Recommendations on optimizing cervical cancer screening in Québec

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Recommendations on optimizing cervical cancer screening in Québec

Direction des risques biologiques
et de la santé au travail

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AUTHORS

Patricia Goggin, MD, MSc
Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec (INSPQ)

Marie-Hélène Mayrand, MD, PhD, FRCSC
Direction des risques biologiques et de la santé au travail, INSPQ
Départements d'obstétrique-gynécologie et de médecine sociale et préventive, Université de Montréal
Hôpital St-Luc, Centre hospitalier universitaire de Montréal (CHUM)

WITH THE COLLABORATION OF

Manon Auger, MD, FRCPC, Cytopathology, McGill University and McGill University Health Centre (MUHC)

François Coutlée, MD, FRCPC, Molecular Virology Laboratory, Hôpital Notre-Dame, CHUM

Majorie Deschênes, MD, FRCPC, Centre hospitalier affilié universitaire de Québec (CHA)

Diane Larocque, MSc, Physical health, Centre de santé et de services sociaux (CSSS) de Laval

Christiane Lemay, MT, Cytology, CHA

Christine Pakenham, B Ed, ministère de la Santé et des Services sociaux (MSSS)

Léo-Roch Poirier, M Sc, INSPQ

Louise Rochette, M Sc, INSPQ

Michel Roy, MD, FRCSC, Centre hospitalier universitaire de Québec (CHUQ)

Denise Vanasse, MT, Cytology, Centre hospitalier universitaire de Sherbrooke (CHUS)

SCIENTIFIC ADVISORY COMMITTEE

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EXTERNAL REVIEWERS

Eduardo L. Franco, PhD, Division of Cancer Epidemiology, McGill University

Robbi Howlett, Ph D, Ontario Cervical Screening Program, Cancer Care Ontario

GRAPHIC DESIGN

Amélie Dugué, Direction des risques biologiques et de la santé au travail, INSPQ

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We would also like to highlight the outstanding contributions of the late Dr. Bernard Duval from the Institut national de santé publique du Québec. A man of vision, skill and commitment, he contributed to the implementation of measures to more effectively control cervical cancer and thus improve the health of many women exposed to the human papillomavirus.

SUMMARY

In 2007, the Comité sur l'immunisation du Québec (CIQ) recommended the establishment of a human papillomavirus (HPV) immunization program with the main objective of reducing the incidence of cervical cancer. In its recommendation paper, the CIQ pointed out the importance of measuring the impact of such a program and the necessary complementarity that should exist between the immunization program and cancer screening activities. However, it was not within the organization's mandate to issue specific recommendations regarding screening.

The present recommendation paper is an extension of the CIQ's recommendations. Its objectives are to clarify the relevance of cervical cancer screening now that vaccination is on its way, to document the current weaknesses in screening, and most of all, to identify the conditions, strategies and means to maximize the effectiveness and efficiency of cervical cancer screening in Québec.

The analysis of current screening weaknesses was based on the model of Zapka et al., which describes cancer control activities according to a continuum of care, and on the results of a meta-analysis permitting an assessment of the relative importance of the main reasons screening fails. Potential solutions identified through a literature review were discussed and improved upon in small working group meetings. The recommendations proposed by the document's authors were then discussed in a meeting expanded to include representatives from various areas of expertise involved in cancer and its prevention (epidemiology, public health, obstetrics-gynecology, oncology, cytology, pathology, virology, primary care medicine, blood-borne and sexually transmitted infections, immunization). A first draft of the document was submitted for comment to all these stakeholders as well as to outside readers. This document constitutes an enhanced version with consensus reached on the recommendations it contains.

The first part of the report reviews the key scientific data pertaining to the issue and examines relevant Québec data. The second part presents several potential solutions identified through a review of scientific literature and discussed with our partners. The third part includes the recommendations emanating from these discussions. The conclusion reiterates the document's key points and the commitment of the Institut and its partners to pursue the work required to implement these measures.

To briefly summarize the recommendations: the top three recommendations address structuring measures such as the need to address screening according to a multidisciplinary, decompartmentalized approach to ensure direction in terms of cervical cancer prevention, to contribute to transforming the current opportunistic approach to screening into an organized approach, and to become equipped with essential tools, such as an information system so that evidence is used to evaluate and adjust interventions. Recommendations 4 and 5 directly deal with parameters for screening and monitoring abnormal cases that could be implemented in a first phase, and that apply mainly to women not vaccinated against HPV. More work is needed to define the optimal parameters for vaccinated women. Recommendations 7, 8, 9 and 10 cover various measures to improve participation, such as developing a procedure code to enhance the importance clinicians place on screening,

improving access to screening services by having professionals other than physicians perform it, sending personalized invitations to women who do not take part in screening, and developing a public communications plan. Recommendations 11, 12 and 13 address support mechanisms such as providing training for professionals, introducing quality assurance measures, and conducting a periodic assessment of the results of our cervical cancer prevention efforts in order to bring about corrective measures when necessary.

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LIST OF ABBREVIATIONS AND ACRONYMS

AGC	Atypical glandular cells
AIS	Adenocarcinoma in situ
ASC	Atypical squamous cells
ASCCP	American Society for Colposcopy and Cervical Pathology
ASC-H	Atypical squamous cells, cannot exclude a high-grade lesion
ASC-US	Atypical squamous cells of undetermined significance
ASSS	Agence de la santé et des services sociaux (health and social services agency)
CAI	Commission d'access à l'information du Québec (Québec's access to information commission)
CC	Conventional cytology
CIN	Cervical intraepithelial neoplasia
CIQ	Comité sur l'immunisation du Québec (Québec's immunization committee)
CCHS	Canadian Community Health Survey
CCPN	Cervical Cancer Prevention Network
CSSS	Centre de santé et de services sociaux (health and social services centre)
CTFPHC	Canadian Task Force on Preventive Health Care
DRBST	Direction des risques biologiques et de la santé au travail
FDA	Food and Drug Administration
FMOQ	Fédération des médecins omnipraticiens du Québec (Québec Federation of General Practitioners)
GMF	Groupe de médecine de famille (Family medicine group)
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
INSPQ	Institut national de santé publique du Québec (Québec public health institute)

LBC	Liquid-based cytology
LSIL	Low-grade squamous intraepithelial lesion
MSSS	Ministère de la Santé et des Services sociaux (Québec's department of health and social services)
PCP	Preventive clinical practices
PQDCS	Programme québécois de dépistage du cancer du sein (Québec breast cancer screening program)
RAMQ	Régie de l'assurance maladie du Québec (Québec's medicare system)
SOGC	Society of Obstetricians and Gynaecologists of Canada
STI	sexually transmitted infection
WHO	World Health Organization

1 INTRODUCTION

1.1 BACKGROUND

Despite the remarkable progress since the introduction of cervical cancer screening services in recent decades, every year in Québec close to 300 women still suffer from cervical cancer and about 80 die from it.

The first human papillomavirus (HPV) vaccine was licensed in Canada in July 2006. This quadrivalent vaccine provides protection from types 16 and 18, which are responsible for about 70% of cervical cancers, and types 6 and 11, associated with the majority of condyloma acuminata (anogenital warts) and with recurrent respiratory papillomatosis. A bivalent vaccine, providing protection from types 16 and 18, may be licensed shortly.

In fall 2007, the Comité sur l'immunisation du Québec(CIQ) recommended to the province's department of health and social services (MSSS) the implementation of an HPV immunization program focused mainly on an intervention strategy in schools aimed at adolescents and preadolescents.(1) The primary objective of this program is to reduce the incidence of cervical cancer and mortality associated with it over the long term. A short-term objective is to prevent cervical cancer precursors. The program began in fall 2008 and targets elementary school girls in Grade 4, with a catch-up program in schools for girls in Level 3 at high school, and in clinical settings for those under the age of 18 not reached through in-school vaccination programs.

However, even with good vaccination coverage, current vaccines alone will not eradicate the disease, for several reasons:

- These vaccines are preventive and have no impact on pre-existing infections. Moreover, the risk of prior infection from a high-risk type of HPV is high among women who are already sexually active, which represents a large percentage of the female population;
- Although a certain degree of cross protection from other genotypes has been shown, current vaccines do not provide protection from all high-risk genotypes for cervical cancer; vaccinated individuals remain at risk although they are at lower risk.

Opting for a vaccination strategy in schools, which targets extensive coverage in a population that is "naive" in terms of the infection, maximizes the prevention potential. However, attaining the objectives will be far from immediate; there is a long period of time between acquisition of an infection and observing its effects. Thus, the full impact of this strategy on the incidence of cervical cancer may not be achieved for at least 20 years. The CIQ has therefore reiterated the need to maintain cervical cancer screening activities; however, it was not within its mandate to issue precise recommendations on this issue.

To assess the impact of the vaccination program, monitoring the incidence of cervical cancer precursors will be essential since at the moment, this is one of the very few clinical result indicators for judging the program's effectiveness. The implementation of an HPV vaccination program therefore requires that synergy be developed among the various players involved in cervical cancer prevention.

This document complements the CIQ's recommendation paper by proposing ways to optimize cervical cancer screening so that when combined with vaccination, we can foresee the eradication of this disease in the future, in the most efficient way possible.

1.2 MANDATE GIVEN TO THE INSTITUT NATIONAL DE SANTÉ PUBLIQUE DU QUÉBEC (INSPQ)

In 2007, in response to a request from Dr. Philippe Couillard, then Minister of Health and Social Services, Dr. Richard Massé, then President and CEO of the INSPQ, gave the latter's Direction des risques biologiques et de la santé au travail (DRBST) the mandate to produce recommendations on steps to be taken to optimize cervical cancer screening in Québec.

This recommendation paper falls within the context of the new HPV infection vaccination program. However, its perspective is broader than that of screening vaccinated women; it covers women in general. It has also taken into account earlier work on cytology-based cervical cancer screening carried out by the INSPQ (Direction des systèmes de soins et politiques publiques) and the MSSS (Direction de la prévention clinique et de la biovigilance).

In connection with the CIQ's recommendations on cervical cancer prevention through an HPV vaccination program and the submission of a study design for evaluating this program, this report on optimizing screening is based on the work of a committee of Québec experts in terms of the various facets of cervical cancer screening and the clinical case management of abnormalities detected during screening according to the evidence and the scientific consensus established within the committee.

1.3 OBJECTIVES OF THE REPORT

The report's objectives are to:

- Document the main weaknesses in current screening and the conditions favourable to maximizing the effectiveness and efficiency of screening;
- Propose strategies and ways to improve screening from the perspective of global cervical cancer prevention.

2 METHODOLOGY

2.1 CHOICE OF THE CONCEPTUAL MODEL FOR CONDUCTING A SITUATIONAL ANALYSIS

The summary of the disease's natural history and discussion of the potential effectiveness of screening are based on syntheses of previously published knowledge, especially the *Vaccine* monographs of 2006[2] and 2008,[3] to which dozens of experts from around the world contributed.

The analysis of screening weaknesses was based on the conceptual model proposed by Zapka et al.,[4] which looks at the quality of care throughout the cancer control continuum and on the results of a meta-analysis dealing more specifically with reasons for screening failure.[5]

2.2 CONSULTATION PROCESS AND DEVELOPMENT OF RECOMMENDATIONS

For each of the three main weaknesses identified (low participation of women, non-optimal performance of current screening tests, and lack of follow-up after a screening test with abnormal results), a series of measures were first of all identified in the scientific literature then discussed in small working groups. Efforts were subsequently undertaken to explore the feasibility and acceptability of various approaches.

The preliminary results of this analysis and potential solutions were discussed and validated on May 15, 2008 during a meeting that included a number of individuals involved in cervical cancer control (epidemiology, public health, obstetrics-gynecology, oncology, cytology, pathology, virology, primary care medicine, blood-borne and sexually transmitted infections, and immunization).

A more detailed analysis was then carried out and a full report addressing the issue and its challenges, and including proposals was sent to forum participants in the summer of 2008. The current version has taken into account the comments received during this consultation.

3 CERVICAL CANCER SCREENING IN QUÉBEC: A PORTRAIT OF THE SITUATION

To understand the issue of cervical cancer screening, a brief knowledge synthesis is presented. This section also includes a description of current cervical cancer screening in Québec and addresses the following points:

- The etiology of cervical cancer and the disease's natural history;
- Epidemiological data on cervical cancer;
- The screening test used;
- Recommendations regarding screening and follow up for abnormal cases ;
- Evidence of the effectiveness of cervical cancer screening;
- The relevance of screening in the wake of vaccination;
- Methods for organizing screening in industrialized countries;
- The history of screening in Canada and in Québec.

3.1 THE ETIOLOGY OF CERVICAL CANCER AND THE DISEASE'S NATURAL HISTORY

HPV is now recognized as the main causal agent of cervical cancer and studies have shown that it is present in 99.7% of cases.[6] There are over 40 HPV genotypes that can infect the anogenital area, among which about 15 have carcinogenic properties. Types 16 and 18 in particular are associated with about 70% of the cases of cervical cancer.[7]

By and large, genital infections caused by HPV are frequent and may affect more than 70% of sexually active people during their lifetimes. Their prevalence is particularly high in the early months and years following the onset of sexual relations and HPV infection is considered the most frequent sexually transmitted infection.[8,9]

While HPV infections are frequent, studies on their evolution show that most of these infections disappear spontaneously in less than 18 months and that a persistent infection enhances the risk of cancer. However, it normally takes a number of years and sometimes decades between the first observable changes at a cellular level and an invasive cancer, which explains why cervical cancer is uncommon before the age of 30 and practically non-existent in women less than 20 years of age. This slow evolution also explains why screening has had so much success in cervical cancer prevention.

The following diagram describes the main stages of carcinogenesis in cervical cancer. Cervical intraepithelial neoplasia (CIN) is divided into three categories according to the thickness of the epithelium affected by cellular changes: CIN1, CIN2, and CIN3.

Figure 1 Main stages of carcinogenesis

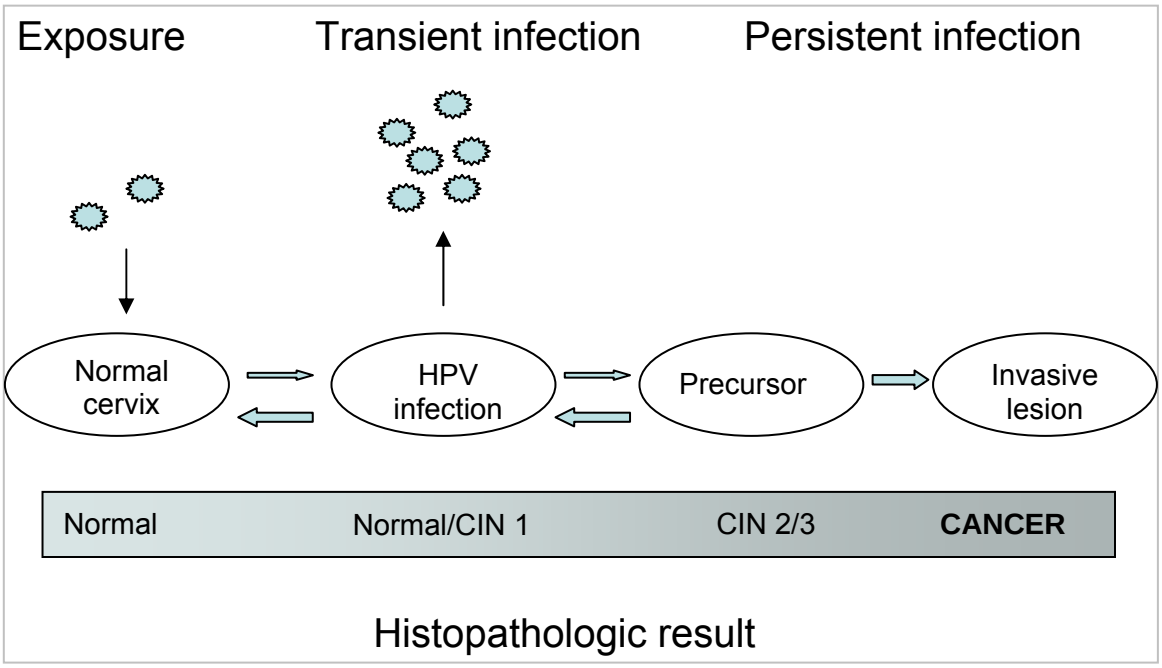


Diagram adapted from IARC Handbooks of Cancer Prevention, Volume 10, "Cervix screening." IARC Press, 2005. Chapter 1, page 49.[10]

The presence of a cervical intraepithelial lesion confirmed in pathology does not mean that this lesion will inevitably lead to invasive cancer. Based on a review of studies published over the previous 40 years, Östör estimated that a minority of grade 1 intraepithelial neoplasia (CIN 1, lesions involving only one third of the thickness of the epithelium) had progressed to a higher grade and that regressions were frequent.[11] High-grade lesions such as CIN 3 (lesions involving the full thickness of the epithelium but confined by the basement membrane) have a higher risk of evolution, but this risk remains difficult to assess given that treatment is generally suggested to women with this condition.

Table 1 Likelihood of the evolution of cervical cancer precursors according to Östör (1993)

CIN grade	Regression	Persistence	Progression towards CIN 3	Progression towards invasive cancer
CIN 1	57%	32%	11%	1%
CIN 2	43%	35%	22%	5%
CIN 3	32%	< 56%	-	> 12%

The most relevant data on the risk of developing high-grade lesions comes from a recent retrospective study of a cohort of women from New Zealand having presented CIN 3-type lesions between 1965 and 1974 and who, it was later realized, had not been treated according to usual standards of care.[12] Among the 143 women with CIN 3-type lesions, the cumulative risk of invasive cervical cancer or vaginal vault was 13% after 5 years, 20% after 10 years, 26.1% after 20 years, and 31.3% after 30 years. The risk was even higher when a follow-up examination performed 6 to 24 months later showed persistence of the lesion

(19.9% after 5 years and 50.3% after 30 years). This data confirms the slow evolution of lesions and the fact that they can be transient. Conversely, the risk of invasive cancer after 30 years of monitoring was only 0.7% among women having undergone the treatment deemed appropriate at the time of the diagnosis.

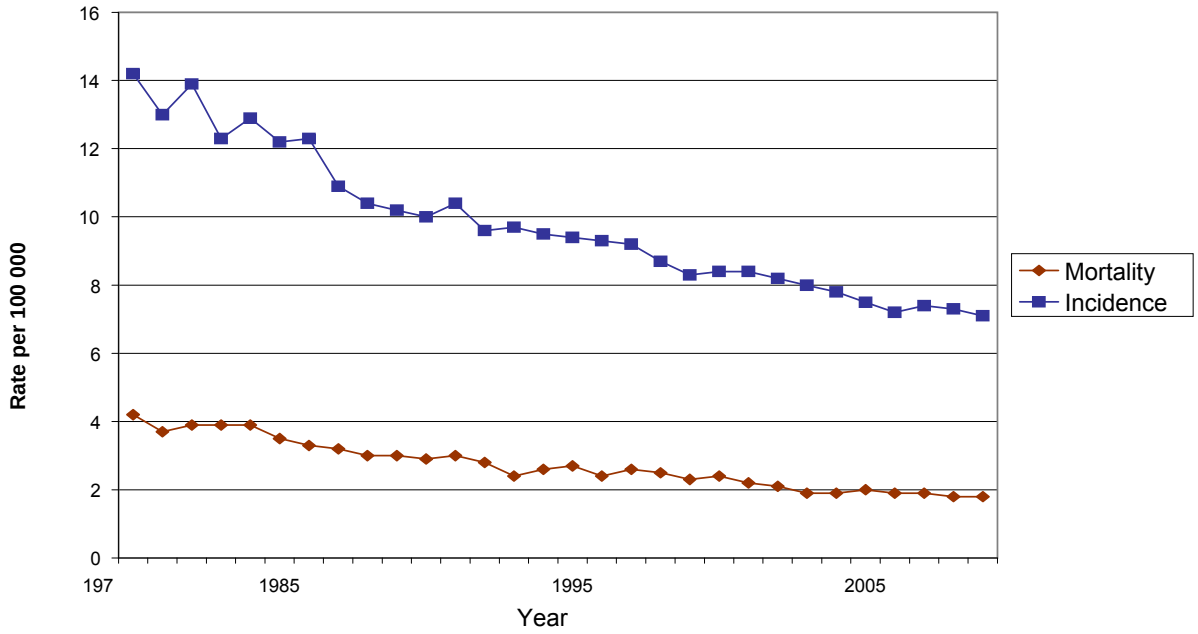
Further information on HPV infection and means of prevention is available in a document published by the INSPQ in 2003.[13]

3.2 EPIDEMIOLOGICAL DATA ON CERVICAL CANCER

Cervical cancer is still a major health problem worldwide, and is the second most common type of cancer among women, after breast cancer, with some 493 000 estimated cases in 2002.[14,15] The majority of cases now occur in developing countries. In Canada, as in a number of industrialized countries providing large-scale screening services, substantial gains have already been made in terms of reducing the incidence of and mortality associated with cervical cancer. From 1963 to 1966, the incidence rate in Canada was estimated at 27.1 per 100 000.[1(16)] From 1979 to 2004, the age-standardized incidence rate in Canada went from 14.2 to 7.5 per 100 000, and the mortality rate from 4.2 to 1.9 per 100 000, reductions of 47% and 55% respectively.[17]

The following figure illustrates the reductions in incidence and mortality rates observed in Canada over the past 25 years, based on this data.

