Guidelines on Cervical Cancer Screening in Québec

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et de la santé au travail

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FOREWORD

Cervical cancer screening through cytological smear analysis, or the Pap test, has been conducted in Québec and elsewhere in the world for more than 40 years. Since this measure was introduced, it is estimated that the incidence of cervical cancer and mortality related to it have declined by over 70% in countries with high screening participation rates. In Canada, the most recent recommendations on screening from the Canadian Task Force on Preventive Health Care (CTFPHC) date back to 1994. The development and dissemination of new guidelines were one of the recommendations contained in the report on optimizing cervical cancer screening prepared by the Institut national de santé publique du Québec (INSPQ) in 2009.(1) In 2010, with the agreement of the Collège des médecins du Québec, the Ministère de la Santé et des Services sociaux (MSSS) gave the INSPQ the mandate to draft these guidelines.

Recent discoveries pertaining to human papillomavirus (HPV), now recognized as the cause of cervical cancer, have led to the development of new molecular techniques for detecting infections from this virus. A number of clinical studies have shown that oncogenic HPV detection tests are more sensitive than the cytological test for screening. Consequently, several settings are currently studying the possibility of using this type of test as the initial approach and restricting cytological analysis to the triage of positive cases only. However, since the specificity of HPV detection tests is relatively lower, studies are underway to establish effective and efficient triage strategies.

Given the uncertainties surrounding the follow-up algorithms associated with this strategy, and the considerable repercussions of such a change not only on laboratories but also on all screening parameters (such as the interval between tests), the *Recommendations on Optimizing Cervical Cancer Screening in Québec* proposed testing this new screening approach in an organized manner so it can be evaluated before being applied on a large scale. That is why the guidelines presented herein address screening through cytological testing, the approach currently used in Québec.

SUMMARY OF RECOMMENDATIONS ON CERVICAL CANCER SCREENING BY CYTOLOGICAL TESTING[1]

Population targeted by the screening

All women who are sexually active or were in the past.

Sexual activities include all types of genital contact, with or without vaginal penetration, with male or female partners.

At what age should screening begin?

The recommended age to begin screening is 21.

However, screening can be delayed for women who have not yet had sexual activity at this age. Exceptionally and based on the clinical context, screening may begin earlier, for example among immunodepressed young women.

How often should one have a screening test?

The recommended interval between screening tests is two to three years.

At what age should screening be stopped?

Among women who have had screening tests regularly, screening may cease at the age of 65 if the results of the last two tests conducted in the previous 10 years were negative.

Any other situation should be addressed in an individualized manner based on the timing of the last test, the results of the last test, and the woman's specific situation. *It is not necessary to continue cervical cancer screening in women who have had a complete hysterectomy for a benign condition.*

What should be done in the case of abnormal screening test results?

If the result is equivocal (ASC-US result):

It is not recommended that all women with equivocal (ASC-US) results be referred to colposcopy, but that a triage strategy, varying according to age, be applied:

- **Before the age of 30**: Repeat the cytological test 6 and 12 months later. Refer to colposcopy if one or the other of these cytological tests show a result of ASC-US or worse.
- **From the age of 30**: Perform an oncogenic HPV detection test[2] and refer to colposcopy if the result is positive. When the HPV test result is negative, repeat the cytological test after 12 months.

In the case of any other abnormal results, the woman must be referred to colposcopy.

[1] Whether the test is performed by traditional smear (on a slide) or liquid-based.

[2] A generic test approved by Health Canada must be used. While waiting for the test to be available in the public system, the same approach used for women under the age of 30 can be applied.

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LIST OF ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AGC	Atypical glandular cells
AIS	Adenocarcinoma *in situ*
ASC-US	Atypical squamous cells of undetermined significance
ASC-H	Atypical squamous cells, cannot exclude a high grade lesion
CDC	Centers for Disease Control and Prevention
CEPO	Comité de l'évolution des pratiques en oncologie
CIN	Cervical intraepithelial neoplasia
CTFPHC	Canadian Task Force on Preventive Health Care
CPG	Clinical practice guidelines
HC2	Hybrid Capture 2
HPV	Human papillomavirus
HSIL	High grade squamous intraepithelial lesion
INSPQ	Institut national de santé publique du Québec (Québec public health institute)
LSIL	Low grade squamous intraepithelial lesion
MSSS	Ministère de la Santé et des Services sociaux (Québec's department of health and social services)

1 INTRODUCTION

Cervical cancer is a major health issue, ranking as the second most frequent cancer among women throughout the world.(2) Fortunately, its incidence now ranks 13th among Canadian women, thanks to sustained screening efforts. Nonetheless, it remains the second most frequent cancer among Canadian women 25 to 44 years of age.(3) In Québec, it is estimated that 270 women were diagnosed with cervical cancer in 2010 and that 65 died of it.(4)

The effectiveness of cervical cancer screening is undeniable, and is based on the fact that screening enables cancer precursors to be detected and treated. However, since the discovery of the causal link between HPV and this cancer, our understanding of the natural evolution of the disease has progressed. Data show that while infections caused by HPVs are very frequent during the first years following the beginning of sexual activity, the majority of these infections are transient and disappear spontaneously within 12 to 18 months. Among the 40 or so HPVs that can infect the anogenital area, about 15 are potentially oncogenic and are identified as “high risk.” Persistent infection by one of these types of HPV increases the risk of cervical cancer, but usually several years, even decades, go by between the persistent infection and the emergence of an invasive cancer. This long time frame allows the detection of cellular abnormalities through the analysis of cytological smears from the cervix. Effective treatments can then halt the progression of the carcinogenic process. Thus, cervical cancer screening not only enables cancers to be detected at an earlier stage and mortality to be reduced, it also reduces the incidence of this cancer.

While it appears theoretically possible to prevent nearly all cervical cancers through screening, a number of reasons explain why screening programs do not succeed in doing so. Among the main reasons of note are the low participation of certain groups of women in screening, the limited sensitivity of the cytological test for detecting all cervical cancer precursors, and inadequate follow up of women who have had abnormal results.(5) It has also been observed that opportunistic screening approaches, currently used in Québec, are not as efficient because they are less apt to reach all women and often result in overscreening women with the least risk. Over-treating lesions likely to disappear spontaneously can result in significant morbidity.

