Cost-effectiveness of High-risk Human Papillomavirus Testing for Cervical Cancer Screening in Québec, Canada

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ABSTRACT

Objectives: Human papillomavirus (HPV) testing is not widely used for triage of equivocal Pap smears or primary screening in Québec, Canada. Our objective was to evaluate the cost-effectiveness of cervical cancer screening strategies utilizing HPV testing.

Methods: We used a lifetime Markov model to estimate costs, quality of life, and survival associated with the following strategies: 1) cytology; 2) cytology with HPV testing to triage equivocal Pap smears; 3) HPV testing followed by colposcopy for HPV-positive women; 4) HPV testing with cytology to triage HPV-positive women; and 5) simultaneous HPV testing and cytology. Cytology was used in all strategies prior to age 30. Outcome measures included disease incidence, quality-adjusted life-years saved (QALYs), lifetime risk of cervical cancer, and incremental cost-effectiveness ratios.

Results: All strategies incorporating HPV testing as a primary screening test were more effective and less expensive than annual cytology alone, while HPV testing to triage equivocal Pap smears annually was very cost-effective ($2,991 per QALY gained compared to annual cytology alone). When compared to cytology every three years, HPV-based strategies cost an additional $8,200 to $13,400 per QALY gained.

Conclusion: Strategies incorporating HPV testing are not only more effective than screening based on cytology alone but are also highly cost-effective. Provincial policy-makers should evaluate incorporating HPV-based strategies into current cervical cancer screening guidelines.

Key words: Human papillomavirus; cervical cancer; cost-effectiveness; health economics; screening

La traduction du résumé se trouve à la fin de l'article.

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Cervical cancer prevention in Canada has benefited from opportunistic screening and organized screening programs.[1] Canadian cervical cancer incidence rates have decreased from 14.2 per 100,000 women in 1979 to an estimated 7.1 per 100,000 in 2008.[2] Age-standardized mortality rates have also declined during this period.[2] The decline in cervical cancer incidence and mortality is largely due to widespread screening using Papanicolaou (Pap) smears, which allows for the detection of cellular changes and early treatment of cervical lesions. Despite the decline in incidence and mortality, cervical cancer continues to constitute an important public health burden with an estimated 1,300 new cases and 380 cervical-cancer related deaths in Canada in 2008.[2]

High-risk (HR) HPV testing has recently been evaluated in a number of trials for cervical cancer screening,[3-7] either as a stand-alone test or in conjunction with the Pap smear. A large Canadian trial comparing HPV testing with conventional Pap testing found that the sensitivity of HPV testing for cervical intraepithelial neoplasia (CIN) 2,3 was 95% compared to a sensitivity of 54% for Pap testing.[3] Due to its higher sensitivity, HPV testing has the potential to improve outcomes and/or reduce costs through longer screening intervals.

There are currently no Québec-specific guidelines for cervical cancer screening and treatment, and the province relies on opportunistic rather than organized screening. Most cervical cancer screening activities in Québec take place within the public sector and are based primarily on conventional cytology. Consideration of HPV-based screening approaches is underway in Québec; however, the cost-effectiveness of such alternatives has not been established.

Our objective was to determine the cost-effectiveness of several cervical cancer screening strategies utilizing conventional cytology and HR-HPV testing in Québec.

METHODS

We developed a lifetime Markov Monte Carlo simulation model of the costs, quality of life, and survival associated with screening and treating invasive cervical cancer and its precursors. We assumed that all women would be screened using Pap smears before age 30.

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Table 1. Input Variables and Sources

