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THE SOCIETY OF OBSTETRICIANS
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Canadian Consensus Guidelines on Human Papillomavirus

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Abstract

Objective: To promote guidelines for health care providers on the key aspects of HPV infection and the management of HPV-related disease in the new era of vaccine availability.

Evidence: Medline and Cochrane databases were searched for articles from January 1995 to March 2007 on subjects related to HPV infection, HPV vaccination, HPV-related disease, Pap testing, and specific consideration of management.

Values: The quality of evidence is rated using the criteria described in the report of the Canadian Task Force on the Periodic Health Examination. Recommendations for practice are ranked according to the method described in this report.

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Preamble

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The development of new HPV vaccines has re-energized the evaluation of HPV-related disease and greatly increased the need to clearly understand the biologic features of HPV and related disease so as to inform decision-making on the role of HPV vaccination. These guidelines are designed to summarize the key aspects of HPV infection and allow the clinician to be well informed in managing HPV-related disease in the new era of vaccine availability.

Abbreviations Used in This Guideline

ACIS	adeno-carcinoma in situ
AGC	atypical glandular cells
AGCUS	atypical glandular cells of undetermined significance
ASC-H	atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion
ASC-US	atypical squamous cells of undetermined significance
CI	confidence interval
CIN	cervical intraepithelial neoplasia
EGWs	external genital warts
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
HSV	herpes simplex virus
LBC	liquid-based cytology
LSIL	low-grade squamous intraepithelial lesion
Pap	Papanicolaou
PCR	polymerase chain reaction
RRP	recurrent respiratory papillomatosis
SCC	squamous cell carcinoma
STI	sexually transmitted infection
VIN	vulvar intraepithelial neoplasia

HPV infection is the most common STI, affecting approximately 550 000 Canadians annually. The virus is spread by skin-to-skin contact. HPV infection is so common that most women are likely to be in contact with one or more of the subtypes of this virus at some time in their lives. Herpes simplex and bacterial vaginosis may facilitate cutaneous and mucosal entry of the virus. The prevalence of HPV infection rises rapidly after the onset of sexual activity and then declines with age.

Most infections are unnoticed and resolve spontaneously within 24 months. Classic genital HPV lesions include benign genital warts and cervical, vaginal, anal, and vulvar cancers. Concurrent oral, hand, and genital HPV infection is frequent. Drugs (steroids), diseases (such as diabetes, renal failure, and HIV infection), and cigarette smoking compromise the immune system and may potentiate the problem. Persistent infection with HPV 16 or 18, although infrequent, may lead to cervical dysplasia and cancer.

Almost all cervical and vaginal cancers and a large proportion of vulvar, anal, and oral cancers are associated with high-risk, oncogenic strains of HPV. Low-risk HPV types cause genital warts, RRP, and oral or conjunctival papillomas.

HPV infection is difficult to prevent in sexually active adults, and preventing transmission is much more difficult to achieve with HPV infection than with other STIs. Vaccination may represent the best primary prevention method, as condoms have limited efficacy without consistent use, and abstinence is unacceptable to many. Pap testing may represent the best secondary prevention method.

New paradigms for prevention and diagnosis will evolve as scientists, regulatory agencies, and private-sector companies share agendas. Since Canada provides universal health care to its population, it is our responsibility to seek sound information and promote constructive strategies. Canadian researchers have a strong international presence in the fight against HPV. Integration of HPV vaccination and screening registries would contribute to the study of HPV infection and profoundly affect the history of cervical cancer.

Summary Recommendations

Chapter 1: Epidemiology and Natural History of HPV Infection

There are no recommendations for Chapter 1.

Chapter 2: Clinical Manifestations and Diagnosis of HPV-Related Disease

1. In the presence of EGWs in a prepubertal child, sexual abuse should be considered. IIIA
2. The diagnosis of EGWs in children does not require biopsy. IIIA
3. Cytology of the cervix as a screening test should not be done in women whose cervix exhibits signs and symptoms of cervical cancer. IIIA
4. Patients should be referred for assessment and follow-up when the Pap smear results include ASCUS, ASC-H, AGC, LSIL, HSIL, or any cancer cells, whatever the cell type. IA
5. In a situation of doubt about cancer, need for a biopsy, or warts that are massive, atypical, and/or non-healing, neoplasia should be suspected if a lesion has any of the following features: pigmentation, bleeding, persistent ulceration, persistent pruritus, or recalcitrance. IA
6. Cytology results showing a new diagnosis of cervical cancer should mandate a patient appointment within 3 weeks in a colposcopy clinic, for HSIL and AGC within 6 weeks. IIIA

Chapter 3: The Role of HPV Testing

1. Reflex HPV DNA testing is recommended only for women aged 30 years or more with ASCUS and should be used only as an adjunct to cervical cytology, to reduce the false-positive rate of conventional cytology and increase the negative predictive value of testing. IA
2. There is no indication for HPV testing in women younger than 30 years and therefore it should not be done. IA
3. Because of the high prevalence of high-risk HPV types in women with LSIL, HSIL, and SCC, triage by means of HPV testing should not be done. IA
4. More research should be done to better characterize natural and acquired immunity after HPV infection and vaccination and to redesign screening strategies to focus on identifying women with persistent infection. IIIA

Chapter 4: Prevention

1. Counselling and other educational activities should stress (a) that abstinence is the most efficient way to prevent HPV infection but must include avoidance of not only penetration of the vagina or the anus but also any anogenital contact and the sharing of sex toys, (b) that condoms have some efficacy against HPV infection only if used consistently, and (c) that disappearance of lesions is no guarantee that the patient is not still contagious. II-2B
2. Caesarean section does not prevent neonatal HPV and should be reserved for women for obstetrical indications. II-2B
3. Partner referral does not reduce the risk of re-infection and is not indicated as a preventative measure. II-2B

4. Cervical cancer screening by cytology should be considered a secondary prevention method, intended to discover precancerous lesions and diminish the risk of their progression to cancer. IA
5. Smoking cessation should be strongly recommended to women with an HPV infection or any stage of an associated disease. IA

Chapter 5: Screening for Cervical Cancer

1. The provincial and territorial governments of Canada should implement a publicly funded, organized, population-based cervical cancer screening system in order to move from opportunistic towards organized screening. IA
2. Recommendations for best evidence screening practice based on pan-Canadian data should be made and updated regularly in collaboration between specialty societies and governmental agencies. IA
3. The existing screening systems are successful in reducing the incidence in mortality of cervical cancer and should be preserved without major alterations. IA
4. An HPV vaccination database should be integrated with a cervical cancer screening database, in order to ensure evaluation of vaccination utility at a population level. IA
5. Type-specific HPV testing should be made available within an appropriate algorithm to eligible women in all provinces and territories. IIIA
6. LBC should be made available in all provinces and territories and facilitate reflex HPV testing when appropriate. IA
7. Cervical cancer screening programs should focus on implementing innovative and effective strategies to increase recruitment of women in populations with low rates of screening, such as Aboriginal groups, older women, newcomers to Canada, and marginalized women. IA

Chapter 6: Treatment of External Genital Warts and Pre-invasive Neoplasia of the Lower Genital Tract

1. The management of EGW should include counselling on epidemiology, prevention of infection, and choice of treatment modalities. IIIA
2. A 0.5% solution of podophyllotoxin may be used for self-applied treatment but not in the urethra, vagina, cervix, or anus and not during pregnancy. II-2B
3. In the management of EGW, imiquimod application is preferred when extensive laser treatment requiring general anaesthesia would otherwise be indicated. II-2B
4. In the management of EGW, laser vaporization should be used only when less aggressive treatments have failed. II-2B
5. When EGWs are atypical or do not respond to topical therapy, VIN should be ruled out by biopsy or excision. II-2B
6. EGWs in children should be managed by a professional experienced in both EGWs and the psychosocial implications of the diagnosis. IIIA
7. Therapy for EGWs in immunosuppressed patients involves both correction of the immunosuppression and a combination EGW treatment that includes both ablative and excisional approaches. II-2B

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care*

Quality of evidence assessment†	Classification of recommendations‡
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	I. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. *Can Med Assoc J* 2003;169(3):207-8.

†The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.*

‡Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.*

- 8. Pregnant patients with extensive warts, patients who are immunosuppressed, and patients who are resistant to therapy should be referred to an expert in EGW management. II-2B
- 9. TCA is a first-line therapy for EGW and may be used in the vagina and safely during pregnancy. II-2B

- 3. HPV vaccination is recommended for females aged 9 to 26 years against high-risk HPV types 16 and 18 for prevention of cervical cancer. IA
- 4. HPV vaccination is recommended for females aged 9 to 26 against low-risk HPV types 6 and 11 for prevention of external genital warts. IA

Chapter 7: Cost-Benefit Analysis of HPV Vaccination

- 1. Government agencies should advocate for public funding to evaluate the cost-benefit analyses reported thus far for the HPV vaccines. IIIA
- 2. Additional sensitivity analyses of HPV vaccines should be done urgently, along with examination of the cost-effectiveness of male vaccination in alternative strategies, such as with different ages at vaccination and with catch-up vaccination. IIIA

Chapter 8: Vaccines

There are no recommendations for Chapter 8.

Chapter 9: Counselling

- 1. A diagnosis of HPV infection or its complications results in a wide range of emotional responses. Physicians should assess the impact the diagnosis has had on the patient and help her work through the emotional responses. IIIA
- 2. Health care providers should proactively discuss issues of sexuality with their patients. IIIA

Epidemiology and Natural History of HPV Infection

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INTRODUCTION

In the genital tract, HPV is primarily transmitted by skin-to-skin contact, and certain genotypes are trophic in both men and women. This can result in subclinical infection of the skin over the entire genital region, which can be detected by HPV DNA testing. A small proportion of those infected will manifest either benign or malignant disease. This chapter will review the epidemiologic aspects of HPV infection and the natural history of HPV disease, primarily in the female genital tract.

EPIDEMIOLOGIC ASPECTS OF HPV INFECTION

HPV infections are ubiquitous. Epidemiologic evaluation is challenging, as many infections are not clinically recognized, yet the virus can be transmitted sexually and can cause disease. The HPV types that infect the female genital tract can cause EGWs (condyloma acuminata), precancerous and cancerous lesions of the cervix, and cancers of the lower genital tract. HPV has been implicated in cancers of the anus, vulva, vagina, and head and neck. Of the more than 100 types of HPV involved in human disease, approximately 40 are thought to infect the genital tract.¹

Determination of the incidence and prevalence of HPV infection can be based on detection of HPV of specific types, the frequency of disease caused by HPV, or both. Cervical cancer has been well evaluated in many countries, and there are databases in some provinces of Canada that have followed the incidence of cervical dysplasia and cancer. However, the literature is less complete for EGWs and disease related to nononcogenic HPV. Recent studies done in conjunction with large-scale vaccination trials are providing useful epidemiologic data and improving our understanding of HPV-related disease.

Studies evaluating the presence of HPV DNA by PCR have shown some variability in age distribution. They have generally confirmed the highest prevalence as being in young groups. Some studies have supported a second peak at 45

years or greater,²⁻⁴ however, a simple decline by age has been seen in other studies.

Comprehensive Canadian data have been published that are based on a study of women attending for Pap smear screening at family practice clinics.⁵ The overall prevalence of HPV of any type was 13.3% and the prevalence of oncogenic types 9.6%. The highest rates for oncogenic types were in the age group 20 to 24 years and the lowest in the group 40 to 44 years; the rates increased again at 45 to 49 years. The rate for those 15 to 19 years old was 15.7%.

Recent data for British Columbia, generated from a population-based study, revealed that 17% of women were infected with HPV overall, 14% with high-risk types and 6% with low-risk types. These data supported the high incidence in young women—26% in those less than 20 years old—but did not show an increase again until the age group above 70 years. The distribution of types, in decreasing order of frequency, was 16, 6, 18, 56, and 90.

Ontario data show a high incidence of HPV acquisition, 25%, over an average of 14 months in women 15 to 19 years old.⁶ A Brazilian/Canadian study showed similar data.⁷

Genital Warts

Clinically visible warts are present in approximately 1% of sexually active adults.⁸ The incidence of visible genital warts in an Ontario study was found to be 1.1%.⁵ Data from the United States suggest that genital warts are the most common STI.⁹ HPV 6 and 11 cause 80% to 90% of condylomata acuminata; types 42, 43, and 44 contribute most of the additional cases.

Cervical Dysplasia and Cancer

The rates of cervical cancer and dysplasia vary greatly between developed and developing nations. Canada has low rates of cervical cancer but high rates of pre-invasive disease owing to our reasonably effective strategies for Pap smear screening. Differences among the provinces in data collection and smear programs have meant difficulty

collecting complete nationwide data. The annual rate of new diagnoses of cervical cancer in Canada is 8.9/100 000 and the annual mortality rate is 2.5/100 000.¹⁰ It was estimated that 1350 Canadian women would be diagnosed with cervical cancer and 390 would die from the disease in 2006. Because of the low age of women with cervical cancer, the burden is high: cervical cancer is the greatest single cause of life-years lost due to cancer in the developing world, at 2.7 million years.

Most cervical cancers are squamous cell carcinomas, but with the relative success of Pap smear screening in many Western countries, the proportion of adenocarcinomas is increasing, as Pap smear screening is not highly effective at detecting adenocarcinoma or its precursors. The annual rate of new diagnoses of adenocarcinoma of the cervix may be as high as 1.83/100 000 in Canada.¹¹

The link between HPV and cervical cancer has been solidly shown. Most cases of cervical cancer can be found to be attributable to HPV infection.¹² In a pooled analysis of 1918 patients with cervical cancer, HPV DNA was detected in 90.7%. A more sensitive assay detected HPV DNA in 96.6% of patients compared with 15.6% of controls. The most frequent types detected, in decreasing order of frequency, were 16, 18, 45, 31, 33, 52, 58, and 35. On the basis of both epidemiologic and comparison phylogenetic classification, the 30 genital HPV types have been classified into high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), possibly high-risk (26, 53, and 66), and low risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108).¹³

Distinct Populations

A summary of data from the published literature suggests that HPV is sexually transmitted between women.¹⁴ Thus, recommendations on Pap smear screening and vaccination should not vary for this group.

HIV-positive women carry HPV at high rates (67%) and have higher rates of cervical dysplasia.^{15,16} Some studies suggest that the cervical dysplasia progresses faster to invasive cancer, in direct relation to the degree of immunocompromise. The high rates appear to be related to HIV virus load, whereas the association with immune status and HPV persistence is modest.^{15,17–19}

Inuit women of Nunavut have higher rates of cervical cancer than Canadian women in general in other provinces and territories. Cervical cancer is the most common cancer of women in this region, representing 35% of all cancers diagnosed. The prevalence of oncogenic HPV in this population is 26% and is inversely related to age.²⁰

Non-cervical HPV Infection

Among non-cervical genital cancer and cancers of the head and neck, the proportions related to HPV infection vary. However, this area of study is evolving. Cancer of the vulva is rare, with an annual rate of new diagnoses of 0.5 to 1.5/100 000. HPV is associated with 20% to 50% of cases and is more frequent in younger women than in older women. Cancer of the vagina is even more rare, with an annual rate of new diagnoses of 0.3 to 0.7/100 000; 40% of cases are attributable to HPV.

High proportions of anal cancer in both women (95%) and men (83%) are associated with HPV infection.²¹ Cancer of the penis is rare, with an annual rate of new diagnoses of 1/100 000; HPV DNA is associated with 40% to 50% of all penile cancers, types 16 and 18 being implicated.

Cancers of the mouth and oropharynx have highly variable incidence rates around the world owing to variations in tobacco and alcohol use. The highest rates in males are in northern and eastern France; the highest rates in females are in India and Pakistan. In these cancers, HPV seems to contribute to the risks related to tobacco and alcohol use. It is estimated that 20% of oropharyngeal cancers and 10% of laryngeal and esophageal cancers are attributable to HPV.²²

RRP occurs in 4.3/100 000 children and 1.8/100 000 adults in the United States.²³ It is estimated that 1 in 400 children born to women with genital infection with HPV types 6 or 11 will have subsequent RRP.

NATURAL HISTORY OF HPV INFECTION

HPV is a DNA virus with a small genome of 8000 base pairs. In the genital tract, HPV infects the basal cells of the stratified squamous epithelium and the metaplastic cells of the transformation zone of the cervical squamocolumnar junction. Depending on the HPV genotype and the host/virus interaction, there can be asymptomatic infection or clinical manifestations of EGWs or early cervical dysplastic changes.

Acquisition of HPV and Immune Response

HPV is acquired from direct skin-to-skin contact. Anogenital contact, but not necessarily intercourse, is required for acquisition of the genital subtypes. Co-infection with more than one type has been seen, and the risk of acquiring a specific HPV type is not substantially decreased among those with prior infection with a phylogenetically related type.²⁴

The virus enters the epithelium, usually through a break in the skin, and then infects the basal and parabasal cells, where it exists as an episome and replicates in the nuclei. As the cells mature up the epithelium, they are filled with HPV particles and are infectious. Viral assembly occurs in the

surface epithelial cells. When these are shed, viral particles are found on the skin surface. The virus then uses the host cell machinery to replicate. The result is papilloma-like projections with heaped-up cell growth. As viral replication proceeds, early and then late proteins are translated, which result in creation of progeny viruses that are shed at the epithelial surface. The time from infection to release of virus is approximately three weeks. However, the period between infection and appearance of lesions can be weeks to months.²⁵ There is essentially no inflammatory response, which permits immune evasion in the early stages of infection.²⁶

The host's immune response is initially the innate response, primarily interferon-based, which then triggers circulating humoral and cell-mediated responses. A cell-mediated immune response is required for HPV containment and lesion regression.^{9,27} In addition to the immune evasion permitted by the intracellular and epithelial location of the virus, HPV can induce a local immune deficiency by depletion of intraepithelial lymphocytes, Langerhan's cells, and CD4+ cells with down-regulation of cytokine production. People with cell-mediated immune dysfunction have higher rates of HPV infection and are more likely to manifest large, multifocal, and dysplastic lesions.

Clearance or Persistence of HPV

The role of the immune system in regression of HPV infection is not fully understood, but in regressing genital warts an infiltration of CD4 and CD8 cells and macrophages is seen. It is likely that this is a systemic T cell response to specific early proteins of HPV (E2 and E6). This appears to occur in animal models and can perhaps be extrapolated to the human situation.²⁸

Genital HPV infection appears to be extremely common in young sexually active women, and 80% of these infections appear to clear; that is, HPV DNA can no longer be detected on the mucosal or epithelial surface. The time required for clearance appears to vary with different HPV genotypes, ranging from 5 to 6 months for low-risk types and 8 to 14 months for high-risk types.^{7,29,30} It is unclear whether the virus is completely eliminated in some cases or whether it remains latent in basal cells and can reactivate under immune-permissive conditions. The risk of carcinogenesis appears to be directly related to the persistence of viral replication of oncogenic types. The definition of transient or persistent infection has not been well worked out, but most studies have assessed for the presence of viral DNA by PCR at 6-month intervals.³¹

Risk Factors for Acquisition and Persistence

Low age is associated with high rates of HPV infection, the peak age being less than 25 years.⁴ Number of sexual

partners and age of the sexual partner for women increase the risk of acquisition of HPV.³² HPV infection has also been associated with current and past cigarette smoking but is not correlated with the amount smoked. The possible association of oral contraception with HPV infection has been very difficult to assess, as oral contraception is highly associated with sexual activity.³³

Genital Warts

Genital warts in women may develop throughout the lower genital tract, including on the cervix. Multiple sites are common. In people with normal immune function, visible warts and evidence of viral replication are gone by approximately 18 months.²⁶

Cervical Dysplasia and Cancer

Infection with oncogenic HPV may result in integration of viral DNA into the host genome, interference with ordered cell growth, immortalization of cells, and cancer. The mechanism is interference of HPV E6 and E7 proteins with the normal cell regulatory functions. Persistence of oncogenic HPV viruses is required for the cellular changes associated with cervical dysplasia. Pap smear screening is designed to detect such changes before progression, which permits ablative therapy to remove the abnormal cells.

Non-cervical HPV Infection

There are no adequate screening programs to prevent non-cervical genital cancer and cancers of the head and neck. Thus, the advent of vaccines is particularly important. Many SCCs of the vagina are preceded by vaginal intraepithelial neoplasia.

Although RRP is considered benign, there are descriptions of malignant transformation. The more typical clinical course is recurrent obstruction requiring laser laryngoscopy and bronchoscopy every 2 to 3 months. Weekly surgical intervention can be required for rapidly growing papillomas.²³

REFERENCES

- Muñoz N, Castellsagué X, de Gonzalez A, Gissmann L. HPV in the etiology of human cancer. *Vaccine* 2006;24(S3):S1–S10. Epub 2006 June 23.
- Kulasingam LS, Hughes JP, Kiviat NB, Mao C, Weiss NS, Kuypers JM, et al. Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: comparison of sensitivity, specificity, and frequency of referral. *JAMA* 2002;288:1749–57.
- Cuschieri KS, Cubie HA, Whitley MW, Seagar AL, Arends MJ, Moore C, et al. Multiple high-risk HPV infections are common in cervical neoplasia and young women in a cervical screening population. *J Clin Pathol* 2004;57:68–72.
- Herrero R, Hildensheim A, Bratti C, Sherman ME, Hutchinson M, Morales J, et al. Population-based study of human papillomavirus infection and cervical neoplasia in rural Costa Rica. *J Natl Cancer Inst* 2000;92:464–74.
- Sellers JW, Mahony JB, Kaczorowski J, Lytwyn A, Bangura H, Chong S, et al. Survey of HPV in Ontario Women Group. Prevalence and predictors of human papillomavirus infection in women in Ontario, Canada. *CMAJ* 2000;163:503–8.

