HUMAN PAPILLOMAVIRUS (HPV) INFECTION

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HUMAN PAPILLOMAVIRUS (HPV) INFECTION

LITERATURE SURVEY AND EXPERT CONSULTATION FROM A PUBLIC HEALTH PERSPECTIVE

DIMENSIONS AND NATURE OF THE HPV INFECTION, PREVENTION AND PUBLIC HEALTH IMPACT

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GLOSSARY

AGUS	Atypical glandular cells of undetermined significance
AHCPR	Agency for Health Care Policy and Research
AIN	Anal intraepithelial neoplasia
ALTS	ASCUS/LSIL Triage Study
ASCCP	American Society for Colposcopy and Cervical Pathology
ASCUS	Atypical squamous cells of undetermined significance
ASHA	American Social Health Association
CDC	Centers for Disease Control and Prevention
CIS	Carcinoma in situ
CIN	Cervical intraepithelial neoplasia
DNA	Deoxyribonucleic acid
DSTDP	Division of Sexually Transmitted Diseases Prevention
FDA	Food and Drug Administration
HC II	Hybrid Capture II Test
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
HR HPV	High-risk human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
IARC	International Agency for Research on Cancer
LEEP	Loop electrosurgical excision procedure
LR HPV	Low-risk human papillomavirus
LSIL	Low- grade squamous intraepithelial lesion
MRNA	Messenger ribonucleic acid
MSM	Men who have sex with men
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NPV	Negative predictive value
Pap test	Papanicolaou test
PCR	Polymerase chain reaction
PPV	Positive predictive value
RLU	Relative light units
SIL	Squamous intraepithelial lesion
SOGC	Society of Obstetricians and Gynecologists of Canada

SPF	Short PCR fragment
STD	Sexually transmitted disease
STI	Sexually transmitted infections
VaIN	Vaginal intraepithelial neoplasia
VIN	Vulvar intraepithelial neoplasia

INTRODUCTION

Human papillomavirus (HPV) infection is recognized as one of the most common – if not *the* most common – sexually transmitted infections. The association between HPV and cervical cancer has also been recognized, while more recently it has been associated with some other types of cancer, primarily those in the genital region.

Our understanding of HPV has advanced considerably in the past decade. In fact, we now speak of human papillomavirus *infections* since there are roughly 100 viruses of varying pathogenecity. New technologies used for detection are being developed with increasing speed, new treatments are available and research on therapeutic or preventive vaccines continues to show promise.

Nonetheless, there is no doubt that HPV infections are a major public health problem.

Recognizing the magnitude of a public health problem is the first step in prevention. However, it is important to fully understand the various components of this problem in order to identify the strategies and means of intervention that are most likely to make a real impact on population health. Thus, preventing cervical cancer and other cancers associated with HPV infection has unquestionably become a major public health objective. While considerable advances have been observed over the past several decades in reducing the incidence of cervical cancer thanks to the general use of the Pap test to detect cervical cancer, it would not be wise to believe that the incidence will continue to decline without improved preventive measures. Preventing other HPV-associated cancers has also become an increasingly major concern. Nor can we overlook the impact of human immunodeficiency virus (HIV) on the evolution of the HPV infection. Besides the morbidity associated with cancers caused by HPV, we are also seeing a greater recognition of the morbidity associated with the infection itself, particularly the psychological impact on those infected. Finally, the understanding of the limited resources of the health care network forces us to consider, more than ever, the cost-effectiveness of any preventive or curative measures we may develop.

We have therefore conducted a survey of the scientific literature to present an overall portrait of the situation, taking into consideration the various aspects of the problem. However, faced with the extremely rapid expansion of HPV-related knowledge, not to mention results that are sometimes inconsistent with published studies and the growing complexity of technological aspects, we sought to validate our literature survey by enlisting a panel of Quebecer experts.