Variable*	Base-case Value	Range	Source
Population variables			
Age-specific prevalence (years) of HR HPV infection (%)		0.5-2x baseline	Mayrand,[9] Richardson[10]
<30	21.8		
30-39	12.7		
40-49	5.9		
50-59	4.8		
60-69	3.8		
Mortality data			
5-year survival rates (% alive at 5 years)			NCDB commission on cancer[17]
FIGO stage I	85	84-86	
FIGO stage II	55	53-58	
FIGO stage III	41	39-44	
FIGO stage IV	12	10-15	
Disease-specific utilities			Sanders[16]
HPV infection	1	0.8-1	
CIN 1	0.97	0.8-1	
CIN 2,3	0.97	0.5-1	
FIGO stage I cervical cancer (during treatment)	0.79	0.25-1	
FIGO stage II-IV cervical cancer (during treatment)	0.62	0.25-1	
Screening tests	Sensitivity	Specificity	
Conventional cytology			CCCaST (unpublished data)†
CIN 1 or worse (%)	33	98	
CIN 2,3 or worse (%)	59	97	
HPV positive			CCCaST (unpublished data)†
CIN 1 or worse (%)	71	95	
CIN 2,3 or worse (%)	98	94	
Cost variables‡			
Cost per clinic visit	$17	$13-$21	RAMQ fee schedule[21]
Diagnostic tests			
Conventional cytology tests	$16	$12-$20	Personal communication [Dr. Patricia Goggin, Institut national de santé publique du Québec, Montréal, QC, June 2008]
HPV DNA testing	$25	$18-$31	Personal communication [Dr. François Coutlée, McGill University, Montréal, QC, June 2008]
Colposcopy/biopsy	$105	$79-$131	RAMQ fee schedule[21]
Treatment options			
LEEP	$109	$82-$136	RAMQ fee schedule[21]
Total hysterectomy	$5,916	$4,437-$7,395	

HPV=human papillomavirus, NCDB=National Cancer Database, FIGO=Fédération Internationale de Gynécologie et Obstétrique, CIN=cervical intraepithelial neoplasia, CCCaST=Canadian Cervical Cancer Screening Trial, RAMQ=Régie de l'Assurance Maladie du Québec, LEEP=loop electrode excision procedure, and OCCI=Ontario Case Costing Initiative.

* All variables are annual unless otherwise noted.

† The sensitivity and specificity estimates were calculated from data on women with both HPV and Pap test results available, in both arms of the CCCaST study. These estimates are slightly different than the ones published in Mayrand[3] where the authors also included data on women with only one test available and computed arm-specific estimates.

‡ All costs are in 2007 Canadian dollars ($). The range of values for cost variables represents a variation of ±25% above and below the base-case estimates.

After age 30, the model evaluates the following cervical cancer screening strategies:

1. No screening;
2. Conventional cytology (every 1-3 years) with repeat screening for atypical squamous cells of undetermined significance (ASCUS) results (**cytology**);
3. Cytology with use of HPV testing to triage ASCUS cytology (every 1-3 years) (**cytology+HPV triage**);
4. HR-HPV testing for primary screening (every 3 years) followed by colposcopy for all HPV-positive women (**HPV only**);
5. HR-HPV testing for primary screening (every 3 years) with use of cytology for triage of HPV-positive women (**HPV+cytology triage**);
6. Co-screening with HPV testing and cytology (every 3 years) (**co-screening**).

Natural history model

Our model, which has been described previously,[8] follows a hypothetical cohort of 100,000 women over their lifetimes beginning at age 13. Distinct health states representing HPV status, CIN, and invasive cervical cancer were used to model the natural history of cervical disease. The time period was divided into monthly Markov cycles during which women could transition between health states based on time-dependent probabilities.

Clinical parameters

The incidence of HPV infection was estimated based on the prevalence of HPV in Québec.[9,10] Women with HPV infection or cervical disease could progress to higher-grade cervical disease, while women with CIN could regress to normal health or have persistent HPV infection without CIN.[11-22]

HPV testing was used to identify the 13 known HR-HPV types. The performance characteristics of cytology and HPV tests were based on data from the Canadian Cervical Cancer Screening Trial (CCCaST).[3] The presence of a cervical lesion was confirmed using colposcopy and biopsy.[23] Treatment varied based on disease status and included loop electrode excision procedure, cryotherapy, hysterectomy, chemotherapy, and radiation therapy.[24] (Refer to Table 1 and Supplementary Appendix 1* for a complete list of model input variables and sources)

Costs and quality of life

We adopted a health care payer perspective and as such included direct medical costs. Micro-costing methods were used to calculate the direct medical costs based on current clinical practice (Table 1 and Supplementary Appendix 1*).[21,22] Utilities were used as quality-adjustment weights to calculate quality-adjusted life-years (QALYs).