6. Sellors JW, Karwalajtys TL, Kaczorowski J, Mahony JB, Lytwyn A, Chong S, et al: Survey of HPV in Ontario Women Group. Incidence, clearance and predictors of human papillomavirus infection in women. *CMAJ* 2003;168:421–5.
7. Franco EL, Villa LL, Sobrinho JP, Prado JM, Rousseau MC, Desy M, et al. Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. *J Infect Dis* 1999;180:1415–23.
8. Simms I, Fairley CK. Epidemiology of genital warts in England and Wales: 1971 to 1994. *Genitourin Med* 1997;73:365–7.
9. Beutner KR, Richwald GA, Wiley DJ, Reitano MV. External genital warts: report of the American Medical Association Consensus Conference. AMA Expert Panel on External Genital Warts. *Clin Infect Dis* 1998;27:796–806.
10. Canadian Cancer Society. Canadian Cancer Statistics. Toronto: National Cancer Institute of Canada; 2006.
11. Liu, S., Semenciw, R., Mao, Y. Cervical cancer: The increasing incidence of adenocarcinoma and adenosquamous carcinoma in younger women. *CMAJ* 2001;164:1151–2.
12. Human Papillomaviruses. IARC Monogr Eval Carcinog Risks Hum 90. Lyons, France: IARC Press; 2005.
13. Muñoz N, Bosch FX, de Sanjose S, Herrero R, Castellsagué X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003;348:518–27.
14. Marrazzo JM, Stine K, Koutsky LA. Genital human papillomavirus infection in women who have sex with women: A review. *Am J Obstet Gynecol* 2000;183:70–4.
15. Palefsky JM. Human papillomavirus infection and anogenital neoplasia in human immunodeficiency virus-positive men and women. *J Natl Cancer Inst Monographs* 1998;15–20.
16. de Sanjose S, Palefsky J. Cervical and anal HPV infections in HIV positive women and men. *Virus Research* 2002;89:201–11.
17. Palefsky J, Minkoff H, Kalish LA, Levine A, Sacks HS, Garcia P, et al. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high risk HIV-negative women. *J Natl Cancer Inst* 1999;91:226–36.
18. Strickler HD, Burk RD, Fazzari M, Anastos K, Minkoff H, Massad LS, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. *J Natl Cancer Inst* 2005;97:577–86.
19. Mbulaiteye SM, Biggar RJ, Goedert JJ, Engels EA. Immune deficiency and risk for malignancy among persons with AIDS. *J Acquir Immune Defic Syndr* 2003;32:527–33.
20. Healey SM, Aronson KJ, Mao Y, Schlecht NF, Mery LS, Ferenczy A, et al. Oncogenic human papillomavirus infection and cervical lesions in aboriginal women of Nunavut, Canada. *Sex Transm Dis* 2001;28:694–700.
21. Frisch M, Fenger C, van den Brule AJ, Sorensen P, Meijer CJ, Walboomers JM, et al. Variants of squamous cell carcinoma of the anal canal and perianal skin and their relation to human papillomaviruses. *Cancer Res* 1999;59:753–7.
22. Spence AR, Franco EL, Ferenczy A. The role of human papillomavirus in cancer: evidence to date. *Am J Cancer* 2005;4:49–64.
23. Benjamin B, Parsons DS. Recurrent respiratory papillomatosis: a 10 year study. *J Laryngol Otol* 1988;108:1022–8.
24. Thomas KK, Hughes JP, Kuyper JM, Kiviat NB, Lee S-K, Adam DE, et al. Concurrent and sequential acquisition of different genital human papillomavirus types. *J Infect Dis* 2000;182:1097–102.
25. Oriel JD. Natural history of genital warts. *Br J Vener Dis* 1971;47:1–13.
26. Stanley M. Immune responses to human papillomavirus. *Vaccine* 2006;24(S1), 16–22.
27. Gunter J. Genital and perianal warts: new treatment opportunities for human papillomavirus infection. *Am J Obstet Gynecol* 2003;189:S3–S11.
28. Ho GYF, Bierman R, Beardsley L, Chang CJ, Burd RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 1998;338:423–8.
29. Brown DR, Shew ML, Qadadri B, Neptune N, Vargas M, Tu W, et al. A longitudinal study of genital human papillomavirus infection in a cohort of closely followed adolescent women. *J Infect Dis* 2005;191:182–92.
30. Giuliano AR, Harris R, Sedjo RL, Baldwin S, Roe D, Papenfuss MR, et al. Incidence, prevalence, and clearance of type-specific human papillomavirus infections: the Young Women's Health Study. *J Infect Dis* 2002;186:462–9.
31. Trottier H and Franco EL. The epidemiology of genital human papillomavirus infection. *Vaccine* 2006;24S1:1–4.
32. Tarkowski TA, Koumans EH, Sawyer M, Pierce A, Black CM, Papp JR, et al. Epidemiology of human papillomavirus infection and abnormal cytologic test results in an urban adolescent population. *J Infect Dis* 2004;189:46–50.
33. Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. *J Clin Virol* 2005;32S:16–24.

Clinical Manifestations and Diagnosis of HPV-Related Disease

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INTRODUCTION

Most HPV infections are transient. Most transient and persistent infections have no symptoms or signs apart from abnormal results of laboratory tests. Immuno-compromised patients, such as those with advanced HIV disease, have more severe manifestations—more lesions or earlier progression to cancer. The HPV genotypes are classified as low-risk or high-risk for cervical cancer.¹ The low-risk genotypes persist in the body for shorter periods than the high-risk genotypes; the mean carriage time is also shorter.² Some low-risk genotypes are, however, considered carcinogenic for humans at sites other than the cervix, such as the larynx, vulva, or penis. Many patients are infected with more than one genotype at a time or in succession. This chapter focuses on patients with normal immune function.

SPECTRUM OF DISEASE CAUSED BY LOW-RISK HPV

External Genital Warts

Typical EGWs present as exophytic fronds or cauliflower-like to papular growths (*condylomata acuminata*) on anogenital skin or mucous membranes, or both. They are frequently multiple, asymmetric, and polymorphic. They occasionally cause bleeding, pruritus, and local discharge.

Lesions not caused by low-risk HPV must be considered in the differential diagnosis (Table 2.1).³ Sebaceous glands may extend onto the inner surface of the labia minora, around the clitoral area, onto the penile shaft, or onto the inner surface of the foreskin. Vestibular papillae (*micropapillomatosis labialis*) are usually quite symmetric rather than randomly distributed and of homogeneous rather than heterogeneous form and size.

Most EGWs are caused by HPV 6 and 11.⁴ The diagnosis rarely poses a problem when the lesions are numerous. There is usually no need for biopsy unless the wart is atypical, in which case cancer must be eliminated. Application of acetic acid to the skin or lesions (acetowhitening) is not

recommended in primary care and has no value in screening for subclinical warts.

Children with EGWs are more likely to present because a care provider has noted an abnormality or the child complains of vague symptoms of genital irritation. This diagnosis in children does not involve HPV DNA typing or biopsy, except when there are atypical or persistent lesions.⁵

The diagnosis of EGWs in a prepubertal child raises the concern of sexual abuse. The commonly accepted upper age limit for perinatal transmission is 12 to 24 months.⁶ The likelihood of sexual abuse rises with age. The positive predictive value of EGWs for sexual abuse is 50% in children 4 to 8 years of age and 70% in children over 8.⁶ Adams,^{7,8} in her classification of signs of abuse, describes EGWs at this age as suggestive of, but not definitive for, sexual abuse.

In all cases, an experienced practitioner should conduct a non-leading interview with the child, when possible, as well as interview the parents or caregivers. Assessment by means of external genital and anal examination for signs of sexual abuse is indicated. There is no clear age below which sexual abuse is never a concern for children with EGWs, but, most commonly, in the child less than 4 years of age, the infection is a result of vertical or other means of transmission. However, in any child, if there is an abnormality on genital or anal examination, another STI, psychosocial or behavioural indications of abuse, or parental concern, advice from the local children's aid society or a medicolegal expert should be sought or a referral be made to child protective services.^{6,9,10}

The possibility of sexual abuse should also be investigated when a child presents with non-genital HPV infections, such as oral or laryngeal warts and papillomatosis.⁶

Immunocompromised patients have more EGWs, and they are harder to clear. These patients also have a higher risk for HPV-related cancers.

Table 2.1 Lesions to be considered in a differential diagnosis of EGWs³

Normal variations
Sebaceous glands
Vestibular papillae, skin growths on Hart's line
Lesions caused by infection
Condylomata lata (due to secondary syphilis)
Molluscum contagiosum
Conditions of the skin and mucosa
Intradermal nevi
Skin tags
Seborrheic keratoses
Anogenital intraepithelial neoplasia and cancer

Recurrent Respiratory Papillomatosis

Respiratory papillomatosis frequently recurs. It has two peaks of incidence, one peak after birth and one in young adulthood. Most infant patients with respiratory papillomas present with hoarseness, weak cry, and signs of partial airway obstruction that include stridor, tachypnea, chest retractions, and nasal flaring. Others present with chronic cough, paroxysms of choking, recurrent respiratory infection, or failure to thrive. These features often lead to a misdiagnosis of asthma, laryngitis, bronchitis, or croup.¹¹ These patients are frequently seen by many physicians before the correct diagnosis is made. The triad of factors indicating high risk for juvenile onset are vaginal delivery, maternal age less than 20 years, and first-born status.¹² Caesarean section is not fully protective and represents too much risk compared with the incidence of the disease.^{13,14}

Abnormal Pap Smears

Recent unpublished research shows that low-risk HPV is associated with 10% to 25% of abnormal cervical smears, ASC-US and LSIL being the most frequently associated smear results. Rarely are HSIL, AGC/AGCUS, and cancer associated with low-risk HPV. The cytologist or pathologist cannot differentiate smears associated with low-risk HPV from those associated with high-risk HPV on the basis of cell morphology. ASC-US and LSIL results should be evaluated according to local guidelines.

SPECTRUM OF DISEASE CAUSED BY HIGH-RISK HPV

High-risk HPV causes transient infection in many patients. These infections last longer than those caused by low-risk HPV but usually resolve spontaneously within 2 to 3 years.¹⁵ Persistent infection with high-risk HPV is associated with anogenital cancers, especially cervical cancer¹⁶; the

association is greater in women than in men, even for anal cancer. Other cancers are associated with high-risk HPV but will not be discussed in these guidelines.

Flat Warts

Flat warts, also known as bowenoid papulosis or warty VIN, are usually caused by high-risk rather than low-risk HPV. They can be seen on the skin of the genitalia as slightly raised, papular or macular lesions with or without keratinization and brown, grey, or blue pigmentation.

Cervical Cancer and Its Precursors

High-risk HPV is the necessary but insufficient cause of cervical cancer. Most high-risk HPV infections of the genitalia are totally silent clinically until precancerous or cancerous changes occur. Cervical cancer may cause spontaneous or postcoital bleeding. Viral testing may detect symptomatic infections much more readily than cytology. Most of the precursor stages can be diagnosed by Pap smear or viral testing.

Vaginal Cancer

Vaginal cancer can give rise to abnormal cervical smears. It can cause spontaneous or postcoital bleeding and, in advanced cases, coital pain.

Vulvar Cancer

Lesions of the vulva evolve over many years. Most vulvar cancers are preceded by VIN.¹⁷ Some VIN lesions are unifocal, others are multifocal. They can be hyperpigmented or hypopigmented. They may ulcerate and bleed. They may be warty or quite flat. They itch, so they may present as chronic vulvar itching; scratching may alter the clinical presentation. Not all vulvar cancers are related to HPV, although many of the patients have a history of abnormal cervical smears. About half of vulvar cancers arise on lichen sclerosus, lichen planus, or lichen simplex. The differential diagnosis should include nevi. Most of the lesions are asymptomatic. Therefore, a good vulvar inspection should be done before a vaginal and cervical exam with a speculum. Biopsy should be performed to eliminate advanced disease. A fair proportion of women with vulvar cancer smoke and should be advised to stop smoking as soon as possible.

Anal Cancer

The anus comprises a transformation zone. Anal cancer can present as difficulty with defecation, bleeding, or pain. At this point, most disease is in late stage. High-resolution anoscopy helps to make the diagnosis of significant lesions and to perform directed biopsy. Plain anoscopy is helpful in the presence of gross disease but does not help with intraepithelial lesions.

LABORATORY TESTING

HPV infection can be detected and managed in various ways that are usually progressive in their intensity. The place of specific viral testing in primary care is discussed in another chapter. Type-specific serology is available for research purposes only and is not recommended for clinical use in primary care at this time.

Cytology

Cytology of the cervix is a screening test and should be done only in asymptomatic women. Women with symptoms or with cervical abnormalities for which cancer cannot be excluded should be referred for colposcopy and in-depth evaluation. A smear should not be taken before colposcopy, because the procedure could obscure the colposcopic field for some time.

The Pap smear is the mainstay of primary screening for cervical cancer. It should be performed with a cervical broom turned three times in a counter-clockwise fashion or with both an endocervical brush turned three times and a long-tipped Ayre's spatula rotated once on the os of the cervix. Excessive mucous on the cervix should be cleaned off before the specimen is taken. The specimen can be put in a liquid specifically designed for LBC or can be smeared on a glass slide. If a broom is used, the secretions should be stroked once across the slide. If a brush and spatula are used, the brush should be unrolled on the upper part of the slide from left to right, and the spatula should be stroked on the lower part of the slide from left to right, without returning on the smeared material.

The Bethesda System classification of 2001 should be used to report the results. Interpreting the results involves three steps. First, the smear's adequacy should be evaluated. If the smear was unsatisfactory, attention should be given to the reason. If the number of cells from the transformation zone was insufficient, the pathologist can still give a result with reservation, but this situation is insufficient for the patient to be recalled before she is due for her next Pap smear. If the pathologist asks for a recall, consider the woman as if she had not had a Pap smear and recall her. Any other reason for an unsatisfactory smear should be evaluated and appropriate action taken or the situation noted in the chart. Second, read whether there were normal or abnormal cells. Third, recognize test results that warrant referral for proper assessment and follow-up: ASC-US, ASC-H, AGC, LSIL, HSIL, and any cancer cells, whatever the cell type.

Biopsy

Patients with any lesions suspected of being high grade or cancerous should be sent directly to an experienced

colleague for biopsy without an attempt to treat, swab, or scrape the lesion, which might temporarily hinder the pathologist's reading of the submitted material.

Colposcopy

This diagnostic procedure is performed for women with abnormal smears or with signs or symptoms suggestive of cancer. Examination of the vulva, vagina, and cervix is done with a speculum and magnification. Acetowhitening of abnormal tissue will augment the contrast. Application of Lugol's iodine may also help detect some changes. Directed biopsy can be performed afterward. Endocervical curettage can be done when glandular disease is suspected or the transformation zone is not visualized in its entirety.

Anoscopy

Anoscopy should be considered in patients with anal warts. Directed biopsy can be done. Anal Pap smear and viral testing is being studied as a method of screening for anal cancer. This may be particularly important for HIV-positive patients and maybe for women with cervical HSIL.

Urethroscopy

Urethroscopy can be considered for patients with extensive urethral warts not amenable to other forms of therapy or for patients with urinary flow problems. Directed biopsy can be done.

WHEN TO REFER

Patients should be referred in a situation of doubt about cancer, need for a biopsy, HIV positivity, or warts that are massive, atypical, or non-healing. Neoplasia should be suspected if a lesion has any of the following features: pigmentation, bleeding, persistent ulceration, persistent pruritus, or recalcitrance. Women with abnormal cervical smears should undergo colposcopy. Women with HSIL and cancer should be given high priority in colposcopy clinics.

RECOMMENDATIONS

1. In the presence of EGWs in a prepubertal child, sexual abuse should be considered. IIIA
2. The diagnosis of EGWs in children does not require biopsy. IIIA
3. Cytology of the cervix as a screening test should not be done in women whose cervix exhibits signs and symptoms of cervical cancer. IIIA
4. Patients should be referred for assessment and follow-up when the Pap smear results include ASCUS, ASC-H, AGC, LSIL, HSIL, or any cancer cells, whatever the cell type. IA

5. In a situation of doubt about cancer, need for a biopsy, or warts that are massive, atypical, and/or non-healing, neoplasia should be suspected if a lesion has any of the following features: pigmentation, bleeding, persistent ulceration, persistent pruritus, or recalcitrance. IA
6. Cytology results showing a new diagnosis of cervical cancer should mandate a patient appointment within 3 weeks in a colposcopy clinic, for HSIL and AGC within 6 weeks. IIIA

REFERENCES

1. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12–9.
2. Frazer IH, Cox J, Mayeaux EJ, Franco EL, Moscicki AB, Palefsky JM, et al. Advances in prevention of cervical cancer and other human papillomavirus-related diseases. *Pediatr Infect Dis J* 2006;25:S65–S81.
3. Expert Working Group on Canadian Guidelines for Sexually Transmitted Infections. Genital human papillomavirus (HPV) infections. In: Canadian guidelines on sexually transmitted infections. 2006 ed. Ottawa: Public Health Agency of Canada; 2006. p. 160–73. Available: http://www.phac-aspc.gc.ca/std-mts/sti_2006/pdf/05sti2006e_e.pdf.
4. Brown DR, Schroeder JM, Bryan JT, Stoler MH, Fife KH. Detection of multiple human papillomavirus types in condylomata acuminata lesions from otherwise healthy and immunosuppressed patients. *J Clin Microbiol* 1999;37:3316–22.
5. Jayasinghe Y, Garland SM. Genital warts in children: What do they mean? *Arch Dis Child* 2006;91:696–700.
6. Sinclair KA, Woods CR, Kirse DJ, Sinal SH. Anogenital and respiratory tract human papillomavirus infections among children: age, gender and potential transmission through sexual abuse. *Pediatrics* 2005;116:815–25.
7. Adams JA. Approach to the interpretation of medical and laboratory findings in suspected child sexual abuse: a 2005 revision. *APSAC Advisor* 2005;17:7–13.
8. Adams JA. Medical evaluation of suspected child abuse. *J Pediatr Adolesc Gynecol* 2004;17:191–7.
9. Hornor G. Ano-genital warts in children: Sexual abuse or not? *J Pediatr Health Care* 2004;18:165–70.
10. Sinal SH, Woods CR. Human papillomavirus infections of the genital and respiratory tracts in young children. *Semin Pediatr Infect Dis* 2005;16:306–16.
11. Shykhon M, Kuo M, Pearman K. Recurrent respiratory papillomatosis. *Clin Otolaryngol* 2002;27:237–43.
12. Shah KV, Stern WF, Shah FK, Bishai D, Kashima HK. Risk factors for juvenile onset recurrent respiratory papillomatosis. *Pediatr Infect Dis J* 1998;17:372–6.
13. Shah K, Kashima H, Polk BF, Shah F, Abbey H, Abramson A. Rarity of cesarean delivery in cases of juvenile-onset respiratory papillomatosis. *Obstet Gynecol* 1986;68:795–9.
14. Kosko JR, Derkay CS. Role of cesarean section in prevention of recurrent respiratory papillomatosis: Is there one? *Int J Pediatr Otorhinolaryngol* 1996;35:31–8.
15. Richardson H, Kelsall G, Tellier P, Voyer H, Abrahamowicz M, Ferenczy A, et al. The natural history of type-specific human papillomavirus infections in female university students. *Cancer Epidemiol Biomarkers Prev* 2003;12:485–90.
16. Kjaer SK, van den Brule AJC, Paull G, Svare EI, Sherman ME, Thomsen BL, et al. Type specific persistence of high risk human papillomavirus (HPV) as indicator of high grade cervical squamous intraepithelial lesions in young women: population based prospective follow up study. *BMJ* 2002;325:572.
17. Joura E. Epidemiology, diagnosis and treatment of vulvar intraepithelial neoplasia. *Opin Obstet Gynecol* 2002;14:39–43.

The Role of HPV Testing

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INTRODUCTION

The management and prevention of cervical cancer should change definitively with DNA testing for high-risk HPV, which is more sensitive than cytology whether used for triage, primary screening, or post-therapeutic surveillance. However, study of long-term benefit and potential iatrogenic impact is still required. At present, HPV DNA testing has been implemented in some Canadian jurisdictions only as an adjunct to cervical cytology. Canadian health care providers will do well to closely follow the rapidly unfolding developments in cervical cancer prevention and HPV testing.¹⁻⁴

ONCOGENIC, OR HIGH-RISK, HPV

Cancer of the cervix (squamous cell and adenocarcinoma) represents the life-threatening burden of disease attributable to HPV.³ The cause of those cancers, and their immediate precursors (severe dysplasia and carcinoma in situ), is high-risk HPV.⁵

Of the 100 known HPV types that can infect humans, at least 15 are considered carcinogenic, and three others are considered possibly carcinogenic.⁶⁻⁸ (See Table 3.1) These 8-kb double-stranded DNA viruses are host- and tissue-specific. Little information exists on the prevalence, incidence, or natural history of infection with multiple HPV types. Although multiple types are present in 20% to 30% of HPV infections, cervical cancer is believed to be a monoclonal event related to a single HPV type.⁹

NEW PARADIGMS IN SCREENING STRATEGIES

The new era of prophylactic HPV vaccination mandates the urgent development of new paradigms in triage, screening (interval and modality), and post-therapeutic strategies, with consideration of the following facts. We usually observe clearance within 18 months of HPV infection, and the infection is usually of no clinical consequence.^{10,11} Prevalence and clearance depend on age and immune competence.¹² Whether done for triage, primary screening, or post-therapeutic surveillance, HPV DNA testing is

uniformly more sensitive, although less specific, than cytologic screening, owing primarily to the detection of transient infection.^{13,14} Cancer of the cervix is a rare result of persistent HPV infection but in developing countries represents the greatest cause of years of life lost because of death from cancer.¹⁵ After HPV 16 and 18, the six next most common carcinogenic HPV types are similar worldwide.¹³ Once vaccination has been instituted, Pap cytology reading performance may decrease, resulting in lower sensitivity and specificity, because of the lower expected prevalence of lesions.³ Cervical cancer is almost 100% preventable.

HPV typing is not useful for patients with EGWs, which are most likely caused by nononcogenic types. The detection of low-risk types 6 and 11 represents identification of HPV infection rather than markers of cancer and its precursors and is thus unwarranted for clinical use.

EMERGING TESTS FOR DETECTING HIGH-RISK HPV

As HPV cannot be propagated in tissue culture, its accurate identification relies on molecular biology technique. Morphologic, serologic, and clinical findings allow only inference of its presence. The presence of genetic material (DNA) from high-risk HPV can be assessed from cell samples by a variety of signal detection procedures⁸ and sampling sources.

DNA Typing Assays

In epidemiologic studies, two methods involving molecular signal amplification technology are widely used for HPV detection. Health Canada has approved only the Hybrid Capture assay (Digene, Gaithersburg MD), version hc2, for the triage of women with ASC-US cytology results.^{8,16} This assay is not genotype-specific: it probes for a pool of 13 carcinogenic HPV types. HPV DNA can also be detected by PCR with the use of generic or consensus primers.^{13,14,17} This technique is more sensitive than the Hybrid Capture hc2 assay, allowing identification of specific HPV types and variants.^{8,13,18-20} It awaits final clinical validation. Both techniques are amenable for high-throughput, rapid, automated testing (e.g., Hybrid Capture can test up to 96 samples in less than 2 h). Because HPV 16 and 18 are responsible for

Table 3.1. Carcinogenic and possibly carcinogenic types of HPV⁶⁻⁸

Carcinogenic types	
Species α -9:	16, 31, 33, 35, 52, and 58
Species α -7:	18, 39, 45, 59, and 68
Species α -5:	51 and 82
Species α -6:	56
Species α -11:	73
Possibly carcinogenic types	
Species α -11:	53*
Species α -5:	26
Species α -6:	66

*Found occasionally in CIN 2/3 but rarely in invasive cancer. It is very prevalent. Screening for this type is, therefore, not useful, because it has low specificity and a low positive predictive value.

70% of cervical cancers, with trivial differences among countries, and for 60% of CIN 2/3 lesions worldwide,²¹ we expect that HPV-specific genotyping will play a key role in clinical management and monitoring in the near future. However, at present it should be restricted to research endeavours.

Other Tests

Other tests and tools that could be instrumental in the triage of HPV-positive women are being developed or validated. The candidates include HPV-specific genotyping (e.g., the Amplicor HPV test kit, Roche Diagnostics, Mississauga ON and Nutley NJ), evaluation of viral load by real-time PCR,² mRNAs encoding for E6 or E7 oncoproteins that could differentiate episomal from integrated HPV onco-gene transcripts,^{22,23} epithelial proliferation biomarkers (e.g., p16^{ink}),^{24,25} cell-cycle-regulating immunostaining markers (e.g., cdc6 or mcm5 proteins),²⁶ susceptibility HLA persistence¹⁰ or prognostic markers,^{26,27} sophisticated microarray DNA- or RNA-based diagnostics,^{28,29} and serologic tests.^{8,14} Clinical application should be withheld pending validation with evidence of high reproducibility and acceptable sensitivity, specificity, and positive and negative predictive value.

Sample Sources

Considering the central role of high-risk HPV in cervical neoplasia and the robust body of scientific knowledge already accumulated, screening for HPV DNA in cell samples from the genital tract appears to be an important strategy for Canada that needs to be further defined as screening technologies evolve. Meanwhile, Pap screening with glass slides or LBC remains the standard method of screening for cervical cancer in Canada. Both techniques are suitable for HPV testing. However, from traditional glass slides, one can only infer the presence of HPV, whereas the residual

fluid in LBC samples with a cytologic diagnosis of ASC-US can be used for reflex triage testing for high-risk HPV DNA.¹⁶ The basic rules of sampling must be respected: a lack of cells in specimens could lead to false-negative results. Concurrent LBC and high-risk HPV DNA testing has been approved for primary screening in the United States but not in Canada. The question of whether individual consent should be required for the HPV DNA testing warrants further societal debate.

Specific high-risk HPV DNA testing with the Hybrid Capture hc2 assay may be useful after a Pap smear has been obtained but before acetic acid or iodine is applied. The collection technique is similar to that of a Pap smear: remove excess mucous, insert a brush 1 to 1.5 cm into the cervical os, make three full turns in a counter-clockwise direction, insert the brush to the bottom of the transport tube, snap off the shaft, carefully cap the tube, and ship the tube at room temperature within two weeks.