The goal of these guidelines is to help clinicians carry out preventive clinical practices by proposing screening parameters that are backed by the best scientific data available. The analysis of these data, and the recommendations that stem for the analyses have been validated and endorsed by the Québec scientific community, as representing the best possible balance between the advantages and disadvantages of screening. Nonetheless, these guidelines should not replace one’s professional judgment in specific circumstances. Furthermore, since screening refers to activities carried out on asymptomatic individuals, simple recourse to a screening test may be insufficient when a woman has a visible lesion or worrisome symptoms. These guidelines will also be used to develop communication tools to inform the public and health professionals about cervical cancer screening.

2 METHODOLOGY

The method used to develop these guidelines was drawn from a framework for developing and assessing the quality of clinical practice guidelines (CPG) prepared by the AGREE Research Trust,(6) a consortium resulting from international collaboration. The AGREE II instrument is a generic tool addressing 23 elements divided into six domains: scope and purpose, stakeholder involvement, rigour of CPG development, clarity and presentation, applicability, and editorial independence.[3]

The procedure used to meet the various quality criteria proposed by this instrument resembles the one proposed in 2009 by the Comité de l'évolution des pratiques en oncologie (CEPO), distributed in Québec by the Direction de la lutte contre le cancer.[4] A special scientific committee was formed to draft the practice guidelines. The committee, coordinated by the Institut national de santé publique du Québec, was composed of professionals from different disciplines involved in screening (gynecology-obstetrics, family medicine, nursing sciences, medical technology, anatomical pathology, gynecological oncology, microbiology, and public health). Each member completed a form to declare his or her conflicts of interest (see Appendix 1), and no relationship with a company was deemed sufficiently significant to exclude members from the decision-making process.

Particular attention was paid to the formulation of the key questions, since the work was not for the purpose of demonstrating the relevance or effectiveness of cervical cancer screening, but to specify the parameters and methods to be applied by clinicians. These questions focused on the age at which screening should begin, the age at which screening should stop, the interval between tests, the best strategy for the triage of equivocal results, and a certain number of secondary elements.

A literature review had been conducted in 2007 in preparation for the *Recommendations on Optimizing Cervical Cancer Screening in Québec*.(1) The project's two editors updated this literature review to compile evidence supporting the merit of the options retained for each parameter. No restrictions on the type of study were applied during the research to maximize the chances of finding information useful for justifying the choice of parameters. The list of specific questions and the research strategy are presented in Appendix 2.

The search for publications in databases was completed by examining the bibliographical references of retrieved articles deemed the most relevant, a reverse search of new studies citing these studies, as well as an examination of various sources of grey literature and information available on the Web sites of cervical cancer screening programs and health authorities producing guidelines in Canada or abroad.

Given the abundance of documentation identified, particular attention was given to articles published in the last three years, but no restrictions were placed on language or time in the case of very specific questions.

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[3] The instrument is available online at: http://www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf.

[4] The document is available at: http://www.msss.gouv.qc.ca/sujets/prob_sante/cancer/download.php?f=d3e7a25c2934c0d51f66241aeaec49cb.

In addition to articles addressing the parameters guiding the clinical application of screening, a number of other recent studies shedding significant light on the natural progression of the disease as well as data on the incidence of cervical cancer obtained from the people in charge of the Québec Tumour File were also consulted to assess the risk of disease. Updating the scientific data continued until the end of March 2011.

Screening for cervical cancer using a cytological test differs from screening for other cancers in that its current practice has not been based on the results of randomized clinical trials, and that its screening parameters were initially defined on an empirical basis. With advances in knowledge on the natural progression of the disease, and given the conclusions of numerous studies on screening, a number of health authorities recently revised their standards regarding screening, or are about to do so.[5] These sources were also consulted. Although a certain convergence in the approaches of these different bodies has been observed in recent years, there are still significant discrepancies between the practice in North America and that of organized European screening programs. These differences are likely related to the organization of services or the practice's legal framework.

Since the information sources were numerous and of a diverse nature, it was not possible within a reasonable timeline to attribute an evidence level to each of the studies or to prepare a structured summary of all the studies on which the recommendations would be based. Furthermore, since a number of uncertainties remain regarding the impact of the various options, and there is still little Québec data on the advantages and risks of these options, the application of a scale to qualify the strength of the recommendations was replaced by a deliberative process within the scientific committee on the various options, taking into account both the best scientific evidence and the contextual factors. The final positions taken were the result of consensus.

Lastly, the document with the proposals was submitted for consultation to the various professional orders concerned as well as to a number of professional organizations and the Québec Division of the Canadian Cancer Society. The guidelines proposed should thus meet the concerns of all stakeholders.

[5] In 2009, the Canadian Task Force on Preventive Health Care was reactivated and undertook the development of new guidelines on cervical cancer screening.

3 SCREENING PARAMETERS

This section addresses the various screening parameters, such as the choice of technology, the age at which screening should start and stop, as well as the interval between tests. Providing guidance is essential not only to maximize screening efficiency and effectiveness, but also to reduce the negative aspects and risks for women.

As previously mentioned, initially cervical cancer screening parameters were defined on an empirical basis. The numerous clinical and epidemiological studies carried out since the development of oncogenic HPV detection tests (or HPV tests, to simplify) have helped us better understand the natural progression of the disease and enabled these initial parameters to be adjusted. Data from countries that have introduced organized screening programs with information systems to analyze their results provide another source of valuable information to assess the advantages and risks associated with the different strategies.

3.1 THE CHOICE OF TECHNOLOGY FOR THE CYTOLOGICAL TEST

The cytological smear can involve the conventional (specimen spread on a slide)[6] or the liquid-based method. The two techniques have similar performances in terms of detecting high-grade lesions.(7) Liquid-based cytology has the advantage of allowing a reflex HPV test to be conducted using the residual liquid in the case of an ASC-US result, but such results do not occur sufficiently frequently per se (≤ 5% of results) to justify its use among all women. Liquid-based cytology may also provide certain advantages in terms of the organization of laboratories, but it is more costly, and an exhaustive analysis of the cost/benefit relationship of this method was beyond the competence and mandate of the working group that drafted these guidelines.