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Table 2. Clinical and Economic Outcomes Associated with Different Cervical Cancer Screening Strategies

Screening Strategy*	Average Annual Incidence of Cervical Cancer in Québec†	Average Annual Number of Cervical Cancer Deaths in Québec†	QALE (Years)‡	Average Lifetime Costs ($)‡	ICER Compared to No Screening ($/QALY)§	ICER Compared to Annual Cytology ($/QALY)	ICER Compared to Triennial Cytology ($/QALY)
No screening	1282	746	17.7817	$368	–	–	–
Cytology only (Every 3 yrs)	339	129	17.8196	$753	$10,161	–	–
Cytology+HPV triage (Every 3 yrs)	291	105	17.8215	$750	$9,616	–	Dominates‖
Cytology only (Annual)	191	54	17.8259	$926	$12,653	–	$27,460
HPV+cytology triage (Every 3 yrs)	163	40	17.8263	$809	$9,924	Dominates	$8,358
Co-screening (Every 3 yrs)	163	39	17.8263	$843	$10,668	Dominates	$13,433
Cytology+HPV triage (Annual)	147	33	17.8270	$930	$12,397	$2,991	$23,919
HPV only (Every 3 yrs)	145	33	17.8272	$815	$9,863	Dominates	$8,158

QALE=quality-adjusted life expectancy, ICER=incremental cost-effectiveness ratio, QALY=quality-adjusted life year, and HPV=human papillomavirus.

* Following are descriptions of the screening strategies listed above:
- Cytology only: Women with abnormal cytology results were referred for repeat screening (ASCUS) or follow-up colposcopies (LSIL/HSIL).
- Cytology+HPV triage: HPV testing was used to triage women with equivocal (ASCUS) cytology results.
- HPV+cytology triage: HPV testing was used for primary screening with use of Pap testing for the triage of HPV-positive women.
- Co-screening: Both HPV testing and Pap smears were used for primary screening.
- HPV only: All HPV-positive women received colposcopies.

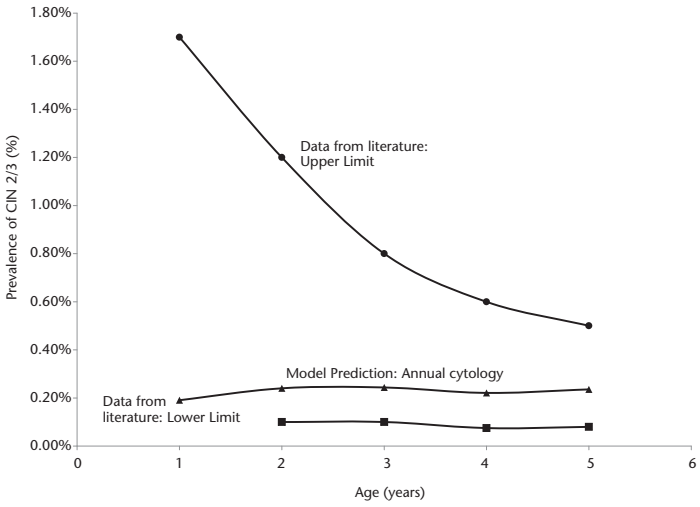
† For this analysis, we have used a population of approximately 3 million women in Québec.
Source: http://www.stat.gouv.qc.ca/donstat/societe/demographie/struc_poplt/201_07.htm

‡ Please note that the ICER calculations are based on costs with two decimal places and life expectancy values with six decimal places, so the presented results are slightly different than what one would calculate using the costs and life expectancy values in the table above.

§ The ICER is calculated as the ratio of the difference in costs to the difference in effectiveness between two screening strategies.

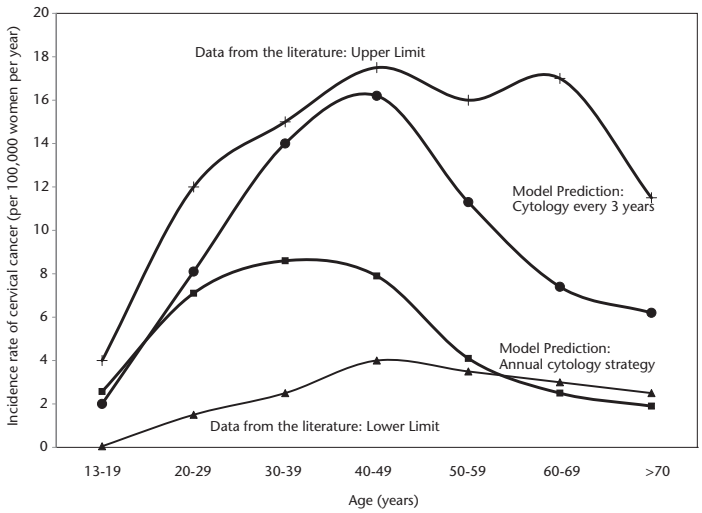
‖ A dominant strategy is less expensive and more effective than the strategy to which it is being compared.