Self-collection of samples for high-risk HPV DNA testing warrants serious further consideration.^{2,8,16,30-32} In contrast to cytology, HPV testing requires less precise sampling to reach 74% sensitivity and 84% specificity.³²

Urine specimens also have been identified as an alternative for screening.³³

CURRENT STRATEGY FOR HIGH-RISK HPV DNA TESTING

In Canada, the current strategy for high-risk HPV DNA testing pertains to a very specific indication: triage of women aged 30 years or more who have ASC-US, to decide whether to refer for diagnostic colposcopy.^{34,35} ASC-US is an equivocal anomaly: 5% to 10% of women with this cytologic diagnosis prove to have high-grade cervical lesions.¹⁶ As 31% to 60% of women with ASC-US are infected with high-risk HPV, DNA testing for these types has about 99% negative predictive value. A study comparing three

strategies to triage women with ASC-US (colposcopy, HPV DNA testing, and cytology) eloquently illustrated this new paradigm.³⁶ The sensitivity of HPV DNA detection in identifying HSIL was 96.3% (95% CI 91.6% to 98.8%), with 56.1% of women referred for colposcopy, compared with 44.1% (95% CI 35.6% to 52.9%), with 6.9% referred, for single repeat cytology. Sensitivity with a lower cytology triage threshold, ASC-US or above, was 85.3% (95% CI 78.2% to 90.8%), with 58.6% of women referred for colposcopy. HPV detection was particularly helpful in women aged 30 years or more.³⁷ Additionally, two meta-analyses have confirmed the accuracy of high-risk HPV DNA testing in triage of women with ASC-US.^{38,39} The Pan-Canadian Forum on Cervical Cancer Prevention and Control recommended the development of a national algorithm using the Hybrid Capture hc2 assay as an adjunct to cervical cytology in women aged 30 years or older with ASC-US.³⁴ A woman with ASC-US and a negative result of HPV DNA testing should be able to return to regular screening and not need to undergo colposcopy.¹⁶ This balanced strategy, with higher sensitivity and similar specificity (63% versus 62%) when compared with repeat cytology,^{38,40} avoids unnecessary and stressful diagnostic procedures and reduces costs to the health care system.^{14,17,41,42}

RATIONALE FOR OR AGAINST HIGH-RISK HPV DNA TESTING

Primary Screening

It is expected that primary screening for cervical cancer and precursor conditions will rapidly evolve toward high-risk HPV DNA testing, either alone or in combination with cytology. Compared with cytology, high-risk HPV DNA testing has uniformly higher sensitivity (95% versus 84%) but slightly lower specificity (60% versus 85%) for the detection of CIN 2/3.⁴³ Indeed, the Hybrid Capture hc2 assay used alone can detect 23% more CIN 2/3 lesions or cancer than cytology alone^{8,16} but is 6% less specific.¹⁴ A meta-analysis reviewing 24 large cross-sectional studies comparing the accuracy of high-risk HPV DNA screening with cytologic screening of asymptomatic women yielded a sensitivity for the former of 89.3% (95% CI 85.2% to 93.4%) and a pooled specificity of 87.8% (95% CI 85.5% to 90%; range 81% to 95%).³⁸ The sensitivity of cytology across studies is highly variable (19% to 76%), whereas that for HPV testing is uniformly high (85% to 100%).^{44,45} Combining cytology and the Hybrid Capture hc2 assay yielded sensitivity and specificity of 99.2% (95% CI 97.4% to 100%) and 87.3% (95% CI 84.2% to 90.4%), respectively, with ASC-US as the cut-off for positivity.^{8,16} This translated into a 4.7% increase in sensitivity of the hc2 assay for CIN 2/3 and a 5.7% loss of specificity.

High-risk HPV testing has the potential to safely allow an increase in screening intervals and automation, Pap cytology being reserved for triage of HPV-positive women, thus lowering costs while improving accuracy in prevention programs.^{1,8} The current true benefit of high-risk HPV testing lies in its ability to lower the false-negative rate of conventional cytology and increase the negative predictive value of testing (the likelihood of having no disease if the result is negative), to 97% to 100%.⁴⁶

Inefficient in the Young

HPV acquisition varies by age, with a peak prevalence of HPV positivity in the late teens or early 20s. Thereafter, the prevalence declines but high-risk type persistence increases, leading to severe dysplasia in the late 20s (the median age of women with CIN 3 is 27 to 30 years) and to cervical cancer more than 10 years later.^{47,48} Cofactors for persistence and progression are being studied. The risk for HPV infection is cumulative. Among women who are initially free of HPV DNA, the virus is acquired by up to 3% per month. Among women 15 to 19 years of age, the cumulative incidence exceeds 40% three years after the beginning of sexual activity.^{11,49–52} HPV detected under the age of 30 years likely represents an incident infection, which may clear spontaneously within 6 to 18 months, whereas in those above age 30 years HPV detection is more likely to represent persistent infection. We need to develop strategies that will focus on identifying women with persistent infection, as the odds ratio of high-grade lesions is 28.4 times higher (95% CI 8.4% to 119.0%) for persistent HPV infection compared with incident infection.⁵³

Not Useful in Triage for Women with LSIL, HSIL, or SCC

Triage by means of high-risk HPV testing of women with cytologically demonstrated LSIL, HSIL, or SCC is not useful, as these women will be referred for colposcopy. LSIL yields positive results for high-risk HPV DNA in more than 80% of cases⁸ but with low specificity: 16% in women aged up to 29 years and 30% in women older than 29 years.^{54,55} The American Society for Colposcopy and Cervical Pathology recommends referring women with LSIL to colposcopy.⁵⁶ Because of the high prevalence of high-risk HPV DNA in LSIL, DNA testing is unwarranted. When type-specific high-risk HPV DNA tests are approved, detection of type 16 could prove useful for the triage of women with LSIL.⁵⁷

Potentially Helpful in AGC Follow-up

Colposcopy, cervical biopsy, and endocervical curettage should help to clarify the management of AGC. For women aged 35 years or older or with the clinical suggestion of endometrial neoplastic lesions (e.g., those with genetic

susceptibility, abnormal bleeding, chronic anovulation, or cytologic findings of psammoma bodies or histiocytes), additional endometrial sampling is warranted. Only after these investigations have ruled out neoplasia might high-risk HPV DNA testing be helpful, as a negative result would allow for less aggressive follow-up.

Possible Role in Post-Therapeutic Surveillance

A review of 16 studies yielded compelling evidence for using high-risk HPV DNA testing for surveillance after conservative treatment of CIN with either local ablation or excision.^{39,40} Treatment failure with CIN occurs in 5% to 15% of patients.^{41,42} HPV DNA testing can predict treatment failure in 67% to 100% of cases (average 94.4%, 95% CI 90.9% to 97.7%) with a pooled specificity of 75.0% (95% CI 68.7% to 81.4%).^{8,40} Exploration of the same possibility after therapy for invasive carcinoma is under way.³

Not Required Before and After HPV Vaccination

Currently, type-specific high-risk HPV DNA testing before vaccination or as follow-up has not been advocated. Routine high-risk HPV testing is not recommended before or after vaccination. However, we need to better characterize natural and acquired immunity after HPV infection and vaccination. The integration of HPV vaccination and screening registries represents a wonderful opportunity for policymakers to study this viral infection and to really affect the history of cancer of the cervix.

Psychosocial Issues

Fortunately, public and political awareness of HPV as the viral cause of cervical cancer is increasing⁵⁸ and is likely to influence prevention and screening paradigms. Multifaceted challenges, including anxiety, confusion, and concerns about trust in relationships, warrant clear communication and accurate health education to ensure better comprehension and quality of life.² To make informed choices, women will need to understand the role of HPV infection.

MANAGEMENT OF CASES POSITIVE FOR HIGH-RISK HPV DNA

Currently, high-risk HPV DNA testing in the absence of abnormal cytologic findings is not indicated. However, since we hope to modify primary screening with virologic tools in the near future, and since the technology is available, it is useful to examine several clinical scenarios that may arise.

Positive DNA but Negative Cytology Results

For women aged 30 years and older, repeating both tests in 12 months is the preferred strategy. If both results are then negative, a return to routine screening is recommended, but if either result is positive, colposcopy is recommended.^{2,53}

Persistent infection is the real risk factor; waiting for 12 months permits clearance of an innocuous infection. If HPV persists, the odds ratio for high-grade lesions is 28.4 times greater than with an incident infection⁵³ and more accurate than colposcopy in predicting cancer risk.^{59,60}

Among sexually active adolescents and women under the age of 30, there is a very low incidence of invasive cancer of the cervix but a very high prevalence of high-risk HPV DNA positivity.⁶¹ There is no need for high-risk HPV testing in adolescence. Triage for ASC-US with repeat cytology in six months is the preferred method, as HPV DNA testing would result in a large number of young women being referred for colposcopy despite their low risk of cervical neoplasia. If an inadvertent positive HPV DNA result has been disclosed, repeat cytology alone in six months is suggested.

Atypical Squamous Cells of Undermined Significance

HPV DNA testing or repeat cytology is acceptable for managing women aged 30 or older with ASC-US. If either test is then positive, colposcopy is recommended. Women with ASC-US who are under age 30 years are best served by repeat cytology in six months.

SPECIAL ISSUES

Pregnancy

There is no evidence that cancer of the cervix or its precursors are modified by pregnancy.¹⁷ HPV DNA testing, repeat cytology, and colposcopy are all acceptable methods for managing pregnant women 30 years or older with ASC-US. When HPV DNA testing or repeat cytology is used, the management options are identical to those described for nonpregnant women except that it is preferable to defer colposcopy until at least six weeks post partum unless invasive cancer is suspected.

Management of HSIL, AGC, and SCC should be reserved for clinicians who are experienced in colposcopic evaluation of pregnant women.

Vaccination against HPV during pregnancy is not recommended and should be postponed. If pregnancy is discovered once any of the vaccine doses has been given, the remaining dose(s) should be delayed until completion of pregnancy and breastfeeding and then resumed as soon as possible, the second and third doses being separated by at least 12 weeks. There is no indication, however, of undue risk to the pregnancy or a need for pregnancy interruption.⁹

Postmenopausal Women

The use of reflex HPV DNA testing with ASC-US in this population may be highly efficient and would result in relatively few women being referred for colposcopy.⁶²

Aboriginal Women and Recent Immigrants

The Aboriginal population in Canada could benefit from targeted prevention measures, as the incidence of high-risk HPV in Nunavut is nearly twice that in the other Canadian provinces and territories.⁶³

Little information is available about recent immigrants, their culture, and their integration into our health care system. Efforts are warranted to collect such information.

HIV Infection or Other Causes of Immunosuppression

Host immunity is complex. Several studies have reported a high prevalence (20% to 70%) of high-risk HPV positivity in HIV-infected women.⁶⁴ Clearance seems to be CD4-dependent. In this population, there is evidence that HPV infection is likely to persist and may include multiple viral types. Screening and management need further research that considers the impact of antiretroviral therapy.⁸ Self-collected samples have yielded promising results in this population.³¹

Vaccination against HPV can be considered for individuals immunocompromised as a result of disease or medication. However, the immunogenicity and efficacy of the vaccine in this population is unknown at present and could be inferior.⁹

SOGC Clinical Tip

High-risk HPV DNA testing in the absence of abnormal cytologic results is not indicated.

SOGC Clinical Tip

Detection of HPV in a woman under age 30 years likely represents incident infection, which may clear spontaneously, whereas after 30 years it probably represents persistent infection.

SOGC Clinical Tip

In patients immunocompromised by disease or medication, HPV infection is likely to persist and may include multiple viral types. Screening, management, and vaccination need further research.

RECOMMENDATIONS

1. Reflex HPV DNA testing is recommended only for women aged 30 years or more with ASCUS and should be used only as an adjunct to cervical cytology, to reduce the false-positive rate of conventional cytology and increase the negative predictive value of testing. IA
2. There is no indication for HPV testing in women younger than 30 years and therefore it should not be done. IA
3. Because of the high prevalence of high-risk HPV types in women with LSIL, HSIL, and SCC, triage by means of HPV testing should not be done. IA
4. More research should be done to better characterize natural and acquired immunity after HPV infection and vaccination and to redesign screening strategies to focus on identifying women with persistent infection. IIIA

REFERENCES

1. Franco EL, Mayrand M-H, Trottier H. Cervical cancer prevention—promises and perils in a changing landscape. *Oncol Exchange* 2006;5(3):9–14.
2. Cuzick J, Mayrand MH, Ronco G, Snijders P, Wardle J. New dimensions in cervical cancer screening. *Vaccine* 2006;24(Suppl 3):S90–S97.
3. Franco EL, Cuzick J, Hildesheim A, de Sanjose S. Issues in planning cervical cancer screening in the era of HPV vaccination. *Vaccine* 2006;24(Suppl 3):S171–S177.
4. Garnett GP, Kim JJ, French K, Goldie SJ. Modeling the impact of HPV vaccines on cervical cancer and screening programmes. *Vaccine* 2006;24(Suppl 3):S178–S186.
5. Bosch FX, Lorincz A, Muñoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002;55:244–65.
6. de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. *Virology* 2004;324:17–27.
7. Coglianò V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F. Carcinogenicity of human papillomaviruses. *Lancet Oncol* 2005;6:204.
8. Villa LL, Denny L. Methods for detection of HPV infection and its clinical utility. *Int J Gynaecol Obstet* 2006;94(Suppl 1):S71–S80.
9. National Advisory Committee on Immunization. Statement on human papillomavirus vaccine. *Can Commun Dis Rep* 2007;33(ACS-2):1–32 Available at <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07pdf/acs33-02.pdf>. Accessed 2007 May 31.
10. Sellors JW, Karwalajtys TL, Kaczorowski J, Mahony JB, Lytwyn A, Chong S, et al. Incidence, clearance and predictors of human papillomavirus infection in women. *CMAJ* 2003;168:421–5.
11. Sellors JW, Mahony JB, Kaczorowski J, Lytwyn A, Bangura H, Chong S, et al; Survey of HPV in Ontario Women Group. Prevalence and predictors of human papillomavirus infection in women in Ontario, Canada. *CMAJ* 2000;163:503–8.
12. Moscicki AB, Ellenberg JH, Crowley-Nowick P, Darragh TM, Xu J, Fahrath S. Risk of high-grade squamous intraepithelial lesion in HIV-infected adolescents. *J Infect Dis* 2004;190:1413–21.
13. Coutlée F, Mayrand MH, Provencher D, Franco E. The future of HPV testing in clinical laboratories and applied virology research. *Clin Diagn Virol* 1997;8:123–41.
14. Coutlée F, Rouleau D, Ferenczy A, Franco E. Human papillomavirus testing. *Can J Infect Dis* 2005;16:83–91.

15. Yang BH. Cervical cancer as a priority for prevention in different world regions: an evaluation using years of life lost. *Int J Cancer* 2004;109:418–24.
16. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 consensus guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2002;287:2120–9.
17. Kornegay JR, Roger M, Davies PO, Shepard AP, Guerrero NA, Lloveras B, et al. International proficiency study of a consensus L1 PCR assay for the detection and typing of human papillomavirus DNA: evaluation of accuracy and intralaboratory agreement. *J Clin Microbiol* 2003;41:1080–6.
18. Bauer HM, Greer GE, Manos MM. Determination of genital human papillomavirus infection by consensus polymerase chain reaction amplification. Vol 1. In: Herrington CS, McGee JOD, eds. *Diagnostic Molecular Pathology, a Practical Approach*. Oxford, England: IRL Press; 1992.
19. Gravitt PE, Peyton CL, Alessi TQ, Wheeler CM, Coutlée F, Hildesheim A, et al. Improved amplification of genital human papillomaviruses. *J Clin Microbiol* 2000;38:357–61.
20. van Doorn LJ, Quint W, Kleter B, Molijn A, Colau B, Martin MT, et al. Genotyping of human papillomavirus in liquid cytology cervical specimens by the PGMV line blot assay and the SPF(10) line probe assay. *J Clin Microbiol* 2002;40:979–83.
21. Clifford G, Franceschi S, Diaz M, Muñoz N, Villa LL. HPV type-distribution in women with and without cervical neoplastic diseases. *Vaccine* 2006;24(Suppl 3):S26–S34.
22. Klaes R, Woerner SM, Ridder R, Wentzensen N, Duerst M, Schneider A, et al. Detection of high-risk cervical intraepithelial neoplasia and cervical cancer by amplification of transcripts derived from integrated papillomavirus oncogenes. *Cancer Res* 1999;59:6132–6.
23. Molden T, Kraus I, Karlsen F, Skomedal H, Nygard JF, Hagmar B. Comparison of human papillomavirus messenger RNA and DNA detection: a cross-sectional study of 4,136 women > 30 years of age with a 2-year follow-up of high-grade squamous intraepithelial lesion. *Cancer Epidemiol Biomarkers Prev* 2005;14:367–72.
24. Bulten J, van der Avoort IA, Melchers WJ, Massuger LF, Grefte JM, Hanselaar AG, et al. P14ARF and p16INK4A, two products of the same gene, are differently expressed in cervical intraepithelial neoplasia. *Gynecol Oncol* 2006;101:487–94.
25. Nieh S, Chen SF, Chu TY, Lai HC, Lin YS, Fu E, et al. Is p16(INK4A) expression more useful than human papillomavirus test to determine the outcome of atypical squamous cells of undetermined significance-categorized Pap smear? A comparative analysis using abnormal cervical smears with follow-up biopsies. *Gynecol Oncol* 2005;97:35–40.
26. Taskiran C, Aktas D, Yigit-Celik N, Alikasifoglu M, Yuce K, Tuncbilek E, et al. CYP1A1 gene polymorphism as a risk factor for cervical intraepithelial neoplasia and invasive cervical cancer. *Gynecol Oncol* 2006;101:503–6.
27. von Knebel-Doeberitz M, Syrjanen KJ. Molecular markers: how to apply in practice. *Gynecol Oncol* 2006;103:18–20.
28. Sopov I, Sorensen T, Magbagbeolu M, Jansen L, Beer K, Kuhne-Heid R, et al. Detection of cancer-related gene expression profiles in severe cervical neoplasia. *Int J Cancer* 2004;112:33–43.
29. Wilting SM, Snijders PJ, Meijer GA, Ylstra B, van den Ijssel PR, Snijders AM, et al. Increased gene copy numbers at chromosome 20q are frequent in both squamous cell carcinomas and adenocarcinomas of the cervix. *J Pathol* 2006;209:220–30.
30. Belinson JL, Qiao YL, Pretorius RG, Zhang WH, Rong SD, Huang MN, et al. Shanxi Province cervical cancer screening study. II: Self-sampling for high-risk human papillomavirus compared to direct sampling for human papillomavirus and liquid based cervical cytology. *Int J Gynecol Cancer* 2003;13:819–26.
31. Petignat P, Hankins C, Walmsley S, Money D, Provencher D, Pourreaux K, et al. Self-sampling is associated with increased detection of human papillomavirus DNA in the genital tract of HIV-seropositive women. *Clin Infect Dis* 2005;41:527–34.
32. Ogilvie GS, Patrick DM, Schulzer M, Sellors JW, Petric M, Chambers K, et al. Diagnostic accuracy of self collected vaginal specimens for human papillomavirus compared to clinician collected human papillomavirus specimens: a meta-analysis. *Sex Transm Infect* 2005;81:207–12.
33. Alameda F, Bellosillo B, Fuste P, Musset M, Marinoso ML, Mancebo G, et al. Human papillomavirus detection in urine samples: an alternative screening method. *J Low Genit Tract Dis* 2007;11:5–7.
34. Stuart G, Taylor G, Bancej CM, Beaulac J, Colgan T, Franco EL, et al. Report of the 2003 pan-Canadian forum on cervical cancer prevention and control. *J Obstet Gynaecol Can* 2004;26:1004–28.
35. Expert Working Group on Canadian Guidelines for Sexually Transmitted Infections. Genital human papillomavirus (HPV) infections. In: Canadian guidelines on sexually transmitted infections. 2006 ed. Ottawa: Public Health Agency of Canada; 2006. p. 160–73. Available: http://www.phac-aspc.gc.ca/std-mts/sti_2006/pdf/05sti2006e_e.pdf.
36. Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *J Natl Cancer Inst* 2001;93:293–9.
37. Sherman ME, Schiffman M, Cox JT. Effects of age and human papilloma viral load on colposcopy triage: data from the randomized Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS). *J Natl Cancer Inst* 2002;94:102–7.
38. Arbyn M, Buntinx F, Van Ranst M, Paraskevaidis E, Martin-Hirsch P, Dillner J. Virologic versus cytologic triage of women with equivocal Pap smears: a meta-analysis of the accuracy to detect high-grade intraepithelial neoplasia. *J Natl Cancer Inst* 2004;96:280–93.
39. Arbyn M, Paraskevaidis E, Martin-Hirsch P, Prendiville W, Dillner J. Clinical utility of HPV-DNA detection: triage of minor cervical lesions, follow-up of women treated for high-grade CIN: an update of pooled evidence. *Gynecol Oncol* 2005;99(Suppl 1):S7–S11.
40. Arbyn M, Sasieni P, Meijer CJ, Clavel C, Koliopoulos G, Dillner J. Clinical applications of HPV testing: a summary of meta-analyses. *Vaccine* 2006;24(Suppl 3):S78–S89.
41. Kuhn L, Denny L, Pollack A, Lorincz A, Richart RM, Wright TC. Human papillomavirus DNA testing for cervical cancer screening in low-resource settings. *J Natl Cancer Inst* 2000;92:818–25.
42. Schiffman M, Herrero R, Hildesheim A, Sherman ME, Bratti M, Wacholder S, et al. HPV DNA testing in cervical cancer screening: results from women in a high-risk province of Costa Rica. *JAMA* 2000;283:87–93.
43. Sherman ME, Lorincz AT, Scott DR, Wacholder S, Castle PE, Glass AG, et al. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. *J Natl Cancer Inst* 2003;95:46–52.
44. Cuzick J, Clavel C, Petry KU, Meijer CJ, Hoyer H, Ratnam S, 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.
45. Ronco G, Segnan N, Giorgi-Rossi P, Zappa M, Casadei GP, Carozzi F, et al. Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial. *J Natl Cancer Inst* 2006;98:765–74.
46. Franco EL. Primary screening of cervical cancer with human papillomavirus tests. *J Natl Cancer Inst Monogr* 2003;31:89–96.
47. Burchell AN, Winer RL, de Sanjose S, Franco EL. Epidemiology and transmission dynamics of genital HPV infection. *Vaccine* 2006;24(Suppl 3):S52–S61.
48. Moscicki AB, Schiffman M, Kjaer S, Villa LL. Updating the natural history of HPV and anogenital cancer. *Vaccine* 2006;24(Suppl 3):S42–S51.