Cytological test results are expressed according to Bethesda terminology version 2001,(8) presented in Appendix 3.

When a biopsy is performed, abnormal results are generally communicated using the following terms: grade 1 or low-grade intraepithelial neoplasia (CIN1), grade 2 or moderate intraepithelial neoplasia (CIN2), grade 3 or severe intraepithelial neoplasia (CIN3), adeno-carcinoma in situ (AIS), or invasive carcinoma.[7]

3.2 AGE TO BEGIN SCREENING

Until recently, the tendency in North America was to begin screening at the age of 18 or at the start of sexual activity. It is now acknowledged that this practice is not only futile, since cervical cancer is practically non-existent before the age of 20 and indeed very rare before the age of 25, but also beginning screening too early can cause disadvantages among young

[6] People less familiar with the sampling and transportation techniques may wish to consult the AQESSS Web site: http://msi.aqesss.qc.ca/methodes/afficher.aspx?id=117&kw=.

[7] In certain studies, pathology results are expressed using different terminology, resembling Bethesda terminology, i.e. low-grade lesions (equivalent to CIN1) or high-grade lesions (grouping CIN2 and CIN3 together).

women. In fact, genital infections caused by HPVs are frequent in the initial years following the start of sexual activity, and the risk of having cytological abnormalities is quite high. However, these lesions are most often low-grade lesions (LSIL) or equivocal results (ASC-US). The majority (≥ 90%) of these lesions disappear spontaneously in less than 24 months. Thus, any subsequent intervention (control exam, colposcopy, biopsy, and at times treatment) has nothing but disadvantages for the vast majority of women involved. Studies have even shown that certain treatments have negative obstetrical consequences, such as an increase in premature deliveries and a higher risk of neonatal mortality.(9) Only a small minority of women will benefit from these interventions aimed at slowing the progression of disease because progression typically occurs over a period of 10 years or more.(10)

To determine the optimal time to begin screening, the following factors were taken into consideration:

- the age of first sexual activity among young women in Québec;
- the risk of contracting an oncogenic HPV infection according to the time since the start of sexual activity;
- the risk of developing cervical cancer after having contracted an oncogenic HPV infection and the risk of developing cervical cancer after having been diagnosed with a severe precursor (CIN3), in function of time;
- the risk of cancer according to age, based on Québec cervical cancer incidence data by age;
- the recommendations of other health authorities in North America and elsewhere in the world.

Recent data from the 2008 Québec Population Health Survey (QPHS 2008) showed that 52% of young people aged 15 to 17 had already had sexual activity.(11) Among girls this age, 51% had been sexually active in the past 12 months,[8] but the survey did not determine the proportion of young girls who had sexual activity at a younger age. Although it is recognized that the prevalence of HPV infections is highest among women under the age of 25(12,13) and that the cumulative risk of contracting such an infection throughout one's lifetime is very high (70% to 80% or higher), not all women will be infected during the first year following the start of sexual activity. HPV infections identified as "low risk" also occur. In a prospective study of female students from the Montréal region (median age of 21 years), the cumulative risk of contracting an infection from an oncogenic type of HPV was 12.7% after one year [95% CI 9.6%-15.8%] and 29% after two years [95% CI 24.3%-33.4%].(14)

One of the best sources for assessing the risk of cancer or severe cervical lesions (CIN3+) following an HPV infection is prospective studies that were designed to compare the performance of cytology and HPV testing as screening tests. Further analysis of such studies has focused on the risk of developing disease according to initial screening test results. The combination of results from seven European studies conducted in six countries and including 24 295 women indicate that the cumulative risk of CIN3+ lesions after six years among

[8] Source: Linda Cazale, Institut de la statistique du Québec, personal communication, December 14, 2010.

women who had negative results on an HPV test (by the Hybrid Capture [HC2] or the polymerase chain reaction [PCR] method) is 0.27% [95% CI 0.12%-0.5%], whereas it is 0.97% [0.53%-1.3%] after negative results on a cytological test.(15) Cancer cases were not presented separately. If these results are transposed to young women who are beginning sexual activity, the risk of severe cervical lesions (CIN3+) following an oncogenic HPV infection would therefore be very low (about 1 per 400) during the first six years.

The time period between the acquisition of an HPV infection and the appearance of cervical cancer is long but difficult to measure accurately because severe cervical lesions are usually treated. Indirect sources must thus be used to estimate it. In a New Zealand study of 143 women with CIN3 type lesions, who it was later realized had not been treated according to the usual care standards, the cumulative risk of cervical cancer or cancer of the vaginal vault was 13% after five years, 20% after 10 years, 26.1% after 20 years, and 31.3% after 30 years.(16) This data confirms the slow progression of severe pre-neoplastic lesions and the fact that they can be transient. A British study estimated that the disease progression from a type CIN3 lesion to invasive cancer among young women aged 20 to 24 would not exceed 1% per year.(17) This rate is similar to that obtained in an earlier meta-analysis of high-grade cytological lesions (HSIL), i.e. 1.4% in 24 months.(18)

Given that the median age when sexual activity starts is between 15 and 17, that the risk of contracting an HPV infection is high during subsequent years (but not necessarily over the course of the first two years), and the very low probability of a rapid progression to a cervical cancer precursor (CIN3) or cancer before at least five or six years, it seems reasonable to delay the age at which screening should begin. In North America, most health authorities have revised their screening standards, now recommending starting screening at the age of 21, whereas in Europe, the recommendations vary from ages 21 to 30.

Members of the working group consider 21 to be a reasonable age for beginning screening among women, generally speaking. Nonetheless, screening could be delayed a few years among women who have not yet had sexual activity by the age of 21. Conversely, it could be advanced a few years in certain circumstances, such as when the initial sexual activity occurs at a very early age or in the case of immunosuppression due to an HIV infection, an organ transplant, or certain chronic diseases (see the section on specific populations). The presence of genital warts (condyloma), however, does not in and of itself justify earlier screening, because genital warts are related to different types of HPVs (identified as low-risk) than cancer-causing ones.