Figure 2 Incidence and mortality rates for cervical cancer in Canada, 1979-2004 with projections to 2008



[1] World population standardized rate.

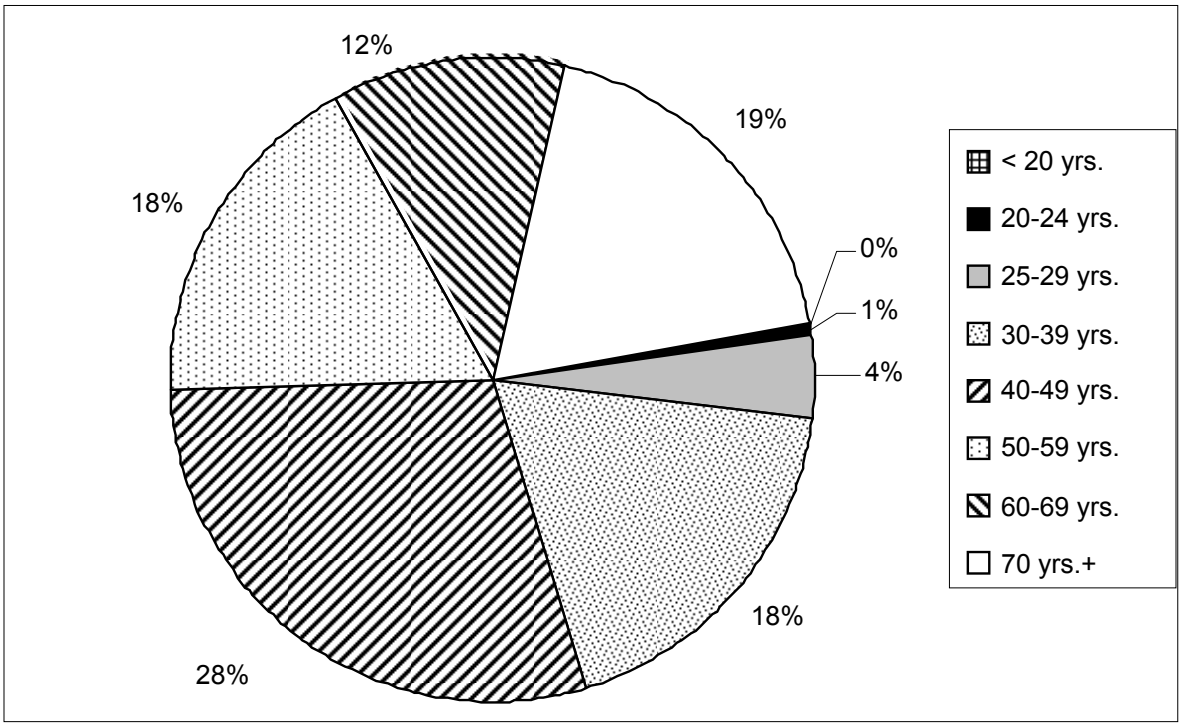
In 2008, the National Cancer Institute of Canada estimated that about 1300 Canadian women, including 280 women from Québec, would be diagnosed with cervical cancer during the course of the year. The following table summarizes the most recent statistics on cervical cancer taken from this report for Canada and for Québec, specifically.

Table 2 Canadian and Québec cervical cancer statistics

	Canada	Québec
Number of estimated cases for 2008	1300	280
Frequency ranking of this type of cancer among women	13th	13th
Age-standardized incidence rate[2]	7 per 100 000	6 per 100 000
Number of estimated deaths for 2008	380	70
Age-standardized mortality rate	2 per 100 000	1 per 100 000
Estimated 5-year relative survival (%)	74%	

A more in-depth examination of cervical cancer data reveals that although this is the second most frequent type of cancer among Canadian women aged 20 to 44,[18] the vast majority of cases (95%) occur among women aged 30 and over, while only 1% of this cancer occurs before the age of 25. The following diagram illustrates the distribution of the cervical cancer cases observed in Québec from 2001 to 2005 by age group.

Figure 3 Distribution of cervical cancer cases in Québec by age group (2001-2005)

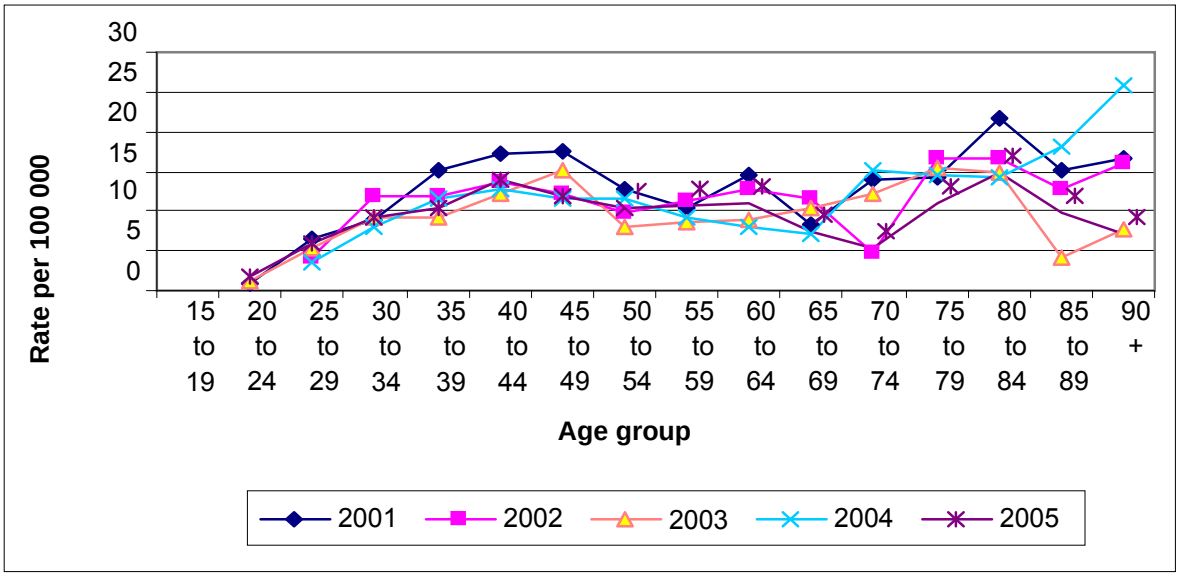


Source: Québec tumour registry (Fichier des tumeurs du Québec).

[2] The rates are adjusted for the age distribution of the Canadian population in 1991.

The graphic presentation of incidence rates by age group for the years 2001 to 2005 confirms the minimal risk of cervical cancer before the age of 30 and the somewhat bimodal distribution of the cancer, with a first spike in incidence from ages 35 to 50 and a second among women aged 75 and over.

Figure 4 Incidence of cervical cancer by age group, Québec (2001-2005)



3.3 THE SCREENING TEST USED

Introduced during the late 1950s, cervical cytology or the Papanicolaou test, commonly known as the Pap test, was quickly incorporated into standard health care procedures and became widely accepted as an effective mass screening test. In Québec, this screening test is used almost exclusively.

Traditionally, the Pap test, which we also call conventional cytology to differentiate it from another more recent form of cytology which will be discussed later, is performed as follows: a wooden spatula or a tiny brush is used to gather cells on the surface of the cervix. This sampling must be done under direct vision, by targeting the area of the cervix at greatest risk for a precancerous lesion. The specimen is spread on a slide. A fixative is added to conserve the cellular morphology. In the cytology laboratory, the slide is dyed then examined under a microscope to look for cellular changes consistent with precancerous lesions or cancer. These changes must then be reported to the attending physician.

A great deal of effort has been devoted to standardizing the nomenclature of cytological results. In North America and a number of other regions, the 2001 version of Bethesda terminology is now used.[19] This classification includes an assessment of the quality of the specimen. In fact, each report includes a mention specifying that the sample is satisfactory and is adequate for the evaluation or that the specimen is unsatisfactory and no results can be obtained. In the latter case, the reason is indicated (for example, cellular inadequacy, excess inflammatory material). Each specimen is then given a general dichotomous categorization. The results of a normal specimen will be recorded as “negative for

intraepithelial lesion or malignancy," while an abnormal specimen will be identified as having "epithelial cell abnormalities."

The following table summarizes the cytological terminology for precancerous and cancerous cervical epithelial cell abnormalities.

Table 3 Cytological classification abbreviations according to the 2001 Bethesda System terminology

Cellular type	Abbreviation	English terminology	French translation proposed by the IARC*
Squamous	ASC	Atypical squamous cells	Atypies des cellules malpighiennes[3]
	ASC-US	Atypical squamous cells of undetermined significance	Atypies des cellules malpighiennes de signification indéterminée
	ASC-H	Atypical squamous cells, cannot exclude a high-grade lesion	Atypies des cellules malpighiennes de signification indéterminée, ne permettant pas d'exclure une lesion malpighienne intrépithéliale de haut grade
	LSIL	Low-grade squamous intra-epithelial lesion (encompassing papillomavirus infection, CIN1)	Lesions malpighiennes intraépithéliales de bas grade
	HSIL	High-grade squamous intra-epithelial lesion (moderate and severe dysplasia, carcinoma in situ; CIN 2 and CIN 3)	Lesions malpighiennes intraépithéliales de haut grade
	Squamous cell carcinoma	Squamous cell carcinoma	Carcinome malpighien
Glandular	AGC	Atypical glandular cells	Atypies des cellules glandulaires
	AIS	Adenocarcinoma in situ	Adénocarcinome in situ
	Adenocarcinoma	Adenocarcinoma	Adénocarcinome

* IARC: International Agency for Research on Cancer. Document available at: http://screening.iarc.fr/atlascytobeth.php?cat=A0&lang=1.

[3] In Québec, in French, the term "épidermoïde" is used more often than "malpighien."

According to a survey of cytology laboratories in Québec conducted by the Association des cytologistes du Québec in 2005, gynecologic cytology analysis results were distributed as follows:

Table 4 Distribution of cytological screening results in Québec according to data provided by 33 cytology laboratories in 2005

Cytological analysis results	Percentage (%)
Normal/benign abnormalities	87.1
Unsatisfactory specimens	1.6
ASC (ASC-US or ASC-H)	4.6
AGC	0.6
LSIL	2.0
HSIL	0.5

Source: Association des cytologistes du Québec. Unverified data. The total is less than 100% due to missing data.

3.4 SCREENING RECOMMENDATIONS

The effectiveness of a screening strategy depends not only on the type of screening test, but also on how the test is implemented. The main parameters to be considered are: target population, age for initiating screening, interval between tests, and age for ceasing screening.

The definition of these parameters varies according to jurisdiction and usually depends as much on scientific and medico-legal considerations (such as fear of recourse in the case of a delayed diagnosis) as organizational ones (integrating the screening test into the annual checkup). As more has become known about the natural history of the disease, recommendations have become more specific, and there has been a growing trend to delay the age for starting screening and to extend the testing intervals.

Currently in Québec there are no specific recommendations pertaining to cervical cancer screening. In the 1997 Québec cancer control program,[20] there was a recommendation for a systematic screening program based on cytology testing every three years, as proposed during a National Workshop on Screening for Cancer of the Cervix in 1989.[21] The screening program was never implemented and the practice of screening annually has been continued by many clinicians.

Table 5 presents the recommendations of major Canadian and American national organizations involved in prevention, followed by the standards recommended in Canada by various provincial screening programs.

In Western and Northern Europe, where cervical cancer screening is done mainly through structured national screening programs, screening standards are much more restrictive, with screening beginning later (at age 25 or even 30, in the case of the Netherlands and Finland) and generally in intervals of three years but that can be up to five years.[22] The age for ceasing screening varies, most often between the ages of 60 and 69. These countries are particularly attentive to questions of efficiency and achieving the right balance between the benefits and inconvenients of population-based screening, whereas in jurisdictions with opportunistic screening (such as the United States and a number of Canadian provinces),

clinicians often tend towards closer intervals and offering screening earlier, even to adolescents, with the goal of detecting all cases, without considering the inconvenients. We will address these two screening approaches in more depth later on. Australia, which has had a structured national screening program since 1991, has opted for an intermediate position, starting screening between the ages of 18 and 20 and ending at age 70, with two-year intervals.[4]

[4] Information on this program may be found by visiting the following site: http://www.cervicalscreen.health.gov.au/internet/screening/publishing.nsf/Content/cervical-1lp.

Table 5 Canadian and American recommendations for cervical cancer screening and the parameters of provincial screening programs in Canada

Organization/ Province (year)	Age for starting screening	Age for ending screening	Screening interval
NATIONAL RECOMMENDATIONS			
Canadian Task Force on Preventive Health Care (1994)	Start of sexual activity or age 18	Age 69	Annual at the start Every 3 years after 2 normal tests More often if high risk*
Cervical Cancer Prevention Network (1998)	Age 18 if sexually active	Age 69	Annual at the start Every 3 years after 2 normal tests, if information system available
US Preventive Services Task Force (2003)	Within the 3 years following the start of sexual relations or at the latest at age 21	Age 65	At least every 3 years
PROVINCIAL SCREENING PROGRAMS			
British Columbia	Sexually active women	Age 69, if at least 3 normal tests in the past 10 years and no history of a significant abnormality	Annual at the start Every 2 years after 3 normal tests Annual if high risk
Alberta	Age 18	Age 69	Annual
Saskatchewan	Age 18	Age 69	Annual at the start Every 3 years after 2 normal tests Annual if high risk
Manitoba	Age 18	Age 69	Annual at the start Every 2 years after 3 normal tests Annual if high risk
Ontario	3 years after the 1st vaginal sexual activity	Age 70 if screening negative over the past 10 years and no history of a significant abnormality	Annual until 3 consecutive normal tests Every 2-3 years after Annual if high risk (immunosuppression or HIV infection)
Nova Scotia	Age 21 or 3 years after the start of sexual relations	Age 75	Annual at the start Every 2 years after 3 normal tests Annual if high risk
Prince Edward Island	Age 18 or at the start of sexual relations	Age 70	At least every 2 years
Newfoundland and Labrador	Women who are sexually active		Annual

* High risk defined as follows: smoker, low socio-economic status, multiple sexual partners or partner with multiple sexual partners, intercourse before age 18.

3.5 FOLLOWING UP ABNORMAL CASES

The follow-up for an individual with abnormal screening results usually begins with a colposcopy. This examination consists of inspecting the cervix using a magnifying lens after the application of acetic acid to identify abnormal vascular patterns. A biopsy and a histopathologic examination of the tissue sampled from the endocervix or the exocervix then confirm the presence or absence de precancerous lesions. In the case of high-grade lesions, treatment generally hinders their progression to invasive cancer. Contrary to breast cancer, where the goal of screening is to detect cancers at an early stage with only a limited impact on incidence, cervical cancer screening has a true preventive impact on cancer, when the appropriate interventions are performed.

As with screening, in Québec there are no specific guidelines for the case management of women with abnormal cytology results or lesions confirmed by histopathologic examination. However, professionals from Québec and elsewhere in Canada have taken part in developing and updating the guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP).[23] These recommendations were developed following an extensive literature review and are based on evidence when available. Moreover, the Society of Canadian Colposcopists, the Society of Gynecologic Oncologists of Canada and the Society of Obstetricians and Gynaecologists of Canada (SOGC) collaborated in the development of these standards. In addition, a survey of Québec colposcopists showed that they were very familiar with these recommendations and over 90% followed them in their practices.[24]

A summary of the ASCCP's recommendations on the case management of women with an abnormal cytology test or a confirmed histologic lesion is presented in Appendix 1.

3.6 EVIDENCE OF THE EFFECTIVENESS OF CERVICAL CANCER SCREENING

No randomized clinical trial has been conducted to show the Pap test's value in reducing mortality or the incidence of cervical cancer. Nonetheless, observational studies are very convincing in terms of the Pap test's effectiveness. In fact, cohort studies, case-control studies, trend studies, and geographic or ecological correlation studies have reported a significant reduction in cervical cancer incidence and mortality since the introduction of screening.[25,26] Also, in a number of countries, including Scandinavia and the United Kingdom, a strong correlation has been shown between a reduction in incidence and the level of screening participation corresponding to the establishment of organized programs.[25,27-33] However, this reduction applies mostly to squamous cell carcinomas, which constitute the majority of cervical cancer types, whereas the incidence of adenocarcinoma (about 15% of cancers) is on the rise in most of these countries.[34]

Since screening has been offered for several decades, it is impossible to accurately estimate the risk of cervical cancer without screening. Nevertheless, it is known that in countries where little or no screening is done, the incidence of cervical cancer is in the order of 25 to 40 per 100 000 women[5] (versus 6 to 7 per 100 000 in Québec and in Canada as a whole). In a modelling study, Canadian researchers estimated that, without screening, the incidence in

[5] GLOBOCAN databank, International Agency for Research on Cancer, available at the following address: http://www.iarc.fr/.

Canada would be 42.22 cases per 100 000 women with a mortality rate of 16.61 per 100 000.[35]

3.7 THE RELEVANCE OF SCREENING IN THE WAKE OF VACCINATION

The advent of HPV vaccination provides a unique opportunity to prevent a large percentage of cancers and precursors caused by HPVs, but this protection is at currently limited to genotypes 16 and 18, responsible for 70% of all cases of cervical cancer, and 50% of severe precursors (CIN 2/CIN 3/AIS). A certain protection from other genotypes exists, but has yet to be accurately quantified. Maintaining screening activities for vaccinated individuals is therefore still recommended.

The majority of adult women will never be vaccinated and will remain at risk of cancer for their entire lifetimes. Screening must thus continue to be very present in this population. Since most of the girls vaccinated are under 18 years of age, it will likely take about 20 years before vaccination has any real impact on the incidence of cancer.[36]

However, as vaccinated cohorts reach adulthood, it is anticipated that the reduction in the prevalence of infections from types 16 and 18 will have an impact on screening test results,[37] particularly with respect to the positive predictive value (i.e. the risk of having the disease when the test is positive). In all likelihood, new screening and follow-up algorithms will have to be proposed for vaccinated women.

There is currently no evidence available enabling us to draft recommendations for the screening of vaccinated women. We must wait for solid modelling studies at the very least, and, especially for firm data on the real results of vaccinating very young girls in preventing cervical lesions in adulthood. For the moment, it is thus justifiable to use the same screening algorithms for vaccinated and non-vaccinated women.

3.8 METHODS FOR ORGANIZING SCREENING

Generally speaking, there are two ways of providing screening services: within an organized program or in an opportunistic way. With an organized program, all elements in the screening process are integrated. These include recruitment and ongoing strategies to maximize participation, screening and management of abnormal cases guidelines, information and quality assurance systems for monitoring and evaluating the program, thus optimizing screening operations and quality. Screening may also be offered to individuals in an "opportunistic" manner, i.e. by offering a screening test to women consulting a health professional. Case management is then left to the discretion of the professional consulted.