49. Ho YF, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women *N Engl J Med* 1998;338:423–8.
50. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. *Vaccine* 2006;24(Suppl 1):S1–S15.
51. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol* 2003;157:218–26.
52. Woodman CB, Collins S, Winter H, Bailey A, Ellis J, Prior P, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *Lancet* 2001;357:1831–6.
53. Cuzick J, Szarewski A, Cubie H, Hulman G, Kitchener H, Luesley D, et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. *Lancet* 2003;362:1871–6.
54. The Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) Group. Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions: baseline data from a randomized trial. *J Natl Cancer Inst* 2000;92:397–402.
55. The ASCUS-LSIL Triage Study (ALTS) Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. *Am J Obstet Gynecol* 2003;188:1383–92.
56. Wright TC Jr, Schiffman M, Solomon D, Cox JT, Garcia F, Goldie S, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. *Obstet Gynecol* 2004;103:304–9.
57. Castle PE, Solomon D, Schiffman M, Wheeler CM. Human papillomavirus type 16 infections and 2-year absolute risk of cervical precancer in women with equivocal or mild cytologic abnormalities. *J Natl Cancer Inst* 2005;97:1066–71.
58. SOGC. Interim statement on HPV immunization / Déclaration provisoire sur l'immunisation contre le VPH. 2007. Available at http://www.sogc.org/media/advisories-20061019_e.asp. Accessed 2007 May 15.
59. Kjaer SK, van den Brule AJ, Paull G, Svare EI, Sherman ME, Thomsen BL, et al. Type specific persistence of high risk human papillomavirus (HPV) as indicator of high grade cervical squamous intraepithelial lesions in young women: population based prospective follow up study. *BMJ* 2002;325:572.
60. Nobbenhuis MAE, Walboomers JMM, Helmerhorst TJM, Rozendaal L, Remmink AJ, Risse EKJ, et al. Relation of human papilloma virus status to cervical lesions and consequences for cervical-cancer screening: a prospective study. *Lancet* 1999;354:20–5.
61. Brown DR, Shew ML, Qadadri B, Neptune N, Vargas M, Tu W, et al. A longitudinal study of genital human papillomavirus infection in a cohort of closely followed adolescent women. *J Infect Dis* 2005;191:182–92.
62. Massad LS, Behbakht K, Collins YC, Cejtin HE. Histologic findings from the cervix among older women with abnormal cervical cytology. *Gynecol Oncol* 2003;88:340–4.
63. Healey SM, Aronson KJ, Mao Y, Schlecht NF, Mery LS, Ferenczy A, et al. Oncogenic human papillomavirus infection and cervical lesions in aboriginal women of Nunavut, Canada. *Sex Transm Dis* 2001;28:694–700.
64. Hankins C, Coutlée F, Lapointe N, Simard P, Tran T, Samson J, et al. Prevalence of risk factors associated with human papillomavirus infection in women living with HIV. Canadian Women's HIV Study Group. *CMAJ* 1999;160:185–91.

Prevention

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INTRODUCTION

Efforts to limit the spread of HPV should be based on evidence. Contrary to bacteria that cause such STIs as chlamydial infection, gonorrhea, and syphilis, and contrary to the bloodborne pathogens that cause such diseases as HIV infection and hepatitis B, not as many methods of preventing transmission of HPV have been shown to be effective.

DEFINITION OF PREVENTION

The World Health Organization in 1948 defined levels of prevention in three successive stages, covering the means to prevent disease, therapy, and, if possible, social reintegration of patients. These objectives have since been adapted to the realm of STI control.¹

PRIMARY PREVENTION

This stage of prevention covers all activities designed to reduce the risk of HPV acquisition and thus to reduce the burden of disease. Considering that HPV is acquired early after sexual debut, primary prevention should start early. Population-based preventive measures should include dissemination of general information about HPV. There are many useful tools to prevent HPV infection, but they need to be tailored to patients' needs. More than one method may apply to each individual, and the approach may need to change over a person's lifetime, since HPV infection can recur even in stable partnerships. Practitioners need to engage patients in regular re-evaluation of their prevention needs. Individual preventive methods could include the following:

Abstinence

This is the best way to prevent HPV infection and the best method during adolescence. This option may not be acceptable for many but should still be discussed. It should be explained as not only abstinence from penetration of the vagina or the anus but also abstinence from skin-to-skin anogenital contact and from the use of sex toys. Postponing the debut of sexual intercourse may reduce the risk of HPV

infection and cervical cancer, as early coitarche is an enabling cofactor.²

Number of Sexual Partners

Reducing the number of sexual partners limits the risk of both HPV transmission and the acquisition of other cofactors for the development of cervical cancer. But among STIs, HPV infection is unique in its risk with very few partners: up to 60% of women were infected by their first partner.³ With a new partner, waiting before initiating sexual intercourse may augment the possibility of clearance of a previously acquired infection in either partner. Increasing the time between sexual partners may also help in terms of clearance. Choice of sexual activities may influence the risk of HPV acquisition. Nonpenetrative activities such as massage, masturbation, and kissing are not associated with HPV transmission. Anal or genital penetration is associated with transmission. Oral sex may be a risk factor for the development of aerodigestive cancer later in life.⁴

Specific Education

Because HPV awareness is so low, even in high-risk populations such as teens, people cannot adopt an HPV-preventive agenda without specific education. Information that should be available about HPV infection includes its frequency, clinical presentation, complications, modes of transmission, and effective preventive measures. This information should be available at least during visits to health care providers for reproductive and maintenance health care. During adolescence, there is a spectrum of readiness for sexual education, so the information should be repeated and, if provided in the office, in an adolescent-friendly approach. Any information campaign for adolescents should consider their characteristics and be addressed specifically to them.

Appropriate Methods of Contraception

The choice of contraceptive methods may influence the risk of HPV acquisition. Barrier methods have been described, from retrospective studies, as of limited efficacy in the prevention of HPV transmission.⁵ However, recently a prospective trial has shown good efficacy with consistent use.⁶

The protective properties of the condom are rapidly lost when use is not consistent. The condom may also protect against STIs caused by such agents as HIV, *Herpes simplex virus type 2*,⁷ and *Chlamydia trachomatis*,⁸ which are cofactors for cervical cancer; in addition, HIV is associated with anogenital cancer and persistent warts.⁹ The main problem with condoms is that too frequently there is genital contact with or without penetration before the condom is used. This limits the efficacy of this method of HPV prevention because the virus is highly contagious. Also, a condom can slip or break. Condom use in adolescence is often not optimal and not consistent. Therefore, the importance of condom use should be reinforced whenever possible.

Lengthy use of oral contraceptives may marginally augment the risk of cervical cancer.^{10,11} The direct effect of contraceptive hormones on the development of cancer is marginal and controversial and should not constrain physicians from prescribing them or patients from taking them,¹² as higher parity is an equivalent risk factor for cervical cancer.¹¹ Use of oral contraceptives in combination with condoms affords optimal protection against both STIs and unwanted pregnancy.

STI Preventive Measures

General measures to prevent STIs should be used, as other STIs represent minor or major factors enabling progress of persistent infection to cancer, and measures to prevent them are effective.

Vaccination

Vaccination may represent the best primary prevention method.

Caesarean Section

For pregnant women with EGWs, there is no evidence that vaginal delivery increases the risk of RRP in the offspring: many infants with RRP are born to women with no history of warts or abnormal Pap test results. Until new data emerge, Caesarean section should be reserved for women with obstructive disease.

SECONDARY PREVENTION

Secondary prevention covers activities aimed at reducing the risk of complications of HPV infection, shortening the time that patients are contagious, and reducing the number of new cases. With STIs, these activities include identification, referral, and screening of partners. These strategies have been proven effective for reportable STIs such as gonorrhea, chlamydial infection, and syphilis, as well as for diseases caused by bloodborne viruses that are also sexually transmissible, such as HIV and hepatitis B and C. In contrast, secondary prevention strategies for HPV infection

have not been proven effective in preventing virus transmission but also have not been greatly studied. At present they are of limited value.

Identification and Treatment of Disease

Early recognition of HPV infection by means of signs and symptoms of EGWs or abnormal Pap test results may help reduce transmission of HPV and prevent complications. However, HPV infection is mostly asymptomatic, and the possibility that an infected person with signs or symptoms will not transmit the virus is low. Since there is no virucidal treatment, there is no therapeutic way to shorten the contagious period. Adequate treatment of warts and lesions causing abnormal Pap test results will not reduce the risk of transmission, because virus can still be found outside the clinically recognizable areas. Disappearance of lesions is no guarantee of treatment efficacy or viral sterility. Some patients with lesions harbour HPV even after seroconversion to their genotype. Counselling about transmissibility, with a recommendation to avoid intercourse and to have new partners vaccinated before the onset of sexual activity, is of utmost importance.

Screening and Partner Referral

Screening for asymptomatic HPV infections in a new couple before they engage in unprotected sex is of no value since there is no validated test for men. In addition, the cost of testing women is prohibitive, as at least the high-risk and the low-risk probe would have to be used. Finally, this strategy has never been demonstrated to be of value in reducing transmission. Unlike gonorrhea, chlamydial infection, syphilis, and trichomoniasis, partner referral has never been demonstrated to be useful for preventing HPV reinfection of the other partner, nor has it been helpful in preventing infection of new partners. Partner treatment on the basis of exposure cannot be done since there is no such therapy available. In the distant future, a therapeutic vaccine may be available to be administered to sexual partners.

Smoking Cessation

Tobacco smoking may be associated with an increased risk of genital cancers in women.¹¹ Smoking cessation is strongly recommended for women with a diagnosis of HPV infection or any stage of an associated disease.

Postexposure Prophylaxis

In contrast to exposure to HIV infection and hepatitis B by accidental professional contact or chlamydial infection by sexual aggression, there is no available prophylaxis for people exposed to HPV infection by sexual activity.

Testing for Cure

Post-treatment testing for cure of HPV infection, EGWs, pre-invasive lesions, and abnormal Pap test results to prevent transmission does not exist. Serologic testing for individual viral genotype is used mainly for epidemiologic and vaccine efficacy research and is not available outside of research facilities. Some people clear their HPV infection without seroconversion, and others with seroconversion do not clear their infection. Nucleic acid amplification testing has not been validated for use in predicting whether a person is no longer infectious. We can prudently say that a person is less likely to transmit an infection the longer a clinical or laboratory abnormality has been silent. But at present we cannot guarantee that a person who had an infection is no longer contagious.

Cervical Cancer Screening

Cervical cancer screening by cytology can be seen as a secondary prevention method. Its role is to discover precancerous lesions that need follow-up, treatment, or both. Such screening diminishes the risk of progression of a precancerous lesion to cancer but has no role in preventing transmission.

TERTIARY PREVENTION

In the context of HPV infection, tertiary prevention activities aim to reduce the incidence of chronic incapacity due to warts, precancerous conditions, and cancers, as well as their recurrence in a population. We also want to reduce the functional consequences—sexual, societal, familial, mental, and physical—of all manifestations of HPV infection. This subject is covered elsewhere in the guidelines.

CONCLUSION

HPV infection is difficult to prevent in sexually active adults, and preventing transmission is much more difficult to achieve with HPV infection than with other STIs. Vaccination may represent the best primary prevention method, as condoms have limited efficacy without consistent use, and abstinence is unacceptable to many. Pap testing may represent the best secondary prevention method.

RECOMMENDATIONS

1. Counselling and other educational activities should stress (a) that abstinence is the most efficient way to prevent HPV infection but must include avoidance of not only penetration of the vagina or the anus but also any anogenital contact and the sharing of sex toys, (b) that

condoms have some efficacy against HPV infection only if used consistently, and (c) that disappearance of lesions is no guarantee that the patient is not still contagious. II-2B

2. Caesarean section does not prevent neonatal HPV and should be reserved for women for obstetrical indications. II-2B
3. Partner referral does not reduce the risk of re-infection and is not indicated as a preventative measure. II-2 B
4. Cervical cancer screening by cytology should be considered a secondary prevention method, intended to discover precancerous lesions and diminish the risk of their progression to cancer. IA
5. Smoking cessation should be strongly recommended to women with an HPV infection or any stage of an associated disease. IA

REFERENCES

1. Steben M, Turgeon F. La prévention des MTS. Montréal: Presses de l'Université de Montréal, 1994:387-8.
2. Schiffman MH, Bauer HM, Hoover RN, et al. Epidemiologic evidence showing that human papillomavirus infection causes most cervical intraepithelial neoplasia. *J Natl Cancer Inst* 1993;85:958-64.
3. Collins S, Mazloomzadeh S, Winter H, Blomfield P, Bailey A, Younge LS, et al. High incidence of cervical human papillomavirus infection in women during their first sexual relationship. *Br J Obstet Gynecol* 2002;109:96-8.
4. Herrero R. Human papillomavirus and cancer of the upper aerodigestive tract. *J Natl Cancer Inst Monogr* 2003;31:47-51.
5. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sex Transm Dis* 2002;29:725-35.
6. Winer RL, Hughes JP, Feng Q, O'Reilly S, Kiviat NB, Holmes KK, et al. Condom use and the risk of genital human papillomavirus infection in young women. *N Engl J Med* 2006;354:2645-54.
7. Smith JS, Herrero R, Bosetti C, Muñoz N, Bosch FX, Eluf-Neto J, et al. Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. *J Natl Cancer Inst* 2002;94:1604-13.
8. Smith JS, Muñoz N, Herrero R, Eluf-Neto J, Ngelangel C, Franceschi S, et al. Evidence of Chlamydia trachomatis as human papillomavirus cofactor in the etiology of invasive cervical cancer in Brazil and the Philippines. *J Infect Dis* 2002;185:324-31.
9. Ferenczy A, Coutlée F, Franco E, Hankins C. Human papillomavirus and HIV coinfection and the risk of neoplasias of the lower genital tract: a review of recent developments. *CMAJ* 2003;169:431-4.
10. Moreno V, Bosch FX, Muñoz N, Meijer CJ, Shah KV, Walboomers JM, et al. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *Lancet* 2002;359:1085-92.
11. Castellsague X, Muñoz N. Cofactors in human papillomavirus carcinogenesis—role of parity, oral contraceptives, and tobacco smoking. *J Natl Cancer Inst Monogr* 2003;31:20-8.
12. World Health Organization. Comprehensive Cervical Cancer Control: a Guide to Essential Practice. Geneva: WHO, 2006:36.

Screening for Cervical Cancer

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INTRODUCTION

Despite repeated recommendations from national expert groups that comprehensive organized cervical cancer screening programs would be in the public interest,¹⁻⁴ there has been wide variation among the Canadian provinces and territories in their planning and implementation of such systems. As such, there is wide disparity among women in Canada as to how they might benefit from one of the most effective cancer prevention strategies known today, cervical cancer screening. Though cervical cancer, widely believed to be in large part a disease preventable by screening, has been significantly reduced in incidence, it is still diagnosed in more than 1400 women in Canada per year and causes death in about 400 per year.⁵ About 60% of these women have not been screened or have been inadequately screened; disease developed in the others despite screening. Many times this number of women have precursor lesions that can be diagnosed through screening and for which effective treatment is available. It is estimated that organized screening can reduce cervical cancer deaths by 70% or more,⁶ prevent not only the loss of large numbers of life years but also the morbidity and costs of treating advanced disease, and, in many cases, preserve fertility when it might otherwise be lost.

PRINCIPLES AND COMPONENTS OF SCREENING

Screening is intended to identify groups of asymptomatic individuals within a population at risk for a specific condition and to systematically apply a simple test to large numbers of such individuals on the principle that identification of early forms or precursors of the condition can lead to definitive diagnosis and, if the presence of precursors is confirmed, an intervention that is acceptable and cost-effective and improves the outcome.

Whereas spontaneous, or opportunistic, screening occurs on a one-off basis as part of attendance at a routine appointment with a primary health care provider, organized screening is implemented on a population basis and has an information system with specific components to ensure high participation rates, including an invitation to enter the

program, reminders to return for repeat tests, and protocols to facilitate appropriate follow-up of abnormal test results.

The components of an organized screening program include the following:

- Recruitment of the target population, ideally via access to population-based data such as provincial health care rolls.
- Evidence-based recommendations for screening practices, including technologic aspects of the program, screening intervals, and intervention in the case of an abnormal result.
- Recall of those overdue for screening.
- Follow-up of abnormal test results.
- Education and communication that includes the public and all health care professionals involved.
- Quality assurance.

CERVICAL CANCER SCREENING IN CANADA

Until recently, Pap smear cervical cytology was the only screening test available for cervical cancer since the introduction of screening in the 1950s. Two new technologies are being evaluated and introduced to screening programs in Canada: LBC and HPV DNA testing. The status of cervical cancer screening in each province and territory in Canada is outlined in Table 5.1.⁷⁻¹³ As of September 2006, Saskatchewan had a fully implemented organized program, Manitoba had the capacity for a fully organized program that was in the process of stepwise implementation, British Columbia and Nova Scotia had very well developed, if not fully organized, programs, and Newfoundland was moving toward an organized program. Ontario's program was partially organized. New Brunswick had completed a pilot screening project, the results of which were being evaluated, but no provincial program. The Northwest Territories, Nunavut, Quebec, and Prince Edward Island had no program; a program in Prince Edward Island had recently been suspended.

Recommendations regarding initiation, intervals, and cessation of cervical cancer screening vary throughout the developed world and are highly influenced by the degree of

Table 5.1 Status of cervical cancer screening in Canada as of September 2006⁷⁻¹³

Region	Status, type* or Yes/No				
	Program	Recruitment	Recall	Follow-up	Data collection
British Columbia	P	No	Yes (MDs)	Yes (MDs)	Cy,H,Co,L
Alberta†	P	Yes	Yes (MDs & women)	Yes (MDs & women)	Partial
Saskatchewan	O	Yes	Yes (women)	Yes (MDs & women)	Cy, H, Co, L
Manitoba	P	Pending	Pending	Yes (MDs & women) for HSIL	Cy, H, Co, L
Ontario	P	No	No	No	Partial
Québec	No				
New Brunswick	Pilot project				
Nova Scotia	P	No	No	Yes (MDs)	Cy, H, Co, partial L
Prince Edward Island	No				Cy, H
Newfoundland	P	No	Pending	Pending	Cy, L pending
Northwest Territories	No				
Nunavut	No				

*O = organized; P = partially organized; Cy = cytology; H = histology; Co = colposcopy; L = linkages.

†In 2 regional health authorities.

organization of the program. Each program in Canada has developed or adopted its own recommendations, as outlined in Table 5.2.¹⁴ Compliance with the recommendations among clinicians and the public is highly variable. These recommendations apply to women in the general population without a history of lower genital tract neoplasia. Referral for colposcopy is indicated for those with significant cytologic abnormalities: HSIL, ASC-H, AGC, malignant cells, or persistent LSIL. Subsequent management will depend on the final diagnosis and the individual's clinical circumstances. There is little evidence to guide clinicians in best screening practices after diagnosis and treatment of a significant abnormality, but women with high-grade lesions remain at elevated risk even after long-term follow up. It is likely that HPV DNA testing combined with cytology will be appropriate follow-up, but this approach remains to be validated by high-quality clinical evidence.

SPECIAL CIRCUMSTANCES

Pregnancy

There is no evidence that women who are pregnant should be screened any differently than women who are not. If reported abnormalities are sufficient to warrant referral for colposcopy, the procedure should be done by a practitioner with specific expertise in assessing the pregnant cervix. If

interventions are required, every effort should be made to be conservative until the pregnancy is concluded, depending on the clinical circumstances. Biopsy or conization of the cervix during pregnancy should be done only if malignant disease is suspected and cannot be ruled out otherwise and again should be done by a clinician with specific expertise.

HIV Positivity

Women who are HIV positive have an increased likelihood of HPV infection,^{15,16} clearance of which can be impaired by decreased immune competence. Early evidence suggests that CIN is more aggressive and more difficult to eradicate with conservative treatment in these women. However, in HIV-positive women whose immune competence remains intact and those who are effectively treated with highly active retroviral therapy, the risk of HPV infection and the natural history of lower genital tract disease may be similar to those in HIV-negative women. Therefore, increased vigilance is recommended. Hankins et al¹⁵ recommended in 1999 that annual screening was appropriate for women with CD4 counts above $0.50 \times 10^9/L$ in whom two consecutive and adequate Pap smears had been normal. Women with CD4 counts below $0.20 \times 10^9/L$ should have baseline colposcopy and cytology every six months. Management of

Table 5.2 Recommendations for screening in each Canadian program, in comparison with national guidelines¹⁴

	Target population of women (years)	Initiation	Interval in relation to annual Pap test	Cessation age (years)
National guidelines ¹⁴	Age 18+ if ever sexually active	After sexual debut	Every 3 years after normal results twice	70
British Columbia	Age 20–69	After sexual debut	Every 2 years after normal results 3 times	69
Alberta	Age 18–69 if ever sexually active	After sexual debut	Annual	69
Saskatchewan	Age 18–69	Age 18+	Every 2 years after normal results 3 times	69
Manitoba	Age 18+ if ever sexually active	Within 2 years after sexual debut	Every 2 years after normal results 3 times	69
Ontario	Age 20–69 if ever sexually active	Within 3 years after sexual debut	Every 2–3† years after normal results 3 times	70 if adequate screening in previous decade
Nova Scotia	All women ever sexually active	Within 3 years after sexual debut or age 21	Every 2–3 years	75
Prince Edward Island*	Age 20–69	After sexual debut or age 18	Every 2 years	70
Newfoundland	All women ever sexually active	After sexual debut	Annual	None

*The program was recently suspended.

†Three years only if a recall system is in place.

abnormalities should be the same as for HIV-negative women.

Adolescents and Young Women

Not only are the cognitive, behavioural, and social circumstances of adolescents distinct from those of adult women, but also the characteristics and determinants of HPV infection are distinct during adolescence: the risk of HPV infection is highest in adolescence, and the likelihood of cervical cancer, while not zero, is very low. The likelihood of HPV infection is maximal in the first two years after initiation of sexual activity and is further increased with multiple or serial partners and inconsistent or no condom use. Most of these infections will be transient and of little consequence. Therefore, HPV testing should in general be used rarely among adolescents and only to demonstrate persistent infection, not incident infection; such testing should always be done in conjunction with cervical cytology. HPV testing has no role as part of routine STI screening. There is no indication for cervical screening before initiation of sexual activity, regardless of age.¹⁷

When abnormal cytology results or histologically proven dysplasia is detected in adolescents, the likelihood of regression of low-grade lesions is sufficiently high that treatment is rarely indicated. Even higher-grade lesions are more likely to regress in this population; although treatment is generally preferred by clinicians and by patients, if compliance with

follow-up recommendations is likely, a conservative approach with close follow-up may be appropriate.¹⁸ The need for health care providers to avoid a traumatic, embarrassing, or uncomfortable experience is important to facilitate screening compliance in all age groups but perhaps most importantly among adolescents.

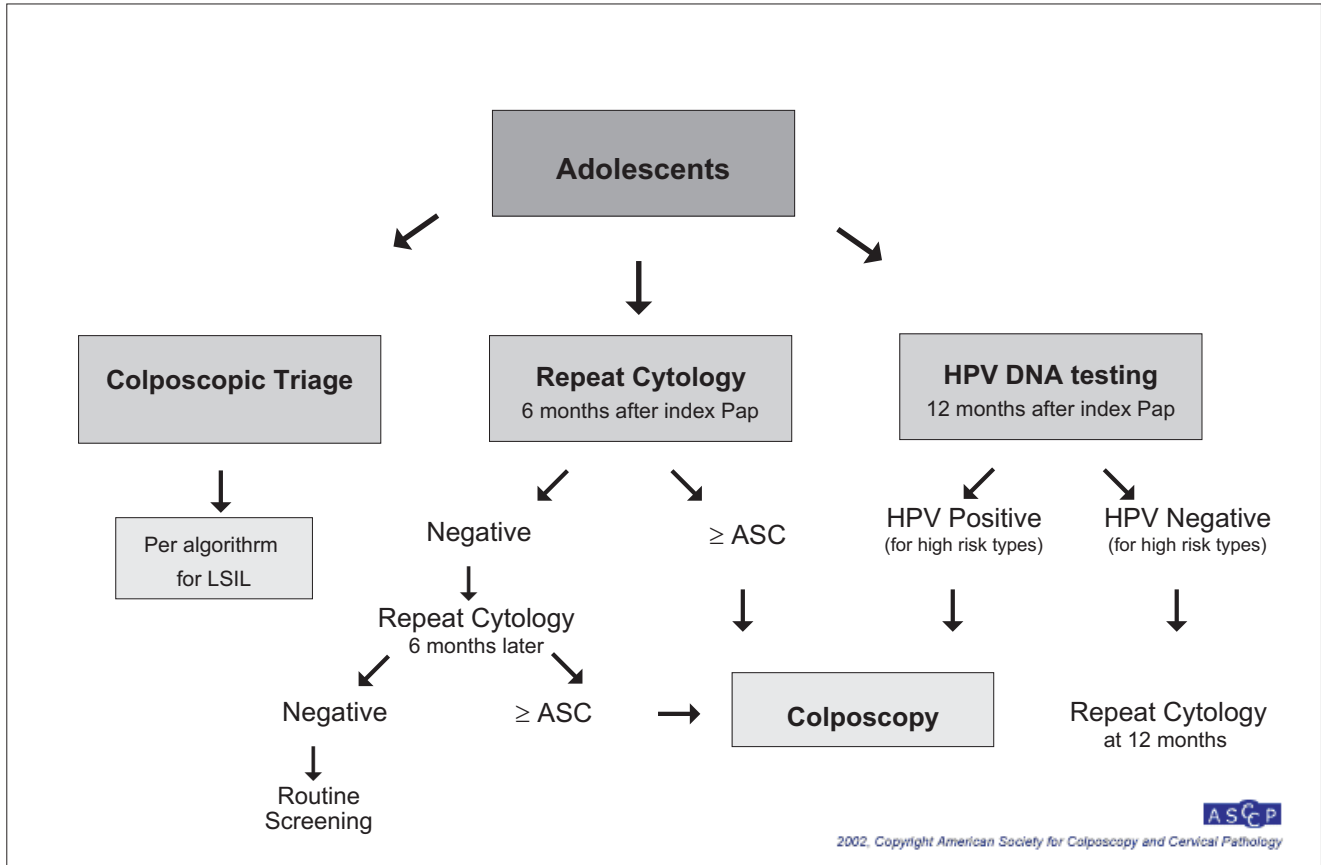
A separate screening algorithm for adolescents has not been adopted by screening programs in Canada. Several such algorithms, such as that in Figure 5.1,¹⁹ have been proposed in other jurisdictions to stress the conservative approach to cervical cytologic abnormalities in this age group and may be worthy of consideration. An even more conservative approach is expected to be published shortly.