The estimated low risk of cervical cancer among young women is corroborated by data on its incidence. In Québec, according to Tumour File data from the years 2001 to 2005, only 1% of cervical cancers appeared among women aged 20 to 24, and 4% among those 25 to 29, which corresponds to 3 and 12 cases per year respectively. During this period, there were no cases reported under the age of 20. A review of data from previous years shows that it is extremely rare to observe cases among women under 20.

In conclusion, the working group recommends that cervical cancer screening should start at age 21, generally speaking.

3.3 AGE TO STOP SCREENING

The following recommendation for the age to stop screening applies to women who regularly undergo screening tests. Any other situation should be addressed on an individual basis according to the time that has elapsed since the last test or the results of the most recent tests. A woman's life expectancy could be another factor to consider when offering the service to elderly women.

Establishing the optimal age to stop screening faces the same challenges as determining the age to begin it: a lack of experimental studies, randomized or not, that have specifically examined this issue, the setting of earlier standards on an empirical basis, and the lack of Québec data to assess the risk of cervical cancer precursors by age. Furthermore, most studies have examined only the impact of variation in age on the incidence of high-grade lesions (CIN2 or CIN3), a less accurate target than the incidence of cancer since some of these lesions can be reversible or remain at this stage.

A review of Québec data on the incidence of cervical cancer in the years 2001-2005 shows that nearly half of the cancers affected women aged 50 and over: 18% among those 50 to 59, 12% among those 60 to 69, and 19% among women 70 and over. Since the progression of cervical cancer can occur over several decades, the risk of having cervical cancer persists to an advanced age, even after menopause and after sexual activity has stopped. However, we know that over half of cervical cancers develop among women who have never had screening tests or for whom the time period since the last test has exceeded the recommended norm.(5) It is likely that older women are overrepresented in this category. In fact, according to statistics from the 2005 Canadian Community Health Survey, the proportion of Québec women who had a Pap test over the course of the three previous years dropped from 67.2% [99% CI 64.5%-69.9%] among women aged 45 to 64 to 49.3% [99% CI 41.9%-56.8%] among women 65 to 69.[9]

Given the lack of high-quality data, two other key elements (in addition to the risk of severe precursors progressing, as discussed in the previous section) were researched to assess at what age a woman who undergoes tests on a regular basis could safely stop being tested, i.e. the risk of having a persistent oncogenic HPV infection and the performance of screening tests after a number of negative results.

A recent review of analyses of the prevalence of infections from all types of HPVs, covering over a million women throughout the world with normal cytology results, shows that the prevalence of these infections is at its maximum among women under the age of 25 with an adjusted rate of 24% [95% CI 23.5% to 24.5%], and then declines steadily to reach a rate of 4.2% [95% CI 4.2% to 4.3%] among women 45 to 54 years of age.(13) Although the number of older subjects included is quite small, in some countries, a second peak in the prevalence of HPV infections was observed among women over 55 (lower than that among women 18 to 25 years of age, however). A number of hypotheses have been proposed to explain this phenomenon: reactivation of a latent infection following hormonal changes caused by menopause, changes in the sexual habits of women of this age (or those of their partners), or

[9] Source: Infocentre de santé publique, ESCC Cycle 3.1-2005 (data not adjusted for hysterectomy).

a simple cohort effect. In Québec, the only prevalence data available by age including older women comes from the Canadian Cervical Cancer Screening Trial (CCCaST).(19) Prevalence was measured by the HC2 test, which covers 13 oncogenic HPVs. No second peak was noted in Newfoundland or in the Montréal region. The following table presents the data.

Table 1 Proportion of women in the CCCaST study with positive HPV test results by age and region

Age group	Montréal region		Province of Newfoundland	
	N	% HPV test positive	N	% HPV test positive
30-39	1411	4.3	2295	7
40-49	1467	4.5	1932	4
50-59	987	2.9	992	2.5
60-69	339	2.9	244	1.2

In Canada, most provinces and territories advise stopping screening at the age of 69, after two or three negative results over the course of the 10 previous years, but this recommendation has not really been substantiated by evidence.

The low yield from screening among older women with negative results from earlier tests is a well-known phenomenon, but most of the studies reviewed have not enabled us to identify the ideal age to stop screening. In fact, these studies often covered women younger (50 to 60 years of age, or 50 and over without specifying an exact age) than the age usually set in Canada for stopping screening (65-70 years).

The European Union recommends stopping screening at age 60 or 64 (within organized programs, on the assumption that the result of the last test was negative). Some countries extend the interval between tests among older women (every three years between the ages of 25 and 49, then every five years to the age of 64 in the United Kingdom) because they have estimated that the yield is low after a number of negative results. After an exhaustive review of the literature, France recently adopted the standard of 65 as the age at which to stop screening. Data from the CCCaST study also indicate that the risk is quite low after the age of 50, since only 2.9% of women had an oncogenic HPV infection.

In light of the data analyzed, the working group's proposal for women who have had screening tests regularly is to offer to stop screening at the age of 65 if the results of the last two tests performed in the previous 10 years are negative, after having explained the potential benefits and risks. Any other situation must be addressed on an individual basis taking into account the timing of the last test, the results of the last test, and the woman's specific situation, such as the fact of having a new sexual partner in recent years.

3.4 INTERVAL BETWEEN SCREENING TESTS

Performing the cytological test annually has been the standard in North America for a long time. Current knowledge on the natural progression of the disease no longer supports this practice. Not only does the practice add to the costs of screening programs, but it also provides few advantages in terms of detecting additional cases of cancer. Furthermore, it can have an impact on the proportion of women referred for a diagnostic investigation of transient lesions likely to disappear spontaneously, thus increasing the disadvantages for women.

In the absence of randomized clinical trials to determine the optimal interval between tests, the cost/effectiveness ratio of various strategies has often been evaluated through mathematical modeling. However, since the cost of a particular strategy also depends on the range of the population targeted, a variety of strategies based on intervals of two, three, four, or five years can have an acceptable cost/effectiveness ratio, depending on the setting.