We hope that the results of this project will be used to plan measures to prevent human papillomavirus infections and their complications and contribute to the making of sound decisions based on scientific evidence. Nonetheless, considering the number of unanswered questions that were raised over the course of our research, we believe that this step is merely the starting point for an ongoing process of updating our understanding of the situation and establishing close ties between researchers and decision makers.

PROJECT SEQUENCE AND METHODOLOGY

The project took place between May 2001 and October 2002 and consisted of two stages, namely a literature survey and an expert consultation to validate the first stage.

Literature survey

The literature survey was conducted using two primary tools: Medline research of relevant articles and Internet research for other types of documents (monographs, guidelines, scientific presentations, etc.). A total of 342 scientific articles were selected for this project.

Medline research

The main source of articles was the Medline database (via the Pubmed and Medscape Web sites). In the first stage, we surveyed articles published between 1995 and May 2001 using the following key words: HPV, cervical cytology, intraepithelial neoplasia, cervical cancer, genital warts. These were used alone or in combination with the following secondary key words: epidemiology, natural history, screening, prevention. The summaries of articles that, according to their titles, seemed relevant to our exercise were read and sorted according to relevance and quality of research. Preference was given to original articles that presented study results over articles reviewing literature, without altogether excluding this latter category of articles. For diagnostic, treatment and prevention aspects, randomized and prospective studies were preferred, although transversal studies were also included in the final selection. The selected articles were read entirely, with individual summaries of highlights drawn up for the most of them, organized by theme. When there was insufficient data for certain aspects, research was expanded to include earlier works. As well, articles that were often referred to as basic reference were retrieved and included in the selection. Consequently, the research extended back to the 1970s in certain areas.

A parallel research strategy attempted to obtain literature and findings of Quebec and Canadian experts, particularly in the fields of epidemiology, prevention and testing. This was conducted either by using additional key words (Canada or Quebec) or by searching additional studies by the already identified Canadian experts.

Following this initial research, weekly updates were conducted in order to include the most recent relevant articles.

Medline research was not limited to English; articles in French, Spanish, Italian and German were also surveyed and, if relevant, included in the selection.

Internet research

Extensive Internet research was conducted parallel to the Medline research, in order to identify monographs, guidelines, scientific papers, conference summaries and other available and pertinent scientific documents. Using Copernic (Copernic Technologies Inc), the following key words and expressions were used: papillomavirus, HPV screening, cervical cancer screening, HPV prevention, cervical cancer prevention, VPH, virus du papillome humain, cancer du col de l'utérus. Copernic searched Internet sites in English, French, Spanish, Italian and German, although the majority of relevant texts were in either English or French. The Internet search allowed to retrieve a total of 49 documents, of which 16 were articles or guidelines and 33 were conference abstracts presented after the year 2000.

Participation at international symposiums

Participation at two international symposiums resulted in an additional 28 scientific presentations selected.

The first international symposium was the 14th symposium of the International Society for Sexually Transmitted Diseases Research (ISSTDR) held in June 2001 and attended by the project manager. The second symposium was the 19th International Papillomavirus Conference held in September 2001 and attended by the research assistant.

Expert consultation

Upon completion of the literature survey, a reference document was produced, as was a summary containing the highlights of the review. Analyzing the literature data helped identify some responses to questions of public health interest. Our analysis was submitted to a group of experts for validation and comments. The Delphi method for building consensus was chosen for the consultation process.

The Delphi method

Well-known among specialists in development of medium- and long-term strategies, this method uses an open-ended questionnaire to gather qualified opinions from a panel of experts in various domains. The feedback-based procedure avoids confrontation between the experts and provides the possibility of keeping the elicited opinions anonymous. The Delphi method was developed in the United States in the early 1950s and consists of collecting and condensing the existing knowledge of experts, in a dynamic and scientific manner.

A number of specialists are asked to fill out a questionnaire pertaining to the research domain of interest. The responses are then condensed and used to develop a new questionnaire that is in turn distributed a second time. A third and fourth round may also follow the same procedure. Thus, with each round, participants are able to offer their personal opinions while considering the essence of the other opinions in the group. Participants may alter or may maintain their original opinions. In this way, the final opinions and advice expressed are not credited to one participant in particular. This iterative process produces results in a highly synthesized form.