Screening After Hysterectomy

Women who have undergone total hysterectomy for benign conditions, do not have a history of cervical dysplasia, and have a negative and adequate prior screening history do not require screening after their hysterectomy.

EFFECT OF CERVICAL CANCER SCREENING PROGRAMS

There is ample evidence that spontaneous cervical cytology screening has contributed substantially to the prevention of invasive carcinoma of the cervix and that organized screening can realize even more significant reductions.²⁰ Numerous reports clearly document a statistically significant decrease in the incidence and mortality rates of cancer of

Figure 5.1. Management of women with LSIL in special circumstances¹⁹

the cervix when screening is introduced into a population.²¹ Quinn and colleagues reported that mortality was reduced by almost half (from 6.1 to 3.7/100 000) 10 years after the 1988 implementation of an organized cervical screening program in Britain; the decline in incidence rate is shown in Figure 5.2.²²

In their analysis of cervical cancer mortality in Britain with and without screening, Peto et al refer to the “cervical cancer epidemic” averted by effective screening that would have resulted from increased HPV transmission owing to changes in sexual behaviour and less frequent use of barrier forms of contraception.²³ Among women aged 20 to 34 years, a population in which cervical cancer mortality increased three-fold between 1967 and 1988, the death rate declined from 2.20/100 000 in 1983–1987 to 1.03/100 000 in 1998–2002. This success was directly related to implementation and subsequent enhancement of a population-based organized screening program that now includes recruitment, recall, and follow-up.

Similar reductions in cervical cancer mortality due to screening programs have been observed in Canada, most remarkably in British Columbia, the province with the first

program and screening rates two to five times those of the other provinces.²⁴ Reductions in cervical cancer incidence and mortality have repeatedly been shown to be proportional to rates of participation in screening.^{6,25}

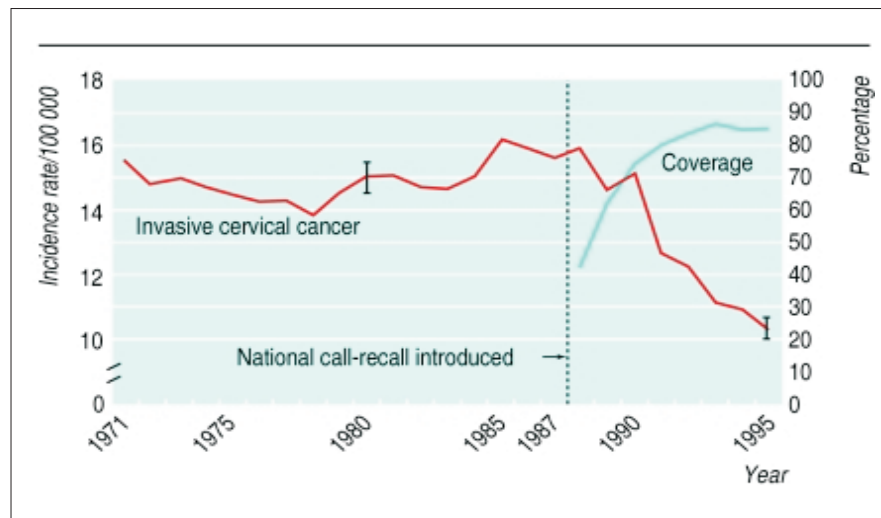
PERFORMANCE OF CERVICAL CYTOLOGY SCREENING

Table 5.3 summarizes the benefits and limitations of cervical cytology testing.^{22,23,26–29} The multifactorial nature of the cervical cancer detection system means that failure is possible at many levels.

Failure to Undergo Screening

Failure to undergo screening may be due to such reasons as lack of knowledge, lack of access, and failure of the clinician to offer screening. There is little information regarding predictors of screening in Canada other than higher income and educational level, lower age, ethnicity, fear or anxiety, and health status likely play a role. In self-reported data from the 1996–1997 National Population Health Survey, Maxwell et al³⁰ found that 72% of women reported a test within the previous three years and that Pap test use varied little across provinces but was less common among older and single women, those with lower education, a spoken

Figure 5.2. Decrease in incidence of invasive carcinoma of the cervix in Britain after the implementation of an organized cervical screening program



Reproduced from Quinn et al²² with permission of the publisher.

language other than English, a birthplace outside Canada, and negative health and lifestyle characteristics. Miller et al³ noted that family physicians and gynaecologists, student health centres, and family planning clinics have primarily been responsible for cervical screening, in the absence of invitations and reminders to women, clinicians, or both, and have relied on antenatal and postnatal screening visits, annual health examinations, and visits for contraception prescription renewals as opportunities to offer screening. Such an approach excludes recent immigrants, Aboriginal women, and those past childbearing age, all of whom are considered to be at above-average risk. Ideally, recruitment and follow-up strategies include specific strategies to target populations with a high likelihood of failure to attend for screening.

Failure of the Screening Process

Such failures include the following:

- Inadequate specimen: interference due to inflammation or menstrual debris, lesion not sampled (sample subepithelial, taken up inside the canal, etc.), squamocolumnar junction not accessible to sampling or not thoroughly sampled, specimen handled poorly, inexperienced clinician.
- Noncompliance with screening guidelines in terms of intervals or follow-up by the patient or clinician, sometimes owing to a laboratory communication problem.
- Laboratory errors in screening and interpretation.
- Errors in follow-up of abnormal results.

Performance of cervical cytology as a screening test, in terms of sensitivity, specificity, and positive and negative predictive values, depends on the techniques used to obtain and handle the specimen, the adequacy of the microscopic examination, the prevalence of cervical disease in the population studied, and the effectiveness of communication of the result to the clinician. In general, both the sensitivity and the specificity of an individual cervical cytology test are low; positive and negative predictive values are also suboptimal. A meta-analysis of 62 cytology studies conducted between 1984 and 1992 found a mean sensitivity of 58% (range 11% to 99%) and a mean specificity of 68% (range 14% to 97%).²⁶ A more recent systematic review found sensitivity and specificity ranges of 30% to 87% and 86% to 100%, respectively.²⁷ These inadequacies predispose to false-negative results, with failure to identify women who have cervical cancer, and false-positive results, which lead to unnecessary interventions and procedures. Serial testing improves sensitivity and diminishes the impact of the false-negative rate.

A truly negative result is one in which the test shows no malignant cells and no evidence of dyskaryotic cells and accurately reflects the absence of cervical disease. False-negative results, in which evidence of underlying disease is not detected, arise because of inadequate sampling of the area at risk or because abnormal cells in the specimen are missed or misinterpreted; however, repetition of the Pap test usually compensates for these sources of error by improved specificity³¹: if an abnormality is missed on one test, it is likely to be detected with the next.

Table 5.3. Benefits and Limitations of Cervical Cytology Testing^{22,23,26–28}

Benefits	Limitations
Good for screening; adaptable to widespread use	Must be repeated to be effective
Cost-effective	Requires laboratory and health system infrastructure to support collection, processing, interpretation, and reporting to clinicians
Acceptable to most patients	
Detects precancerous and cancerous lesions	Low sensitivity and specificity; suboptimal positive and negative predictive values
False-positive rate less than 1%	False-negative rate ~ 15% to 40%
If spontaneous screening, effective in reducing incidence and mortality	
If organized screening, further reduces incidence and mortality	

More than 50% of new cases of cervical cancer are diagnosed in women who are seldom or never screened.³² The failure rate of cervical cytology is highest in the presence of invasive cancer and can be 50%,²⁷ which emphasizes the need to biopsy any visible lesions of the cervix rather than depend on cytology. Even if associated with a normal Pap test result, a cervical lesion suspicious for cancer requires biopsy for accurate diagnosis.

Improved sensitivity, specificity, and predictive values are possible with LBC in place of conventional Pap cytology.^{33,34} Compared with cytology, HPV DNA testing as a primary screening test in some settings shows greater sensitivity and a very high negative predictive value, although a lower specificity. According to the International Agency for Research on Cancer, “there currently exists sufficient evidence that primary HPV testing can be expected to be at least as effective as conventional cytology” in reducing cervical cancer incidence and mortality.²¹ Applying the two techniques in sequence or in combination may be the optimal test when resources are adequate. Trials are ongoing or imminent of triage by HPV testing of women with abnormal Pap test results, as is currently recommended for women over the age of 30 years with ASC-US, and by cervical cytology for women with positive results of HPV testing. It is likely that integration of HPV testing into screening will allow later initiation and decreased frequency of cervical screening. If so, information systems and communication with women and their health care providers will become increasingly important to the effectiveness of screening.

Loss to follow-up of patients with abnormal Pap test results is an important cause of failure. Depending on the jurisdiction, the rate of loss often ranges between 20% and 40%.^{35–37} Prolonged screening intervals may contribute to this source of screening failure; in this circumstance, a registry and reminder letters to women, their clinicians, or both,

may be even more important than when more frequent screening is recommended.

TERMINOLOGY OF CERVICAL CYTOLOGY REPORTING

Most provinces use the 1991 revision of the Bethesda System³⁸ for classifying cervical cytology results in reporting the results of Pap tests. Ontario and Nova Scotia have implemented Bethesda 2001 terminology.³⁹

A standardized system of cytologic interpretation and terminology is an important part of our ability to understand the nature of cervical cancer precursors, to clearly communicate the results of cytologic tests, and to compare results among centres. The Bethesda System was developed in 1988⁴⁰ and revised in 1991, 2001, and 2006 (report pending). The revisions reflect our evolving understanding of the pathogenesis of cervical disease as interpreted from cytology specimens.³⁹ The Bethesda System of reporting includes three distinct components: (a) a statement of specimen adequacy (satisfactory versus unsatisfactory), (b) a general categorization (normal versus abnormal), and (c) the interpretation (non-neoplastic findings versus neoplastic findings [ASC-US, LSIL, HSIL, AGC, AIS, squamous carcinoma, adenocarcinoma, other]).

The strength of the Bethesda System is that it provides uniform, well-defined diagnostic terminology to facilitate unambiguous communication between the laboratory and the clinician.⁴¹ It also requires an evaluation of specimen adequacy. This rigorous standardization also allows for development and continuous flow of meaningful treatment algorithms and assessment of outcomes. The system does not include comprehensive guidelines on how to manage abnormalities, although educational notes and suggestions from the laboratory to the clinician are encouraged (<http://www.cytopathology.org/NIH>).

Table 5.4. Advantages and Disadvantages of LBC

Advantages	Disadvantages
More efficient for clinician, who does not have to prepare the slide	Training or retraining needed for cytotechnologists and cytopathologists
Collecting satisfactory specimen less dependent on clinician technique; lower proportion of unsatisfactory specimens	High cost of conversion and implementation of the technology in the lab
More homogeneous samples	Higher cost per test
Monolayer specimen easier to read; reduced interpretation time; increased lab productivity	
Greater sensitivity and specificity	
Allows for adjunctive/reflex HPV-DNA testing of same sample	

CERVICAL SCREENING TECHNOLOGY

Conventional Cytology

Conventional glass slide cytology remains the most common screening test for cervical cancer available to women in Canada. Effectiveness depends in large part on thorough sampling of the transformation zone of the cervix, the anatomic part at risk for cancer, with a sequential or a single-instrument technique under direct and complete vision. A single slide is sufficient for the entire specimen. When fixative is to be used, as in most jurisdictions in Canada other than British Columbia, it should be applied to the slide immediately after the cells are spread from both sides of the brush or spatula in a thin layer. Many studies have shown the sensitivity and specificity of conventional cytology to be less than ideal. Nanda et al²⁷ concluded from their systematic review that conventional Pap testing is less efficient at discriminating between women who have disease and those who do not than is generally believed; that although specificity was found to be high, the sensitivity estimates were much lower than is generally believed; and that cost-effectiveness models of cervical cancer screening should use more conservative estimates of Pap test sensitivity. However, with serial use, performance improves, and thus cervical cytology remains highly effective in reducing cervical cancer incidence and mortality.

Liquid-Based Cytology

LBC is a variation of conventional cytology. Two techniques are available: ThinPrep (Cytoc Corporation, Boxborough MA) and SurePath (formerly AutoCyte; TriPath Imaging, Burlington NC). The sample is collected in a manner similar to that of conventional cytology, with a cervical spatula, an endocervical brush or broom, or a combination, but is placed in a vial containing cell-preserving fluid. For ThinPrep, the spatula or brush is rinsed in the contents of the vial; with SurePath, the collection device is retained in the vial along with the sample. In this way,

virtually all cellular material is available to the laboratory for analysis.⁴² After the sample has been treated to remove cellular debris such as blood and mucous, a thin layer of the cells is deposited onto a slide. For both LBC techniques, slide preparation is automated, but ThinPrep slides are stained and examined in the usual way under a microscope by a cytologist, whereas SurePath slides can be examined by automated primary screening.

A meta-analysis showed that unsatisfactory specimens were significantly less likely for LBC than for conventional cytology, ranging from 0.1% to 1% and 0.1% to 12%, respectively.⁴² In an Ontario study, the proportion of unsatisfactory LBC specimens was half that of conventional cytology specimens.⁴³ The same meta-analysis also reported only slight improvements in sensitivity and specificity with LBC compared with the Pap test.⁴² The relative utility of LBC compared with conventional cytology will vary from setting to setting (e.g., high-risk versus low-risk populations) and with study design (e.g., split-sample versus direct-to-vial studies; historical-control versus other-control studies).^{22,44}

Ontario is the only Canadian jurisdiction in which LBC is currently used within a cervical cancer screening program. Newfoundland and British Columbia will implement LBC in the near future. In all other jurisdictions, specimens are collected for conventional cytology. The cost of transition to LBC is a challenge to all programs, but, as outlined in Table 5.4, the benefits include a significant increase in the proportion of satisfactory specimens and, therefore, a decreased need for repeat visits and potential loss to follow up, as well as availability of a residual specimen for reflex HPV DNA testing.

HPV DNA testing

HPV DNA testing has not been integrated into screening in Canada. Only in Newfoundland and Labrador is it funded by the provincial health care system, and then only if ordered by a gynaecologist or obstetrician. It is considered an option in Ontario and is widely available, in contrast to

the rest of Canada. HPV testing is recommended as a triage mechanism for the management of ASC-US among women over the age of 30 years. See Chapter 3 for a detailed discussion.

FROM SCREENING TO PREVENTION

The quadrivalent vaccine against the two HPV strains thought to be responsible for at least 70% of cervical cancer and the two strains responsible for most genital warts is now available in Canada, and another vaccine, effective against the same two oncogenic strains, is in the approval process. Although these vaccines will have an impact on screening in the future (as will changes in screening technology such as LBC, HPV DNA testing, and possibly other innovations such as molecular testing for preneoplastic conditions), no changes in screening practices are expected in the short term. Both vaccines have proven highly immunogenic, without significant adverse effects, and highly effective against CIN 2/3 (a surrogate for invasive cervical cancer) in large study populations. Published data for the quadrivalent vaccine show sustained immunogenicity for up to five years, with no indication of erosion of immunity in the study populations.⁴⁴ Only ongoing experience will determine whether booster doses will be necessary to preserve immunity. Long-term data will also inform the possibility or advisability of changes in screening practices.

Predicting the impact of HPV vaccination on screening strategies is complex. Most importantly, the unvaccinated population will remain at risk of invasive cancer and its precursors and will continue to require population-based screening for many years to come. Even women who are vaccinated will remain at risk of cervical neoplasia arising from the HPV types not covered by the vaccine. The recommendations for use of the quadrivalent vaccine published in February 2007 by the National Advisory Committee on Immunization included the strong statement that even “these [vaccinated] women should still expect to take part in the currently recommended cervical cancer screening programs.”⁴⁵

As the vaccinated population becomes demographically dominant and the high-risk types wane in frequency, it will likely become more challenging for screening cytotechnologists and cytopathologists to distinguish significant early changes in cytology specimens from those that are inconsequential. The volumes of cervical cytology specimens will likely diminish, necessitating changes in laboratory workflow, training requirements, and quality-assurance procedures.

Registration and tracking of vaccination status, preferably integrated with screening databases, will be very important to provide appropriate screening advice and interventions

to individuals and also to inform population surveillance strategies and to evaluate effectiveness of the vaccine(s). It is difficult to argue that implementation of a strategy that could prevent most of the 1400 cases of cervical cancer diagnosed in Canada annually is not prudent; however, the cost-effectiveness of this expensive new technology remains to be proven, although it has been extensively modelled, as discussed in detail in Chapter 7. The cost per case of cancer prevented or year of life saved will depend on uptake of the vaccine, delivery systems adopted, age at initiation and frequency of screening, savings in screening costs and costs ensuing from screening-detected abnormalities, and effectiveness of the vaccine(s) in preventing cervical cancer.⁴⁶

The challenges and opportunities of vaccination in developing countries, low-resource environments that in large part have little or no screening available, are even more complex. In jurisdictions that lack screening systems, have resultant high rates of cervical cancer, and face difficult resource-allocation decisions, HPV vaccination may be a more efficacious choice than screening.

RECOMMENDATIONS

1. The provincial and territorial governments of Canada should implement a publicly funded, organized, population-based cervical cancer screening system in order to move from opportunistic towards organized screening. IA
2. Recommendations for best evidence screening practice based on pan-Canadian data should be made and updated regularly in collaboration between specialty societies and governmental agencies. IA
3. The existing screening systems are successful in reducing the incidence in mortality of cervical cancer and should be preserved without major alterations. IA
4. An HPV vaccination database should be integrated with a cervical cancer screening database, in order to ensure evaluation of vaccination utility at a population level. IA
5. Type-specific HPV testing should be made available within an appropriate algorithm to eligible women in all provinces and territories. IIIA
6. LBC should be made available in all provinces and territories and facilitate reflex HPV testing when appropriate. IA
7. Cervical cancer screening programs should focus on implementing innovative and effective strategies to increase recruitment of women in populations with low rates of screening, such as Aboriginal groups, older women, newcomers to Canada, and marginalized women. IA

REFERENCES

- Walton RJ, Blanchet M, Boyes DA, Carmichael J, Marshall KG, Miller AB, et al. Cervical cancer screening programs. *Can Med Assoc J* 1976;114:1003–33.
- Canadian Task Force on Cervical Screening Programs: Cervical cancer screening programs: summary of the 1982 Task Force report. *Can Med Assoc J* 1982;127:581–9.
- Miller AB, Anderson G, Brisson J, Laidlaw J, Le Pitre N, Malcolmson P, et al. Report of a national workshop on screening for cancer of the cervix. *Can Med Assoc J* 1991;145:1301–25.
- Parboosingh EJ, Anderson G, Clarke EA, Inhaber S, Kaegi E, Mills C, et al. Cervical cancer screening: Are the 1989 recommendations still valid? National Workshop on Screening for Cancer of the Cervix. *Can Med Assoc J* 1996;154:1847–53.
- Health Canada. Cervical cancer screening in Canada: 1998 surveillance report. Ottawa: Minister of Public Works and Government Services Canada; 2002.
- Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet* 1987;1:1247–9.
- BC Cancer Agency. Cervical Cancer Screening Program, 2005 Annual Report. Available at www.bccancer.bc.ca/PPI/Screening/Cervical/2004+CCSP+Annual+Report.htm. Accessed 2006 Sept 5.
- Alberta Cervical Cancer Screening Program. Alberta Clinical Practice Guideline for Cervical Cancer Screening, 2006 Update. Available at www.cancerboard.ab.ca/acssp/resources.html. Accessed 2006 Sept 5.
- Saskatchewan Cancer Agency. Prevention Program for Cervical Cancer. Available at http://www.scf.sk.ca/PPCC/PPCC_web/Prevention%20Program%20For%20Cervical%20Cancer%20Frame.htm. Accessed 2006 Sept 5.
- Manitoba Cancer Care. Manitoba Cervical Cancer Screening Program, the Fundamentals, September 2000. Available at <http://www.cancercare.mb.ca/MCCSP/index.shtml>. Accessed 2006 Sept 5.
- Cancer Care Ontario: Ontario Cervical Screening Program Report 1997–2000. Available at <http://www.cancercare.on.ca/documents/Report97–2000Eng.pdf>. Accessed 2006 Sept 5.
- Cancer Care Nova Scotia. Pap Test Information, Office Manual for Health Professionals, Quick Reference Card, 2006. Available at <http://www.cancercare.ns.ca/inside.asp?cmPageID=323>. Accessed 2006 Sept 5.
- PEI Pap Screening Program, 2003 Report. Available at <http://www.gov.pe.ca/infopei/index.php3?number=62340&lang=E>. Accessed 2006 Sept 5.
- Johnson K. Periodic health examination, 1995 update: 1. Screening for human papillomavirus infection in asymptomatic women. Canadian Task Force on the Periodic Health Examination. *CMAJ* 1995;152(4):483–93. Available at <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=7859196>. Accessed 2006 Sept 5.
- Hankins C, Coutlée F, Lapointe N, Simard P, Tran T, Samson J, et al. Canadian Women's HIV Study Group. Prevalence of risk factors associated with human papillomavirus infection in women living with HIV. *CMAJ* 1999;160:185–91.
- Spitzer M. Lower genital tract intraepithelial neoplasia in HIV-infected women: guidelines for evaluation and management. *Obstet Gynecol Surv* 1999;54:131–7.
- Moscicki AB. Impact of HPV infection in adolescent populations. *J Adolesc Health* 2005;37(Suppl):S3–S9.
- ACOG Committee Opinion: Evaluation and management of abnormal cervical cytology and histology in the adolescent. *Obstet Gynecol* 2006;107:963–8.
- American Society for Colposcopy and Cervical Pathology. Consensus guidelines for the management of women with cytological abnormalities. *JAMA* 2002;287:2120–2129. <http://www.asccp.org/pdfs/consensus/algorithms.pdf>. Accessed 2007 May 30.
- Nieminen P, Kallio M, Anttila A, Hakama M. Organised vs. spontaneous Pap-smear screening for cervical cancer: a case-control study. *Int J Cancer* 1999;83:55–8.
- IARC Working Group on the Evaluation of Cancer-Preventive Strategies. Evaluation. In: Cervix cancer screening [IARC handbooks of cancer prevention 10]. Lyon, France: International Agency for Research on Cancer; 2005.
- Quinn M, Babb P, Jones J, Allen E. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *BMJ* 1999;318:904–8.
- Peto J, Gilham C, Deacon J, Taylor C, Evans C, Binns W, et al. The cervical cancer epidemic that screening has prevented in the UK. *Lancet* 2004;364:249–56.
- Benedet JL, Anderson GH, Matisic JP. A comprehensive program for cervical cancer detection and management. *Am J Obstet Gynecol* 1992;166:1254–9.
- Sigurdsson K. Effect of organized screening on the risk of cervical cancer: evaluation of screening in Iceland. *Int J Cancer* 1993;54:563–70.
- Fahey MT, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. *Am J Epidemiol* 1995;141:680–9.
- Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med* 2000;132:810–9.
- Sawaya GF, Sung HY, Kearney KA, Miller M, Kinney W, Hiatt RA, et al. Current approaches to cervical-cancer screening. *N Engl J Med* 2001;344:1603–7.
- Saslow D, Runowicz CD, Solomon D, Moscicki AB, Smith RA, Eyre HJ, et al. American Cancer Society. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. *Cancer J Clin* 2002;52:342–62.
- Maxwell CJ, Bancej CM, Snider J, Vik SA. Factors important in promoting cervical cancer screening among Canadian women: findings from the 1996–97 National Population Health Survey (NPHS). *Can J Public Health* 2001;92:127–33.
- Mayeaux EJ Jr, Harper MB, Abreo F, Pope JB, Phillips GS. A comparison of the reliability of repeat cervical smears and colposcopy in patients with abnormal cervical cytology. *J Fam Pract* 1995;40:57–62.
- Colgan TJ, Clarke A, Hakh N, Seidenfeld A. Screening for cervical disease in mature women: strategies for improvement. *Cancer* 2002;96:195–203.
- Monsonego J, Autillo-Touati A, Bergeron C, Dachez R, Liaras J, Saurel J, et al. Liquid-based cytology for primary cervical cancer screening: a multi-centre study. *Br J Cancer* 2001;84:360–6.
- McNeeley SG Jr. New cervical cancer screening techniques. *Am J Obstet Gynecol* 2003;189(Suppl):S40–S41.
- Sarfati D, Cox B, Jones RW, Sopoaga T, Rimene C, Paul C. National audit of women with abnormal cervical smears in New Zealand. *Aust N Z J Obstet Gynecol* 2003;43:152–6.
- Peterson NB, Han J, Freund KM. Inadequate follow-up for abnormal Pap smears in an urban population. *J Natl Med Assoc* 2003;95:825–32.
- Gage JC, Ferreccio C, Gonzales M, Arroyo R, Huivin M, Robles SC. Follow-up care of women with an abnormal cytology in a low-resource setting. *Cancer Detect Prev* 2003;27:466–71.
- Solomon D. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA* 2002;287:2114–9.