At the moment, with the exception of Australia, which is questioning the cost/effectiveness of its current policy of screening every two years (20), and a number of Asian countries, most organized screening programs have adopted a policy of screening every three years (France, Italy, Denmark, Norway), every five years (Finland, the Netherlands), or at a progressive interval of three to five years according to age group (Sweden, United Kingdom). In the United States, where screening is done in an opportunistic manner, the standard regarding the interval between tests proposed in 2009 by the American College of Obstetricians and Gynecologists (ACOG) was two years between the ages of 21 and 29, regardless of the type of cytological test (conventional or liquid-based) used, and then every three years after three consecutive negative results. In Canada, the standards vary from one to three years according to the province or territory, but a number of them are under review.

While a trend to adopt an interval of three years seems to prevail in settings that have established organized screening approaches with invitation and reminder mechanisms, such mechanisms are not yet available in Québec. Furthermore, the cytological test's sensitivity was only 55% in the Canadian centres that took part in the CCCaST study. On the basis of the data available, the working group recommends that screening tests be spaced two to three years apart.

In the absence of evidence supporting the annual repetition of tests in the initial period of screening and given the low risk of cancer before the age of 25, it does not appear necessary to repeat the first screening test one year later, unless the quality of the specimen is of insufficient quality to provide a result.

4 FOLLOW-UP OF WOMEN WITH ABNORMAL SCREENING TEST RESULTS

Appropriately following up every woman with abnormal results is part of a screening strategy. A colposcopic evaluation with a biopsy of the cervix and/or the endocervix remains the preferred approach for most cytological lesions. However, the working group focused on two situations because recommendations for their follow-up have evolved over recent years and they are more likely to vary according to the setting: low-grade cytological lesions (LSILs) and equivocal results (ASC-US). In all other cases of abnormal cytological results (AGC, ASC-H, HSIL, AIS, cancer), women must be referred for a colposcopic evaluation at the time the result becomes available.

4.1 FOLLOWING UP EQUIVOCAL RESULTS

ASC-US cytological results represent an equivocal category, most often of a benign nature, but occasionally associated with high-grade lesions (6-12%) or even cancers (0.1-0.2%).(21)

Three strategies have been proposed for following up ASC-US results from a cytological test: immediate colposcopy, repeating the cytological test at 6 and 12 months with referral to colposcopy if one of the results is again positive, or triage through an HPV test (detecting the presence of oncogenic HPV DNA), referring only women with positive results to colposcopy.(22)

Because the best case management strategy is the one that maximizes the detection of high-grade lesions while minimizing the number of women who have to undergo more invasive exams (because the risk of severe lesions remains low), an immediate colposcopy is not an appealing option since it requires many invasive exams.

The ALTS study (*ASCUS and LSIL Triage Study*), a randomized trial comparing the three strategies led by a team from the National Cancer Institute and involving 3488 women in the United States, was one of the first to show that a single HPV test performed when an ASC-US result is obtained is an effective option for detecting high-grade lesions.(23)

The effectiveness of ASC-US results triage using HPV testing is now the subject of consensus in the scientific community given that this strategy enables a higher number of high-grade precursors to be detected than the strategy of repeating cytological tests, and it results in a lower rate of referrals of women to colposcopy. This measure was one of the recommendations of a pan-Canadian forum on cervical cancer prevention in 2003, at least in the case of women aged 30 and over.(24) The most recent systematic review on the subject, which included 20 studies, concluded that the sensitivity of ASC-US cytological results triage by HPV testing was 93% and its specificity 63% for detecting high-grade lesions. On average, the sensitivity of the HPV test was 14% above that of a cytology test repetition strategy.(25) Moreover, this strategy alleviates problems of compliance associated with multiple visits.

However, the fact that cancers and type CIN3 lesions are rarer among young women and that HPV infections are more frequent in this age group raises the question of the relevance of conducting ASC-US triage through HPV testing regardless of the woman's age.

A closer examination of the ALTS study results indicates that among women aged 23 to 28, the strategies based on cytological test repetition or HPV testing result in a similar frequency of referral to colposcopy (64% and 65%). Furthermore, these two strategies have a sensitivity close to that of immediate colposcopy in detecting type CIN3+ lesions (88% for the cytological test and 96% for the HPV test). The situation is different among women 29 and over. In fact, in this age group, the sensitivity of the three strategies was similar (91% for the cytological test, 94% for the HPV test, 100% for colposcopy, in theory), but the HPV test resulted in referrals to colposcopy among only 31% of women, compared to 50% for the strategy of cytological test repetition.(26) Also of note, in this study, the cytological test was repeated only once. If the test were repeated twice, the number of referrals to colposcopy would likely be even higher. This difference in the frequency of referrals by age if a triage strategy based on HPV testing were chosen is confirmed by a meta-analysis that demonstrated that up to 77% of young women under the age of 30 had positive HPV test results following an ASC-US result, compared to about 25% among women over the age of 30.(27)

Three economic studies having more specifically analyzed the cost/effectiveness ratio of this strategy based on age also indicate that this strategy is more efficient among women over the age of 30(28,29) or 35(30).

In Canada, three other provinces currently recommend the triage of ASC-US results by HPV testing as the favoured option, and the three reserve it for women 30 and over. This working group also recommends this approach.

The following table summarizes the indications for screening and the triage of ASC-US results by age.

Table 2 Indications for screening and the triage of equivical (ASC-US) results by age

Age	Screening	Triage of ASC-US results
< 21 years	Not indicated (with some exceptions)	Repetition of the cytological test at 6 and 12 months if a screening test has been done Referral to colposcopy if ASC-US or more severe results from one of the cytological tests
21-29 years	Cytological test every 2 or 3 years	Repetition of the cytological test at 6 and 12 months Referral to colposcopy if ASC-US or more severe results from one of the cytological tests
30-65 years	Cytological test every 2 or 3 years	HPV test If +: referral to colposcopy If -: repeat the cytological test after 1 year
≥ 66 years	Cytological test if indicated (absence of prior screening or recent screening, last results unknown)	HPV test If +: referral to colposcopy If -: repeat the cytological test after 1 year

4.2 FOLLOWING UP LOW-GRADE CYTOLOGICAL LESIONS (LSIL)

The challenge regarding case management in the case LSIL results is similar to that posed by ASC-US results, i.e. to minimize the number of invasive exams while maximizing the detection of high-grade lesions. It must be stressed, however, that the frequency of this diagnosis (≤ 2%) is much lower than that of ASC-US. The frequency of severe precursors determined by biopsy is slightly higher in women with an LSIL result, as compared to those with an ASC-US (not triaged).