Currently in North America, screening is most often offered in an opportunistic manner, whereas Northern Europe and countries such as Australia often advocate organized approaches. While it is possible to achieve a high coverage rate with an opportunistic approach, its low level of efficiency is especially criticized because of the over-screening of low-risk women, common with this type of approach.[38-40] In fact, according to the law of diminishing returns, over-screening low-risk women increases costs substantially, while providing only marginal benefits.

There are few studies that specifically quantify the added value of an organized approach versus an opportunistic approach in terms of incidence or mortality results, when there is comparable participation in each approach. Difficulty also stems from the fact that a number of European countries with established organized programs tolerate a certain form of opportunistic (or spontaneous) screening in addition to screening by invitation.[41] However, in a case-control study in Finland, it was estimated that the organized screening had more impact than spontaneous screening.[42]

On the other hand, modelling studies have clearly shown that increasing the participation rate had a greater impact on the incidence of cancer than reducing the interval between tests,[43-48] as well as being a more efficient strategy. Organized programs pay particular attention to the participation rate and generally obtain better results in terms of coverage. In the Netherlands, for example, when the program was in the implementation phase, participation rates were estimated at 91% among women invited to take part in the program versus 68% among those who had not yet received an invitation during the same time period.[49]

The following table summarizes the main characteristics of these two approaches, established by a group of screening experts from the United Kingdom, Australia and the United States.[50]

Table 6 Comparison of screening approaches (adapted from Miles et al., 2004)

Characteristics	Organized program with population-based approach	Opportunistic approach
Underlying health system	Systems based on universal health care coverage (ex: United Kingdom, Netherlands, Scandinavian countries)	Varied systems, either predominantly public (France, Switzerland, etc.), mixed or private (United States)
Choice of screening test	Determined by the governmental authority and chosen to maximize efficiency	Determined by professional authorities and influenced by suppliers and patient preferences
Access to new technologies	Process of adopting new technologies slower due to the necessity of demonstrating cost-effectiveness	Quicker, less conditional on the demonstration of a cost-effective relationship
Attention given to the sensitivity of the test (detection potential)	Yes, but from a collective perspective, taking coverage into account	Essential, to maximize the benefits for the individual
Attention given to the specificity of the test (risk of false positive)	Yes, because it is essential to minimize the disadvantages from a collective perspective	Less important
Interval between tests	Determined to maximize efficiency	Variable, chosen to maximize individual protection
Quality assurance (QA)	Core function Performance indicators and ongoing monitoring of activities	Variable, often left to local authorities
Recruitment of clientele	Active, with target group and methods identified Affected by the quality of population registries Participation rate often > 80%	Passive, requires interaction with the health care system and education of clientele (subject to supply and demand). Greater risk of irregularity. The overall screening rate may be high, but at the expense of an over-screening of certain clienteles
Equitable access	Essential, economic barriers reduced (without eliminating all the cultural and logistical barriers)	Secondary Socio-economic barriers often observed
Benefits	Maximized for the population Greater potential for reducing the incidence and mortality (better coverage, abnormal case follow-up, quality assurance)	Maximized for individuals who use screening Abnormal case follow-up may be lacking
Risks or disadvantages	Minimized for the population	Little consideration given
Organizational aspects	More difficult to implement in settings where an opportunistic approach already exists and if professionals not very interested Public health infrastructure and core funding required	Offering screening depends on the interest of professionals No central authority for monitoring results Less efficient and more costly

3.9 THE HISTORY OF SCREENING IN CANADA AND IN QUÉBEC, SPECIFICALLY

Cervical cancer screening was introduced in Canada in the 1950s. Subsequently, numerous efforts to improve screening were undertaken.(51) Beginning in 1973, Canada's Conference of Deputy Ministers of Health examined the need to develop cervical cancer screening programs. In 1976, the Walton Task Force recommended that health authorities support the introduction of comprehensive cervical cancer screening programs, and that women be encouraged to participate in them. In 1982, this task force again analyzed the situation and recommended measures designed to improve the quality and sensitivity of the methods used, the recruitment of women never having had a screening test, and the creation of registries. In 1989, during a national workshop on cervical cancer screening, the problems related to recruiting women, inadequate screening tests, follow-ups and case management of women with abnormalities, and too frequent testing were raised once again. Participants recommended the adoption of an organized screening approach. In 1995, a workshop entitled Interchange '95 was organized with Health Canada's support to review the situation in terms of provincial efforts and to identify obstacles in implementing the recommendations previously issued and still deemed relevant. Emphasis was placed on three essential components required for an organized program: quality improvement, recruitment, and information systems. The Cervical Cancer Prevention Network (CCPN) was formed on this occasion, informally grouping federal, provincial and territorial government representatives with representatives from professional organizations and the community.

In 2003, a pan-Canadian forum was organized by the CCPN to review new screening technologies.(52) In 2006, as part of the Canadian Strategy for Cancer Control, it was proposed that a Screening and Early Detection Action Group be put in place to maximize the positive repercussions of screening efforts in Canada (Canadian Strategy for Cancer Control, 2006).

Despite all these efforts, the degree to which screening programs are organized varies substantially among the provinces and territories. Québec and New Brunswick are the only provinces that have not put in place any component of an organized cervical cancer screening program, although New Brunswick has conducted a pilot project in several regions. The following table presents an overview of the situation in Canada as of early 2007.

Table 7 Summary of cervical cancer screening policies in Canada by province and territory, excluding Québec (2007)[6(53)]

Canada	Start of the program	Test	Recruitment, call-back and follow-up	Databank (DB)
British Columbia	1949	Pap test	Opportunistic recruitment by health care professionals The program: routine call-back and follow-up with a professional if abnormal or unsatisfactory results	Only 1 cytology laboratory (600 000 analyses/year) Central DB for cytology, colposcopy and histology Linkage with cancer registry
Alberta	2000	Pap test	Opportunistic screening (physicians and nurses)	Central DB for cytology (not all labs), DB for colposcopy, possibility of linking with cytology, no histology DB
Saskatchewan	2003	Pap test	Letters of invitation sent to women. Contact, if necessary, with the professional for following up abnormal or unsatisfactory specimens	DB for recruitment of the population Central DB: cytology, colposcopy and histology
Manitoba	2000	Pap test	Program sending letter to the professional, if high-grade abnormal results, if results of the colposcopy not registered in the information system in the expected time interval	Central DB pour cytology, colposcopy and histology Linkage with cancer registry
Ontario	2000	Recommends liquid-based cytology;* conventional Pap test acceptable option	Opportunistic	Central DB, voluntary transmission of test results (≈ 85%), no histology results

* Liquid-based cytology is an alternative for the conventional Pap test, in terms of slide preparation. A detailed discussion of this technique follows in section 5.3.2.

[6] This document is currently being updated by the Public Health Agency of Canada.

Table 7 Summary of cervical cancer screening policies in Canada by province and territory, excluding Québec (2007) (continued)

Canada	Start of the program	Test	Recruitment, call-back and follow-up	Databank (DB)
New Brunswick	Pilot projects in 4 districts	Pap test	Recruitment by professionals	
Nova Scotia	1991	Pap test	Opportunistic recruitment Program sending letter to the professional, if high-grade abnormal results, if results of the colposcopy not registered in the information system in 16 weeks	Central DB for cytology (7 labs) and colposcopy, no routine histology
Prince Edward Island	2001	Pap test	No notice to professionals or invitations to women	Central DB (only 1 lab) may be linked with a separate histology DB
Newfoundland and Labrador	1998 (pilots) 2003	Pap test		DB grouping Pap test results from 4 laboratories in the province
Northwest Territories		Liquid-based cytology	Recruitment by professionals (family physicians or nurses)	Analyses in 1 laboratory in Edmonton, results to the professional
Nunavut		Liquid-based cytology	Recruitment by professionals (family physicians or nurses)	Analyses in 1 laboratory in Edmonton, results to the professional only

In Québec, a systematic analysis according to the World Health Organization's criteria for implementing screening programs, listed below, was conducted in 1997 as part of the development of Québec's cancer control program (Program québécois de lutte contre le cancer).[20] A recommendation to establish an organized approach for cervical cancer screening was then issued. Nonetheless, the program was never implemented, and screening continues to be carried out in an opportunistic manner.

Recommended criteria for putting in place a systematic cancer screening program, according to the Québec cancer control program (Program québécois de lutte contre le cancer)

Significant problem: The cancer targeted leads to significant mortality and morbidity.

Adequate tests: Screening and diagnostic tests are sufficiently accurate.

Effective treatment: Treatments capable of positively changing the course of the disease are available.

Acceptable risks: The risks and disadvantages associated with the tests and treatments are acceptable when compared to the anticipated benefits.

Demonstrated reduction in mortality: There is convincing evidence that screening is effective in reducing mortality.

Reasonable cost/effectiveness ratio: The costs of the program are reasonable when compared to the expected benefits.

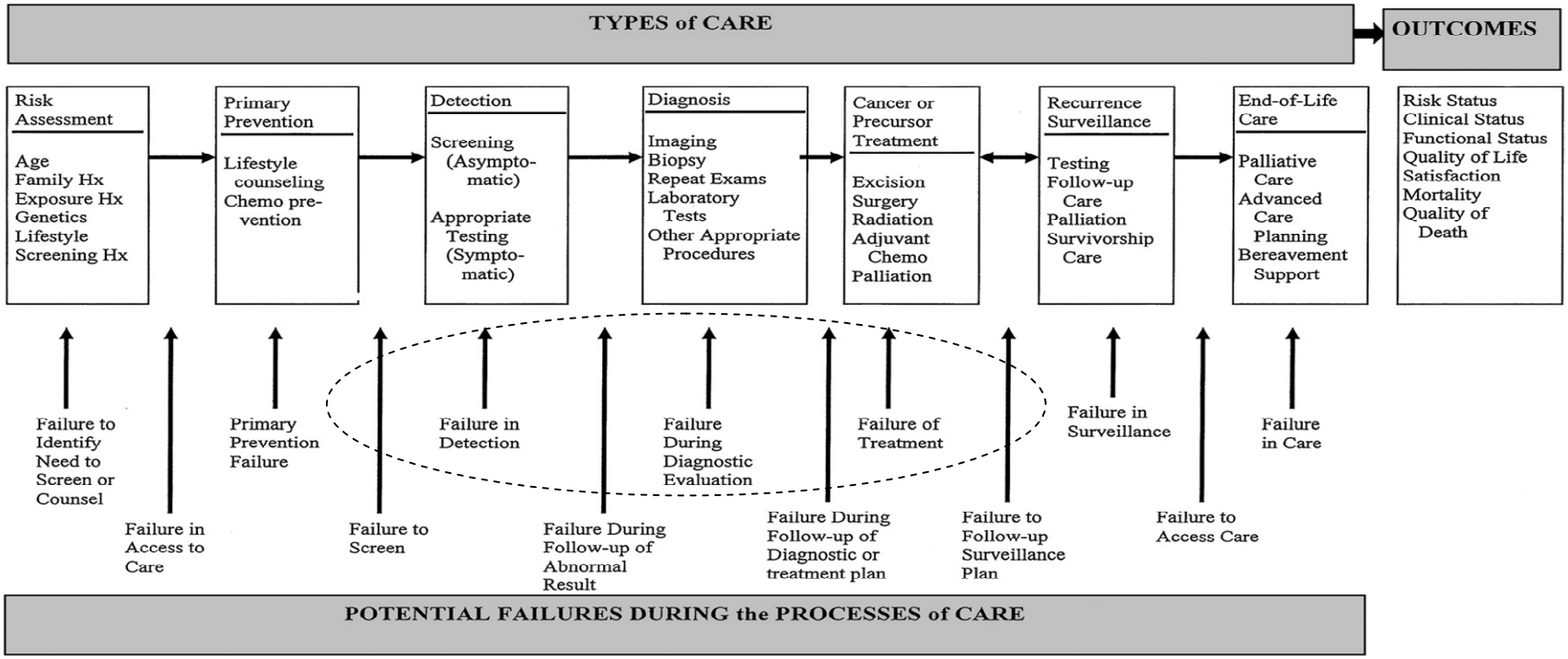
4 THE MAIN WEAKNESSES IN SCREENING

The natural history of the disease and the slow evolution of lesions caused by the HPV in particular, lead us to believe that, theoretically, a prevention strategy based on periodic screening should enable this disease to be eradicated. However, although screening services have been available for a number of decades, many cases of cervical cancer continue to be observed every year. In Québec, there are close to 300 new cases per year.

Several researchers have attempted to grasp the reasons behind a diagnosis of cervical cancer by examining the clinical pathway of women affected by this cancer, according to a continuum of services for cancer control, as described by Zapka et al.[4] and illustrated in the following diagram.

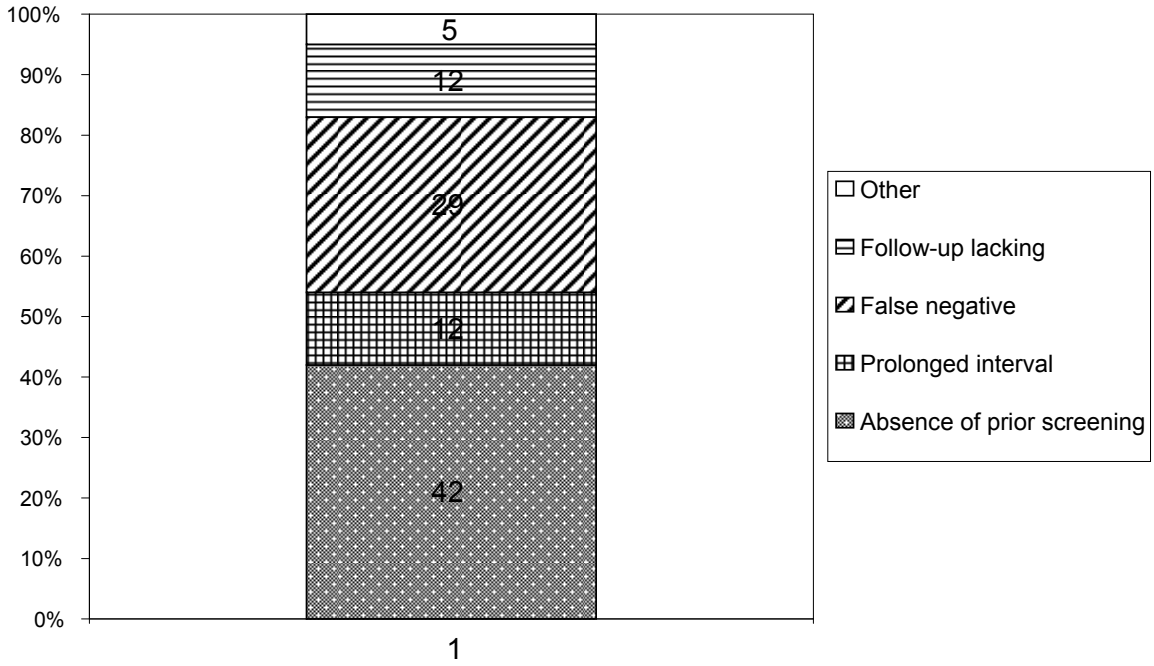
Prior to the advent of HPV vaccination, primary prevention measures such as sexual health education (advocating the wearing of condoms, limiting the number of sexual partners) played only a very incidental role in controlling this disease, primarily due to the high prevalence of HPV infections in the population, the often asymptomatic nature of HPV genital infections, and the limited effectiveness of the condom in preventing the transmission of the infection.[54] It is thus only beginning at the screening stage that an analysis of weaknesses can be conducted.

Figure 5 Continuum of services in cancer control according to Zapka et al., and fragile links applicable to cervical cancer control



According to a systematic review of 42 studies (all conducted in developed countries) and a recently published meta-analysis,[5] the absence of prior screening is still the main reason for failure to prevent cervical cancer. That combined with a too-long interval between screening tests explains 54% of invasive cervical cancer cases. Detection errors in the screening tests are the second most common reason. Shortcomings in following up cases and other reasons, such as treatment failure, explain 12% and 5% of the cases, respectively. The following diagram illustrates the distribution of the main causes of failure, according to the meta-analysis.

Figure 6 Distribution (%) of the main reasons for failure in countries that offer screening, according to the meta-analysis by Spence et al.



In the following sections, we will examine in greater detail the factors associated with the main causes of cervical cancer screening failure.

4.1 INADEQUATE PARTICIPATION OF THE POPULATION

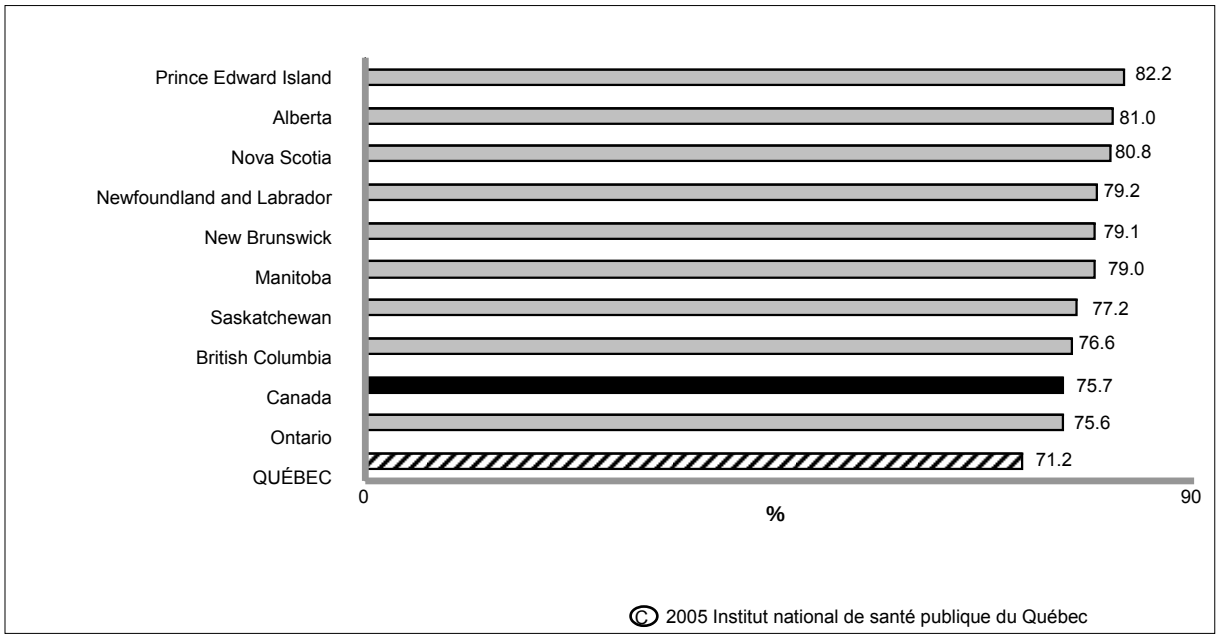
This section will deal more specifically with the situation in Québec.

According to data obtained from the MSSS, 1 215 108 cytology exams (Pap tests) were performed in Québec in 2005. This number has been relatively stable for several years. The quantity of exams performed outside the public system is estimated to be negligible.

In the absence of a screening program and a specific information system, it is difficult to establish the exact percentage of women having used screening services according to the intervals normally recommended in Canada. Moreover, there is no specific procedure code for the sampling in the Medical Procedures File of the Régie de l'assurance maladie du Québec (RAMQ). The data used to establish participation rates essentially come from periodic health surveys, with the limitations inherent in this type of measurement (memory bias, social desirability, the telescoping effect over time in terms of estimating the interval since the last test). In general, self-report data tends to overestimate the actual rates of screening test use.[55]

The following diagram presents overall screening participation rates in 2003 in Canada by province based on data from the 2003 Canadian Community Health Survey (CCHS).