Figure 1a. Model validation: Age-specific prevalence of CIN 2,3*



* The line with triangles shows the age-specific prevalence of CIN 2,3 predicted in the model. The line with squares and the line with circles show respectively the lowest and highest prevalence values in the literature.[26]
CIN denotes cervical intraepithelial neoplasia.

Figure 1b. Model validation: Age-specific incidence of cervical cancer*



* The line with squares shows the age-specific incidence of cervical cancer predicted in the model for the annual cytology strategy. The line with circles shows the incidence of cervical cancer in the model assuming cytology is done every three years. The line with triangles and the line with crosses show respectively the lowest and highest cervical cancer incidence rates seen in the literature.

Health states for CIN and cervical cancer were associated with decreased utility.[16] Age-specific utilities were based on data from the WHO-CHOICE program.[18]

Model outcomes

Primary outcome measures included QALYs saved, total costs, lifetime risk of cervical cancer, and incremental cost-effectiveness ratios (ICERs). Future costs and health outcomes were discounted to present values at a rate of 5% per year.[25] All modeling was conducted using TreeAge Pro 2007 release 1.5 (TreeAge Software, Williamstown, MA).

Sensitivity analysis

We conducted one-way sensitivity analyses to assess the robustness of model results. Ranges for the sensitivity analysis for clinical variables were based on the literature and input from clinical experts (Table 1 and Supplementary Appendix 1*). The range of values for cost variables represents a variation of ±25% above and below the base-case estimates.

Because of the lack of precise data on compliance and loss to follow-up for HPV-based strategies, we assumed 100% compliance and no loss to follow-up for all strategies in the base case. We conducted extensive sensitivity analyses on loss to follow-up and compliance, assuming that 16% of women will never be screened, 70% of women will be screened as recommended, and 18% of women will miss follow-up colposcopies (details provided in Supplementary Appendix 2*).[19,20]

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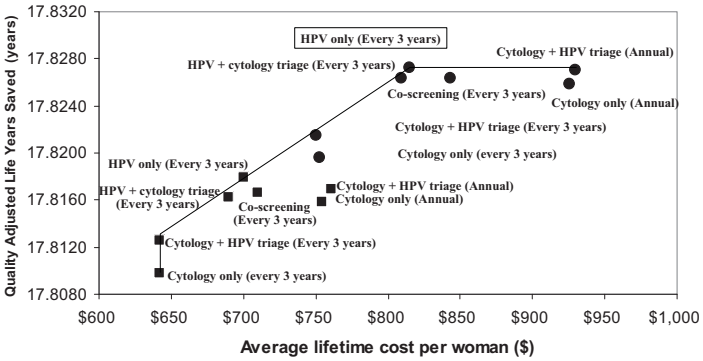
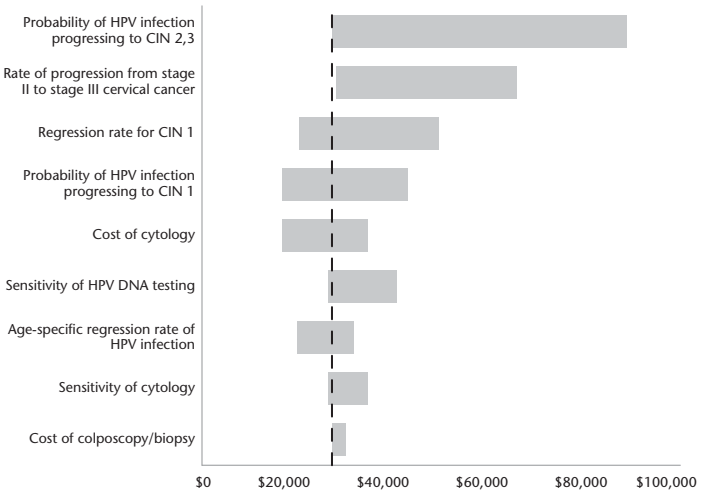
Figure 2. Costs and outcomes associated with various screening strategies assuming no loss to follow-up and either 100% compliance (●) or real-world compliance (■)



HPV=human papillomavirus.