The ALTS trial cited above is the most extensive study with the objective of determining a reliable triage method for LSIL results. The portion of the study pertaining to the follow-up of LSIL results was stopped prematurely. In fact, in the HPV testing group, over 80% of the women had positive results (75% among women over the age of 30), which made this triage strategy inefficient. In terms of the strategy of repeat cytological testing, when the positivity threshold for referral to colposcopy was set at HSIL results, close to half of the CIN3 lesions were not detected. When the positivity threshold was set at ASC-US results, the sensitivity rose to 98.9% (two repetitions), and 87.4% of the women were referred to colposcopy. The authors have concluded that no triage strategy is efficient and that the 15% risk of high-grade lesions justifies referring women with LSIL results to colposcopy.(23) Another study conducted in Great Britain has shown that if an HPV test triage protocol for LSIL results were implemented, 82% of women aged 20 to 34 and 73% of women 35 to 64 years would be referred to colposcopy, which raises doubts about the usefulness of this strategy.(31) Similar

results were obtained in Sweden, where a cost/effectiveness analysis showed that the option of immediate colposcopy prevailed over all other strategies, regardless of age group.(29) A single study concluded that the triage of LSIL results by HPV testing among women over the age of 35 could be an alternative option to immediate colposcopy. However, this conclusion was based primarily on a ROC (Receiver Operating Characteristic) comparison of women aged 35 and under with that of women over the age of 35. It is thus not surprising that the performance of the triage strategy involving HPV testing was less effective among women under the age of 35. The study did not compare triage by HPV testing with immediate colposcopy.(32) Arbyn's meta-analysis confirms that the high frequency of positive HPV test results among women under the age of 30 (77%-89%) and among those over 30 (69%-75%) limits the usefulness of triage by HPV testing.

In the face of such unconvincing data to back a proposal for a triage strategy for low-grade lesions, this working group recommends referring all women with these results to colposcopy.

5 SPECIFIC POPULATIONS

Screening indications and methods were reviewed to establish whether an adjustment to the guidelines would be appropriate in certain situations. In the case of any situation not addressed herein, consultation with a specialist in the field may be necessary.

5.1 PREGNANT WOMEN

As cervical cancer can appear among women of reproductive age, it is not impossible to discover cervical cancer or a precursor during pregnancy.(33) Prenatal visits thus provide a good opportunity to reach women for a screening test. However, pregnancy in and of itself does not justify repeating a test performed according to the recommended interval when the result of the last test was normal.

Furthermore, there is no evidence that the risk of progression from a grade 1 intraepithelial lesion (CIN1) to a more severe lesion (CIN2/3), or from a severe lesion (CIN2/3) to invasive cancer is greater during pregnancy. The regression of lesions is frequent during the post-partum period.(34-37) During pregnancy, follow-up of abnormal results thus remains essentially the same, i.e. the indications for referral to colposcopy are identical. During the diagnostic exam, certain interventions could be delayed until after delivery.

5.2 WOMEN WHO HAVE HAD A HYSTERECTOMY

A number of studies as well as a systematic review of the topic(38) support the recommendation to stop screening among women who have had a complete hysterectomy (cervix removed) when the intervention was done for a benign condition. In fact, the risk of vaginal cancer is extremely low, and the yield of the cytological test among this population is thus minimal.

However, women who have had a subtotal hysterectomy, i.e. whose cervix has been left in place, must be screened in the same manner as the general population.

When a hysterectomy has been performed for cervical cancer or a precancerous lesion, monitoring over a period of several years could prove necessary since the risk of vaginal cancer is higher.(38,39) Follow-up must be conducted on an individualized basis according to the attending physician’s recommendations.

5.3 IMMUNODEPRESSED WOMEN

Women with immunosuppression following an HIV infection, an organ transplant, or the long-term consumption of certain medication to treat an auto-immune disease or cancer run a higher risk of anogenital cancer than the average woman. The risk following an HIV infection has been studied the most.

Among HIV-infected women, a higher risk has been found in terms of the incidence, prevalence, and persistence of HPV infections, and the incidence of cervical precursors, invasive cancer, and the post-treatment recurrence of lesions.(40-42) In 1993, cervical cancer was included by the US Centers for Disease Control and Prevention (CDC) in the

clinical conditions associated with an AIDS diagnosis. Since 1996, access to more effective antiretroviral drug treatments has provides a better control of HIV infections. However, the impact of the treatment on the risk of evolution to a high-grade lesion is not yet well understood.

The screening recommendations reviewed were primarily based on expert opinions. The American, Canadian, British, and Australian organizations consulted all recommend annual screening in cases of immunosuppression, as soon as the diagnosis is made. Some bodies also recommend repeating the first test after six months, but the data supporting this practice come essentially from an economic study done by modelling in the United States.(43)

Some have proposed a colposcopy at the time of HIV diagnosis, at each visit or HPV testing. These strategies were analyzed more specifically in a large cohort study involving 1534 seropositive women from seven countries, who were examined periodically using a cytological test, an immediate colposcopy, and an HPV test.(44) After having studied the performance of the different tests, the authors concluded that the sensitivity of the colposcopy was equivalent to that of the cytological test, which limits its usefulness. The economic analysis conducted in the United States in 1999(43) demonstrated that recourse to colposcopy for screening is also more expensive, without contributing real benefits (dominated option).

There is currently no clear consensus on the use of HPV test as either a complementary screening test or for the triage of ASC-US results, since HPV infections are frequent among immunodepressed women and the positive predictive value of the test is lower. However, in a second economic study conducted in the United States,(45) the addition of HPV testing to the cytological test for the first tests and an adjustment to the screening interval based on the results (i.e., annually when the results of the HPV test are negative, but every six months when the results are positive) resulted in a cost/utility relationship of US$10 000 to US$14 000 per quality-adjusted life-year saved (versus no screening). This option is more complex to introduce, however.