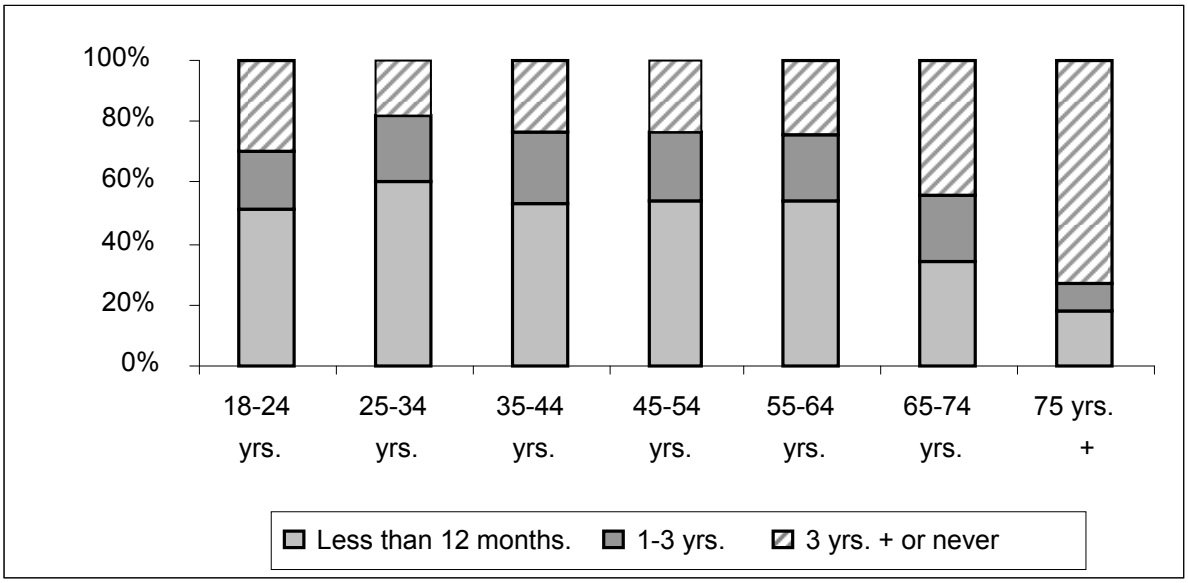
Figure 7 Percentage of women aged 18 to 69 having had a Pap test within a three-year period, Québec, other Canadian provinces and Canada, 2003



This data shows that at 71.2% the overall screening rate in Québec in 2003 was the lowest of all the Canadian provinces; the average for Canada was 75.7%.

The diagram below shows the screening rate in 2003 by age group and interval. The rate has been adjusted to take into account the percentage of women having had a hysterectomy earlier and who were no longer part of the target population. The rate for young women under the age of 18 is not known because they were not included in the survey.

Figure 8 Pap screening rates in Québec by age and interval, 2003



Overall, 16% of women who participated in the survey had never had a prior screening test, which represents 365 000 individuals province-wide. When women whose last test dated back more than three years are included, the number of women whose screening frequency was inadequate in 2003 rises to 530 000.

The same data show that among women less than 65 years of age having participated in screening, most had had a screening test over the past 12 months, which suggests that in Québec, when women take advantage of screening, most do so on an annual basis.

The following table presents more detailed population-based estimates.[56]

Table 8 Estimates of the number of women having had a screening test by age group and interval, Québec (2003)

Last Pap test	18-24 years	25-34 years	35-44 years	45-54 years	55-64 years	65-74 years	75 years +	Total
< 12 months N %	163 813 51%	276 154 60%	277 554 53%	234 006 54%	141 545 54%	55 123 34%	21 552 18%	1 169 747 51%
1-3 years N %	62 429 19%	100 320 22%	119 387 23%	99 299 23%	59 039 22%	33 664 21%	11 036 9%	485 173 21%
> 3 years or never N (%)	530 000 (28%)							

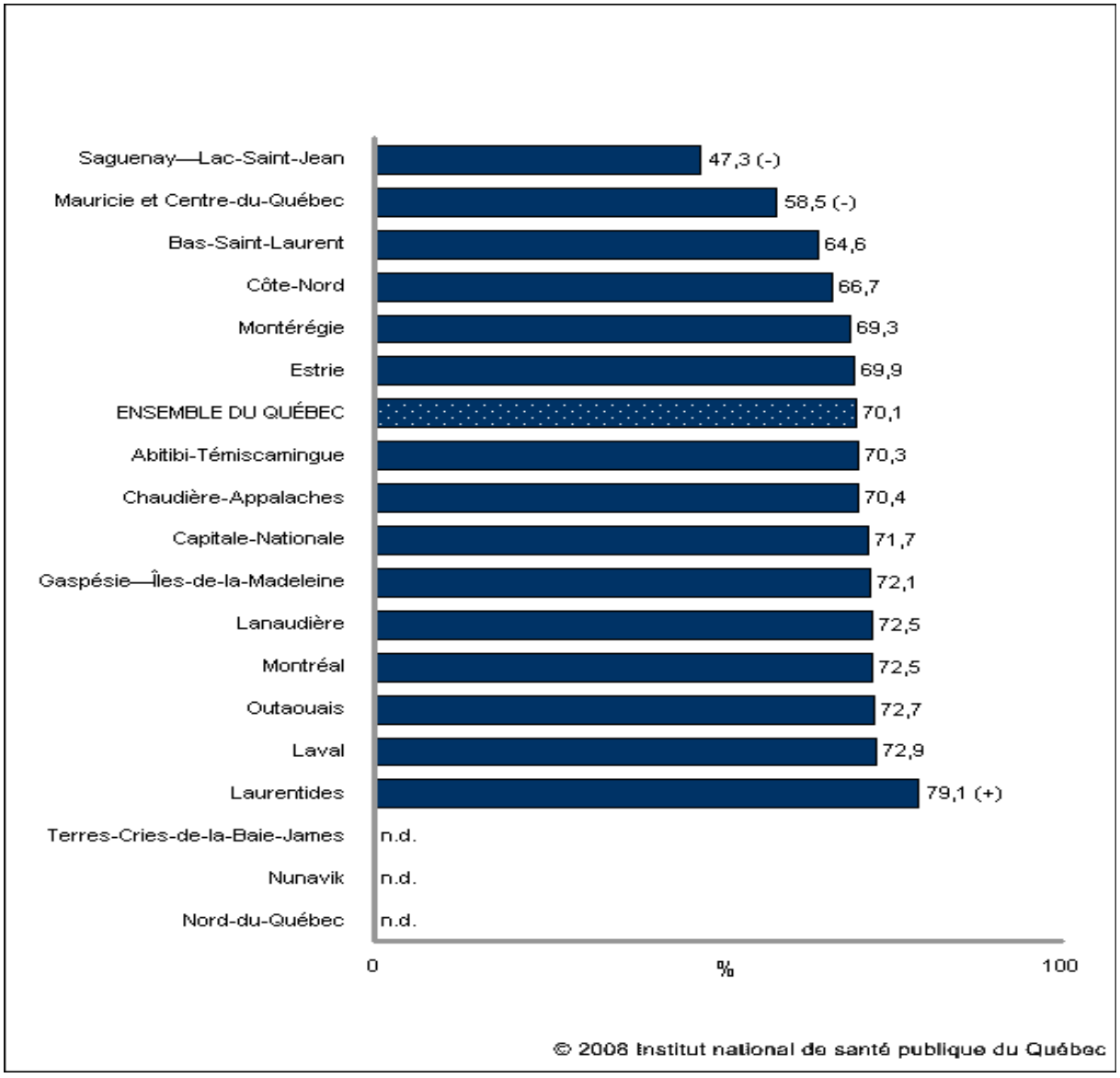
In Québec, according to the same data, there is little variation among health regions. Only the Laurentides (81%) and Outaouais (84%) regions have an overall participation rate that is statistically higher than the provincial average.

Numerous studies on screening determinants have been published throughout the world in the past. More specifically in Canada, one study of data from the Canadian health survey conducted in 1998 showed that the risk of not having had a recent screening examination was higher among women who were older, had a lower level of education, were of non-European ethnic origin, were allophone, were unmarried or living alone, and used few preventive services in general.[57]

In Québec, a detailed analysis of data from the 2003 Canadian survey shows that low household income, the absence of a family doctor, the fact of experiencing a language barrier (speaking neither French nor English), a low level of education, and the fact of living alone for older women are the most correlated factors with the probability of being under-screened or unscreened. On the other hand, the vast majority of under-screened or unscreened women did not necessarily have these characteristics and 70% of them had a family doctor.[56]

A preliminary analysis of Québec data from the last Canadian Community Health Survey conducted in 2005 (cycle 3.1) shows similar results regarding the overall participation rate (70.1%) and rates by age group. As illustrated in the following diagram, the rates by region are also very similar, with the exception of three regions, two of which now have rates that are statistically below the average and one which has a rate statistically higher than the average.

Figure 9 Variation in cervical cancer screening rates by Québec health region, 2005[7]



[7] Source: http://www.inspq.qc.ca/Santescope/element.asp?NoEle=721.

4.2 SUBOPTIMAL SENSITIVITY OF THE SCREENING TEST

Despite the definite success of conventional cytology screening in reducing the incidence of and mortality from cervical cancer, this test has significant limitations. Nanda et al. published an extensive review on the subject.[58] After having assessed hundreds of studies, the authors concluded that only 94 studies evaluating the performance of the Pap test were of sufficient quality to be included in their systematic review. Among these studies, only 12 included a population of women who were screened and who had had their results verified by colposcopy and biopsy. Among the seven studies with data that allowed a calculation of Pap test performance in identifying high-grade lesions (CIN 2+), some sensitivity estimates were as low as 23%. In five of these seven studies, sensitivity was less than 75%. Specificity varied from 91% to 98%. This review highlighted the lack of available data for accurately assessing the performance of a commonly used test. Variability in performance of the test was also noted. The low sensitivity of the Pap test led professional organizations to recommend frequent test repeats. Given the natural history of the disease, the screening interval could definitely be extended if a more sensitive test were used.

Since the publication of Nanda et al.'s report, numerous studies have been published to compare the performance of the Pap test with a new test, the HPV test. One of the advantages of these studies is that they have provided new data on the performance of cytology from better quality studies. Table 9 summarizes the performance of cytology in a screening context (ASC-US positivity threshold for identifying CIN 2+ lesions), where colposcopy was used as the norm in populations with health care standards comparable to ours. The table shows that sensitivity for identifying high-grade lesions varies from 20% to 86%, with a very low positivity threshold (ASC-US) for cytology.

Table 9 Pap test sensitivity in a screening context in studies comparing cytology to the HPV test in North America and Europe*

Study (year)	Country	Size*	Ages	Type of cytology	Pap test sensitivity
Cuzick (1999)[59]	United Kingdom	2988	≥ 35	CC	86%
Ratnam (2000)[60]	Canada	2098	18-69	CC	40%
Schneider (2000)[61]	Germany	4761	18-70	CC	20%
Clavel (2001)[62]	France	1550	≥ 30	CC	58%
Clavel (2001)[62]	France	4121	≥ 30	LBC	84%
Kulasingam (2002)[63]	United States	760	30-50	LBC	38%
Cuzick (2003)[64]	United Kingdom	10 358	30-60	CC	77%
Petry (2003)[65]	Germany	7908	30-60	CC	44%
Cochand-Priollet (2005)[66]	France	1757	Average age 33 yrs.	CC LBC	60% 65%
Agorastos (2005)[67]	Greece	1296	≥ 17	CC	50%
Bigras (2005)[68]	Switzerland	13 842	≥ 16 (96% > 30)	LBC	59%
Ronco (2006)[69]	Italy	22 760	25-60	LBC	74%
Mayrand (2007)[70]	Canada	10 154	30-69	CC	55%

***** When more than one article reported results for the same population, the most comprehensive report was used. When an article gave more than one sensitivity estimate, the estimates adjusted for verification bias were chosen, as well as those applying to women over the age of 30 where the positivity threshold of the cytology was ASC-US or the equivalent, and that of the histology was CIN2 +.

CC = conventional cytology.

LBC = liquid-based cytology.

Given this context, it is not surprising to learn that in their review of the subject, Spence et al. determined that up to 30% of women with a diagnosis of invasive cancer had had a recent screening test interpreted as normal.[5] This study also observed that the percentage of patients with a screening test interpreted as a false-negative varies according to the milieu. In the United States, where screening is opportunistic, this percentage is 36% whereas it is only 11% in Europe (in countries with organized screening and quality control).

4.3 WEAKNESSES IN FOLLOWING UP ABNORMAL CASES

To prevent cancer, it is essential that women with abnormal screening test results have the appropriate follow-up within an acceptable time frame. Treatment, then identification of failures and recurrences, are also essential. Spence et al. estimated that 11.9% of invasive cancers could be attributed in errors in follow-up.

There are many causes of errors in follow-up. An abnormal result may not have been communicated to the attending physician or to the patient. The attending physician may have failed to recommend the appropriate follow-up. At the time of diagnostic assessment, the colposcopist may have missed a lesion or not treated it appropriately. Finally, the woman may have refused an examination or not shown up for the appointment.

Without an information system, there is currently no data available in Québec to document this section but a study on this subject is underway by researchers from McGill University in collaboration with the INSPQ.

4.4 EFFICIENCY CONCERNS

Cervical cancer screening mobilizes significant resources and is an important component of the current economic burden relating to cervical cancer control. American researchers who analyzed data from a Health Maintenance Organization have shown, for example, that cervical cancer treatment represented only 10% of the total costs of cervical cancer control in their milieu. However, screening costs represented 63%, following up abnormal cases 17%, and false positive results 9%.[71]

In Québec, 1.2 million cytology tests are performed per year. The cost of screening alone was estimated at $32.2 million for 1995 during work to develop the Québec cancer control program.[20] In 2007, with costs of $13 per screening test (cytological analysis only) and $65 for a first colposcopy, minimum costs would be over $20 million for these two interventions only, to which control examinations, medical fees and treatments would have to be added.

Costs of this scale should raise efficiency concerns. We know that opportunistic screening often results in over-screening low-risk individuals. An analysis of Québec data from the 2003 survey (Table 8, p. 27) shows that a large percentage of screened women had a Pap test in the previous year (51%), which is a higher percentage than we would observe if 100% of the women had a test every three years (which would result in 33%). In Québec, screening adolescents is also a very widespread practice.

Over-screening also affects human resources. In a survey conducted by the Association des cytologistes du Québec in the summer of 2008, the median time line from the moment the specimen arrived in the laboratory to determination of the results was 45 days, but could be up to six months in certain places. A reduction in over-screening could have a positive impact on laboratory processing times and the shortage of human resources.

5 POTENTIAL SOLUTIONS

5.1 IDENTIFICATION AND ANALYSIS OF SOLUTIONS

Improving cervical cancer screening can be considered from a number of perspectives. Scientific literature details several specific methods for improving participation. Most of the studies come from the United States and adapting them to the Québec context is not always clear. First, data on the effectiveness of these interventions is limited, and data on efficiency is almost non-existent. In the case of complex interventions, it is particularly difficult to evaluate the contribution of the various components. In addition to measurable clinical effectiveness among individuals, other factors must also be considered in the choice of intervention, such as equity, acceptability, and feasibility in our milieu.

Using the interventions reviewed as a basis, preliminary work was carried out by a small group[8] to research other plausible and previously tested methods in the field of prevention, and to explore the advantages and disadvantages (or limitations) and feasibility of these interventions. A number of these methods come from the Québec breast cancer screening program (Programme québécois de dépistage du cancer du sein or PQDCS), the only organized cancer screening program currently in place in Québec.

Potential solutions were submitted for discussion during a meeting on May 15, 2008 of an expanded group, which involved over a dozen participants from various fields (managers or heads of programs, family doctors, obstetricians/gynecologists, epidemiologists, etc.). Individual consultations continued after the meeting to document the additional options identified during this meeting.

The process was essentially the same for screening parameters. Hypotheses were established based on the scientific literature, improved in a small working group[9] and submitted for discussion during a meeting involving additional stakeholders from clinical, laboratory, public health and mathematical modelling settings. The options were analyzed by considering the ideal situation or acceptable alternative solutions, and taking into account the future evolution of screening. After the May 15 meeting, discussions continued with certain participants to better document the potential for improving screening through quality assurance measures.

[8] Those who took part in the study of measures to improve participation in screening were: Patricia Goggin, Diane Larocque, Marie-Hélène Mayrand, Christine Pakenham, Léo-Roch Poirier and Louise Rochette.

[9] Those who took part in the study of screening parameters and abnormal case follow-up were: Manon Auger, Marie-Hélène Mayrand, Louise Rochette, Michel Roy, Chantal Sauvageau and Denise Vanasse.

5.2 SCREENING PARTICIPATION

This section includes a description of the main measures likely to improve screening participation, an analysis of their advantages and limitations, and a brief discussion of their feasibility. Few interventions targeting or specifically assessing a reduction in over-screening were identified in the literature. However, reducing over-screening should remain an important concern if we want to avoid further clogging the system, unnecessarily extending wait time for obtaining services, and preventing the morbidity associated with any useless procedure.

Interventions can be described according to whether they target the health care system, professionals (physicians or nurses, usually) or the population targeted by screening.

5.2.1 Interventions targeting the health care system

The establishment of a cervical cancer screening procedure

In recent years, screening participation appears to have reached a plateau. However, according to data analyzed from the 2003 Canadian Community Health Survey, most women who had not been screened recently had an attending physician.(56) The low level of importance placed on cervical cancer screening and the fact that some male doctors have dropped gynecological examinations, possibly due to fear that patients may incorrectly interpret the examination, may have contributed to a reduction in screening offered by physicians.

The establishment of a specific procedure, combined with remuneration conditions for primary care physicians, could act as an incentive for offering screening in a more systematic manner. This would not constitute a precedent because, since 2007, two preventive medical procedures have been established for general practitioners (medical support for smoking cessation and preventive interventions related to blood-borne and sexually transmitted infections).[10]

The identification of screening procedures would also facilitate an evaluation of the proposed screening policy, which cannot be done presently because the screening procedure is integrated into the medical exam or consultation. Currently, we have to rely on health survey data to estimate the rate at which women participate in screening. However, this method of measuring participation is not only imprecise, it is about to disappear as the majority of Canadian provinces (8/10) are in the process of establishing organized programs with specific information systems.

The establishment of such a procedure could also contribute to reducing over-screening, and limit the additional cost of implementing such a measure, if it were associated with remuneration conditions such as age or interval. Clear guidelines to define these remuneration conditions are thus necessary. Moreover, the description of the procedure should deal more with counselling and sampling as such, rather than the type of analysis

[10] A description of the remuneration and its conditions may be found on the following Web site: http://www.ramq.gouv.qc.ca/fr/professionnels/manuels/100/011_b1_acti_clini_preven_acte_omni.pdf.

conducted on the sample (which is the laboratory's business), and should be flexible enough to allow for its evolution.

The cost of such a measure has yet to be assessed as does the rate to be negotiated between the MSSS and the Fédération des médecins omnipraticiens du Québec (FMOQ), to which general practitioners are affiliated. Terms and conditions must also be defined for identifying screening procedures when sampling is done by other professionals (obstetricians/gynecologists, nurses, or medical technologists) or by general practitioners remunerated according to other conditions than fee-for-service (on salary or on hourly rate).

The implementation of an information system specifically for screening women and conducting follow up

Among the actions recognized and evaluated as most effective, sending personalized invitations to women appears to be one of the most relevant. However, given the current relatively high use of screening services, this approach could result in significant waste were invitations sent to everyone, without considering prior screening experience. To specifically target women who have never received screening or whose screening intervals exceed the recommended standard, it is essential to have the use of a population registry and screening procedure records. Access to a population registry, and not to local patient records (such as in family medicine groups or cytopathology departments), is required to reach women who do not have an attending physician or who are simply not in the system.

The establishment of an information system on cervical cancer screening that includes examination data would enable an assessment not only of the screening results but also of the interventions carried out on a woman (or by a physician) thus reducing the risk of loss or delay in following up abnormal cases. The data obtained through this information system is also essential to evaluate the impact of technological change (eventual integration of new screening tests) and of HPV vaccination.

The extent to which elements in electronic medical records (Québec health records containing standarized laboratory data, including cytology and pathology results) and the Panorama public health information system (including vaccination status data) could be integrated to facilitate the development of an information system specific to cervical cancer screening must be explored.