39. Henry MR. The Bethesda System 2001: an update of new terminology for gynecologic cytology. *Clin Lab Med* 2003;23:585–603.
40. The 1988 Bethesda System for Reporting Cervical/Vaginal Cytological Diagnosis. National Cancer Institute Workshop. *JAMA* 1989;262:931–4.
41. Franco EL, Duarte-Franco E, Ferenczy A. Prospects for controlling cervical cancer at the turn of the century. *Salud Publica Mex* 2003;45(Suppl 3):S367–S75.
42. National Institute for Health and Clinical Excellence. Cervical cancer—cervical screening (review): Liquid-based cytology for cervical screening (review). Technology appraisal TA69. 2003. Available at <http://guidance.nice.org.uk/TA69>. Accessed 2007 May 30.
43. Colgan TJ. Programmatic assessments of the clinical effectiveness of gynecologic liquid-based cytology. *Cancer* 2003;99:259–262.
44. Villa LL, Costa RLR, Petta CA. Efficacy of a prophylactic quadrivalent human papillomavirus (HPV types 6/11/16/18) L1 virus-like particle (VLP) vaccine through up to 5 years of follow-up. *Br J Cancer* 2006;95:1459–66.
45. National Advisory Committee on Immunization. Statement on human papillomavirus vaccine. *Can Commun Dis Rep* 2007;33(ACS-2):24.
46. Garnett GP, Kim JJ, French K, Goldie SJ. Modeling the impact of HPV vaccines on cervical cancer and screening programmes. *Vaccine* 2006;24(Suppl 3):178–86.

Treatment of External Genital Warts and Pre-invasive Neoplasia of the Lower Tract

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INTRODUCTION

Many modalities are available for the treatment of EGWs. None provides 100% chance of clearance or 0% chance of recurrence. The choice of treatment depends on the wart type, location, and number; patient preferences; and special circumstances, such as childhood, pregnancy, and immunosuppression. Before EGW treatment is begun, the physician should fully assess the entire lower genital tract, including performing a Pap smear, to rule out the presence of a cervical lesion. If the warts are atypical in appearance, VIN must be ruled out by biopsy or excision. The approach to treating pre-invasive disease of the lower genital tract is covered briefly at the end of this chapter. Invasive cervical cancer is managed by subspecialists, and discussion of treatment is beyond the scope of these guidelines. Treatment of HPV lesions and counselling should go hand in hand. Counselling is addressed in a separate chapter.

SOGC Clinical Tip

Before EGW treatment is begun, the physician should fully assess the entire lower genital tract, including performing a Pap smear, to rule out the presence of a cervical lesion.

CURRENT APPROACH TO EGW TREATMENT

Spontaneous regression of EGWs occurs in approximately 10% to 30% of patients.^{1,2} However, because regression may take up to six months, all patients with an EGW diagnosis could be offered treatment. Most women will elect to undergo treatment. The type of treatment chosen (Table 6.1) often depends on the location and extent of the EGWs, as well as on the age, sex, and pregnancy status of the patient.^{3,4} The patient also has a choice between self-applied and provider-applied treatment. The goals of treatment are

to remove the visible lesions and reduce the psychological consequences of having EGWs.

Self-Applied Treatment

Podophyllotoxin works as an antimetabolic agent, interfering with cell division and damaging tissues in which cells are reproducing. It is applied as a 0.5% solution (Condyline [Canderm Pharma, St-Laurent QC] or Wartec [Pharmascience, Montreal QC]) to warts, but not to the surrounding skin, every 12 hours, 3 days a week, for up to 6 weeks. It is more efficacious and has a lower rate of side effects than provider-applied 10% to 25% podophyllum resin (podophyllin).⁵ With use of the 0.5% solution, EGWs clear 45% to 88% of the time, but the recurrence rate is high, at 60%.⁶ Podophyllotoxin should not be used internally for treatment of cervical, urethral meatal, vaginal, or anal warts. Nor should it be used in pregnancy, as the agent accumulates in the fetus.⁷ It is both teratogenic and oncogenic in mice but has never been shown to be teratogenic or oncogenic in humans.⁷ Inadvertent use during pregnancy should be stopped, and the container should be stored at room temperature in a secure location, away from children, to avoid accidental ingestion.

Imiquimod is a cellular immunomodulator that acts by inducing inflammatory cytokines to suppress HPV infection, thus reducing the HPV load at the site of application.⁸ It is supplied as a 5% cream (Aldara; 3M Pharmaceuticals, St. Paul MN) in small, single-use sachets and can be applied topically to the lesions 3 times a week for up to 16 weeks. It is useful for first episodes and in cases refractory to other treatment. In one study, it completely cleared EWGs in 72% of female patients, and approximately 81% of those with persistent warts had more than a 50% reduction in wart size. During a 12-week follow-up period, only 13% of those with complete clearance experienced a recurrence.⁹ The main side effects are local erythema and erosion at the site of application. These side effects are usually mild to moderate, and treatment is generally well tolerated.

Table 6.1. EGW treatment modalities

Modality	Advantages	Disadvantages
Patient-applied		
Podophyllotoxin (0.5% solution)	Low cost, low toxicity	Variable penetration, contraindicated in pregnancy, ulceration, precise application difficult
Imiquimod (5% cream)	Easier to use, efficacious, low recurrence rate	High cost, delayed response
Provider-applied		
Trichloroacetic acid (85%)	Low cost, safe in pregnancy, easy to use, low potential for systemic reactions	Pain, variable penetration, ulceration
Cryotherapy	Safe in pregnancy, easy to use, no systemic reactions	Pain, ulceration
Laser vaporization	Efficacious, precise, no systemic reactions	High cost, training needed, pain, long healing time
Interferon	Antiviral, antiproliferative, immunostimulant	High cost, questionable efficacy, pain, systemic reactions

*The choice of therapy depends on the number of warts, their location, and their appearance (whether they are keratinized).

Imiquimod has not been harmful to the fetus in animal studies but is not licensed for use during pregnancy. Imiquimod application is the preferred therapy when the patient has multiple warts covering a large area. Because of its efficacy and the associated low recurrence rate, it should be tried before extensive laser treatment that requires local or general anaesthesia.⁹

SOGC Clinical Tip

Many patients prefer self-applied therapy for initial treatment of EGWs. Imiquimod is the topically applied agent with the lowest associated risk of recurrence.

Provider-Applied Topical Treatment

Podophyllum resin (10%–25%) removes warts by destroying infected tissue with a locally destructive and antiproliferative action.³ Use of the resin is decreasing in view of other safer and better topical agents.¹⁰ Systemic toxicity has been reported with use of the resin, and this agent is contraindicated in pregnancy because it is both teratogenic and oncogenic in mice.⁷ The European guidelines for the management of anogenital warts have removed podophyllum resin from the list of treatments for EGWs.^{11,12}

Trichloroacetic acid causes cellular destruction by chemical coagulation of cellular proteins.¹³ It is applied directly on the warts. The surrounding skin should be protected by the application of petroleum gel. There is no need to wash off the agent. Treatment can be repeated weekly for 4 to 6

weeks. Although trichloroacetic acid is well tolerated, it may produce blisters and ulcerations. It is safe for use during pregnancy.³

SOGC Clinical Tip

When using 85% trichloroacetic acid, apply petroleum gel to the surrounding skin to reduce the risk of more extensive local erosion

Provider-Applied Ablative Treatment

If topical therapy fails, VIN must be ruled out by biopsy or excision. An ablative treatment should then be used. Initial success rates with the following ablative forms of therapy are good, 70% to 97% of patients reporting clearance after treatment. Recurrence rates of up to 50% have been reported.³ Side effects may include bleeding, pain, itching, swelling, and scarring. Except for cryotherapy, all these modalities require at least local anaesthesia.

Cryotherapy with liquid nitrogen, carbon dioxide, or nitrous oxide and cryoprobes delivers treatment at a moderate cost with a good response rate. The damage is usually limited to the epidermis. It is especially useful when the EGWs are exophytic.

Surgical excision of the warts with a scalpel or an electrosurgical loop may be selected for large exophytic warts or when histologic diagnosis is required.

Electrosurgical destruction includes the techniques of electrofulguration and desiccation of the lesion.

Electrocautery (i.e., with a heated probe as opposed to an electrical current) causes more tissue damage and should be avoided.

CO₂ laser therapy is particularly useful in the treatment of EGWs that are large or have not responded to other therapy. It requires the use of highly specialized, expensive equipment that may not be available in all clinics. Special training in the effective and safe use of this equipment is also required, as in unskilled hands laser therapy can cause severe tissue damage and lead to scarring and vaginal or rectal perforation.¹⁴

Other Provider-Applied Treatment

In the past, α - and β -interferon were administered intralesionally, topically, and systemically for resistant or recurrent lesions that had not responded to other treatments. Clinical trials have shown that interferon therapy can be effective for EGWs.¹⁵ The side effects of direct delivery of the drug make treatment unacceptable to most women, and therefore interferon is rarely used for EGWs.¹⁶

SOGC Clinical Tip

For biopsy of the vulva, after local anaesthesia take the lesion between the thumb and the index finger to form a fold of skin, so the biopsy instrument can better “bite” the lesion. A Keyes punch biopsy instrument may also be used.

Treatment of Children

As discussed in detail in Chapter 2, the diagnosis of EGWs in children under the age of 12 years often raises concerns of sexual abuse. Referral for assessment to an experienced health care provider or to child protective services should be considered.

Many warts spontaneously regress in children, and careful consideration should be given to whether treatment is truly indicated. Although imiquimod is not approved for use in children, anecdotal experience is accumulating attesting to its safety, efficacy, and overall tolerability. Podophyllotoxin (0.5% solution) is a reasonable option and can be applied by caregivers or health care providers. The dosing schedules for these two agents are similar to those described for adults. Local reactions may occur. Care should be taken to store these agents out of the reach of small children. When destructive or caustic therapy is indicated, it should be performed with some form of sedation, analgesia, or anaesthesia.

SOGC Clinical Tip

In all children with EGWs, the possibility of sexual abuse must be considered. Evaluation by an expert or consultation with child protective services should be considered

Treatment During Pregnancy

EGWs often enlarge and proliferate during pregnancy and usually regress post partum. Treatment is often not necessary, and lesions may be managed expectantly. If the care provider and the woman elect treatment, the goal is to minimize discomfort and psychological burden. Vertical transmission during labour occurs in 30% of cases, but persistent infection in the neonate is uncommon.¹⁸ The risk of neonatal laryngeal papillomatosis after vaginal delivery is 1:400 to 1:1000.¹⁹ There is no evidence that treatment of EGWs reduces the risk of transmission to the infant or of neonatal laryngeal papillomatosis.²⁰ Caesarean section is not recommended for the purpose of preventing vertical transmission and is reserved for cases of large EGWs that might obstruct labour or result in heavy bleeding.²¹

Topical application of trichloroacetic acid and ablative treatments are safe.³ Podophyllum resin is contraindicated in pregnancy because teratogenicity has been reported in mice.⁷

Imiquimod cream has been used successfully, without side effects, in pregnancy,²² but it is not licensed for this use. In animal studies, no teratogenic or toxic effects on the fetus have been observed.²³ In the limited number of cases reported, no fetal adverse effects have been observed. Given the limited information available, imiquimod should be prescribed cautiously in pregnancy.

SOGC Clinical Tip

In pregnancy, EGWs are often managed expectantly. If treatment is elected, application of trichloroacetic acid and ablative treatments are safe.

Treatment of Immunosuppressed Individuals

HPV infection and in particular EGWs have been best studied in HIV-positive individuals and to a much lesser extent in people with other states of immunosuppression. HPV genotypes 6 and 11 are five times more prevalent and EGWs three times more common in HIV-positive women than in HIV-negative women.²⁴ The odds ratios for HPV 6 and 11 infection compared with no HPV infection among HIV-infected women range from 4.9 to 8.8 in those with CD4 cell counts of 200/ μ L or greater and 5.3 to 12.8 in

those with lower CD4 counts.²⁵ The incidence of EGWs is 5.01 per 100 person-years for HIV-seropositive women compared with 1.31 for HIV-seronegative women.²⁵ Large and often multiple warts occur with increased frequency in HIV-infected individuals.

Correction of the immunosuppressed condition, if possible, should be part of the management approach. Generally, antiretroviral therapy decreases the incidence of EGWs. However, worsening of EGWs has been described as a component of the immune reconstitution syndrome seen early after initiation of antiretroviral therapy.^{25,26} Standard regimens of EGW treatment can be tried, but typically the response is slow and relapse is more frequent.²⁷ Combination treatment that includes an ablative or excisional approach is often required. The approach should be individualized. Imiquimod has had mixed results in HIV-infected individuals. A systematic review in 2002 concluded that it was ineffective in HIV-seropositive individuals.²⁸ More recent studies have suggested however that the responses to treatment, as measured by total clearance, partial response, and frequency of adverse effects, are similar in HIV-infected and HIV-noninfected individuals.²⁹

When to Refer to a Specialist

Patients with lesions that are resistant to initial therapy or that are ulcerated, bleeding, or atypical in appearance, as well as pregnant patients with extensive warts, children, and immunosuppressed patients, should be referred to an expert in EGW management.

Treatment of Dysplastic Lesions of the Cervix, Vagina, and Vulva

HPV is the primary cause of dysplastic lesions of the vulva, vagina, and cervix. Treatment of these cytologically and histologically confirmed lesions is beyond the scope of these guidelines. Readers are referred to the American Society of Colposcopy and Cervical Pathology guidelines for contemporary recommendations.³⁰

Referral for colposcopy is indicated in any of the following circumstances: ASC-US or LSIL in two consecutive Pap smears at least six months apart; ASC-H; HSIL; ACG; ACIS; positive result of a test for high-risk HPV; abnormal-looking cervix, even if the cytology results are normal.

Treatment of histologically confirmed LSIL at colposcopy is at the discretion of the colposcopist and is based on consideration of age and lesion size. HSIL requires treatment by cryotherapy, loop electrosurgical excision procedure (LEEP), laser ablation, or in some circumstances cervical conization.

RECOMMENDATIONS

1. The management of EGW should include counselling on epidemiology, prevention of infection, and choice of treatment modalities. IIIA
2. A 0.5% solution of podophyllotoxin may be used for self-applied treatment but not in the urethra, vagina, cervix, or anus and not during pregnancy. II-2B
3. In the management of EGW, imiquimod application is preferred when extensive laser treatment requiring general anaesthesia would otherwise be indicated. II-2B
4. In the management of EGW, laser vaporization should be used only when less aggressive treatments have failed. II-2B
5. When EGWs are atypical or do not respond to topical therapy, VIN should be ruled out by biopsy or excision. II-2B
6. EGWs in children should be managed by a professional experienced in both EGWs and the psychosocial implications of the diagnosis. IIIA
7. Therapy for EGWs in immunosuppressed patients involves both correction of the immunosuppression and a combination EGW treatment that includes both ablative and excisional approaches. II-2B
8. Pregnant patients with extensive warts, patients who are immunosuppressed and patients who are resistant to therapy should be referred to an expert in EGW management. II-2B
9. TCA is a first line therapy for EGW and may be used in the vagina and safely during pregnancy. II-2B

REFERENCES

1. Weck PK, Buddin DA, Whisnant JK. Interferons in the treatment of genital human papillomavirus infections. *Am J Med* 1988;85:159-64.
2. Rudlinger R, Smith IW, Bunney MH, Hunter JA. Human papillomavirus infections in a group of renal transplant recipients. *Br J Dermatol* 1986;115:681-92.
3. Beutner KR, Ferenczy A. Therapeutic approaches to genital warts. *Am J Med* 1997;102:28-37.
4. Kraus SJ, Stone KM. Management of genital infection caused by human papillomavirus. *Rev Infect Dis* 1990;12(Suppl 6):S620-S32.
5. Kinghorn GR, McMillan A, Mulcahy F, Drake S, Lacey C, Bingham JS. An open, comparative, study of the efficacy of 0.5% podophyllotoxin lotion and 25% podophyllotoxin solution in the treatment of condylomata acuminata in males and females. *Int J STD AIDS* 1993;4:194-9.
6. Maw R. Critical appraisal of commonly used treatment for genital warts. *Int J STD AIDS* 2004;15:357-64.
7. von Krogh G, Longstaff E. Podophyllin office therapy against condyloma should be abandoned. *Sex Transm Infect* 2001;77:409-12.
8. Stanley MA. Mechanism of action of Imiquimod. *Papillomavirus Report* 1999;10:23-9.
9. Edwards L, Ferenczy A, Eron L, Baker D, Owens ML, Fox TL, et al. Self administered topical 5% imiquimod cream for external anogenital warts. *Arch Dermatol* 1998;134:25-30.

10. Fox PA, Tung MY. Human papillomavirus: burden of illness and treatment cost considerations. *Am J Clin Dermatol* 2005;6:365–81.
11. Von Krogh G, Lacey CJ, Gross G, Barrasso R, Schneider A; European Course on HPV Associated Pathology (ECHPV); European Branch of the International Union against Sexually Transmitted Infection and the European Office of the World Health Organization. European guideline for the management of anogenital warts. *Int J STD AIDS* 2001;12(Suppl 3):40–7.
12. Longstaff E, von Krogh G. Condyloma eradication: self-therapy with 0.15–0.5% podophyllotoxin versus 20–25% podophyllin preparations—an integrated safety assessment. *Regul Toxicol Pharmacol* 2001;33:117–37.
13. Zhu WT, Blauvelt A, Goldstein BA, Leonardi C, Penneys NS. Detection with the polymerase chain reaction of human papillomavirus DNA in condylomata acuminata treated in vitro with liquid nitrogen, trichloroacetic acid, and podophyllin. *J Am Acad Dermatol* 1992;26(5 pt 1):710–4.
14. Duus BR, Philipsen T, Christensen JD, Lundvall F, Sondergaard J. Refractory condylomata acuminata: a controlled clinical trial of carbon dioxide laser versus conventional surgical treatment. *Genitourin Med* 1985;61:59–61.
15. Syed TA, Khayyami M, Kriz D, Svanberg K, Kahlon RC, Ahmad SA, et al. Management of genital warts in women with human leukocyte interferon-alpha vs. podophyllotoxin in cream: a placebo-controlled, double-blind, comparative study. *J Mol Med* 1995;73:255–8.
16. Friedman-Kien AE, Eron LJ, Conant M, Growdon W, Badiak H, Bradstreet PW, et al. Natural interferon α for treatment of condylomata acuminata. *JAMA* 1988;259:533–8.
17. Grussendorf-Conen EI, Jacobs S. Efficacy of imiquimod 5% cream in the treatment of recalcitrant warts in children. *Pediatr Dermatol* 2002;19:263–6.
18. Tenti P, Zappatore R, Migliora P, Spinillo A, Belloni C, Carnevali L. Perinatal transmission of human papillomavirus from gravidas with latent infections. *Obstet Gynecol* 1999;93:475–9.
19. Tseng CJ, Liang CC, Soong YK, Pao CC. Perinatal transmission of human papillomavirus in infants: relationship between infection rate and mode of delivery. *Obstet Gynecol* 1998;91:92–6.
20. Silverberg MJ, Thorsen P, Lindeberg H, Grant LA, Shah KV. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. *Obstet Gynecol* 2003;101:645–52.
21. Expert Working Group on Canadian Guidelines for Sexually Transmitted Infections. Genital human papillomavirus (HPV) infections. In: Canadian guidelines on sexually transmitted infections. 2006 ed. Ottawa: Public Health Agency of Canada; 2006. p. 160–73. Available at http://www.phac-aspc.gc.ca/std-mts/sti_2006/pdf/05sti2006e_e.pdf.
22. Einarson A, Costei A, Kalra S, Rouleau M, Koren G. The use of topical 5% imiquimod during pregnancy: a case series. *Reprod Toxicol* 2006;21:1–2.
23. Frega A, Stentella P, De Ioris A, Piazzze JJ, Fambrini M, Marchionni M, et al. Young women, cervical intraepithelial neoplasia and human papillomavirus: risk factors for persistence and recurrence. *Cancer Lett* 2003;196:127–34.
24. Silverberg MJ, Ahdieh L, Muñoz A, Anastos K, Burk RD, Cu-Uvin S, et al. The impact of HIV infection and immunodeficiency on human papillomavirus type 6 or 11 infection and on genital warts. *Sex Transm Dis* 2002;29:427–35.
25. Massad LS, Silverberg MJ, Springer G, Minkoff H, Hessel N, Palefsky JM, et al. Effect of antiretroviral therapy on the incidence of genital warts and vulvar neoplasia among women with the human immunodeficiency virus. *Am J Obstet Gynecol* 2004;190:1241–8.
26. Ratnam I, Chiu C, Kandala NB, Easterbrook PJ. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1-infected cohort. *Clin Infect Dis* 2006;42:418–27.
27. De Panfilis G, Melzani G, Mori G, Ghidini A, Graifemberghi S. Relapses after treatment of external genital warts are more frequent in HIV-positive patients than in HIV-negative controls. *Sex Transm Dis* 2002;29:121–5.
28. Moore RA, Edwards JE, Hopwood J, Hicks D. Imiquimod for the treatment of genital warts: a quantitative systematic review. *BMC Infect Dis* 2001;1:3. Available at <http://www.biomedcentral.com/1471-2334/1/3>. Accessed 2007 May 15.
29. Cusini M, Salmaso F, Zerboni R, Carminati G, Vernaci C, Franchi C, et al. 5% imiquimod cream for external anogenital warts in HIV-infected patients under HAART therapy. *Int J STD AIDS* 2004;15:17–20.
30. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ; ASCCP-Sponsored Consensus Conference. 2001 consensus guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2002;287:2120–9.