Studies on the relationship between CD4 counts or the taking of antiretroviral medication and the incidence or evolution of pre-neoplastic cervical lesions have provided complex results.(46,47) For some, the risk among seropositive women having a CD4 count above 500 per µl would be practically identical to that of seronegative women. Generally speaking, restoring the immune system seems to have more impact on the evolution of low-grade lesions than on that of high-grade lesions, but the number of high-grade lesions found was often limited. It thus seems premature at the moment to make recommendations that would vary according to the treatment or degree of immunosuppression.

The working group recommends that annual screening be proposed to all sexually active women with immunosuppression following an HIV infection, organ transplant, or other chronic condition, regardless of their age.

Women with equivocal (ASC-US) or abnormal results should be referred to a colposcopy clinic for assessment.

6 INDICATIONS FOR HPV TESTING

Indications for HPV testing are expected to evolve rapidly, for both screening and the follow-up of abnormal results. At the current time, besides an indication for the triage of ASC-US results among women over the age of 30, this test can be used to guide the monitoring of women treated for a high-grade lesion. Use of HPV testing as the primary screening test is also under study in a number of settings. However, the follow-up algorithms as well as basic screening parameters, such as the optimal interval between tests have yet to be determined.

In a certain number of situations, **conducting an HPV test is clearly not indicated** at the present time. These situations are:

- the diagnostic investigation of other cytological abnormalities (HSIL, AGC, etc.);
- making a decision to be vaccinated for HPV or not;
- the diagnostic investigation of genital warts in a symptomatic woman or one who has had sexual contact with an individual having genital warts;
- the screening of sexually transmitted infections.

In settings that use HPV testing in conjunction with the cytological test for screening, such as the United States, this indication is recommended only for women aged 30 and over, at a frequency that must not be less than every three years.(48)

At the moment, all HPV tests approved for clinical use target only oncogenic HPVs. While there are also tests that detect low-risk HPVs, such as those that cause genital warts, they should only be used in a research context. Tests not validated as screening tests should not be used outside of a research context, in which women must be clearly informed of the experimental nature of the test.

7 CONCLUSION

The field of research on best strategies for screening and follow-up of abnormal results is very active, and it is likely that other approaches will have to be examined in the coming years. We only have to think of the use of tests enabling the type of HPV to be accurately detected through genotyping and the various molecular markers enabling the risk to be more accurately determined. The present recommendations must therefore be updated in the very near future.

Furthermore, the first cohorts of women vaccinated in schools will soon reach the proposed age to start screening. Since HPV vaccines are very effective in reducing persistent infections and cervical cancer precursors, the screening approach for these women will have to be reviewed. For the moment, the same strategy that applies to non-vaccinated women should be applied.

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APPENDIX 1

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

Each member of the working group completed a potential conflicts of interest disclosure form.

The following members declared no potential conflict of interest:

- **Manon Auger**
- **Michel Labrecque**
- **Sylvain Mailhot**
- **Anne-Marie Martel**

The other members made the following declarations:

Lyne Cloutier has received unrestricted research grants from Novartis (2008-2009) and Schering-Plough (2008-2009); she has also been invited by Merck (2008-2010), BMS (2008-2010), Boeringher (2008-2010) and Novartis (2008-2010) to be a guest speaker.

François Coutlée has participated in expert opinion meetings with Qiagen (2009) and GlaxoSmithKline (2010). He has received research grants for the evaluation of HPV tests from Roche Diagnostics (2005-2007) and for HPV detection in CIN lesions from Merck (2006-2008). He has been invited by Roche Diagnostics (2009) and Merck (2011) to be a guest speaker.

Marc Dionne has taken part in clinical studies on vaccines with GlaxoSmithKline, Merck, Pfizer, and Sanofi through the research centre at the CHUQ/CHUL.

Patricia Goggin has received free supplies from Roche Diagnostics in the context of a research project (2009) and speaker fees from Merck for a continuing medical education conference (2010). She has collaborated without remuneration in an unrestricted research project whose funds came from Roche Diagnostics (2008-2009).

Marie-Hélène Mayrand had received speaker fees for continuing medical education conferences from Merck and KlaxoSmithKline (on average two per year in last three years). She has received unrestricted research grants from Merck and Qiagen in 2010-2011 (less than 1% of total budget of the project). She has received a research grant from Merck related to her participation in a randomized clinical trial on vaccination (2008-2011). She has collaborated without remuneration in an unrestricted research project whose funds came from Roche Diagnostics (2008-2009).

Philippe Sauthier has been guest speaker at the invitation of Merck, GlaxoSmithKline, and Sanofi.

APPENDIX 2

RESEARCH QUESTIONS AND STRATEGIES

RESEARCH QUESTIONS AND STRATEGIES

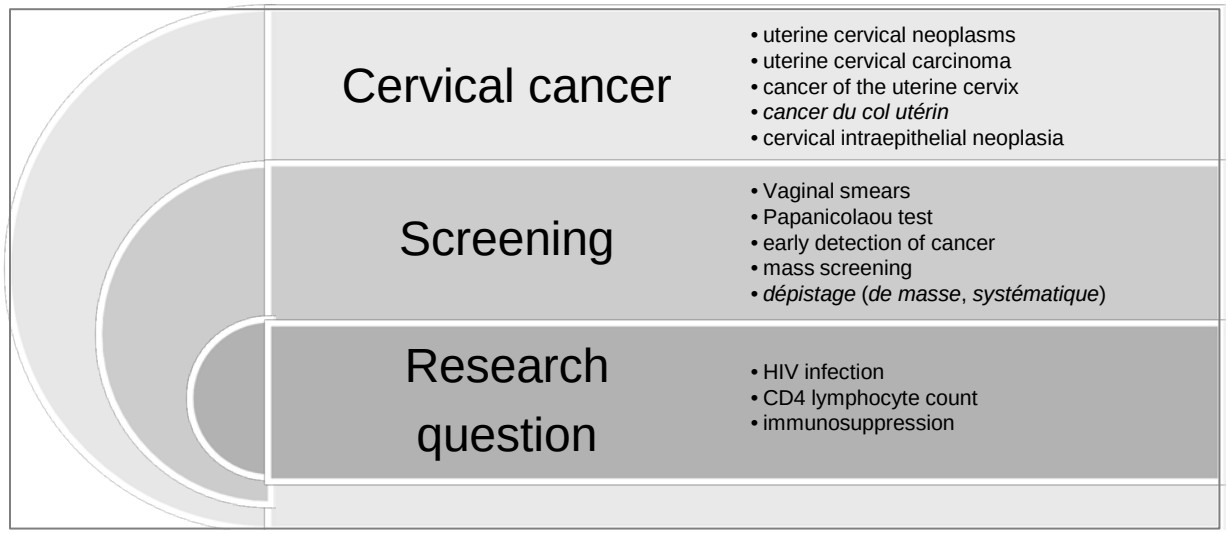
The goal of the research was not to gather data on the effectiveness of cervical cancer screening, which was never an issue, but rather to try to find the best data to support the choice of screening parameters when the cytological test is used.