Reducing barriers to accessibility

The allocation of population-based responsibilities to new authorities established through the recent reform of the health care system, and particularly the creation of health and social services centres (CSSSs), could be a facilitating factor in seeking original solutions adapted to the milieu, depending on whether the barriers are more geographically, organizationally or ethnoculturally based, for example.

Access to a primary care physician is currently a major challenge in Québec. Giving nurses or other professionals, such as medical technologists, responsibility in this area is a measure that has been suggested time and time again to overcome certain barriers to accessibility, especially when cultural factors come into play. Their acceptability for this type of intervention

would no doubt be high. Nonetheless, nurses working in primary care trained to do this type of sampling are still few and far between. However, the legal barrier was lifted with the adoption of Bill 90[11] in 2003. Giving nurses responsibility for taking samples will require clear guidelines to avoid unnecessary testing and the aggravation of over-screening. For example, we would like to avoid young women who are being seen for contraception or for blood-borne and sexually transmitted infection screening being systematically screened for cervical cancer if they are not in the age group targeted by the screening policy. Mechanisms must also be put in place to ensure the follow-up of abnormal cases. A pilot project to better assess this strategy's potential and conditions for success will be launched in the Mauricie et Centre-du-Québec region over the coming year (verbal communication with Lyne Cloutier, project leader, September 9, 2008).

Among other measures to improve accessibility, several authorities have held screening days or events that involve the mobilization of a team of professionals for a limited period of time. This strategy was often used in the 1970s for example, when a mobile team (the Cyto-Québec mobile trailer) travelled across Québec while screening services were still not readily available. A number of Canadian authorities annually organize special screening days in remote regions or underprivileged urban areas. In Québec, as part of Québec's breast cancer screening program (PQDCS), several remote regions receive mobile mammography services. These services are so successful that these regions obtain participation rates equivalent to or even higher than those in a number of regions that have permanent services available year-round.(72)

Performance incentive measures

Finally, another method proposed to give added value to screening among clinicians involves performance incentive measures. This method has been used in the United Kingdom since 1990. General practitioners are given a fixed bonus amount when 80% of their patients eligible for screening have had a test in the past five years. From 1991 to 1993, increased screening participation, followed by a subsequent reduction in incidence and mortality of cervical cancer was particularly significant in underprivileged areas and among women 35-64 years of age.(73) After 1993, the improvement in participation was less marked, especially in affluent areas where the rates had already reached a very high plateau. The success of the performance incentive has been explained in part by the greater involvement of nurses in performing sampling.

In 2000-2001, New Zealand also adopted perfomance incentives, including a target for cervical cancer screening.(74) However, a number of experts remain skeptical regarding the true effectiveness of this type of measure, and point out the high cost to the health care system and the risk of harmful effects.(75,76) In Great Britain, it was estimated that one year after implementation of a new performance-based remuneration system in 2004, more than 80% of practitioners met the practice standards, which leads to the assumption that the targets were too easy to attain. Ideally, databases should be available before considering introducing this type of measure.

[11] Act to amend the Professional Code and other legislative provisions as regards the health sector.

In Québec, the mechanisms required to measure results (by professional, group practice or CSSS?) are not obvious, especially in a partial capitation system and in the absence of billing codes for screening sampling. This measure thus appears difficult to implement in the short term.

5.2.2 Interventions targeting health care professionals

The publication of guidelines

The adoption of Québec-specific guidelines adapted to current knowledge could support professional training efforts by limiting the number of different messages. The recommendations of the Canadian Task Force on Preventive Health Care (CTFPHC) date back to 1994.(77) These recommendations are based on knowledge at the time, with a very broad interpretation of the risk factors, contributing to over-screening. The update produced in 1995, on using HPV detection tests for screening(78) is completely outdated, since the majority of solid studies were published after that date.

An update produced in 1998 by a consortium of Canadian professional organizations and provincial representatives (the CCPN) essentially issued the same message, but insisted on the creation of organized screening programs.(79) Nonetheless, until recently, the SOGC continued to maintain its recommendation for screening on an annual basis, in the absence of call-back mechanisms.

Over the course of recent years, with the establishment of organized screening programs in Canada, a number of provinces have issued new guidelines that take into account the evolution of knowledge on the disease's natural history and include, as was the case in Ontario in 2005, options with HPV detection tests.[12]

Even though several Québec professionals took part in recent work by the SOGC to produce an HPV infection prevention guide, the section addressing screening(80) mostly contains general principles on organizing screening rather than real screening guidelines for clinicians. Thus, in Québec, there is currently a huge void in terms of screening guidelines in a context of rapidly evolving knowledge. With the commercialization of an HPV vaccine and the introduction of a vaccination program, the absence of a strong message relating to screening could lead to the assumption that screening is simply no longer necessary.

The INSPQ's work in preparing this report on screening presents an ideal context for developing guidelines, since the work is based on evidence and the process brings together a vast number of professionals involved in screening. The key screening parameters recommended by the group of experts are presented later on. However, the passive distribution of guidelines may be insufficient to generate behavioural change, especially If the change is significant. A proactive distribution through several forums and repeated over time is a vital condition for integrating them in practice. Moreover, the cooperation of the Collège des médecins du Québec (CMQ) could be sought to ensure additional support.

[12] www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13104.

As previously mentioned by a number of authorities, and to avoid any contradictory message, the success of a change in screening such as extending the interval between tests is conditional upon the implementation of an integrated screening information system enabling women to be called back. The guidelines and organization of services should thus be consistent with one another. With a purely opportunistic approach, as is the case now, clinicians could be tempted to maintain the highest level of caution and err towards over-screening rather than risk legal action for negligence.

Another element to be considered in disseminating new screening guidelines, which could promote their acceptance by the targeted clientele, would be to plan clear messages explaining the changes. Many women have developed the habit of having an annual screening test and they could perceive any initiative to change this routine as a simple effort to rationalize resources to the detriment of their health. It is essential that the messages disseminated to workers and those intended for women be consistent.

Professional development

The recent announcement of an HPV vaccination policy in Québec and the implementation of a public vaccination program in autumn 2008 present an ideal context for updating the knowledge of primary care physicians with respect to the diseases caused by HPV and cervical cancer screening. A 2007 survey conducted in four Canadian provinces, including Québec, was able to identify major gaps in knowledge among general practitioners, pediatricians and obstetricians/gynecologists regarding the epidemiology of diseases caused by the HPV and the effectiveness of screening.[81] One of the major training needs identified is related to the various impacts of vaccination on screening activities.

Reaching all the health care workers with professional development activities remains a difficult task. However, the adoption of screening guidelines and the introduction of HPV vaccination could serve as a point of departure for a mass campaign targeting primary care practitioners (including nurses and medical technologists). The two screening and vaccination components could be integrated into a cervical cancer prevention approach. Expanding training methods to include interactive workshops and online training in cooperation with the professional orders concerned should be considered in order to reach the greatest possible number of health care workers.

The experience acquired from launching Québec's breast cancer screening program (PQDCS) has also taught us that measures to encourage the adoption of changes in practice may be required for several years and that training future practitioners must not be neglected.

Support for preventive clinical practices

Preventive clinical practices (PCP) constitute a set of interventions (counselling, screening, immunization, chemoprophylaxis) that a health professional (clinician) conducts with a patient with the goal of promoting health and preventing diseases, injuries and psychosocial problems.[82]

Providing support for PCPs is an action strategy in Québec's 2003-2012 public health program.[83] This strategy is based on the fact that three quarters of the Québec population annually consult physicians in their offices at least once a year (an average of four times), in addition to being in contact with other health professionals, providing many opportunities for integrating prevention in daily practice. Thirty interventions have been specifically targeted because they are supported by category A or B recommendations according to CTFPHC standards. Cervical cancer screening via the Pap test is among these measures. Responsibility for supporting PCPs among clinicians is under the jurisdiction of regional public health branches, in collaboration with health and social services centres (CSSS).

According to a recent MSSS survey on the status of implementing PCPs since the province established its public health program in 2003, cervical cancer screening has one of the lowest implementation statuses, 1.8 on a scale of 1 to 4.[82] As mentionned earlier, the absence of a clear policy on cervical cancer screening and the lack of concrete measures promoting screening (or reducing barriers) among health care workers has definitely contributed to this weak performance. With the advent of HPV vaccination and a clearer picture of the interventions required to improve screening, this is an ideal time to give greater priority to this strategy and to ensure that the people responsible for implementing PCPs and those responsible for cervical cancer prevention are in contact with one another. There would also be potential benefit from working on this matter in concert with the FMOQ and its affiliated organizations.

5.2.3 Interventions targeting women

A personalized invitation to women from their attending physicians or from another health-related authority (CSSS or ASSS)

According to a literature review, one of the most effective ways to enhance participation is to send personalized letters to women inviting them to have a screening test.[84-86]

These letters could be sent by attending physicians, but the computer-based infrastructure required to generate these letters automatically when the time comes is currently rarely available. In addition, there is little potential control over this way of doing things, especially in the absence of incentives. Finally, physicians, groups of physicians, such as family medicine groups (GMF), and network clinics can only invite women who are already part of their practice, which has little impact on reaching women with no attending physician.

The best strategy to reach all women, including those without an attending physician, is to identify them through population records, such as that of the Régie de l'assurance maladie du Québec (RAMQ). This approach is already used by Québec's breast cancer screening program (PQDCS), with the approval of Québec's access to information commission (CAI). Given that nearly half of the women may already have had a screening test over the course of the past year, a system that combines population records and a screening test registry would allow invitations to be targeted only to those women not having had a screening test during the recommended interval (two or three years, for example) and who fall within the targeted age group for receiving an invitation.

Having local (CSSS) or regional (public health branches of ASSS) authorities send women invitation letters presupposes the existence of clear guidelines pertaining to the target group (age, interval, follow up of abnormal cases) and that services are ready and waiting for them. Mechanisms would have to be put into place to take in orphan patients, not only for conducting the sampling, which could be performed by nurses or medical technologists, but also for ensuring abnormal cases are followed up with appropriate medical supervision.

In a context where the opportunistic approach has been functioning for a number of years with a certain degree of success, this strategy should probably be regarded as a complement to the screening services already offered by family doctors and obstetricians/gynecologists, rather than as the sole way to access screening. Thus, attending physicians should be involved in the plan and promote it among their patients, rather than viewing the invitation strategy as a competitive system.

Given that the screening standards would essentially be different from current practices, especially in terms of adolescents and young women, a communications plan addressing the target clientele and training for health care workers would be required to dissipate any confusion in this regard. Authorities who could respond to questions from women or health care workers should be identified and prepared to do so.

According to the working group members who studied strategies to improve screening participation, having a public health authority send invitation letters to women who have not had a recent screening test is the most promising approach to boost participation. However, it is also the most demanding in terms of organization, because it encompasses all the other aspects discussed earlier (guidelines, training of health care workers, reducing barriers to accessing services, communications plan, etc.).

Mass communication strategies

Using the mass media, such as television, radio and newspapers to promote screening is a relatively costly strategy whose effectiveness cannot be guaranteed if it is not combined with an increased offer by clinicians or a reduction of barriers to accessing services. Harmonizing the messages intended for the public with those aimed at health care workers is also essential to avoid any contradiction in messages.

According to a systematic review of community-type interventions relevant to public health in Canada published in 2002,[87] the mass media is especially useful for building awareness in the population and for enhancing knowledge, but more targeted interventions are usually required to generate behavioural change.

The autumn 2008 implementation of a public vaccination program could provide the ideal context to talk about screening and combine certain objectives. Using a known personality as the spokesperson for or advocate of screening promotion activities could be considered to enhance the visibility of an eventual cervical cancer prevention program. Establishing an association with a credible, well-known organization, such as the Canadian Cancer Society, could also be considered.

Local or more targeted information campaigns

Local information or promotional campaigns are easier to organize than mass information campaigns and may provide the opportunity to better respond to local accessibility issues. In several Québec regions, such campaigns are organized by the breast cancer screening program, for example during visits by mammography mobile units.

As was mentioned for mass media, it is difficult to use this approach in an isolated fashion and the underlying conditions remain essentially the same (the need for clear guidelines and training for health care workers to harmonize the messages, enhanced offer of services to take in orphan patients, etc.).

In the absence of a province-wide policy for cervical cancer screening, leaving the initiative under the jurisdiction of regional or local communities could lead to disparities among regions and compromise the integrity of the message being delivered.

Exploring ways of working in partnership with Québec's breast cancer screening program (PQDCS)

When Québec's cancer control program (Programme québécois de lutte contre le cancer) was developed in 1997-1998, it was proposed that plans be made to harmonize an eventual cervical cancer screening program with the breast cancer screening program[20] since there is a partial overlap in the target clientele (women aged 50-69). Currently, all these women receive a personalized invitation to participate in the breast cancer screening program shortly after their 50th birthday, and participants whose test results are normal systematically receive invitations every two years after. The fact that this process is already in place and that a lower cervical cancer screening participation rate is observed among older women gives merit to this recommendation. Nonetheless, while certain common approaches in communicating with women seem easy enough to imagine, a full integration of the two programs in terms of services and information systems appears hard to envisage in the short term.

The production of educational material

Simply making educational material available in medical clinics, pharmacies and other public places is not known to be a very effective measure. However, the effectiveness of educational material could be increased if the material were accompanied by a personalized invitation letter from an official and credible source.

5.3 THE SCREENING TEST

Since nearly 30% of failures to prevent cervical cancer can be attributed to screening test errors, it goes without saying that optimizing screening in Québec cannot rely solely on an increase in the participation of women in screening activities, but must also try to improve screening test performance. Simply put, two avenues are possible: improving the performance of the current test or replacing it with a new test. The following sections assess the possibilities provided by these two avenues.

5.3.1 Improving the conventional Pap test

Although it is one of the most commonly used tests and appears to be very simple, the conventional Pap test requires several delicate steps in order to perform well. For this reason improving performance of the test presents such challenges.

Professional development

Were the conventional Pap test to continue to remain the screening test used in Québec, efforts would be required at a number of levels. Professional development begins with health care workers taking samples for analysis purposes and covers the following aspects: visualizing the cervix, identifying the transformation zone, taking the sample, smearing onto a slide and fixation. The quality of the sample is vital to obtaining valid screening test results.

Quality control

Better structured quality control measures should be put into place in cytology laboratories in order to standardize supervision of the professional practice within well-identified performance targets. Appendix 2 presents the proposed guidelines for the performance evaluation of Québec cytology laboratories in an organized screening context. These recommendations are based on those published for the United Kingdom, Europe and Canada. The proposed recommendations were developed by Drs. Majorie Deschênes and Manon Auger, both pathologists, in consultation with medical technologists Denise Vanasse and Christiane Lemay.

Concentration of cytology screening activities

The performance of cytology laboratories is connected, in part, to the volume of specimens examined, the internal and external quality controls in place, and the technologies used. Some jurisdictions (British Columbia, for example) have opted to centralize the interpretation of gynecological cytologies. This choice can result in economies of scale, facilitate the assessment of new technologies, and improve ongoing training and quality control. This is not the situation that currently prevails in Québec, where about 40 cytology laboratories under the jurisdiction of the MSSS and a number of private laboratories interpret the analyses of gynecological cytologies.

The decentralization of cytology laboratories has potentially significant advantages, however, such as reducing delays, reducing the risk of clerical errors, and facilitating access to cytological results during follow-up by the same local health services network. Decentralization also enables a cyto-histologic correlation to be performed on an ongoing basis, an essential aspect of quality control. In the majority of institutions, the demographic concentration around existing cytology laboratories provides a sufficent population base to ensure work for a minimal number of cytologists in appropriate professional practice.

Another aspect to consider in evaluating the degree of concentration of gynecologic cytology activities is the impact the closing this service would have on the non-gynecologic cytology of each institution, whose requests come mainly from specialized clinics (pneumology, urology, breast, etc.) and require a rapid response. Offering services in gynecologic cytology ensures

an optimal analysis volume for hospital cytologists so they keep up their skills in microscopic reading and in detecting abnormal cells.

Thus, concentrating gynecologic cytology activities in a limited number of institutions cannot be recommended at this stage without a more in-depth examination of all the consequences of such a move in the Québec context.

5.3.2 Changing the test

The limitations of the Pap test (its lack of reproducibility and limited sensitivity) have led to numerous research efforts to assess alternative technologies. In order to be concise, below we detail the two options with the characteristics required to be considered as potential Pap test replacements: liquid-based cytology (LBC) and the HPV detection test. Other technological developments, such as automated cytology slide reading systems, genotyping and molecular markers, will be presented more succinctly.

5.3.2.1 Liquid-based cytology (LBC)

LBC is a variant of the conventional Pap test in terms of the stages of sample preparation. The sampling is done in the same way as for a conventional Pap test but, instead of being spread onto a slide, the specimen is transferred to a flask containing a cellular fixative, then sent to the laboratory where it is treated to remove blood and debris. It is then spread onto a slide in a thin layer. The results are expressed in an identical manner to those from conventional cytology.

The main commercialized tests in Canada are the ThinPrep™ test from the Hologic company (formerly Cytyc), and the SurePath™ test from the DB Diagnosis company (formerly TriPath).

Initial studies on the performance of LBC concluded that it was superior to conventional cytology in terms of the test's sensitivity. However, its precise sensitivity remains difficult to establish due to verification bias and the variable comparison threshold values used in the studies. Moreover, performance discrepancies could vary according to the severity of the lesions. The specificity of the two screening methods (conventional cytology and LBC) was generally recognized as similar.

Later, several systematic reviews were conducted by independent researchers and health technology assessment agencies in Canada, the United States, Australia, New Zealand and Europe.[35,88-91] The two most recent were published in early 2008. By meticulously reviewing the data available and paying particular attention to the quality of the study design, their conclusions were different in terms of the effectiveness and the cost-effectiveness of LBC. They both judged the quality of the evidence available to compare the performance of the conventional Pap test to LBC to be poor. In terms of comparing the sensitivity and the specificity of the two tests, these reports concluded that there wasn't enough data available to reach a conclusion or that a possible advantage in terms of sensitivity was very modest, when the goal was the identification of high-grade lesions later proven by biopsy.

While contesting the superiority of LBC in terms of accuracy, a number of researchers nonetheless admit that LBC could have other advantages, such as a reduced number of unsatisfactory specimens and a reduction in time required for microscopic reading. LBC also provides the possibility of using the residual fluid to conduct a HPV detection test or other complementary analyses such as immunocytochemical markers. These potential advantages must be examined in the context of limited material and human resources. Liquid-based cytology may also avoid having the patient undergo the discomfort of a second gynecological exam when complementary tests prove relevant (ASC-US triage).

Some studies noted a lower percentage of unsatisfactory specimens with LBC.[92,93] For example, in a pilot study, the UK National Institute for Clinical Excellence observed a reduction in the percentage of unsatisfactory specimens from 9.1% to 1.6% after the introduction of LBC. However, this advantage could be marginal when the unsatisfactory specimen rate is low to start with, as in the study by Davey et al.[90] (0.75%). According to a survey of Québec cytology laboratories conducted by the Association des cytologistes du Québec in 2005, the average unsatisfactory specimen rate in the 28 laboratories was only 1.6%. There is thus little likelihood that the introduction of LBC in Québec would provide a significant advantage in terms of the number of unsatisfactory samples.

A comparison of the cost-effectiveness profiles of LBC and conventional cytology has been undertaken in various areas. In Canada, an in-depth study conducted by the Canadian Agency for Drugs and Technologies in Health concluded that an LBC screening strategy (including HPV tests for ASC-US triage) every two years was superior (less expensive and better impact on health) to the current practice of annual conventional cytology.The following table summarizes the advantages and disadvantages of LBC versus conventional cytology.

