cured in 82.7% (mean follow-up 32 mo)
Ruge et al, Denmark, 1991[69]	Randomized controlled trial	CO_2 laser therapy v. standard therapy	50 women with HPV infection on Papanicolaou smear	6-mo follow-up: cure rate 100% in laser therapy group and 72% in control group

tection and prevention are others. Older chemical treatments may be more acceptable to some patients than the newer, more invasive and expensive techniques such as laser vaporization. No therapy exists for nonvisible HPV infection, thus there is little value in screening for such latency.

Adverse effects of HPV screening

As with any medical testing procedure, despite the intention to benefit patients, some adverse effects must be considered in screening for HPV infection. These include the following.

- Morbidity of testing and treatment. Although Papanicolaou testing alone has few adverse effects apart from usually minor discomfort, the need for repeat testing, colposcopy, various destructive therapies and possible surgery may have a negative impact on the individual.
- A significant increase in the number of Papanicolaou smears and referrals for colposcopy (on a population basis) would result in large financial and other costs to society, including the increased depletion of resources to deal with the necessary testing and treatment.
- Most people with HPV infection are probably asymptomatic, and diagnosis of HPV infection may produce a significant labelling effect in many individuals. Of major importance is the knowledge that HPV infection is sexually transmissible. Although it may be in a dormant state for many months or years, considerable distress may follow once an otherwise healthy person becomes a "patient."

Recommendations (Table 5)

Given the prevailing state of imprecise diagnostic testing for HPV infection, the uninterpretable risk of subsequent morbidity and the general ineffectiveness of treatments of HPV infection, fair evidence exists to support the recommendation that screening for HPV infection be excluded from the routine periodic health examination of asymptomatic women (grade D recommendation).

The present screening recommendations for cervical cancer do not include specific testing for HPV infection beyond the recommendations for Papanicolaou testing. In the event of an abnormal result further testing (e.g., repeat Papanicolaou testing, colposcopy and biopsy) is at the discretion of the attending physician, often guided by the advice of the testing laboratory. Mass repeat testing of all atypical smears may add too great a burden on existing facilities. Current criteria for recall testing are appropriate for balancing false-negative and false-positive rates for Papanicolaou testing alone as a screening procedure, and the addition of further diagnostic tests to the present routine would add little to the effort to reduce the incidence of cervical cancer. In addition, further testing would considerably increase monetary costs, stretch the existing system beyond its capacity (especially with a rapid increase in the number of referrals for colposcopy) and likely increase morbidity considerably in terms of quality of life for many people, without adding established benefit.

Future research into HPV infection (see Research priorities) should be encouraged, since the ultimate aim of HPV screening — the reduction in the incidence of cervical cancer — continues to be a major research priority. Ultimately, any recommendations regarding HPV screening must be re-examined in the light of findings from further research, since so many current issues remain unresolved.

Validation

Attendees at a national workshop on screening for cervi-

Table 5: Summary of manoeuvre, effectiveness, levels of evidence and recommendation for the screening of HPV infection in asymptomatic women

Manoeuvre	Effectiveness	Level of evidence*	Recommendation*
HPV screening (beyond Papanicolaou testing for cervical cancer) using any of the diagnostic tests mentioned in Table 3	HPV infection is associated with risk and grade of cervical cancer	Cohort[9,41–43] and case–control[10,11] studies (II-2)	Fair evidence to exclude from the periodic health examination (D)
	The natural history of untreated HPV infection is poorly understood, and there is no effective therapy for long-term success	Randomized controlled trials[59,65–67,69] (I), cohort study[68] (II-2) and case series[62–64] (III) for various therapies	
	Diagnostic manoeuvres have poor test characteristics regarding HPV 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	Case series[9,11,20,53–58] (III)	

*For descriptions of levels of evidence and classification of recommendations see Appendix 1 in part 1 of the 1992 update (*Can Med Assoc J* 1992; 147: 443).

cal cancer, held in Ottawa Nov. 27 to 29, 1989, briefly considered HPV infection and cervical cancer.[14] They concluded that there was insufficient evidence to add specific tests for HPV infection to routine screening for cervical cancer. Like the Canadian task force, the US Preventive Services Task Force has made no specific recommendations regarding screening for HPV infection separate from the recommendations for cervical cancer screening.

Research priorities

1. Refining a diagnostic method that will be sensitive, specific, noninvasive and appropriate for large-scale screening purposes to identify the type of HPV present or to predict which lesions are likely to progress to cervical cancer.
2. Defining precisely the incidence of HPV infection in the general population.
3. Assessing the risks associated with specific HPV genotypes for progression to cervical cancer.
4. Identifying cofactors that influence HPV transmission and that may promote carcinomatous changes in cervical lesions.
5. Finding effective treatments for people with HPV infection for whom it can be determined that treatment will produce a net benefit.
6. Developing immunologic therapies, especially a possible vaccine, for HPV infection.
7. Determining the efficacy and cost-effectiveness of screening for HPV infection.

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