The **core questions** were the following:

General theme	Specific questions
Natural evolution of the disease	Which elements in the natural evolution of the disease can help us understand the risk of cancer by age and the rate of progression of lesions? For example: ▪ the risk of acquiring a high-risk HPV ▪ the time line between the acquisition of the infection and the appearance of the different lesions ▪ the proportion of spontaneous regression of these different lesions ▪ the time period for progression from the different lesions to invasive cancer.
Age at which screening should begin	▪ What is the risk of cervical cancer among young women, in Québec in particular? ▪ What proportion of Québec adolescents are sexually active? ▪ What are the consequences of overscreening and overtreatment?
Age at which screening should stop	▪ What is the risk of cancer among older women? ▪ What is the prevalence of HPV infection among older women in Québec? ▪ In Québec, is there a second peak in the prevalence of HPV infection, as in other countries? ▪ What is the current screening practice among older women in Québec? (compliance indicator) ▪ What is the yield of screening, according to the number of previous tests and the results of these tests?
Interval between tests	▪ What degree of safety can be expected after negative results from a cytological test, by number of years? ▪ Is the sensitivity of the cytological test in Québec known? ▪ What do economic studies on the cost/effectiveness ratio of the various intervals teach us? ▪ More specifically, which ones have data providing support for the choice of an interval of two or three years? ▪ What data provides justification for the annual repetition of tests in the initial years?
Adapting standards for particular situations	▪ Can screening be stopped after a hysterectomy? ▪ Are there adaptations to make in the case of immunosuppression or pregnancy?
Triage of ASC-US results via the HPV test	▪ Should this strategy be proposed to all women or be reserved to women aged 30 (25-35) and over?

The OvidSP database (encompassing the EMBASE, PubMed, and EMBR databases) was consulted a number of times as the **primary** documentary **research strategy**, with a combination of terms from the MeSH thesaurus and terms in everyday English and French

regarding three (at times four) concepts combined, as the figure below illustrates (partial list of the terms uses as an illustration for immunosuppression):



In addition to the primary research strategy, on a number of occasions throughout the year between the start and end of the work the document's two editors initiated queries of the Pubmed database for specific questions.

- Among the other sources of data consulted were the following: Québec Tumour File for the number of cases and distribution by age group (Michel Beaupré, personal communication)
- Web sites:
  - Infocentre de santé publique (screening rate by age group, proportion of adolescents sexually active over the course of the past year)
  - Screening programs in other Canadian provinces, Australia, Great Britain, France (Haute Autorité de santé)
  - American Society for Colposcopy and Clinical Pathology (ASCCP)
  - Centers for Disease Control and Prevention (CDC)
  - US Preventive Services Task Force
  - Canadian Task Force on Preventive Health Care

APPENDIX 3

MODIFIED QUÉBEC VERSION OF 2001 BETHESDA TERMINOLOGY

MODIFIED QUÉBEC VERSION OF 2001 BETHESDA TERMINOLOGY[10]

1 SPECIMEN TYPE

CONVENTIONAL SMEAR OR SINGLE-LAYER PREPARATION (LIQUID-BASED CYTOLOGY)

2 SAMPLE QUALITY

SATISFACTORY
Presence or absence of transformation zone or glandular endocervical components or any other quality indicators (presence of blood or inflammation partially masking the cells, etc.)

UNSATISFACTORY (SPECIFY THE REASONS)

3 GENERAL CLASSIFICATION (OPTIONAL)

Absence of intraepithelial lesion and malignancy (negative)

Abnormal epithelial cells

Other

4 AUTOMATED REVIEW (if used)

5 HPV SCREENING TECHNIQUES (if used)

6 INTERPRETATION

ABSENCE OF INTRAEPITHELIAL LESION AND INVASIVE CARCINOMA

- **Normal smear**
- **Micro-organisms**
  Trichomonas vaginalis
  Mycotic components consistent with *Candida*
  Shift in vaginal bacterial flora suggestive of bacterial vaginosis
  Bacteria morphologically consistent with *Actinomyces*
  Cellular changes consistent with *Herpes simplex* virus infection
- **Other changes (optional)**
  Reactive benign changes (inflammation, intrauterine contraceptive device, radiation, etc.)
  Atrophy
  Post-hysterectomy presence of benign glandular cells

[10] Adapted by Québec's pathology quality assurance committee (Comité en assurance de la qualité en pathologie du Québec).

ABNORMAL EPITHELIAL CELLS

- **Squamous cells**

  Atypical squamous cells of undetermined significance (ASC-US)

  Atypical squamous cells of undetermined significance, cannot exclude high-grade squamous intraepithelial lesion (ASC-H)

  Low-grade squamous intraepithelial lesion (LSIL)

  High-grade squamous intraepithelial lesion (HSIL)

  High-grade squamous intraepithelial lesion with changes suggestive of an invasive squamous carcinoma

  Invasive squamous carcinoma

- **Glandular changes**

  Atypical glandular cells (endocervical, endometrial or of undetermined origin)

  Atypical glandular cells likely neoplastic (endocervical or of undetermined origin)

  Endocervical adenocarcinoma *in situ*

  Adenocarcinoma (endocervical, endometrial, or other)

- **Other**

  Endometrial cells with no significant atypia in a woman over the age of 40

7 SUGGESTION FOR FOLLOW-UP (optional)

8 COMMENTS (EDUCATIONAL NOTES)

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