The Delphi method is particularly effective when dealing with issues for which, due to their nature, knowledge is approximate and incomplete.

Compared to the usual group consultation techniques, the Delphi method is beneficial for the following reasons:

1. **The number of people consulted:**
    This method allows consultation of a greater number of participants, thereby obtaining a broad diversity of expertise – a clear advantage over telephone conferencing or committee meetings.

2. **Anonymity:**
    Using a formal questionnaire reduces, if not eliminates, the likelihood of dominant personalities overwhelming the process, which is often the case in direct interactions.

3. **Controlled feedback:**
    The exercise consists in a series of steps between which a summary of the previous stage is transmitted to participants, allowing them to revise, if they wish, their earlier positions.

Consultation procedure

Potential participants were identified either as Quebec authors of relevant scientific publications or scientists recommended by other experts. The initial list consisted of 18 experts – 2 gynecologists, 2 pathologists, 2 microbiologists, 4 epidemiologists and/or public health experts, five non-medical researchers and 2 general practitioners. One person refused to participate and 10 agreed to participate in the Delphi group.

For each of the 18 consultation questions, suggested answers or comments were proposed based on the analysis of the literature survey. The experts were asked to offer an opinion on these propositions and to offer their own recommendations or thoughts. They could also raise additional questions for consideration by other participants in the second round of consultations. In all, 342 scientific articles were included in our project.

An acceptable level of consensus was reached after two rounds of questionnaires.

For analytical purposes, the following definitions were used:

Unanimity: All experts agree

Consensus: Agreement among at least seven experts and no more than one clearly expressed opposing view

Lack of consensus: Agreement among fewer than seven experts or more than one clearly expressed opposing view.

CHAPTER 1: LITERATURE SURVEY

1.1 EPIDEMIOLOGY

1.1.1 Prevalence of HPV infection

The prevalence of HPV infection varies by country and studied population: HPV is detected in the cervix of 5 to 50% of asymptomatic women of reproductive age (Franco 1997, Table 1, Appendix 1). In analyzing the results of epidemiological studies, it is important to note that the tests did not perform equally well, some being less sensitive than others (i.e. Hybrid Capture tube test) or susceptible to contamination (i.e. PCR) (Cuzick 1999).

Italy and Spain have the lowest prevalence of HPV infection – approximately 5% of the general population (De Sanjosé 2000, Muñoz, 1996, Tenti 1999). In the majority of other countries, between 10 and 20% of the population is infected (Muñoz, 1996, Kjaer 1990, Clavel, 1998, Franco 1999, Herrero 2000, Muñoz 2001).

Young women are most at risk of HPV infection. For example, studies of American female university students or young women indicate a particularly high prevalence of HPV, namely between 26 and 39% (Ho 1998, Kotloff 1998, Peyton 2001).

Among men, the prevalence of HPV varies from 3% in Spain to 39% in Brazil (Franceschi 2002).

The seroprevalence of HPV (Table 2, Appendix 1) is not an especially reliable indicator of the extent of the epidemic since it does not distinguish between earlier infection (cured or not) and current infection. As well, only about half those people infected develop circulating antibodies (Shah 1997). In the United States, the NHANES III study identified a 13% HPV 16 seroprevalence in the general population, higher among women (17.9%) and among those of African origin (19.1%) (Stone 2000). In a group of 672 American women, the HPV 16 seroprevalance was 22.2% (Daling 1996), while among the mostly male patients of an STI clinic in New Orleans, 36.1% carried antibodies against HPV 16 and 31.6% carried antibodies against HPV 6 and 11 (Slavinsky 2001). In Finland, 24% of pregnant women in 1983-84 and in 1990-1991 carried antibodies against HPV 16 (Kibur 2000).