In September 2005, LBC via the ThinPrep™ method received approval from the Food and Drug Administration (FDA) in the United States as a technique superior to conventional cytology for detecting glandular abnormalities (AGCs). Although these abnormalities represent less than 1% of cytological analysis results, cervical adenocarcinomas are recognized as being the most difficult to detect with cytology, have a poorer prognosis and, contrary to squamous cell cancers, their incidence is increasing in a number of countries, particularly among young women.[34,94]

Table 10 Advantages and disadvantages of LBC versus conventional cytology

	Advantages	Disadvantages
Conventional cytology	▪ Test simple, not expensive and familiar to health care workers ▪ High specificity ≥ 95% (few false positives)	▪ Average sensitivity at the LSIL/CIN 1 threshold assessed at roughly 50%, thus the frequent necessity of repeating the test (sensitivity increases with the severity of the lesions) ▪ Complex process, involving a number of steps and requiring sophisticated laboratory infrastructure
Liquid-based cytology (LBC)	▪ Less time required to read the slides ▪ Could reduce the number of unsatisfactory specimens for analysis ▪ Possibly enhanced sensitivity for detecting glandular abnormalities, (but contested for epithelial abnormalities) ▪ Specificity equivalent to conventional cytology ▪ Can more easily be associated with automated slide reading systems, for quality control or for screening (even more significant reduction in reading time) ▪ Allows additional tests to be done on the residual fluid (HPV or other STI detection tests, such as chlamydia, herpes simplex, molecular markers…)	▪ More expensive ▪ Additional steps in preparing the slides ▪ Requires redesigning the laboratory and training personnel

If the LBC option were selected, the quality assurance measures explained in the section on cytology would also apply.

5.3.2.2 HPV detection tests

Subsequent to the identification of some types of HPV as the causal agent of cervical cancer, a number of efforts have been made to use this knowledge to improve cancer prevention. The presence of the HPV's DNA can be detected in genital secretions by what is commonly called an HPV test. This detection is possible through two commercially available techniques: the PCR method (Amplicor HPV™), which is based on a polymerase chain reaction, and the signal-amplification technique (Hybrid Capture II™ or HC II test). Most of the independently published studies address performance of the HC II test, which was the first licensed for sale. They all cover a panel of 13 HPV oncogenes, without distinguishing the genotype(s) present. These are semi-quantitative tests, which lend themselves to a certain degree of automation and which are conducted on a liquid-based cytology sample or with a specific kit. The test is

affordable in a mass treatment context (about $25). In Québec, few hospitals offer this technology, reserved almost exclusively for ASC-US triage, but it is accessible in a number of private laboratories at a relatively high cost to women (about $100). Tests now also exist enabling HPV genotyping of infections. These tests enable the exact type(s) present to be determined. For the time being, they are reserved for research and follow-up purposes (see section 5.3.2.4).

Indications for the use of HPV tests are rapidly evolving. They are generally grouped into three types: for the triage of ASC-US lesions (the HPV test is only used for women presenting this result from cytology) to guide case management, for primary screening (the HPV test is the first or only test used), or to guide the case management of women treated for a high-grade, pre-invasive lesion. Below we present the evidence available for the first two indications in greater detail.

ASC-US triage

ASC-US-type cytological lesions form an ambiguous category, most often of a benign nature but occasionally associated with high-grade lesions (6-12%) or even cancers (0.1-0.2 %).[23] The goal of a triage strategy is to avoid sending all women with this cytological result for a more sophisticated diagnostic assessment, since the risk of a significant lesion remains low, and yet to accurately identify those with a higher risk.

Traditionally, cytology was repeated every 4 to 6 months for one or two years and only women with at least a second abnormal cytological test were sent for a colposcopy. The ALTS study (*ASCUS and LSIL Triage Study*), led by a team from the National Cancer Institute and involving more than 5000 women in the United States, was one of the first to show that a single HPV test performed when an ASC-US result was observed was a good option for identifying high-grade lesions.[95] In this study, the sensitivity of the HPV test for identifying high-grade lesions was 96%, compared to 85% for the Pap test (ASC-US threshold). All of the studies on the issue since that time have stressed the superiority of the HPV test. The usefulness of the HPV test for ASC-US triage is now the subject of major consensus within the scientific community[96] and this measure was one of the recommendations of a panCanadian forum on cervical cancer prevention in 2003,[52] at least in the case of women aged 30 and over. The most recent systematic review on the subject, which included 20 studies, concluded that the sensitivity of ASC-US triage by HPV testing was 93% and its specificity 63% for identifying high-grade lesions. On average, the sensitivity of the HPV test was 14% above that of a cytology repetition strategy.[96] Moreover, this strategy alleviates problems of compliance, associated with multiple visits.

Cost-effectiveness studies assessing ASC-US triage in a context where LBC is used invariably favour a triage strategy using the HPV test. In their model applied to the Canadian context, the team of Krahn et al. concluded that, compared to an annual conventional cytology strategy, a strategy of LBC every two years, associated with an ASC-US triage by HPV testing, would result in a reduction in costs and a similar or reduced burden of disease. Even with conventional cytology every two years, the evidence also supported the superiority of triage by HPV testing.[35]

In general, cost-effectiveness meta-analyses and studies have evaluated alternative triage strategies (by HPV testing or repeating cytologies) without considering age. The study by Legood et al.[97] conducted in the United Kingdom has been the only one to examine the question and, in fact, demonstrated a greater efficiency of this strategy among women aged 35 and over compared with those under the age of 35 (£3 735 versus £18 605 per year of life saved), but with the parameters of their screening program, i.e. an interval of three to five years. Although the overall results are conclusive, questions remain regarding the relevance of using the HPV test on women under 30-35 years, given the high frequency of positive HPV tests among young women and the infrequency of progressive high-grade lesions in this group. More studies are required to answer this question.

Primary screening

In primary screening, the HPV test can be used alone or combined with cytology. Recent studies suggest that adding the high-risk HPV detection test to the cervical cytological exam would greatly enhance the screening sensitivity for cervical cancer precursors but would reduce its specificity.[98]

The following table summarizes the characteristics and results of a number of randomized controlled studies that compared the performance of the Pap test to that of the HPV test, when the two tests are used alone or together to detect high-grade pre-invasive lesions.

Table 11 Results of randomized controlled studies comparing the sensitivity of the HPV test to cytology

Publication	Country	Ages	No.	Tests	Main result
Ronco, 2006[69]	Italy	35-60	45 307	LBC+ HPV test vs. CC	Relative sensitivity for LBC+ HPV test vs. CC: 1.47
Bulkmans, 2007[99]	Netherlands	29-56	18 403	CC+ HPV test vs. CC	Relative detection rate of CIN 3+ for CC+ HPV test vs. CC: 1.70, at the outset Relative detection rate of CIN 3+ for CC + HPV test vs. CC: 0.45, 5 years later
Mayrand, 2007[70]	Canada	30-69	10 154	CC vs. HPV test	Sensitivity: HPV test: 94.6% CC sensitivity: 55.4%
Naucler, 2007[100]	Sweden	32-38	12 527	CC+ HPV test vs. CC	Relative detection rate of CIN 2+ for CC and HPV test vs. CC: 1.51, at the outset Relative detection rate of CIN3 + for CC and HPV test vs. CC: 0.58, 4 years later
Kotaniemi-Talonen, 2008[101]	Finland	25-65	61 149	CC vs. HPV test followed by a CC triage	Relative detection rate of CIN 3+ for HPV test vs. CC: 1.10
Ronco, 2008[102]	Italy	25-34	6 788	CC vs. HPV test	Relative sensitivity of HPV test vs. CC: 3.50
		35-60	17 747	CC vs. HPV test	Relative sensitivity of HPV test vs. CC: 1.92

LBC: liquid-based cytology.

CC: conventional cytology.

When each test is considered on its own, the superior sensitivity of the HPV test compared to cytology (conventional or liquid-based) is now the subject of significant consensus. In their meta-analysis comparing the Pap test to the HPV test in primary screening, Arbyn et al. concluded that the HPV test was on average 23% more sensitive than the Pap test and 6% less specific.[96] A systematic review limited to observational studies conducted in Europe and North America also concluded that the HPV test has greater sensitivity (96% vs. 53%). Nonetheless, this same study reported a 6% reduction in specificity if the HPV test was used as the sole test.[103] The impact of lower specificity cannot be neglected. It may cause a significant increase in diagnostic exams, resulting in anxiety, costs, and the ineffective use of human and material resources. For this reason, a screening strategy based solely on the HPV test, and recommending a colposcopy referral at the first HPV test, is not envisaged.

By combining the two tests, the negative predictive value (NPV) would approach 100%, which would allow the intervals between tests to be safely extended.[98] In fact, a negative HPV test, on its own or associated with a negative cytology, provides excellent protection for at least six years.[104] This advantage must be weighed against the fact that this strategy is associated with a significant increase (nearly double) in the number of diagnostic procedures required (per screening episode).

Compared to a strategy based on the HPV test alone, the strategy of combining the two tests is more expensive and provides few advantages.[61] Currently, the United States is the only country that recommends use of the two tests in combination.[105]

Given the large number of transient infections among young women, an HPV screening strategy should be reserved for women aged 30 and over. It was under this condition that in 2003 the American FDA approved use of the HPV test combined with cytology (liquid or conventional) for primary screening.

Compared to cytology testing, which continues to be a laborious test exposed to some subjectivity, the HPV detection test has the appeal of being easier to standardize and therefore applicable to a mass approach. Another advantage of the HPV detection test, which is most relevant in the context of a shortage of resources or when women have personal or cultural barriers about having a gynecological exam is that the test's performance remains acceptable when the sampling is done by the woman herself. Although the sensitivity of a HPV detection test in detecting high-grade lesions generally remains below that of a specimen taken by a clinician, it is at least equivalent to, if not higher than that of conventional cytology.[106-108] This characteristic of HPV detection tests has been put to the test in the Netherlands. The screening participation rate was increased by 10% by mailing a self-sampling kit to women who had not responded to the initial invitation by letter.[109]

The HPV detection test is still rarely used in Québec. Used almost exclusively to manage abnormal cases during screening and in rare settings, the introduction of such a screening test on its own or combined with cytology poses a particular challenge in terms of communication with the public and health care workers. This is especially true given the negative connotation that could be associated with a test to detect a sexually transmitted infection. However, with the arrival of HPV vaccines, the public interest piqued by vaccine manufacturers' marketing campaigns could affect the demand for such tests.

The following table outlines the main advantages and disadvantages of the use of the HPV detection test in screening compared with cytological screening.

Table 12 Comparison between primary screening using cytology and using the HPV detection test

	Advantages	Disadvantages or limitations
Cytological screening	▪ Test simple to administer and familiar to clinicians and women ▪ High specificity ≥ 95% ▪ In the case of LBC, enables the HPV detection test for ASC-US triage to be done using the residual fluid	▪ The moderate sensitivity of a test must be compensated for by repetition on a relatively frequent basis ▪ Highly variable performance depending on the laboratory ▪ Requires a 2nd visit for the HPV detection test (ASC-US triage) if conventional cytology is used
Screening with the HPV detection test	▪ Very high sensitivity ▪ More standardized and automated test than cytology and thus applicable to mass screening ▪ Self-sampling possible	▪ Lower specificity ▪ Not indicated for women under 30 (transient infections) ▪ Lack of knowledge concerning the HPV test ▪ Optimal approach for following up positive cases still to be determined ▪ Strategy to be evaluated in a populational context (target population, interval between tests)

The characteristics of the HPV test summarized in the preceding section (greater sensitivity, easily reproduced, more easily automated, enables self-sampling) are so interesting that we should carefully study whether certain measures could reduce the impact of the disadvantages while maintaining the benefits. For example, different screening algorithms are currently being discussed in order to take advantage of the strong sensitivity of the HPV test, while attaining greater specificity. Various tests used in succession could be an interesting avenue. An HPV test could be performed first on its own, and then in the case of a positive HPV test, followed by a second test such as cytology, using molecular markers (which we will discuss below) or another HPV test allowing the identification of the precise genotype (genotyping). Another option could be to increase the positivity threshold of the HPV test, because it is a semi-quantitative test.[101]

Due to the prevalence and distribution of HPV infection genotypes that vary by population, as well as the cytology performance that varies according to the environment, it is possible that the ultimate choice of screening algorithms based on the HPV test will vary from one country to another to maximize the efficiency and effectiveness of screening activities. In terms of an organized screening program, we believe that like Sweden, Italy, Finland, the Netherlands and British Columbia, Québec should evaluate different screening algorithms based on

promising technologies such as the HPV test. The information gathered in demonstration areas would provide population-based data to solidly guide decision-making.

More recently, modelling analyses have assessed the economic impact of using the HPV test as a primary screening test. In their most recent analysis, a team from Harvard University concluded that, in terms of current recommendations, the use of the HPV test as the primary screening test among women aged 30 and over was the option with the best cost-effectiveness ratio.[110] In a Québec-specific analysis, another team also concluded that a screening strategy using the HPV test following by a cytology triage every three years was less burdensome and more effective than an annual cytology strategy.[111]

Were the HPV test chosen for screening in Québec, quality assurance measures would have to be put in place, as for cytology. Appendix 2 proposes a number of performance indicators.

5.3.2.3 Automated methods for reading cytology slides

Although they can be used with conventional cytology, most automated reading systems are used with LBC. They can be used for quality control or primary screening. These systems require a major financial investment but can significantly reduce the time cytologists devote to reading slides.

According to information gathered at the Eurogin Congress in 2006 and 2008, there are currently two main systems, each with different properties.

The DB FocalPoint™ Slide Profiler system, formerly the AutoPap™ System, developed, produced and supported by Tripath Imaging, is an automated gynecologic cytology slide reading assistant. Its software and algorithms enable the detection of morphological changes associated with epithelial abnormalities, benign cellular changes, infections as well as with the quality of the specimen. First it assesses, classifies, and groups in order the slides most likely to be abnormal rather than normal. The DB FocalPoint™ is the only automated assistant approved by the FDA capable of classifying up to 25% of slides into a separate “no further review” category with enough certainty to archive them directly without requiring their reading by laboratory personnel. The remaining slides must be studied by cytologists. This device was designed to operate 24 hours a day and can treat up to 90 000 LBC slides per year (or about 65 000 conventional slides). Thus, it can have a significant impact on laboratory productivity.

The second system, called the ThinPrep™ Imaging System (Hologic), is the most widely used around the world. It uses algorithms based on cell characteristics, such as size and DNA content. It also increases productivity by pre-locating 22 reading fields per slide and eliminating the need to analyze the other slide fields, unless the cytologist decides otherwise. One device can read 100 000 LBC slides per year. The manufacturer claims that this system improves the detection of LSIL- and HSIL-type lesions compared to manual reading. A new module called MultiCyte™ has been developed to facilitate use in a decentralized context. Liquid-based samples are sent to a central laboratory that prepares the slides and marks localized areas. Marked slides can then be read in secondary laboratories. Another module integrating immunocytochemical markers may be added shortly.

Since technology in this field is evolving very quickly and there are few independent quality studies validating the manfacturers' results, it is extremely difficult to express an opinion on the cost-effectiveness of these technologies. The same conclusion was made in a recent study conducted by British researchers.(112) Assuming equivalent effectiveness, one of the systems analyzed may be efficient, but these preliminary results would have to be confirmed when more information is available. However, the impact of this type of technology on the organization of work is such that the results of an economic evaluation in one specific context would not necessarily be applicable in another.

5.3.2.4 Genotyping

The HPV tests described in the previous section do not permit the exact type(s) of HPV involved to be identified in the case of a positive result. Genotyping has two potential advantages at the clinical level. Firstly, infections from types 16 and 18 appear to have a greater risk of progressing to high-grade lesion.(113,114) It has been suggested that more aggressive follow-up should be considered in these cases. Secondly, in situations in which women have more than one positive HPV test over time, genotyping could permit differentiating successive transient infections by different types from the presence of a persistent infection by the same type. Since the risk of evolving lesions is linked to persistent infections, this distinction could also permit different follow-up.(115)

Few genotyping tests have characteristics enabling them to be used in a clinical laboratory. The Linear Array™ test (Roche Molecular Systems Inc., Branchburg, NJ, United States) and the Inno-LiPA™ test (Innogenetics NV, Ghent, Belgium) are two tests developed for clinical use. These methods permit the simultaneous amplification of a number of types (20-35). A second reaction enables identification of the types present. Enhanced quality control measures must be applied to each step involved in genotyping in order to obtain valid results. Clinical trials on large populations are needed before routine use of these tests.

Immunocytochemical and molecular markers

Since the majority of low-grade lesions identified by cytological screening end up spontaneously regressing and only a minority evolve into high-grade lesions (the true precursor stage of cancer), considerable effort has recently been devoted to finding elements that will allow a better prediction of the evolution of cytological lesions. This would permit closer monitoring of women with lesions most likely to evolve and result in reassurance and less aggressive follow-up for those whose lesions will eventually regress.

There are a number of types of molecular markers. A first category is based on the detection of RNA messengers linked to 5 types of high-risk HPV (types 16, 18, 31, 33 and 45)[13] or to 14 types of high-risk HPV (types 16 and 18 separately and a pool of 12 other high-risk types).[14] The detection of E6 and E7 mRNA points to the transcriptional activity of these oncogenes in cells and enables the identification of women with a real risk of a progression

[13] Test PreTect HPV-Proofer™ developed by the Norchip firm but currently marketed by Invirion Diagnostics and Biomérieux under the name NucliSENS™ EasyQ HPV.

[14] The Gen-Probe company's APTIMA™ HPV assay test.

to a pre-cancerous or cancerous lesion, contrary to the detection of viral DNA, where transient infections cannot be differentiated from evolving infections.

Another category of immunocytochemical markers involves the expression of various oncogene proteins such as p16INK4a[15] and the ProExC™ test developed by Tripath Imaging and already on the Canadian market. The latter test is based on the detection of an overexpression of MCM (minichromosome maintenance) and TOP2A (topoisomerase II alpha) oncoproteins when there is a disturbance in cellular regulation.

The development of such prognostic and diagnostic markers is currently underway in a number of cancer research fields, with promising results. Most of the work on cervical cancer is focused on the evolution of equivocal or low-grade lesions and the usefulness of these markers is determined on the basis of their ability to predict high-grade histologic lesions (CIN 2 or higher). For the moment, this does not involve screening tests as such but a secondary application after screening a cytologic (or histologic in certain cases) abnormality, to improve the test's specificity and cut down the transfers to colposcopy. As another option, these tests could perhaps serve as triage for cases with positive HPV test results, should this test be used in primary screening. A recent study comparing a number of these tests shows that many have a specificity higher than an HPV detection test using the HCII™ test.(116)

Another advantage of these tests is that contrary to HPV detection tests, which are of little predictive value among young women, they are applicable to women of any age. For the moment, all the tests appear to be based on a liquid transport medium.

Results published or presented at conferences to date are highly encouraging, but they have yet to be validated at the populational level.

5.4 FOLLOW-UP OF ABNORMAL CASES

5.4.1 Guidelines

In a context in which screening is primarily cytological, we believe it essential that standardized terminology be used that is based on the 2001 Bethesda recommendations. Below is the recommended follow-up of abnormalities.

ASC-H, HSIL, AGC, AIS, cancer: colposcopic evaluation

LSIL: Colposcopy, except for specific populations. For pregnant women who have had normal results in previous screenings, colposcopy can be postponed until after delivery; for post-menopausal women, triage by HPV test is an acceptable option.

ASC-US: Based on the literature review presented in section 5.3.2, it is essential that the HPV test be available to permit ASC-US triage. For women under 30, triage by repeating a cytology test is an acceptable alternative solution.

[15] Test CINtec™ by MTM Laboratories AG (formerly DakoCytomation).

Regardless of the screening test used, final case management is determined by the histological diagnosis. We propose following the guidelines issued by the ASCCP, which are summarized in Appendix 1.

A strategy for disseminating these guidelines is essential. Moreover, the introduction of an information system would enable an assessment of the extent to which guidelines are followed and the necessary corrections to be made. Finally, professional development efforts could all be oriented in the same direction with clear standards of conduct.

5.4.2 Unique, provincial information system

An information system presenting screening results and diagnostic procedures is an essential safety net to minimize errors in follow-up. A monitoring system could be put in place to send reminder letters to attending physicians and women if no diagnostic procedure has been recorded following an abnormal screening result. Therapeutic procedures could also be monitored in the same manner.