Figure 3. Tornado diagram: One-way sensitivity analysis showing the range of incremental cost-effectiveness ratios (ICERs) comparing cytology every three years with HPV+ cytology triage every three years



The vertical dotted line represents the base-case analysis ICER. A wide bar indicates that the associated variable has a large effect on the results of the model. Note that all variables in the model were included in the sensitivity analyses, but only key variables that the model was most sensitive to are presented in Figure 3.
HPV=human papillomavirus; CIN=cervical intraepithelial neoplasia.

RESULTS

Model validation

To validate the model, we conducted 10 Monte Carlo simulations of 100,000 women each (one million women total). In these simulations, the margin of error was less than 0.61% of total lifetime cost per patient and less than 0.02% of the average life expectancy. The model predicted age-specific prevalence of CIN 2,3 and invasive cervical cancer within the range of values seen in the literature (Figure 1).[26]

Table 2 shows the primary outcomes evaluated in the model. Screening using cytology reduced the annual incidence of cervical cancer by 74-85% while HPV-based screening strategies reduced the annual incidence of cervical cancer by 87-89%, compared to no screening.

All strategies incorporating HPV testing as a primary screening test were dominant strategies compared to annual cytology alone and reduced costs by 9-13%. The HPV-only strategy was the most effective option and a dominant strategy compared to the co-screening strategy and annual cytology (please refer to Supplementary Appendix 3* for additional discussion of the model results) (Figure 2).

Sensitivity analysis

In sensitivity analyses, we examined the impact of reduced compliance and loss to follow-up. As expected, screening strategies with fewer clinic visits and longer screening intervals became more cost-effective (Figure 2). Compared to screening with cytology alone every one or three years, cytology+HPV triage remained cost-effective with ICERs of $5,962 and $74 per QALY gained, respectively. Co-screening, HPV+cytology triage, and HPV only remained dominant strategies compared to annual cytology. Compared to triennial cytology, primary screening with HPV testing remained cost-effective with ICERs in the range of $7,164 to $10,074 per QALY. (Please refer to Supplementary Appendix 2* for additional results from the sensitivity analyses regarding compliance and loss to follow-up.)

Figure 3 shows the results of one-way sensitivity analyses on various input parameters. ICERs were most affected by changes to the risk of progression from HPV infection to CIN, cervical cancer progression rates, and the CIN 1 regression rate.

We conducted threshold analyses on the efficacy and cost of cytology and HPV testing. Varying the price of HPV testing between $18 and $31 (base-case value of $25) did not affect the ranking of strategies. If the sensitivity of HPV testing decreased by more than 20%, HPV+cytology triage was no longer a dominant strategy. As the sensitivity of conventional cytology testing increased, both costs and life-expectancy outcomes increased. However, HPV testing remained a cost-effective option when we increased the sensitivity of cytology by 20%.

Resource utilization

Because the presence of cervical lesions are confirmed based on colposcopy and biopsy, different screening strategies will result in higher or lower numbers of women being referred for these procedures. The HPV-only strategy was the most effective screening strategy we evaluated and dominated annual cytology, annual cytology+HPV triage, and co-screening every three years. However, the HPV-only strategy resulted in approximately 2,000 colposcopies per 100,000 women per year compared to 830 colposcopies with the co-screening strategy and 160-700 colposcopies with the cytology-based screening strategies.

DISCUSSION

To our knowledge, this is the first study to examine the cost-effectiveness of cervical cancer screening strategies in Québec. Our study shows that strategies incorporating HPV testing are more effective than screening based on conventional cytology alone and highly cost-effective, with ICERs considerably less than the per capita GDP (gross domestic product) of Québec.[27]

In addition to effectiveness and cost-effectiveness, practical considerations such as availability of colposcopy resources might impact policy-makers' recommendations. HPV tests have a lower specificity and thus more false-positive test results compared to

cytology tests. These false positive results increase the number of required colposcopies and the overall costs associated with HPV-based screening strategies compared to cytology-based screening strategies. However, the cost of the increased colposcopies is partially offset by a reduction in the total number of screening tests required (due to a lengthening of the screening interval) as well as downstream health care savings as a result of treating fewer cases of cervical cancer. In our analysis, the HPV+cytology triage and co-screening strategies were both more effective and less expensive than annual cytology and required 55-59% fewer colposcopies than the HPV-only strategy.