Cost-Benefit Analysis of HPV Vaccination

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INTRODUCTION

With the advent of a quadrivalent vaccine against HPV, which has now been approved by Health Canada, studies in Canada have weighed the costs against the benefits of vaccination with this agent. In evaluating new interventions, treatments, and vaccines, regulatory agencies have made cost-effectiveness analysis an integral part of decision-making. As a measure of health outcome that combines duration and quality of life, the quality-adjusted life year (QALY) is used in most economic evaluations. Internationally it is well recognized that a cost of approximately \$50 000 or less per life-year saved is indicative of a cost-effective program. The assumptions made in calculating the QALY are crucial.

CLINICAL BURDEN OF HPV INFECTION

Despite the availability of regular screening, cervical cancer represents the second most common cancer in Canadian women aged 20 to 44 years.¹ Each year, there are approximately 1400 diagnoses in Canadian women and 400 deaths (Table 7.1).² Seventy percent of cervical cancer cases are due to HPV 16 and 18.

Infection with high-risk HPV types is also linked to a variety of other cancers. On average each year in Canada, 436 Canadian women receive a new diagnosis of vulvar or vaginal cancer and 128 women die from these diseases.³ The BC Cancer Agency estimated that in 2003 in British Columbia, in addition to 151 cases of cervical cancer, 87 cases of anogenital cancer and 56 cases of head and neck cancer were directly linked to HPV infection, and 78% of them were linked to HPV 16 and 18.⁴

Infection with HPV also causes an estimated 177 000 cases of CIN 1 and 52 000 cases of CIN 2/3 in Canada annually, 26% and 53%, respectively, being attributable to HPV 6, 11, 16, or 18.⁵

Genital warts are very common, affecting 1 in 10 Canadians at some point in their lives.⁶ The annual number of cases among Canadian women has been estimated to be 36 000,⁵ and the prevalence among Ontario women receiving cervical cytologic screening was reported to be 1.1%.⁷ Recent

data from Manitoba indicate that the prevalence of genital warts in Canadian men could be even higher than that in women: 190 versus 142 cases per 100 000.⁸

PSYCHOSOCIAL BURDEN OF HPV-RELATED DISEASE

HPV is a significant source of distress among people with an abnormal Pap test result, a diagnosis of precancerous lesions or invasive cancer, or genital warts. A positive Pap smear or referral for colposcopy can cause long-lasting worry about cancer, affect mood, impair daily activities, disturb sleep, and affect sexual life.⁹ These effects appear to be particularly pronounced in adolescents and young adults.¹⁰ Cervical cancer strongly affects the quality of life during treatment and thereafter.¹¹ People with genital warts frequently experience shame, anxiety, and embarrassment, which can reduce sexual enjoyment and have a negative impact on sexual relationships.^{12,13} Treatment of genital warts can be distressing, embarrassing, and painful.^{14,15} Many people also experience recurrence.^{15,16}

ECONOMIC BURDEN OF HPV-RELATED DISEASE

Screening for, diagnosing, and treating cervical HPV disease and genital warts in Canadian women poses a substantial burden to the health care system, with approximately 38 000 diagnoses of CIN 1, 12 000 diagnoses of CIN 2/3, and 85 000 consultations for genital warts annually (Table 7.2).⁵

The resulting annual economic burden is estimated to be close to \$300 million.⁵ Most of this burden (\$244.5 million) represents the cost of the more than 3.9 million Pap tests that produce negative or false-positive results; the rest (\$53.7 million) is due to true genital or cervical disease. HPV types 6, 11, 16, and 18 are thought to be responsible for 100% of the cost of genital warts (\$9.2 million), 36% of the cost of CIN 1 (total cost \$15.7 million), 61% of the cost of CIN 2/3 (total cost \$14.5 million), and 73% of the cost of cervical cancer (total cost \$13.6) (Table 7.3).

Overall, 62% (or \$33.3 million) of the total cost of true genital or cervical HPV disease in women is attributable to HPV 6, 11, 16, or 18. In comparison, the BC Cancer Agency reported that in 2005 the costs associated with HPV 6, 11,

Table 7.1. Estimated numbers* of new cases and deaths from cervical cancer by province in Canada in 2002²

Province	New cases (n)	Deaths (n)
Newfoundland and Labrador	25	15
Prince Edward Island	10	5
Nova Scotia	55	20
New Brunswick	35	10
Quebec	280	75
Ontario	510	150
Manitoba	45	15
Saskatchewan	45	15
Alberta	170	40
British Columbia	160	50
Total for Canada	1350	390

*Because of rounding of all numbers, the sums for the provinces do not equal the totals for Canada. The estimates for Canada may differ from actual figures and therefore must be compared cautiously with previously published estimates.

16, or 18 were \$37.4 million, or 75% of the total direct costs for the province.⁴ In BC alone, the annual cost of treating and managing diseases due to types 16 and 18 infection amounts to \$28.6 million, or 57% of the total; for types 6 and 11 the cost is \$8.8 million, or 18% of the total, since types 6 and 11 are responsible for 90% of genital warts, 76% of RRP, and 33% of sinonasal papillomas. These estimates do not include indirect costs to patients and families or the cost to the economy of productivity losses resulting from time away from work for diagnosis or treatment.

COST-BENEFIT ANALYSES OF HPV VACCINATION

With the increased cost of vaccine products, cost-effectiveness analyses are needed to justify new programs, especially because long-term recurrent expenditure is involved. In Canada, the first economic analysis was performed when vaccination of health care workers was to be introduced in 1991. Now this type of information is systematically requested. Cost-effectiveness analyses have been done for, among others, pneumococcal vaccination, varicella programs, and immunization strategies for the control of serogroup C meningococcal diseases (Table 7.4).^{17–19} Although budget impact remains a leading criterion for decision-makers, cost-effectiveness analysis determines the predicted marginal cost-effectiveness of programs.

There have been few reports on cost-benefit analyses of the quadrivalent and bivalent HPV vaccines (Table 7.5). In addition to factors that would be included in cost-benefit analyses of any vaccine (such as efficacy, coverage, and duration of protection), a history of HPV infection,

transmission rates, and cervical cancer screening are important variables to be considered in establishing a model for cost-benefit analysis of HPV vaccination. Many variables, such as the duration of protection and the uptake in the population, are unknown at this time for HPV vaccination. The quadrivalent vaccine was designed to protect against HPV types 6, 11, 16, and 18, the bivalent vaccine against types 16 and 18 (oncogenic types only).

Two types of models of HPV-vaccination evaluation are available in the literature: Markov models, which evaluate the natural history of HPV infection; and dynamic models, which evaluate transmission of HPV and the natural history of HPV infection. A third type of model, which incorporates the results of dynamic transmission into the Markov model, is called the hybrid model.

Groups of investigators have examined models to evaluate the cost-effectiveness of HPV vaccination in the United States.^{20–22} With respect to natural history, several factors were taken into account: the target for HPV vaccination, cervical cancer screening percentage, age at vaccination (which across all studies was 12 years), vaccination coverage (70% to 100%), vaccination efficacy (75% to 90%), and duration of protection (10 years or more to lifetime if boosters are given).

Vaccination of Females

The estimated cost per QALY gained varied considerably in the different Markov analyses of HPV vaccination in the United States.^{20–22} And, as discussed by Goldie et al,²² if vaccination efficacy varied between 70% and 100%, the reduction in the lifetime risk of cervical cancer would also

Table 7.2. Estimated annual burden of HPV-related disease in Canada (= 16 million women)⁵

Variable	Median of simulations	80% credibility interval (10% and 90% of simulations)
Health outcomes		
Genital warts*	36 000	(20 000; 60 000)
CIN 1	177 000	(95 000; 260 000)
CIN 2/3	52 000	(29 000; 101 000)
Cervical cancer	1 100	(450; 1600)
Cervical cancer deaths	450	(190; 680)
Health care resources		
Genital wart consultations*	85 000	(45 000; 140 000)
Negative Pap tests	3 743 000	(3 693 000; 3 777 000)
False-positives	161 000	(†; 554 000)
Diagnosed CIN 1	38 000	(18 000; 74 000)
Diagnosed CIN 2/3	12 000	(6 000; 22 000)
Cost (\$ per million)		
Negative Pap tests	212.6	(133.5; 316.7)
False-positives	31.9	(†; 178.8)
Treatment and diagnosis		
Genital warts	9.2	(7.0; 24.6)
CIN 1	15.7	(12.7; 48.8)
CIN 2/3	14.5	(10.5; 57.1)
Cervical cancer	13.6	(†; 64.9)
Total	298.2	(†; 560.2)

*Attributable to HPV 6 or 11.
†Base case is the minimum value of the parameter distribution.

vary, between 46% and 66%, thus leading to a cost per QALY of \$33 700 with 70% efficacy and \$20 600 with 100% efficacy. Despite these variations, all the models demonstrated that HPV vaccination would result in a reduction in HPV-related cervical cancer. They also predicted that compared with current screening practice, vaccinating girls before the age of 12 years appears to be cost-effective.^{20–26}

Because of the large number of equations and inputs, sensitivity analysis is very important in cost-effectiveness analysis. It is most sensitive to cervical cancer screening characteristics such as frequency and age of initiation, as well as duration of vaccine efficacy. It is less sensitive to natural history parameters and screening test characteristics. Most of the studies conducted thus far have been funded by the two pharmaceutical companies who will be or are marketing HPV vaccine, Glaxo Smith Kline (GSK) and Merck. The GSK model produced a cost per QALY of \$32 028 if the HPV vaccine offered protection against only HPV 16

and 18 and \$16 847 if the vaccine offered cross-protection against other oncologic types.²⁴

When transmission dynamics were included, Taira et al²³ found the cost per QALY gained by vaccination of females alone to be \$14 583. They estimated that the lifetime risk of cervical cancer among vaccinated girls would be reduced by 62% and that the number of lifetime cases of cervical cancer related to HPV 16 and 18 would be reduced by 95% in the vaccinated core. They also used a population-based assumption, dividing the population into age and sexual-activity groups. Base-case estimates of the cost per QALY for female-only vaccination ranged from \$0 to \$14 583.^{23,25}

Vaccination Against Low-Risk HPV Types

Recent studies in the United States that used a Markov model obtained a cost per QALY gained ranging from US \$44 889 to US \$12 700,^{20–22} whereas other models produced a cost ranging from less than zero to \$16 847 when including

Table 7.3. Estimated annual burden of disease related to HPV 6, 11, 16, and 18 in Canada

Variable	Burden	Burden attributable to HPV 6, 11, 16, and 18	
		Median of simulations	80% credibility interval (10% and 90% of simulations)
Health outcomes			
Genital warts*	36 000	100%	
CIN 1†	46 000	26%	(19%; 34%)
CIN 2/3	28 000	53%	(39%; 63%)
Cervical cancer	800	73%	(61%; 84%)
Cervical cancer deaths	320	71%	(58%; 83%)
Health care resources			
Genital wart consultations*	85 000	100%	
Negative Pap tests	0	0%	
False-positives	0	0%	
Diagnosed CIN 1†	17 000	44%	(30%; 56%)
Diagnosed CIN 2/3	7 510	61%	(49%; 69%)
Cost (\$ per million)			
Negative Pap tests	0.0	0%	
False-positives	0.0	0%	
Treatment and diagnosis			
Genital warts	9.2	100%	
CIN 1	5.7	36%	(25%; 44%)
CIN 2/3	8.9	61%	(49%; 69%)
Cervical cancer	9.9	73%	(61%; 84%)
Total†	33.3	11%	(10%; 24%)

*Attributable to HPV 6 or 11.
†Attributable to HPV 16 or 18 only: CIN 1 = 36 000; diagnosed CIN 1 = 13 000; total cost = \$17 million.

benefits against HPV 6 and 11.^{24,25} Less than zero per QALY means a cost saving in the Merck model when integrating the benefits of protection against HPV 6 and 11.²³ The best-case estimates would also vary substantially if parameters and assumptions were modified.

Vaccination of Males in Addition

A Merck dynamic model demonstrated that, in Britain, vaccinating both boys and girls with a quadrivalent vaccine before age 12 years, with catch-up vaccination of both sexes by age 24, was the most effective strategy, at a cost of less than Can \$30 000 per QALY gained.²⁷ In the United States, the same strategy was also the most effective, at a cost of US \$20 176 per QALY gained compared with the current practice.²⁵

Study Limitations

None of the studies addressed some possible effects of HPV vaccination, such as the decreased positive predictive value of Pap testing, adverse effects, and behavioural issues. They also did not address other HPV-related cancers, indirect costs, and productivity losses related to diagnosis or treatment. Small changes in a large number of variables might affect results; therefore, more comprehensive sensitivity analysis may be needed. A final issue not addressed is what may occur if the women not vaccinated are the ones who are not screened.

The analyses published thus far were mostly by economists funded by the vaccine manufacturers. Therefore, government agencies need to urgently review the data to confirm or modify assumptions that underpin those results.

Table 7.4. Cost-effectiveness of other vaccine interventions in Canada

Report	Vaccine	Base-case routine scenario	Vaccine cost per unit (no. of doses)	Cost-effectiveness analysis
De Wals et al, 2003 ¹⁷	Seven-valent pneumococcal conjugated vaccine	80% coverage; 4 doses at 2 to 6 months of age	\$58 (4)	Cost per QALY gained \$116 000 (3% discounted rate); net cost to society.
Brisson et al, 2002 ¹⁸	Varicella vaccine	90% coverage; 1 dose at 12 months of age	\$60 (1)	Cost per life-year gained \$44 503 (3% discounted rate);* health payer's perspective.
DeWals et al, 2004 ¹⁹	Serogroup C meningococcal vaccine	90% coverage; 1 dose at 12 months of age	\$50† (1)	Cost per QALY gained \$42 000 (3% discounted rate); societal cost under probabilities of different epidemiologic scenarios.

*Assuming no zoster or breakthrough varicella.

†Assuming joint administration with other vaccines and therefore no additional cost.

Predictions Specific to Canada

The quadrivalent recombinant vaccine costs \$134.95 per dose, or \$404.85 for the full three-dose vaccination regimen. The incremental administrative costs for the delivery of the vaccination program would be minimal in provinces that have school-based programs for hepatitis B vaccination. The Canadian perspective by Brisson et al²⁸ predicted that a vaccine that affords lifelong immunity and is 100% efficacious against infection with HPV 6, 11, 16, and 18 would prevent 9600 cases of genital warts, 3900 cases of CIN 1, 1800 cases of CIN 2/3, 140 cases of cervical cancer, and 50 deaths from cervical cancer over the lifetime of 100 000 Canadian girls vaccinated at age 12. According to this model, 8 Canadian girls would need to be vaccinated to avoid 1 case of genital warts, 14 to avoid 1 case of CIN 1, 31 to avoid 1 case of CIN 2/3, 276 to avoid 1 case of cervical cancer, and 639 to avoid 1 death from cervical cancer. The BC Cancer Agency estimated that if 80% of males and females received the vaccine, almost 12 cases of RRP could be avoided over 25 years in British Columbia alone and that prevention of genital warts and cervical cancer would represent 22% and 74% of the total discounted cost per QALY gained by vaccination.⁴

After incorporation of economic information, the Canadian model predicted that a quadrivalent vaccination program targeting 12-year-old girls would result in a substantial reduction in costs related to the diagnosis and treatment of anogenital warts, cervical dysplasia, and cervical cancer.²⁶ The projected discounted costs avoided per 100 000 Canadian girls vaccinated would total \$7.7 million—\$2.4 million for anogenital warts, \$1.3 million for CIN 1, \$2.2 million for CIN 2/3, and \$1.8 million for cervical cancer. A large proportion of the total cost avoided would be attributable to a reduction in the incidence of CIN 1 and

genital warts linked to the HPV 6 and 11 component of the quadrivalent vaccine.

According to Brisson et al,²⁶ adding the vaccination program to current Canadian screening practices would save 1390 life-years, or 2100 QALYs per 100 000 vaccinated girls, at a cost of \$32.3 million, or \$15 000 per QALY gained. This compares favourably with other publicly funded interventions, such as vaccination with the 7-valent pneumococcal conjugate vaccine (\$116 000 per QALY gained)¹⁷ and the use of letrozole, a novel aromatase inhibitor for the extended adjuvant treatment of women with early breast cancer (\$34 058 per QALY gained).²⁹ The cost-effectiveness of the quadrivalent HPV vaccine is essentially unchanged when the efficacy is reduced to 90% or the discount rate, input costs, or QALYs gained per outcome are varied. Only when the vaccine loses its efficacy after 30 years, vaccination is delayed until age 30, or the vaccine excludes types 6 and 11 do certain simulations produce incremental costs greater than \$50 000 per QALY gained.

CONCLUSION

Overall, vaccination against high-risk HPV types 16 and 18 and low-risk types 6 and 11 is cost-effective in a wide range of models with a wide range of assumptions. HPV vaccination can offer substantial health benefits, but at a cost—about US \$24 000 per QALY gained, according to the US Markov model of vaccinating 12-year-old girls against HPV 16 and 18 with lifetime protection.²² However, the estimated cost per QALY gained with female-only vaccination is more favourable when the prevention of genital warts is included by vaccinating against HPV types 6 and 11 as well—about Can \$15 000 according to the Canadian-based model with vaccine efficacy of 100% and age 12 years for the start of vaccination.²⁶ With the available published information, including that from the only government

Table 7.5. Comparison of cost-effectiveness analyses of HPV vaccination

Variable	Sanders et al ²⁰ (2003)	Kulasingam et al ²¹ (2003)	Goldie et al ²² (2004)	Taira et al ²³ (2004)	GSK ²⁴ (CDC, 2006)	Dasbach et al ²⁵ (CDC, 2006)	Brisson et al ²⁶ (IPV, 2006)
Model	Markov, static USA	Markov, static USA	Markov, static USA	Hybrid,*USA	Markov, static USA	Dynamic USA	Static Canada
HPV types targeted	High-risk	70% of high-risk types	16, 18	16, 18	a) 16, 18 b) 16, 18† c) 6, 11, 16, 18	6, 11, 16, 18	6, 11, 16, 18
Coverage	70%	100%	100%	70%	90%	70%	100%
Age	12 years	12 years	12 years	12 years	12 years	By 12 years	12 years
Efficacy	75%	90%	90%	90%	Types targeted by vaccine, 95%. Other oncogenic types, 30%	6, 11: 90% 16, 18: 100%	100%
Vaccine duration	10 years + 10 years with booster	10 years	Lifetime	10 years + 10 years with booster	Lifetime	Lifetime	Lifetime
Cost	\$300 per series + \$100 for booster	\$200 per series	\$377 per series	\$300 per series + \$100 for booster	\$100 per dose + admin. costs	\$300 per series	\$400 per series
Strategy	Females aged 12 years: 3 doses + booster after 10 years. Cancer screening: 71% every 2 years.	Females aged 12 years. Cancer screening: biennial screening delayed until age 24.	Females aged 12 years. Cancer screening: 67% < 1 year, 28% > 1 year, 5% not screened.	Females aged 12 years. Cancer screening: 71% every 2 years.	Females aged 12 years	a) Females aged 12 years b) F + M aged 12 years plus catch-up of F aged 12 to 24 years. Cancer screening: 0.6% to 60.4% per year.	Females aged 12 years. Cancer screening under current algorithm in Canada.
Reduction in risk‡ (base case)	20%	—	58%	62%	—	75%	61%
Cost per QALY gained	10-year protection, \$22 800 (base case) Lifetime protection, \$12 700	\$44 889§	Vaccine efficacy: 70%, \$33 700 90%, \$24 300 (base case) 100%, \$20 600	\$14 583 (base case)	a) \$32 028 (base case) b) \$16 847¶ c) \$21 443	a) Cost saving b) \$20 176	\$15 000

*Results from the dynamic transmission model were incorporated into the Markov model.

†Plus some protection against other oncogenic types (preliminary results; under investigation).

‡Reduction in lifetime risk of cervical cancer for vaccination compared with current screening practices.

§Per life-year gained with vaccination versus screening but no vaccination.

¶Assumes cross-protection.

agency report published to date,⁴ the most significant avoided costs with HPV vaccination would be those of pre-cancerous conditions of the cervix and nonmalignant disease. Cervical atypia and cancers would represent up to 55% of all costs avoided annually. Genital warts and RRP would make up another 36%.

RECOMMENDATIONS

1. Government agencies should advocate for public funding to evaluate the cost-benefit analyses reported thus far for the HPV vaccines. IIIA
2. Additional sensitivity analyses of HPV vaccines should be done urgently, along with examination of the cost-effectiveness of male vaccination in alternative strategies, such as with different ages at vaccination and with catch-up vaccination. IIIA
3. HPV vaccination is recommended for females aged 9 to 26 years against high-risk HPV types 16 and 18 for prevention of cervical cancer. IA
4. HPV vaccination is recommended for females aged 9 to 26 against low-risk HPV types 6 and 11 for prevention of external genital warts. IA

REFERENCES

1. Marett LD, Froid J, Nishri D, Ugnat AM. Cancer incidence in young adults in Canada: preliminary results of a cancer surveillance project. *Chronic Dis Can* 2002;23(2):58–64.
2. Canadian Cancer Society, National Cancer Institute of Canada, Statistics Canada, Provincial/Territorial Cancer Registries, Public Health Agency of Canada. Canadian cancer statistics 2006. Available at <http://www.cancer.ca>. Accessed 2007 June 8.
3. Statistics Canada. CANSIM Table 102–0522. Deaths, by cause, age group and sex, Canada, 2000–2003, Neoplasms (C00 to D48). <http://www.statcan.ca/english/freepub/84–208-XIE/2002/tables.htm>. Accessed 2007 June 8.
4. BC Cancer Agency. A Population Based HPV Immunization Program in British Columbia, Cancer Prevention Program, 2006. Available at <http://www.bccancer.bc.ca/NR/rdonlyres/3559E2B1–7D72–4D57–952E-E1CDD1E9F6E0/14494/HPVImmunizationReportJanuary172007.pdf>. Accessed 2007 June 8.
5. Brisson M, Van De Velde, Boily MC, De Wals P. The health and economic burden of HPV infection, genital warts, cervical dysplasia and cervical cancer in Canada. Presented at the 23rd International Papillomavirus Conference and Clinical Workshop; 2006 Sept 1–7; Prague, Czech Republic.
6. Akom S, Venne S. Human papillomavirus (HPV) infection. Québec: Institut national de santé publique; 2002 Nov. Available at <http://www.inspq.qc.ca/pdf/publications/374-HumanPapillomavirusInfection.pdf>. Accessed 2007 June 8.
7. Sellers JW, Mahony JB, Kaczorowski J, Lytwyn A, Bangura H, Chong S, et al; Survey of HPV in Ontario Women Group. Prevalence and predictors of human papillomavirus infection in women in Ontario, Canada. *CMAJ* 2000;163:503–8.
8. Kliewer EV, Demers AA, Elliott L, Brisson M. Twenty year trends (1985–2004) in the incidence and prevalence of anogenital warts in Manitoba, Canada: preliminary results. Presented at the 23rd International Papillomavirus Conference and Clinical Workshop; 2006 Sept 1–7; Prague, Czech Republic.
9. Rogstad KE. The psychosocial impact of abnormal cytology and colposcopy. *BJOG* 2002;109:4368.
10. Idestrom M, Milsom I, Andersson-Ellstrom A. Women's experience of coping with a positive Pap smear: a register-based study of women with two consecutive Pap smears reported as CIN 1. *Acta Obstet Gynecol Scand*. 2003;82:756–61.
11. Wenzel L, De Alba I, Habbal R, Kluhsman BC, Fairclough D, Krebs LU, et al. Quality of life in long-term cervical cancer survivors. *Gynecol Oncol* 2005;97:310–7.
12. Maw RD, Reitano M, Roy M. An international survey of patients with genital warts: perceptions regarding treatment and impact on lifestyle. *Int J STD AIDS* 1998;9:571–8.
13. Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private health plans in the United States. *Clin Infect Dis* 2003;36:1397–403.
14. Clarke P, Ebel C, Catotti D, Stewart S. The psychosocial impact of human papillomavirus infection: implications for health care providers. *Int J STD AIDS* 1996;7:197–200.
15. Von Krogh G, Lacey CJ, Gross G, Barrasso R, Schneider A. European guideline for the management of anogenital warts. *Int J STD AIDS* 2001;12(Suppl 3):40–7.
16. Stanley M. Chapter 17: Genital human papillomavirus infections—current and prospective therapies. *J Natl Cancer Inst Monogr* 2003;(31):117–24.
17. De Wals P, Petit G, Erickson LJ, Guay M, Tam T, Framarin A. Benefits and cost of immunization of children with pneumococcal conjugate vaccine in Canada. *Vaccine* 2003;21:3257–64.
18. Brisson M, Edmunds WJ. The cost-effectiveness of varicella vaccination in Canada. *Vaccine* 2002;20:1113–25.
19. De Wals P, Nguyen VH, Erickson LJ, Guay M, Drapeau J, St-Laurent J. Cost-effectiveness of immunization strategies for the control of serogroup C meningococcal disease. *Vaccine* 2004;22:1233–40.
20. Sanders G, Taira A. Cost effectiveness of a potential vaccine for human papillomavirus. *Emerg Infect Dis* 2003;9:37–48.
21. Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *JAMA* 2003;290:781–9.
22. Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch FX, et al. Projected clinical benefits and cost effectiveness of a human papillomavirus 16/18 vaccine. *J Natl Cancer Inst* 2004;96:604–15.
23. Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. *Emerg Infect Dis* 2004;10:1915–23.
24. Chesson HW. Cost effectiveness models of HPV vaccines. Presented at the 2006 National STD Prevention Conference, Jacksonville, Florida; 2006 May 8–11. Recorded presentation with handout available at <http://cdc.confex.com/cdc/std2006/techprogram/P11001.HTM>. Accessed 2007 June 8.
25. Dasbach EJ, Elbasha EH, Insinga RP. Immunization with a quadrivalent HPV vaccine: a cost effectiveness analysis of alternative vaccination strategies in the United States. Presented at the 23rd International Papillomavirus Conference and Clinical Workshop; 2006 Sept 1–7; Prague, Czech Republic.
26. Brisson M, Van De Velde, Boily MC, De Wals P. The potential cost-effectiveness of a prophylactic HPV6/11/16/18 vaccine. Presented at the 23rd International Papillomavirus Conference and Clinical Workshop; 2006 Sept 1–7; Prague, Czech Republic.
27. Insinga RP, Elbasha EH, Dasbach EJ. A preliminary assessment of the cost-effectiveness of a quadrivalent HPV vaccine in the United Kingdom using a multi-type transmission dynamic model. Presented at the 23rd International Papillomavirus Conference and Clinical Workshop; 2006 Sept 1–7; Prague, Czech Republic.
28. Brisson M, Van De Velde, Boily MC, De Wals P. Estimating the number need to vaccinate to prevent HPV related disease and mortality. Presented at the 23rd International Papillomavirus Conference and Clinical Workshop; 2006 Sept 1–7; Prague, Czech Republic.
29. El Ouagari KE, Karnon J, Delea T, Talbot W, Brandman J. Cost-effectiveness of letrozole in the extended adjuvant treatment of women with early breast cancer. *Breast Cancer Res Treat* 2007;101:37–49.