5.4.3 Professional development and quality assurance

A concerted approach to the professional development of primary care physicians and nurses, colposcopists, cytologists and pathologists is vital to ensure that follow-up of abnormal cases remains optimal. Standard training methods (conferences, online courses, etc.) could be established.

The existence of an information system would enable more effective methods to be put in place to improve the quality of the practice, such as an audit or self-assessment of professional practice.[117]

For example, each primary care physician could annually and confidentially be sent:

- the percentage of his/her samples determined to be unsatisfactory (if cytology is used as a screening test);
- the percentage of his/her patients requiring follow-up who went for a diagnostic examination within the predetermined time frame.

Each colposcopist could annually and confidentially be sent:

- the percentage of over- and under-estimated colposcopic impressions;
- the percentage of patients having received an appropriate histologic evaluation;
- the percentage of patients having had a therapeutic procedure appropriate to the diagnosis.

5.5 INEFFICIENCY

One of the basic reasons for the low effectiveness of screening is the over-screening of women with little risk of cervical cancer, such as very young women, those with a recent test that was normal, and women who no longer have a cervix following a hysterectomy for non-neoplastic lesions. In this context, the best way to improve the efficiency of the process is to

precisely define the target population and determine the best criteria for initiating screening, ceasing screening, and the intervals for performing screening.

To refocus activities on the population for which screening will be most useful, new guidelines need be established and distributed to practitioners, together with the other measures outlined in this section. Following a scientific literature review and a review of the most recent epidemiological data, the following principles are proposed for defining the target population and testing frequency.

5.5.1 The population targeted by cervical cancer screening

Since the HPV is the main causal factor of cervical cancer and it is transmitted sexually, screening should target women who are currently or were previously sexually active. Sexual relations with a risk of transmission include activities involving sexual contact without penetration as well as activities between homosexual partners.[118]

However, there is a certain consensus that women who have had their uterus removed (hysterectomy) for non-neoplastic lesions should be excluded from screening. In fact, primary cancer of the vagina is a too rare a condition to justify screening for it.[119] Women having undergone a hysterectomy due to neoplastic or pre-neoplastic lesions in the uterus or vagina could require monitoring tests for a certain time, as clinical follow-up and not for the purpose of screening. A pelvic exam and/or a study of previous records should be conducted when in doubt of the nature or cause of the intervention.

5.5.2 The age for initiating screening

No controlled clinical trial has been done to precisely determine the ideal age to begin screening exams and it would not be ethical to conduct one. However, a number of well-documented elements can assist with decision-making in this area.

Throughout the world, cervical cancer is almost non-existent before the age of 20. The rare cases found among this population are most often rare forms of cancer, unrelated to HPV[120] or that can be explained by in-utero exposure to diethylstilbestrol. Despite changing sexual morals in recent decades, an increase in the incidence of invasive cancer among women under 20 has not been observed.

Although HPV infections are frequent in the early years after the onset of sexual relations, the majority of infections are transient and of no consequence. Cytological abnormalities are more frequent among young women than among older women; however, the abnormalities found among young women are mostly of an equivocal or low-grade type.[121] The majority of these abnormalities will disappear spontaneously without treatment in less than two years.[122] Moreover, it usually takes several years, even decades, before a high-grade lesion progresses to an invasive cancer.

Colposcopic evaluation and treatment of low-grade lesions are not without consequence for young women. The psychosocial impact can be significant and obstetrical consequences may be observed subsequently[123]. Therefore, it is uncertain as to whether the advantages of screening all these lesions outweigh the disadvantages.

For these reasons, there has been a growing trend observed to delay the age for initiating screening and to discourage the screening of adolescents, even though some anecdotal cases of invasive cancer have been reported.

In the United States, where screening is opportunistic, there is a growing trend to favour screening beginning about three years after the start of sexual relations or by age 21 at the latest, rather than when sexual relations begin, as was the case a number of years ago (US Preventive Services Task Force, American College of Obstetricians and Gynecologists, American Cancer Society). Physicians are encouraged to use their clinical judgment in cases of young women who are sexually abused or immunosuppressed.

Not everyone agrees on the relevance of screening women in their twenties. In organized screening programs in Europe, women are generally invited to be screened between the ages of 20 to 25, depending upon the country.[22,41] In Finland and the Netherlands, invitations are extended beginning at age 30, but opportunistic screening before this age is tolerated. In the United Kingdom, in 2003, the minimum age increased from 20 to 25, however there was some protest concerning the risk.[124,125] An analysis of incidence rate trends for cervical cancer precursors caused Icelandic scientists to recommend women be screened in their early twenties.[126] However, in Finland, where the rate of moderate and severe precursors (CIN3) among women aged 15 to 34 increased in the 1990s, the screening policy has remained constant.[127]

Québec has no data available on the incidence of cervical cancer precursors by age to facilitate this type of decision. In the absence of empirical data, the people consulted in the context of this report consider it reasonable to recommend that, for the time being, screening commence at age 21 and be readjusted later as needed.

Since the use of the HPV test in primary screening is not recommended before age 30, an alternative test (cytology) would have to be used before this age if the HPV test were later selected as the principal screening test. Finally, indications for cervical cancer screening should be disassociated from indications for screening for other blood-borne and sexually transmitted infections and from assessments of contraceptive needs.

5.5.3 The age at which to cease screening

Here again, there have been no controlled clinical trials to determine the ideal age to cease screening, which explains the great variability in recommendations. Prior participation in screening and the results of these screening tests are important factors to consider. For example, women with repeated recent normal screening results could stop sooner. In the United States, the medico-legal context is pressuring some organizations such as the American College of Obstetricians and Gynecologists not to prescribe an age for ceasing screening and to take an individual approach.[128] In Europe, invitations may stop at age 60, 64 or 69, depending upon the country.

The choice of test also influences this parameter. The negative predictive value is so high with the use of the HPV detection test or the two tests run concomitantly (cytology and HPV detection tests), i.e. close to 100%, that screening could probably be ceased earlier were this strategy chosen.

It is important to note that the epidemiology of the HPV infection can vary from one area to another and it may be relevant to adjust this parameter based on local epidemiological data. A number of countries observe a second peak in the prevalence of infections caused by HPV around the ages of 45 to 50.[129] Whether this apparent rise in infections will translate into a rise in precursors several years later is unknown at present.

Finally, even if a second peak in the incidence of cervical cancer is observed among older women (see Figure 4, page 9), we do not know to what extent these women had already had screening tests in the past. It is thus not clear that continuing screening among women over the age of 70 provides any advantage when their prior tests were normal. Attention should probably be paid to women never having had a previous test. In addition, with the risk of comorbidity going hand-in-hand with age and the generally late benefits of early cancer detection, balancing the advantages with the disadvantages becomes particularly delicate among older women.

In the absence of clearer empirical data, the group recommends that, for the time being, screening cease to be offered at the age of 69 to women having had recent negative screening test results**,** but that vigilance and individual approaches continue for women who have never had a test or who have not been tested in the last 10 years.

5.5.4 The screening interval

The optimal screening interval is the one that will maximize a reduction in cervical cancer incidence and mortality at costs and disadvantages that are acceptable for both women and the health care system. The optimal interval will also vary based on the screening test chosen. Since the Pap test is the test currently in use, we will begin our discussion of the screening interval by focusing on data surrounding cytological screening.

The current recommended interval for cytology screening varies from one to five years depending upon the policy and the jurisdiction, which clearly demonstrates the difficulty in establishing an absolute standard for this parameter. In 1986, a working group of the International Agency for Cancer (IARC)[130] analyzed data from eight countries and concluded that the benefits for women were almost as high when screening frequency was two or three years as when it was one year, but that the decision had an impact on resources required (see Table 13). This conclusion therefore led a number of authorities to recommend a three-year interval to maximize efficiency. However, few women under the age of 30 were included in this analysis.

Table 13 Reduction in the cumulative incidence of cervical cancer by interval and the number of tests required per woman aged 35 to 64, according to the IARC (1986)

Interval between tests	% reduction in cumulative incidence	Number of tests required
1 year	93.5	30
2 years	92.5	15
3 years	90.8	10
5 years	83.6	6
10 years	64.1	3

Since this data was published, a number of researchers have tried to determine the optimal interval by evaluating the risk of invasive cancer or abnormalities based on different strategies, such as cohort studies,[131-135] case-control studies[136,137] or simulation models.[131,138]

Although methods vary from one study to another in terms of several other factors – such as subject selection, different impact targets (precursors, squamous cell cancer only or all types), an analysis separated by age group or according to the number of prior negative tests – the relative risk of developing an invasive cervical cancer or severe precursors increases, in general, as a function of the time since the last negative screening. However, there is no consensus regarding the difference between intervals of two and three years.

In the study by Miller et al. (2003), the relative risks of cervical cancer at screening intervals of two years (adjusted OR: 2.06 (CI 95% 1.30-3.26)) or three years (adjusted OR: 2.24 (CI 95% 1.28-3.92)) are two times higher than with a one-year interval, with no significant difference when two- and three-year intervals are compared. However, Schindeler et al. (2008) observed that the risks of high-grade cytologic (OR 1.47 CI 95% 1.31-1.66) or histologic (OR 1.64 CI 95% 1.43-1.89) abnormalities were significantly higher when the screening interval was three years, compared to two years. This study was conducted specifically to re-examine the screening policy in place in the Australian program; after the study, the two-year interval was maintained.

Some of these studies also showed that the risk could vary by age.[131,135,137,139] In general, the negative impact of extending the interval tends to diminsh with age, a factor that has led screening programs in the United Kingdom and Sweden to adjust the recommended interval according to age (every three years until age 49, every five years thereafter). Finally, two of these studies as well as a Canadian modelling study conducted before that of the IARC[140] have shown the futility of repeating the first test after one year in young women when the results are normal.

The characteristics of a screening test, such as its sensitivity, have a significant impact on determining the interval. A more sensitive test would enable the interval to be extended, since the problem of false negatives would be reduced. Given the previous discussion on liquid-based cytology (LBC), there is currently not enough evidence to recommend a different interval according to the type of cytology used (conventional cytology or LBC). However,

should the HPV detection test be adopted as the screening test for first-line use, the intervals could be extended.

In summary, while there is some consensus against having a one-year interval for cytological screening, the results diverge for two- and three-year intervals in terms of clinical efficacy. At equal efficacy, a three-year screening strategy would obviously be more efficient. However, if the risk of severe abnormalities increases with the interval, cost-effectiveness studies would be helpful in guiding decision making. With such studies being difficult to conduct in the short term in Québec due to a lack of empirical data on cancer precursors, it would be more prudent to begin with a two-year interval and adjust it as needed afterwards.

Since the negative impact of extending the interval on the risk of cancer or precursors appears less pronounced among older women, longer intervals for these women could eventually be foreseen, as is the case in the United Kingdom and Sweden.

There is no evidence to support annual repetition of the initial test if the results are normal, especially among young women where the incidence of cancer is practically nil.

6 SUMMARY AND RECOMMENDATIONS

With the evolution of knowledge on the disease and the development of new technologies, cervical cancer control is currently experiencing a major change of direction. From a strategy primarily based on screening with the Pap test and treating cervical cancer precursors, the introduction of a systematic vaccination of preadolescents and young women and access to high-performance screening methods now allows us to envisage the eradication of this disease. However, integrating the two strategies (screening and vaccination) poses a real challenge in a context in which cervical cancer prevention affects not only health care workers in these two sectors (screening and vaccination), but also those in primary care, clinical gynecology, laboratories, sexually transmitted infections and cancer control. An integrated, multidisciplinary vision of cervical cancer prevention is critical to the success of this fight.

Recommendation 1

Ensure an **interdisciplinary, integrated** (screening and vaccination) **vision** of cervical cancer prevention and assign clear responsibility for governing the actions to be performed.

We have identified a number of potential strategies to optimize screening. Each of these strategies appears interrelated to one or more of the others, and none is a global solution. Throughout the consultations with various groups of professionals regarding the relevance and feasibility of the interventions, they raised the need to put in place a concerted, organized screening approach, as has been previously proposed by various authorities time and time again, rather than relying on sporadic isolated efforts.

Recommendation 2

Establish an **organized, concerted cervical cancer screening approach**, based on the recognized key principles for such programs.

Cervical cancer control is currently in a crucial period of its evolution. Empirical data is required to define or modify the screening parameters, and to assess the impact of the vaccination strategy. However, at the current time, only cases of invasive cancers are recorded in the Québec tumour registry (Fichier des tumeurs) and this indicator is too delayed for short- and medium-term assessment needs. A monitoring system is needed that includes cervical cancer precursors and the distribution of HPV genotypes in cancers, precursors and in the general population. Moreover, a true information system based on population records is required to specifically invite women who have not had a recent screening test to do so. The information system must include screening test results, diagnostic procedures and treatments. Such an integrated system would help reduce losses in follow-up and errors.

Recommendation 3

Set up an **integrated information system** to make it easier to offer screening and to evaluate screening and vaccination results.

In a context of rapid knowledge development and the availability of new technologies, the lack of clear guidelines for screening parameters constitutes an obstacle to encouraging best practices and avoiding over-screening. HPV tests feature interesting characteristics as front-line screening tests. However, solutions must be found to minimize their disadvantages, especially their lower specificity, before their routine use for screening can be recommended. The implementation of such a measure would also have a significant impact on the organization of laboratory services and training needs.

Recommendation 4

Adopt and distribute **guidelines** for screening parameters, while ensuring they are modified as evidence becomes available. The initially proposed parameters are as follows:

- The screening test remains cytology, given that the impact of implementing alternative tests in the Québec context has not been assessed. Since the evidence on efficacy does not definitively favour liquid-based cytology or conventional cytology, each setting can select either of these methods based on specific organizational factors.
- Screening should start at the age of 21, unless exceptional circumstances indicate otherwise (first sexual relations at a very early age, sexual abuse, immunosuppression or HIV infection). Screening tests are to take place every two years when results have been normal. Repeating the test in all other circumstances should follow the adapted ASCCP recommendations in Appendix 1. Screening may be stopped at age 69 in women having had at least one negative test in the past 10 years.

In terms of integrating new technologies, the committee considers it urgent to assess the impact of the introduction of HPV detection as a primary screening method. This evaluation should be undertaken without delay in a controlled context and in specific areas. On the other hand, efficacy evidence and the cost-effectiveness profile justify the use of the HPV test for the triage of ASC-US lesions. These tests should be made available to all women in Québec free of charge as quickly as possible.

Recommendation 5

Make HPV tests for the triage of ASC-US lesions available to all women in Québec. However, triage by repeated cytologies remains an acceptable option among women under the age of 30.

Recommendation 6

Assess the impact of the introduction of HPV detection as a primary screening method through a **pilot project**.

To improve the participation rate of women in screening, in addition to the preceding general measures, four more specific measures are recommended.

Recommendation 7

Establish a **remunerated procedure code** for primary care physicians, consistent with the cervical cancer screening guidelines.

Recommendation 8

At local and regional levels, explore all means to **facilitate access to screening services**, including involving nurses and medical technologists in taking specimens and holding specific screening days.

Recommendation 9

Implement an **invitation-by-letter procedure using a population-based approach** as soon as the information system to identify non-participating women is in place, guidelines are ratified, and the services to take in women with no attending physician are available.

Recommendation 10

Develop a **communications plan** on HPV and cervical cancer prevention directed at the population that addresses in particular, the complementary nature of screening and vaccination.

To improve the quality of services and reduce the risk of incidents throughout the screening and monitoring/follow-up process, the following measures are proposed.

Recommendation 11

Provide **training** on screening and follow-up to all affected health care workers on an ongoing basis, from the perspective of an integrated vision of cervical cancer prevention.

Recommendation 12

Establish **quality assurance measures** for laboratory personnel based on the working group's recommendations (Appendix 2) and ensure their application.

Recommendation 13

Periodically assess epidemiological data on cervical cancer and its precursors in order to adjust interventions.

The proposals included in these recommendations entail significant structural changes. We believe that the implementation of the key recommendations in this report in a limited number of administrative regions (two) would permit an easier transition from opportunistic screening to an organized program. Screening services (Pap test reading) and diagnostic services (colposcopy) are already centralized in the Estrie and Capitale-Nationale regions. It would therefore be relatively easy to enter screening and diagnosis data into an information system,

particularly at the Centre hospitalier universitaire de Sherbrooke (CHUS), which is already computerized.

This type of more “closed” setting also presents obvious advantages for the controlled introduction and evaluation of new screening technologies.

7 CONCLUSION

Cervical cancer is a disease that lends itself well to screening and that still meets all of the WHO's criteria for a systematic screening approach. With close to 300 new cases of cancer annually in Québec, the fight is far from over.

The shortcomings of screening are well known, with a suboptimal participation of women, imperfect screening tests and weaknesses in following up women with abnormal results.

For each of these shortcomings, solutions have been explored and analyzed with a group of partners. Everyone consulted for this opinion believes that it is important to establish a structured, concerted approach to improve the quality and efficacy of screening in Québec, to be more efficient and to take advantage of technological advances that will be difficult to implement in an opportunistic context.

We believe that with the measures proposed to increase participation, it will be possible to reach coverage rates in Québec comparable to those observed elsewhere in Canada. In addition, a brief analysis of the costs of screening with the proposed parameters (found in Appendix 3) shows that substantial savings could be achieved and that these savings would probably be sufficient to cover the funds required to finance the proposed organizational measures. For the tests alone, a difference of more than $5 million has been noted between the current situation and the option of reaching 75% of eligible women every two years. With a three-year interval, the costs of screening would practically be cut in half compared to the current situation.

In terms of the choice of screening test, it does not seem desirable to immediately base screening on new technology, such as HPV detection tests, before having established the ways to increase participation and to measure the impact of our interventions. The scientific watch will continue and the experience acquired in many countries that have integrated this technology will add to our reflection and help us base a future opinion on solid performance data in a populational context. Moreover, testing this technology in a strictly evaluation context (pilot projects in demonstration areas) will enable us to evaluate its performance in our settings.

While the immunization of young women against certain HPV genotypes adds new tools for disease prevention, the effects of immunization on the incidence of cancer will not be observable for a number of years and a certain form of screening will remain essential even for vaccinated individuals. Since the current recommendations are based on available evidence and aims to guide practice in the coming years, it essentially addresses the optimization of screening among non-vaccinated women. Nonetheless, it appears vital that an integrated vision of cervical cancer prevention be adopted now. Determining the best screening strategy for women vaccinated against HPV is a good example to illustrate the necessary complementary nature of the two approaches.

The INSPQ and its partners would be pleased to be associated once again with the work required to implement these measures.

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APPENDIX 1

SUMMARY OF THE KEY ASCCP RECOMMENDATIONS FOR THE CASE MANAGEMENT OF ABNORMAL CYTOLOGIES

SUMMARY OF THE KEY ASCCP RECOMMENDATIONS FOR THE CASE MANAGEMENT OF ABNORMAL CYTOLOGIES

	General recommendation	Other recommendations for specific populations		
Cytology result		Adolescents	Menopausal women	Pregnant women
ASC-US	Triage with HPV test[16]	Repeat cytology after 12 months	Triage with HPV test would be more efficient	Alternative: Colposcopy postponed to 6 weeks post partum
	OR repeat cytology at 6 and 12 months			
	OR immediate colposcopy			
ASC-H	Colposcopy			
LSIL	Colposcopy	Repeat cytology after 12 months	Alternative: Triage with HPV test or repeat cytology	Alternative: Colposcopy postponed to 6 weeks post partum
HSIL	Colposcopy			
AGC	Colposcopy			
AIS or cancer	Colposcopy			

[16] Preferred option if LBC is used.