Our findings are similar to published reports that have found HPV testing to be more effective than cytology alone and a cost-effective option in developed countries.[13,28,29] Goldhaber-Fiebert et al.[28] found a similar reduction in lifetime risk of cervical cancer (71%) resulting from screening every three years using cytology and HPV testing in the United States. Kim et al.[13] found that using HPV testing to triage equivocal Pap smears was less expensive and more effective than screening using conventional cytology alone in the UK and the Netherlands. Contrary to our findings, Mandelblatt et al.[29] found co-screening to be more effective than HPV testing alone. We assumed a lower sensitivity for cytology and a higher sensitivity for HPV testing than Mandelblatt based on recently available data from the CCCaST study,[3] as well as less aggressive treatment patterns for low-grade disease based on current recommendations, which may explain the differences in our findings.

Our analysis has a number of limitations. First, we combined data on the course of HPV infection and cervical disease from multiple sources with varied study designs. However, we validated our estimates by matching model predictions to data from the literature. Second, precise data on compliance, loss to follow-up for HPV-based screening strategies, and quality of life of HR-HPV-positive women were lacking. To account for this, we conducted extensive sensitivity analyses and found our results to be robust over a wide range of values. Finally, we have not incorporated the effects of HPV vaccination on the screening strategies in our model. Given the recent approval of an HPV vaccine for use in Canada, it will be important to determine how cervical cancer screening strategies should best be utilized in a vaccinated population. Given the likely negative impact that HPV vaccination will have on the performance of cytology relative to that of HPV testing,[30] our results probably reflect a conservative evaluation of cost-effectiveness in the future, when vaccinated cohorts progressively reach screening age. Moreover, it seems unlikely at the present time that significant vaccination coverage will be attained in women over the age of 18, making our analysis relevant for years to come.

Based on our analysis, HPV-based screening strategies are both economical and effective and should merit serious consideration among clinicians and policy-makers as methods to efficiently control cervical cancer in Québec. Provincial policy-makers should evaluate incorporating one or more of these HPV-based strategies into current cervical cancer screening guidelines.

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RÉSUMÉ

Objectifs : Au Québec (Canada), le dépistage du virus du papillome humain (VPH) n'est pas beaucoup utilisé pour le triage des frottis vaginaux suspects ni pour le dépistage primaire. Nous avons voulu évaluer le rapport coût-efficacité des stratégies de dépistage du cancer du col utérin faisant appel au dépistage du VPH.

Méthode : À l'aide d'un modèle de Markov sur la vie entière, nous avons estimé les coûts, la qualité de vie et la survie associés aux stratégies suivantes : 1) cytologie; 2) cytologie avec dépistage du VPH pour trier les frottis suspects; 3) dépistage du VPH suivi d'une colposcopie chez les femmes séropositives pour le VPH; 4) dépistage du VPH avec cytologie pour trier les femmes séropositives pour le VPH; et 5) dépistage du VPH et cytologie simultanément. La cytologie a été utilisée dans toutes les stratégies visant les femmes de moins de 30 ans. Les résultats ont été mesurés selon la fréquence de la maladie, les années de vie pondérées par la qualité (AVPQ) gagnées, le risque à vie de cancer du col utérin et les rapports coût-efficacité marginaux.

Résultats : Toutes les stratégies intégrant le dépistage du VPH comme test de dépistage primaire étaient plus efficaces et moins chères que la cytologie annuelle à elle seule, mais le dépistage du VPH pour trier les frottis suspects une fois l'an était particulièrement rentable (2991 $ par AVPQ gagnée comparativement à la cytologie annuelle à elle seule). Comparativement à la cytologie tous les trois ans, les stratégies axées sur le VPH coûtent 8200 $ à 13 400 $ de plus par AVPQ gagnée.

Conclusion : Les stratégies intégrant le dépistage du VPH sont non seulement plus efficaces que le dépistage uniquement basé sur la cytologie, mais elles sont aussi très rentables. Les stratèges provinciaux devraient donc songer à les intégrer dans les lignes directrices actuelles sur le dépistage du cancer du col utérin.

Mots clés : virus du papillome humain; cancer du col utérin; rapport coût-efficacité; économie de la santé; dépistage