Vaccines

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INTRODUCTION

Trials have investigated prophylactic vaccines designed to prevent HPV-related disease; other trials are ongoing. Therapeutic vaccines are being developed in an attempt to treat those already infected with HPV.

Prophylactic Vaccination

Prophylactic vaccination is carried out with virus-like-particle (VLP) vaccines, which contain no viral DNA. The quadrivalent HPV vaccine Gardasil consists of the L1 capsid protein of each of the 4 HPV types 6, 11, 16, and 18.¹ The protein product self-assembles into a noninfectious VLP that is identical in shape and size to the natural virus.

HPV vaccination has been shown to be highly immunogenic and is very efficacious in preventing persistent HPV infection in women not previously infected with the HPV types used in the vaccine.² When injected intramuscularly, the vaccine induces immunity without actual infection.³ Clinical trials involving monovalent, bivalent,⁴ and quadrivalent vaccines⁵ have shown over 90% protection against persistent HPV infection² and related cervical dysplasia due to the vaccine subtypes in young, healthy people who have not begun sexual activity. Trials have also shown more than 90% efficacy in preventing incident HPV infection.⁶ Antibody response has been excellent in the vaccinated individuals and much greater than with natural infection.⁶⁻⁸ At the end of follow-up, the vaccine-induced antibody titres were 17 and 14 times higher than the titres induced by naturally occurring infection with HPV types 16 and 18, respectively.⁹

In the trials of bivalent vaccine (vaccination against HPV types 16 and 18) there was also some protection against incident infection with HPV types 45 and 31, indicating some cross-protection against phylogenetically related oncogenic HPV types.⁹ Currently there is no evidence for cross-protection against disease induced by HPV types 45 and 31 (e.g., CIN 2/3).¹⁰

The quadrivalent vaccine protects against the two main oncogenic HPV types as well as the two main types

responsible for the development of genital warts. At five years after enrollment, there was 96% protection against persistent HPV infection, and there were no cases of CIN related to HPV 16 or 18 or genital warts related to HPV 6 or 11. After 36 months, 94% remained seropositive for HPV type 6, 96% for type 11, and 100% for type 16. However, only 76% remained seropositive for type 18.^{5,7} The significance of antibody levels and seropositivity is unknown at this time.

FREQUENTLY ASKED QUESTIONS

What is Available?

There is currently one prophylactic vaccine available for use in North America: Gardasil (Merck Frosst).

What Does the Vaccine Protect Against?

Gardasil protects against the two most common oncogenic HPV types (16 and 18), which cause approximately 70% of cases of cervical cancer, and the two common low-risk types (6 and 11) that cause approximately 90% of anogenital warts.^{1,3,10} Cross-protection against phylogenetically related types is under investigation. There is no evidence that this vaccine will have an impact on an existing infection.

For Whom Has the Vaccine Been Approved?

Health Canada, which approved the vaccine July 10, 2006,¹¹ and the National Advisory Committee on Immunization (NACI)¹⁰ recommend it for girls and women aged 9 to 26 years. The NACI recommendations are incorporated into the responses below.

If Clinical Trials Studied Women 16 to 26 Years of Age, Why Is Vaccination Recommended for Those 9 to 26 Years Old?

Ideally the vaccine should be given before sexual debut and thereby before exposure to HPV. Vaccination of younger girls is important, as 20% of girls in grade 9 and 46% of those in grade 11 have had sexual intercourse.^{10,12,13} Vaccination before sexual debut would ensure maximum efficiency against all HPV subtypes covered by the vaccine. Also, immunogenicity data are available for girls 9 to

15 years old from bridging studies.^{1,2,7,9} The similar immunogenicity in those 9 to 15 years old as in those 16 to 26 years old is used to infer efficacy in the younger group, for whom efficacy data are not available.

Why Is Vaccination Approved Only at Age 9 to 26?

NACI recommends the vaccine only for females aged 9 to 26 years.¹⁰ The vaccine is not recommended for girls under the age of 9. Studies are now being done in women older than 26 years. Until the results are available, use of the vaccine in this older group, although not approved, can be considered in individual circumstances.¹⁰

May Boys and Men Be Vaccinated?

The vaccine has been approved for use in males in Australia, Mexico, and the European Union, but not in Canada. There are ongoing studies to find out if the vaccine prevents HPV infection and disease in males. Health Canada may consider licensing the vaccine for use in males if the results show that it is safe and effective in males.

Should Sexually Active Women Be Vaccinated?

The vaccine will not work as well for women exposed to HPV before receiving the vaccine.^{1,2,8} However, because most women will be naive to one or more of the HPV types in the vaccine, they may still benefit from vaccination.^{10,14}

Should Women with a History of HPV Infection Be Vaccinated?

Genital warts, abnormal cervical cytology results, and proven CIN are not contraindications to vaccination.^{2,15} Again, the vaccine will not work as well for those exposed to HPV before receiving the vaccine. However, these women may benefit to some extent because it is unlikely that they have been infected with all four types of the virus covered by the vaccine.^{10,14} Practitioners need to emphasize that the benefits of the vaccine may be limited in these circumstances and that cervical cancer screening needs to be continued according to provincial guidelines.¹⁴

Does HPV Testing Help Determine Whom To Vaccinate?

Neither HPV antibody testing nor testing for low- or high-risk HPV DNA is clinically useful in determining the need for vaccination.¹⁰ Serologic testing is insensitive and unreliable outside of research protocols. If results are positive, DNA testing for HPV identifies only current infection, possibly with more types than are contained in the vaccine, and likely identifies only one or two of the four types contained in the vaccine.¹⁰ Negative results do not rule out previous infection.

Can the Vaccine Be Used To Treat HPV Infection?

Vaccination is not a treatment for HPV infection or related disease.¹⁰

Should Pregnant Women Receive the Vaccine?

Pregnancy should be excluded before the vaccination series is begun. HPV vaccination is not recommended during a known pregnancy, but the safety data to date are reassuring.^{1,10} If a woman finds out she is pregnant after she has started the three-dose vaccine series, she should wait until after the pregnancy to finish the series. Overall, the proportions of pregnancies with an adverse outcome were comparable in women who received Gardasil and those who received placebo.¹ The manufacturer's pregnancy registry should be contacted (800-567-2594) if pregnancy is diagnosed during the vaccination schedule, but there is no need for any intervention.¹⁰

Should Lactating Women Receive the Vaccine?

Because it does not contain active virus, the vaccine appears to be safe in lactating women. It is not known whether vaccine antigens or antibodies induced by the vaccine are excreted in human milk.^{1,10}

Should Clinically Immunocompromised Women Be Vaccinated?

Those with HIV infection, recipients of solid organ transplants, and those receiving long-term immunosuppressant therapy may also receive the vaccine. However, there are no data on safety, immunogenicity, or efficacy.¹ The immune response to the vaccine may be blunted when compared with that of the immunocompetent population.

Should Lesbians Receive the Vaccine?

Vaccination is indicated for all females aged 9 to 26 years.

Does an Intercurrent Illness Preclude Vaccination?

Gardasil can be administered to patients with minor acute illnesses (e.g., diarrhea or mild upper respiratory tract infection, with or without fever). Vaccination should be deferred until a moderate or severe acute illness has resolved.¹

Which Women in the Indicated Age Group Should Not Receive the Vaccine?

Women should not receive the vaccine if they fit any of the following categories¹:

- Acutely ill with temperature above 37.8°C.
- Allergic to yeast or vaccine ingredients.
- Pregnant or trying to get pregnant.
- Have a bleeding disorder and cannot receive injections.

How Effective Is the Vaccine?

The HPV vaccine has been shown to be highly immunogenic.^{5,16} It generates a greater antibody response than natural infection.^{1,10} It is most efficacious in preventing persistent HPV infection in women who have not previously been infected with the HPV strains used in the vaccine.

Is the Vaccine Safe?

One cannot become infected with HPV by vaccination with Gardasil because the vaccine does not contain live virus or viral DNA.¹ The vaccine has been tested in more than 21 000 females 16 to 26 years of age worldwide. These studies have shown no serious side effects attributed to the vaccine. Adverse effects were uncommon, were the same in vaccinated subjects and controls, and consisted mostly of minor side effects such as pain, swelling, and redness at the injection site. The most common complaint was soreness at the injection site, which might last a day or so.¹⁰

What Are the Ingredients of the Vaccine?

The main ingredients in Gardasil are purified proteins of HPV types 6, 11, 16, and 18. The vaccine also contains amorphous aluminum hydrophosphate sulfate, sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection. The vaccine does not contain preservatives, antibiotics, mercury, or thimerosal.¹ The packaging is latex-free. Anyone who is allergic to the ingredients of Gardasil or has had an allergic reaction to the vaccine should not receive or continue to receive the vaccine.¹

Will Vaccine Recipients Be Protected If They Miss a Dose?

It is not yet known how much protection the vaccinee would receive from only one or two doses of Gardasil. For this reason, it is very important that all three doses be given.

Are Booster Doses Required?

Currently there are no data to support a recommendation of booster doses. The vaccine trials have found that vaccinated people are protected for at least five years. More research is being done to find out how long protection will last and whether a booster dose will be needed. The antibody level required for protection is unknown.

How Is the Vaccine Obtained and Stored?

Physicians administering Gardasil need to be familiar with cold-chain storage, quality audit, and handling procedures.¹ The vaccine should be kept in constant cold-chain storage at 2°C to 8°C (not frozen) and protected from light.¹ To ensure the integrity of the vaccine, temperature logs for the office refrigerator need to be kept. The vaccine should not be kept in a home refrigerator.^{17,18}

How Is the Vaccine Administered?

Gardasil is injected into the deltoid muscle in three doses over a six-month period (months 0, 2, and 6). If the patient cannot follow this schedule, it is recommended that the minimum interval between the first and second doses should be one month, and the third dose should be given at least three months after the second dose. All three doses should be given within a one-year period.¹ HPV vaccine may be given at the same time as hepatitis B vaccine.¹ Whether it can be administered with other vaccines is being studied.¹⁰

What Does Vaccination Cost?

Vaccination with Gardasil is currently not publicly funded. The cost of the full three-dose schedule should be discussed with the patient, as the proven efficacy is based on completion of the full schedule. Each dose costs approximately \$135, for a total of \$405, plus pharmacy fees. One should check with the local supplier for more information. The patient should check with her company or employer, as some insurance companies may cover some or all of the cost.

Should Vaccine Administration be Tracked?

It is good practice to keep a log of all those vaccinated and to develop a recall system for return appointments to ensure subsequent injections.

Should Patients Be Informed about the Vaccine?

We have a duty to inform our patients about the availability of any vaccine. The informed-consent discussion should cover risks and benefits of vaccination, possible consequences if vaccination is declined, the fact that the vaccine is currently not covered by any provincial health plan, and the cost to the patient of the entire three-dose program. It is good practice to document in the chart salient information about the discussion.¹⁹

Is Informed Consent Needed for Vaccination?

Health care providers should be familiar with provincial "consent to treat" legislation and rights to confidentiality. Although every effort should be made to involve and educate parents or caregivers, some provinces have no age for consent, and legislation allows adolescents (without reference to age) who have the capacity to understand and consent to medical intervention to receive information and treatment without explicit parental consent or involvement.¹⁹

Should Vaccinated Women Continue to Have Pap Tests?

Cervical cancer screening practices, according to provincial guidelines, should not be altered for vaccinated women, for three reasons:

- 1) the vaccine does not protect against all types of HPV that cause cervical cancer;
- 2) some women may not receive all three doses or may not get them at the right times, so they may not receive the full benefit; and
- 3) women who have already acquired an HPV type represented in the vaccine may not get the full benefit of the vaccine.^{10,14}

CONCLUSION

Information on HPV vaccination is rapidly changing, and what is presented here reflects what was available during the development of these guidelines. HPV is a common human pathogen that may exist in latent, subclinical, and clinically obvious states. Because it is a major immune interactor in the causation of cervical, vaginal, anal, and vulvar warts, dysplasia, and cancer, prophylactic vaccination is the most likely long-term solution to the burden of HPV-related diseases.

REFERENCES

1. Product monograph: Gardasil™ [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine] Suspension for Injection. Active Immunizing Agent. Kirkland QC: Merck Frosst Canada, 2006. Available at http://www.merckfrosst.ca/assets/en/pdf/products/GARDASIL_1055-a_10_06-E.pdf. Accessed 2007 May 30.
2. Stanley M. Prophylactic HPV vaccines. *J Clin Pathol* 2007;Jan 26 doi:10.1136/jcp.2006.040568 [Epub ahead of print].
3. Bosch FX, Manos MM, Muñoz N, Sherman M, Jansen AM, Peto J, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International Biological Study on Cervical Cancer (IBSCC) Study Group. *J Natl Cancer Inst* 1995;87:796–802.
4. Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004;364:1757–65.
5. Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16 and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005;6:71–8.
6. Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, et al. Proof of Principle Study Investigators. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med* 2002;347:1645–51.
7. Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. Efficacy of a prophylactic quadrivalent human papillomavirus (HPV) types 6, 11, 16 and 18 L1 virus-like particle vaccine through up to 5 years of follow-up. *Br J Cancer* 2006;95:1459–66.
8. Mao C, Koutsky LA, Ault KA, Wheeler CM, Brown DR, Wiley DJ, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. *Obstet Gynecol* 2006;107:18–27. Erratum in: *Obstet Gynecol* 2006;107:1425.
9. Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Rotelli-Martins CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised controlled trial. *Lancet* 2006;367:1247–55.
10. National Advisory Committee on Immunization. Statement on human papillomavirus vaccine. *Can Commun Dis Rep* 2007;33(ACS-2):1–32 Available at <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07pdf/acs33-02.pdf>. Accessed 2007 May 30.
11. Public Health Agency of Canada. Available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/phase1-decision/drug-med/nd_ad_2006_gardasil_102682_e.html. Accessed 2007 May 30.
12. Garriguet D. Early sexual intercourse. *Health Rep* 2005;16:9–18.
13. Grunbaum JA, Kann L, Kinchen S, Ross J, Hawkins J, Lowry R, et al. Youth risk behavior surveillance—United States, 2003. *MMWR Surveill Summ* 2004;53:1–96.
14. Frazer IH, Cox JT, Mayeaux EJ Jr, Franco EL, Moscicki AB, Palefsky JM, et al. Advances in prevention of cervical cancer and other human papillomavirus-related diseases. *Pediatr Infect Dis J* 2006;25(Suppl):S65–S81.
15. ACOG Committee Opinion. *Obstet Gynecol* 2006;108:699–705.
16. Block SL, Nolan T, Sattler C. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16 and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. *Pediatrics* 2006;118:2135–45.
17. Guidelines for maintaining and managing the vaccine cold chain. *MMWR Morb Mortal Wkly Rep* 2003 4;52:1023–5.
18. Weir E, Hatch K. Preventing cold chain failure: vaccine storage and handling. *CMAJ* 2004;171:1050.
19. New childhood vaccines. Information Letter. Ottawa:Canadian Medical Protective Association;December 2002;17(4).IL02470E. Available (for members only) at http://www.cmpa.org/cmpapd02/pub_index.cfm?FILE=CMPA_DOCS&LANG=E—59k— Accessed 2007 May 30.

Counselling

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INTRODUCTION

Counselling is defined as a professional relationship and activity in which a person endeavours to help another understand and solve his or her adjustment problems. It can also be the giving of advice, opinion, and instructions to direct the judgement or conduct of another.¹ The goals of counselling are crisis intervention, assistance with coping, promotion of self-care and shared decision-making, and reduction in transmission.

HPV infections and their complications result in a wide range of strong emotional responses, such as disgust, embarrassment, anger, self-blame, fear, betrayal, denial, depression, lowered self-esteem, and diminished sexual desirability. It is important to assess the impact that the diagnosis has on your patients to help them work through their emotional responses.²

COMMUNICATION ISSUES

Realize that nearly all communication is nonverbal. Only a small proportion of the message received is based on what you say. Your tone of voice and body language communicate much more than your words. Therefore, attempt to reduce noises and distractions, and remove obstacles between you and the patient. Sit down, and be aware of your posture and body language; avoid distracting behaviour. Before starting to talk, make eye contact and consider your tone of voice.

PERSONAL BELIEFS AND VALUES

Be aware of your own beliefs, attitudes, and values, which may differ from those of your patient. You need to acknowledge yours to avoid applying them to your patient and thus hindering objective counselling.

THE 5 R'S OF COUNSELLING

To get the best return on your counselling, follow the 5 Rs.³

- **Reach out** to your patient and explore the impact of a diagnosis of HPV infection. Acknowledge that the

patient is upset; allow her to express how she is feeling and determine why she feels this way.

- **Review** what the patient knows: what she was told, what she has read, what her parents and friends are saying about it, and what her preconceptions are about her condition.
- Be a **Resource** and build on or correct the patient's current knowledge: help her find this information by providing written materials or addresses of reliable Web sites.
- **Reassure** the patient that HPV infection is very common and that you will help her to manage it. Most people with the infection will not have disease or complications. Most can be followed and treated. The rate of death is very low and usually occurs in the late stage of disease, very rarely at an early stage if the patient is keeping scheduled follow-up appointments. Most adolescents will clear the infection on their own. Cervical cancer is a rare complication and can be prevented with close monitoring.
- **Reiterate** what you have discussed and book a follow-up appointment for further discussion. There is too much to take in at a single visit. Offer to allow the patient to bring her partner in. Refer her to sources of knowledgeable support, such as a community group, psychologist, sex therapist, or marriage counsellor knowledgeable in this field.

HELP PATIENTS PARTICIPATE IN THEIR CARE

Information can help patients to take control or become active participants in their care. They need and want information on transmission, characteristics of the infection, treatment options, prevention, and the risk of cervical cancer.⁴ Most patients wish to have information personalized to their situation.

Make the point that in more than 90% of cases, EGWs and cervical lesions spontaneously clear within two years. Smoking cessation helps to clear the lesions and decreases the risk of cancer. Condom use may help reduce HPV transmission if compliance is high. Stress that this means

from start to finish, with no unprotected genital-to-genital contact with all activities and partners. Condom use may also reduce the risk that EGWs and cervical lesions will develop. Condoms reduce the transmission of other STI agents, such as HIV, *Chlamydia trachomatis*, and HSV, which are cofactors for CIN as well as unwanted pregnancy.

Many patients have difficulty understanding the concepts of low- and high-risk types of HPV. They also have difficulty differentiating EGWs from Pap smear abnormalities and precancerous or cancerous lesions. Many women cannot distinguish between HPV DNA results and Pap test results. They do not understand that HPV can be present for a long time before it causes cervical cancer. Many women do not understand that the Pap test is used to detect precancerous conditions or cancer of the cervix. There is confusion between HPV and HSV.

The Internet is an important empowerment tool for many patients. Physicians should refer patients to credible Web sites, as many other sites have not updated their content. The Health on the Net stamp of approval may suggest that credible information is available. Specific sites of importance for patients include <http://www.sexualityandu.com> and www.ashastd.org. Sites addressing the specific concerns of professionals include <http://www.sogc.com> and <http://www.asccp.org>.

CULTURAL ISSUES

HPV testing may be seen as an indicator of infidelity or premarital sex. Some cultural groups may not see the need for testing because they do not see themselves as being at risk for STIs. Some religious beliefs may prohibit screening. A positive test result, if considered an indicator of infidelity, may cause marital discord and even excommunication from the family. If the treatment decision, based on the patient's wishes, is different from usual Canadian standards of care, the physician must clearly document this in the chart.⁵

ADOLESCENT SEXUALITY

Adolescents want to discuss issues of sexuality with their health care providers. They also believe that issues related to their sexuality should be important to their health care providers. They are likely to discuss these issues in a nonthreatening environment, but they may not ask for clarification if they do not understand a question. They prefer to be asked questions rather than being expected to volunteer information. They also need reassurance that their privacy will be respected and information will not be shared.⁶

RECOMMENDATIONS

1. A diagnosis of HPV infection or its complications results in a wide range of emotional responses. Physicians should assess the impact the diagnosis has had on the patient and help her work through the emotional responses. IIIA
2. Health care providers should proactively discuss issues of sexuality with their patients. IIIA

REFERENCES

1. Spraycar M, ed. *Stedman's Medical Dictionary*, 26th ed. Baltimore: Williams & Wilkins, 1995.
2. Reitano M. Counseling patients with genital warts. *Am J Med* 1997;102:38–43.
3. Main C. Counselling patients for human papillomavirus. Module 5 in: *Linking human papillomavirus to the practice of immunization*. Ottawa: SOGC: 2006.
4. Anhang R, Wright TC Jr, Smock L, Goldie SJ. Women's desired information about human papillomavirus. *Cancer* 2004;100:315–20.
5. McCaffery K, Forrest S, Waller J, Desai M, Szarewski A, Wardle J. Attitudes towards HPV testing: a qualitative study of beliefs among Indian, Pakistani, African-Caribbean and white British women in the UK. *Br J Cancer* 2003;88:42–6.
6. Rosenthal SL, Lewis LM, Succop PA, Burklow KA, Nelson PR, Shedd KD, et al. Adolescents' views regarding sexual history taking. *Clin Pediatr* 1999;38:227–33.

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