SUMMARY OF THE KEY ASCCP RECOMMENDATIONS FOR THE CASE MANAGEMENT OF WOMEN WITH HISTOLOGIC LESIONS

Histologic diagnosis	Results from previous cytology	Proposed management procedure
CIN 1	ASC-US, ASC-H, LSIL)	HPV test every 12 months or Cytology every 6 months
CIN 1, satisfactory colposcopy	ACG or HSIL	Diagnostic excision or Colposcopic follow-up every 6 months
CIN 1, unsatisfactory colposcopy	ACG or HSIL	Diagnostic excision
CIN 1, adolescents	All	Cytology every 12 months
CIN 2 or 3	All	Treatment (excision or ablation)
CIN 2, adolescents	All	Colposcopy every 6 months suggested Treatment acceptable
CIN 3, adolescents	All	Treatment sugggested, Colposcopy every 6 months acceptable
AIS	All	Hysterectomy if no wish for fertility If fertility desired, conization acceptable
Cancer	All	Referral to a gynecological-oncologist for appropriate treatment

APPENDIX 2

PERFORMANCE INDICATORS

Internal Performance Indicators

Rates of satisfactory and unsatisfactory specimen adequacy

Requisite indicator: At least annually, **the total number of cases and rates of satisfactory and unsatisfactory specimen adequacy** must be calculated for the laboratory. These figures must also be calculated for each professional (physician, midwife, etc.) who collected specimens and the results must be communicated to the professional annually.

Optional indicator*:* Calculation of the total number of cases and rates of satisfactory and unsatisfactory specimen adequacy may also be documented by cytologist.

The rate for each cytodiagnosis

Requisite indicator: The total number and rates of cases for each cytodiagnosis (i.e. negative (including reactional), ASC-US, LSIL, ASC-H, HSIL, AGC, carcinoma and others) must be calculated for the laboratory.

Optional indicators*:* The total number and rates of cases per cytodiagnosis for each pathologist and each cytologist may be calculated.

Screening sensitivity[1-6]

Requisite indicator: At least annually, an evaluation of the sensitivity of the laboratory's gynecological screening interpretation must be calculated for all the cytologic abnormalities together and for the lesions equivalent to or greater than high-grade squamous intraepithelial lesions (HSIL). A false-negative is considered as the failure to identify a lesion equivalent to or greater than a low-grade squamous intraepithelial lesion (LSIL).

Optional indicators*:* Each laboratory, internally, may also calculate the sensitivity of the screening by using the ASC-US as the threshold. An evaluation of the sensitivity of the gynecological screening interpretation of each cytologist should also be calculated if the cytologic results management system permits it.

Screening methods[1-6]

The following methods are recommended to determine the false-negative rate and thus the sensitivity of a laboratory:

- **Targeted rescreening of cases interpreted as negative from high-risk groups** (i.e. atypical clinical history, abnormal gynecological examination, vaginal bleeding, history of cervical or vaginal cancer, history of ASC-US, atypical glandular cells or exposure to DES).
- Retrospective rescreening of cases interpreted as negative in the three years preceding a cytodiagnosis of HSIL, AIS or carcinoma.
- **Rapid screening,** based on one of the methods suggested:
  - Rapid prescreening of all cases received at the laboratory is the preferred method
  - Rapid rescreening of all cases interpreted as negative and unsatisfactory
  - Use of an automated rescreening device.

Positive predictive values

Requisite indicator: The cytology-histology agreement of the HSIL, adenocarcinomas in situ and infiltrating carcinomas must be documented annually.

Optional indicators*:* The cytology-histology agreement of all abnormal cases must also be calculated. A cytology-virology agreement must also be conducted in all laboratories using the HPV test as triage for atypical squamous cells of undetermined significance (ASC-US). The test must be positive in at least 30% of its ASC-US.[7-10]

Publication of internal performance indicators

All this data must be calculated for the province and made public annually so that each laboratory can compare itself with the provincial average.

External Performance Indicators

Each laboratory must annually evaluate its performance using external indicators. Three suggestions are proposed, and each laboratory is free to choose the one that it prefers:

- The College of American Pathologists' (CAP) program: Educational Interlaboratory Comparison Program in Gynecologic Cytopathology – Education Series (http://www.cap.org/apps/docs/proficiency_testing/pap_pt/2008_pap_pt_program_information.pdf)
- The American Society for Clinical Pathology's (ASCP) program: ASCP GYN Assessment: http://www.ascp.org/LongDescriptions/GYNAssessment.aspx.
- The Ontario Medical Association's Quality Management Program – Laboratory Services: http://www.qmpls.org/eqa/EQA%20Program%20Information%20-%202009.pdf

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Parameters (performance indicators) used in the United Kingdom for their organized screening program

	Internal performance indicators	Frequency of the documentation	Details
1	Unsatisfactory specimen rate and case rates for each diagnosis category for the laboratory.	Annual	This data is calculated for the whole province and published annually in a report card in the form of 10-90th percentiles.
2	False-negative rate (no precise definition) for each cytologist and each laboratory.	Annual	Rapid rescreening of 100% of the negative and unsatisfactory cases is recommended but, rapid prescreening is also an accepted method.
3	Evaluation of the screening sensitivity of each cytologist and the laboratory, for all abnormalities as a whole and for lesions equivalent to or greater than HSIL, by using cytodiagnosis of the pathologist as the “gold standard.”	Quarterly	Using rapid rescreening, the laboratory must have more than 90% sensitivity for all abnormalities as a whole and over 95% for lesions equivalent to or greater than HSIL.
4	Cytology-histology agreement (positive predictive value) of HSIL.	Annual	The positive predictive value for HSIL must be between 65% and 90%.

Parameters used in European countries with an organized screening program or using opportunistic screening

	Internal performance indicators	Frequency of the documentation	Details
1	Unsatisfactory specimen rate and case rates for each diagnosis category, calculated for each cytologist, the laboratory and at the provincial level.	Annual	
2	LSIL, HSIL and unsatisfactory specimen rates for the pathologists.	Annual	
3	False-negative rate (no precise definition)		1) Rapid rescreening of 100% of unsatisfactory and negative cases; rapid prescreening of all cases; or automated rescreening. 2) Targeted rescreening of cases from high-risk groups. 3) Rescreening of negative cases preceding a new diagnosis of HSIL (number of years not defined). 4) Rescreening of negative cases and of LSIL in the 3-5 years preceding a diagnosis of invasive carcinoma.
4	Cytology-histology agreement of all abnormal cases.		The positive predictive value of the HSIL must be documented separately.
5	Cytology-virology agreement (if the HPV test is used as ASC-US triage in the laboratory).		The HPV test must be positive in at least 30% of the ASC-US triage.

	External performance indicators
1	IAC proficiency testing
2	EFCS aptitude test

Canadian recommendations 12-13

	Internal performance indicators	Frequency of the documentation	Details
1 *	Total number of cases and satisfactory and unsatisfactory specimen rates, with or without the transformation zone, calculated for each cytologist, the laboratory and each health care provider.	Annual	
2 *	Total number of cases and case rates for each diagnosis category calculated for each cytologist and each pathologist.	Annual	
3	False-negative rate (corresponding to a lesion equivalent to or greater than a LSIL) calculated for each cytologist and the laboratory.	Annual	1) Rescreening of 10% of the negative cytologies or rapid rescreening of 100% of the negative cases. 2) Rescreening of the negative cytologies from the 3 years preceding a diagnosis of HSIL or AIS. 3) Rescreening of cases from high-risk groups.
4 * ' * *	Cytology-histology agreement for ASC-H, HSIL, AIS and carcinomas (positive predictive value).	Annual	
5	Specimen treatment time (time line from the date the specimen was received until the date the final report was issued).	Annual	

	External performance indicators	At least one, choice	
1	CAP program	Bi-annual (10 slides in total)	Educational Interlaboratory Comparison Program in Gynecologic Cytopathology - Education Series: http://www.cap.org/apps/docs/proficiency_testing/pap_pt/2008_pap_pt_program_information.pdf
2	ASCP program	Three times per year (15 slides in total)	ASCP GYN Assessment: http://www.ascp.org/LongDescriptions/GYNAssessment.aspx
3	Ontario Medical Association's Quality Management Program – Laboratory Services		Quality Management Program: http://www.qmpls.org/eqa/EQA%20Program%20Information%20-%202009.pdf

* Should be assessed by 10-year age group (i.e. 21-30; 31-39; 40-49; 50-59; 60-69) and eventually reported separately for HPV-vaccinated and non-vaccinated women.

** Agreement must be done within the 12 months following an abnormal diagnosis.

A quality assurance program for HPV screening must include quality assurance procedures that are applied before and after the test's implementation.

1) Pre-implementation:
   - Only tests validated and approved by Health Canada may be used for this purpose. In-house tests should be prohibited because tests are available that have been properly evaluated and approved. Appropriate literature must support the use of the tests otherwise studies must be conducted to evaluate their performance.
   - Medical technologists must take a supervised training session regarding the methodology used, preferably at the site where the technique will be performed and by experts hired by the company marketing the test.
   - This training is already offered by the two companies currently offering an HPV screening test.
   - The training is followed by a performance test in which positive and negative specimens supplied by the company are sent to the laboratory that is required to correctly analyze the specimens without assistance. Once the results have been verified, the laboratory will be considered certified to conduct this test and can then order the test reagents from the company (this procedure is already in place for HPV tests).
   - Certified medical technologists can train other technologists in the same laboratory who must pass the above-mentioned performance test supplied by the company.

2) Post-implementation:
   - On a daily basis, conduct the positive and negative controls suggested by the manufacturer for each analysis session.
   - Check the quality of the reagents when a new lot of reagents is used.
   - Annually, verify the documentation on equipment calibration and maintenance.
   - Conduct an annual quality control with specimens selected and analyzed at random. This quality control must be carried out by the Laboratoire de santé publique du Québec and include strong and weak positive reagents as well as negative specimens.
   - Monitor the positivity rate in patients with an ASC-US. This rate should not exceed 60% or be under 35%, otherwise, HPV test procedures must be reviewed and the cytopathology laboratory contacted to ensure the quality of the ASC-US diagnosis.
   - Verify the positivity rate of HPV detection in cases of high-grade disease determined by cytology and/or biopsy. This rate should exceed 90%.
   - Assess the time for resolving problems and delays in issuing results when a technique's positive and negative controls fail.
   - Conduct an annual audit and review of the standard operating procedure, to be done by the head of the laboratory.

APPENDIX 3

COST ANALYSIS

Introduction

While not intending to conduct a detailed cost analysis of all the measures proposed, the objective of this supplement is to provide a summary estimate, on an annual basis, of the cost of the current situation of opportunistic screening and the cost of a more organized screening strategy based on different parameters in terms of the target population and screening intervals, while maintaining conventional cytology as the screening test. Only the costs of screening have been considered at this stage.

Methodology

The premises and hypotheses used in the calculations, as well as their information sources are presented below. The estimates do not take into account the advent of vaccinated cohorts, for whom screening recommendations will likely be modified. All the calculations were made using the 2003 Microsoft Office version of Excel.

Premises/Hypotheses	Information sources
Current situation: Number of annual cytologies in public laboratories in Québec: 1 262 500	MSSS (DOSMT) Laboratory data for 2005-2006
% of total cytologies carried out for screening (vs. for control purposes): 95% = 1 199 395 (as compared to the screening rates estimated in the 2003 CCHS survey for the previous year, which indicated 1 169 747 tests)	According to data from the British Columbia program, over a one-year period: 95% of women had 1 cytology 4.7% of women had 2 cytologies 0.1% of women had 3 cytologies[17] Data from the 2003 CCHS survey for validation
Option proposed: ▪ Target population: Women aged 21-69, who have not had a hysterectomy ▪ 2-year interval ▪ Women < 21 years and 70-74 years: small numbers, e.g.: < 21 years: 20 000 > 70 years: 10 000 Population size and hysterectomy rates (%) N % 15-20 years: 282 338 negligible 21-34 years: 708 514 0.1% 35-44 years: 550 358 1% 45-54 years: 625 471 24% 55-64 years: 494 928 36% 65-69 years: 172 495 44% 70-74 years: 143 317 44%	Institut de la statistique du Québec: target population per age group 2003 CCHS: percentage of women having had a hysterectomy by age group Estimate of test volumes among those < 20 years of age and those > 70 years based on data from the British Columbia program /2)
Targeted participation rate: 75%	Applied for the year, taking into account the overall participation rate obtained in the Canadian survey (2003 CCHS)
Cost of cytology testing: $15 or about $13 for the cytology test and $1.80 for the pathology ($14.80 rounded up)	Verbal communication, Dr. Laurent Delorme (DOSMT) and RAMQ for the pathology rate.
Cost of the medical visit for the sampling: $17. In the absence of data on the distribution of tests done by general practitioners or by obstetricians/gynecologists, the same rate is applied to all.	RAMQ, regular rate, examination conducted by a general practitioner (or half of a full exam or one quarter of a major full exam).

[17] 2007 annual report of the screening program available at http://www.bccancer.bc.ca/NR/rdonlyres/A6E3D1EC-93C4-4B66-A7E8-B025721184B2/29784/2007CCSP_Annual_Report1.pdf.

Results

1. Estimate of the actual cost of screening tests (on an annual basis and excluding follow-up of abnormal cases)

Table 1 Current situation

Number of gynecologic cytology exams (according to MSSS data x 0.95)	Unit cost	Subtotal $	Total $
1 199 395	$15 for the cytology	17 990 925	38 380 640
	$17 for the medical visit	20 389 715	

2. Estimate of the cost (on an annual basis and excluding follow-up of abnormal cases) to move to the proposed option:

- Systematic screening offered to women aged 21-69
- Exclusion of women who have had a hysterectomy
- Anticipated participation rate 75%
- Reduced participation for women under the age of 21 (n = 20 000) and aged 70 and over (n = 10 000)

Table 2 Situation proposed in the opinion

Number of gynecologic cytology exams	Unit cost	Subtotal $	Total $
812 148	$15 for the cytology	12 180 713	25 985 522
	$17 for the medical visit	14 104 808	
Difference with the current situation described in Table 1			
- 387 347	$15 for the cytology	- 5 810 212	-12 395 118
	$17 for the medical visit	- 6 284 907	

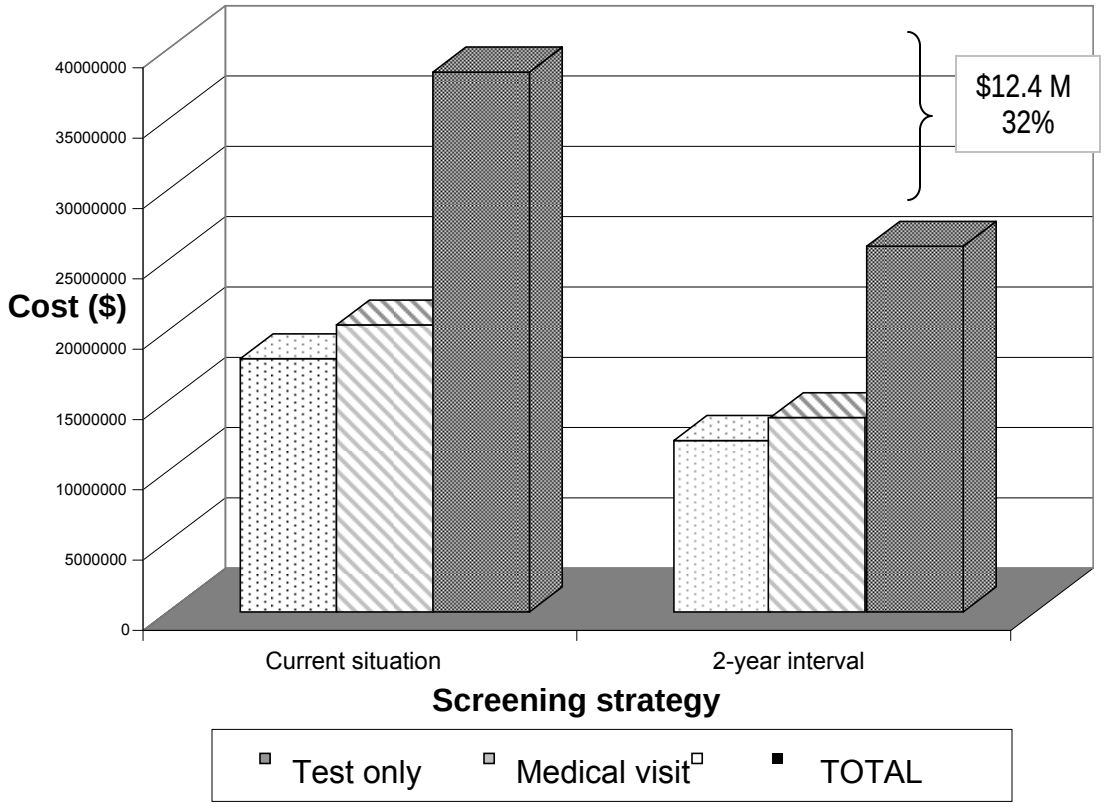
Thus, moving to an organized approach with a two-year test interval would reduced the number of tests by 387 347, while increasing participation to 75% for women in the target group. The overall participation rate in Québec estimated by the survey was 71% in 2003, but this is probably overestimated because it is based on self-reporting.

The cost difference between the two approaches is $12 395 118 per year; if medical visits are excluded and only the tests are considered, the difference is $5 810 212. This is a difference of 32%. We have no idea what percentage of women would go for an annual gynecological exam if the Pap test were no longer recommended at this frequency, and consequently, what would be the real savings in terms of medical visits.

A difference of this scope would likely be sufficient to cover the initial costs associated with organizing the program (information system, coordination, etc) and boosting participation to 75% would increase the impact potential on reducing the incidence of cancer.

The following chart illustrates the differences between the two strategies expressed in percentages.

Figure 1: Variations in costs between the current situation (opportunistic) and the proposed situation with a 2-year interval



3. Sensitivity analyses

A sensitivity analysis was performed by changing the participation rate to 80% and extending the interval between tests (every three years rather than every two years). In fact, even if a two-year screening policy were adopted, it is likely that a certain percentage of women would have their exam between two and three years, due to delays in obtaining appointments with their physicians. With an information system in place to re-invite women who have had normal test results, a three-year interval could be envisaged later on.

The following table summarizes the estimated costs of these strategies, compared to the two preceding situations.

Table 3 Sensitivity analysis

Strategy	Cost of the test ($)	Cost of the medical visits($)	Total cost ($)
1 Opportunistic screening (current) 1- to 3-year interval Participation ≤ 70%	17 990 925	20 389 715	38 380 640
Options assessed			
2 Organized screening, ages 21-69 2-year interval Participation 75%	12 180 713	14 104 808	25 985 522
Difference between 2 and 1: 32%	- 5 810 212	- 6 284 907	- 12 395 118
3 Organized screening, ages 21-69 2-year interval Participation 80%	12 962 761	14 691 129	27 653 890
Difference between 3 and 1: 28%	- 5 028 164	- 5 698 586	- 10 726 750
4 Organized screening, ages 21-69 3-year interval Participation 80%	8 791 841	9 964 086	18 755 927
Difference between 4 and 1: 51%	- 9 199 084	- 10 425 629	- 19 624 713

Discussion

This data confirms that an organized approach with screening standards that are respected (to limit over-screening) would be much more efficient than the current approach, while having a greater impact on health, because it would allow more women to be reached. The potential savings would be substantial and would generously cover the costs of program implementation.

The calculations are limited to the cost of the screening exams. The estimates above could vary slightly if follow-up of abnormal cases were included. In fact, with less frequent screening, the rate of detecting abnormalities could increase and generate more complementary exams. On the other hand, as the rate of ASC-US- and LSIL-type abnormalities is higher among young women than among older women, the fact of delaying screening to the age of 21 for the majority of women could lower the number of colposcopies required overall, without having a negative impact on health, since the majority of these lesions tend to disappear spontaneously without treatment. In the study by Insinga et al. (2004), mentioned in section 4.4 of the opinion on optimizing screening, the costs of initial screening represented a much more significant portion of the overall economic burden of cervical cancer control (63%) than the cost of following up abnormal cases, which only represented 17%, the remainder being divided between treatment costs and costs associated with following up false positives.

The impact of adding the HPV test for the triage of ASC-US lesions has been the subject of a number of economic analyses, including a study conducted by the Canadian Agency for Drugs and Technologies in Health (Krahn et al., 2008) and documented in section 5.3.2.2. of the main report. The potential impact of changing the screening test for another one was also discussed in that section.

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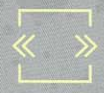

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