1.1.2 Incidence of HPV infection

According to a review by Tortolero-Luna (1999), the incidence of HPV in the general population varies between 8 and 20% per year. In recent longitudinal studies conducted among young women, the annual incidence was between 14 and 24% and 43-55% over 3 years (Table 3, Appendix 1). More specifically, the incidence of HPV 16 infection was 4% over 18 months in tests among the general population of Brazil (Franco 1999) and 4.5% per year in Finland among a group of women younger than 25 (Kibur 2000a).

According to Collins (2002), HPV infection occurs on average 2.6 months after a subject's first sexual intercourse. Subsequently, the incidence of HPV diminishes with age. A study by Kibur (2000a) indicates the annual incidence of HPV 16 infection was 13.8% among women under the age of 17 and 1.3% for those between 23 and 25.

According to Verdon (1997), the lifetime risk of being infected by HPV is 79%. In a group of young college student women, 60% had at least one episode of HPV infection during a follow-up averaging 2.3 years (Ho 1998).

1.1.3   Canadian data on the prevalence and incidence of HPV infection

A number of Canadian studies have looked at, among other components, the epidemiology of HPV infection. For instance, the Sellors study carried out during 1997-1998 among 909 women aged 15 to 49 from across Ontario demonstrated an overall HPV prevalence of 13.3%, using polymerase chain reaction (PCR). The prevalence by age group is presented in Table 1, Appendix 1. The prevalence of visible condylomata in this population was 1.1% (Sellors 2000a).

In a group of 105 Toronto university students in 1990, the prevalence of HPV infection was 18.1% (10.4% HPV 16, 2.9% HPV 6/11 and 4.8% unknown types). The PCR test used identified only HPV 6, 11, 16, 18 and 33 (Rohan 1991). Ratnam (2000) identified a 10.8% prevalence of high-risk HPV among a group of 2098 Newfoundland women between 1996 and 1998. The Hybrid Capture I test was used at the beginning of the study, followed by the more reliable Hybrid Capture II test.

The levels of identified prevalence in these studies are comparable to those in other studies conducted around the world.

The Healey study (2001) looked at the epidemiology of HPV infection among women aged 13 to 79 in Nunavut. In this population, which has an elevated incidence of cervical cancer, the prevalence of infection by high-risk HPV was 26%, more than double compared to other Canadian studies (Table 1, Appendix 1).

In Quebec, two studies estimated the prevalence of HPV infection in the province. The first, conducted by Richardson et al (2002), indicated that the prevalence of HPV infection among 621 Montreal university students was 29% in 1996, 21.8% with high-risk HPVs and 14.8% with low-risk HPV. Another study was conducted between 1992 and 1993 (Richardson et al 2000), among 375 university students, also in Montreal. In this group of young women, the total prevalence of HPV infection, detected using the PCR MY09/MY11, was 22.7%. High-risk HPV types were present among 11.8% of the women, low-risk HPV types 6.2%, while 7.1% of the participants carried unidentified types. In addition, 2.7% of the women had multiple infections, including at least one type of high-risk HPV (Richardson 2000). In the 2002 study, the cumulative incidence over 2 years was 36.4% for all HPV types, 29.2% for high-risk HPV and 23.9% for low-risk HPV. The incidence was highest for HPV 16 (12% over 2 years), HPV 51 (8%) and HPV 84 (8%) (Richardson 2002). According to the Coutlée (1997) study of 287 sexually active subjects, 178 of whom were HIV-positive, the prevalence of oral HPV infection was 11%. In another study, the prevalence of esophageal HPV infection was 17% among a group of HIV-positive subjects, while none of the seronegative subjects had esophageal HPV infection (Trottier 1997).

1.1.4 Distribution of HPV according to type

In general, the most frequent types of HPV are HPV 6/11 and 16 followed by HPV 18, 51, 31, 45 and 53 (Forslund 2000, Kotloff 1998, Kjaer 1990, Muñoz 1996, Muñoz 2000, Ho 2001, zur Hausen 2000). In the study by Forslund (2002), the most frequent high-risk HPV types were HPV 16 and 31. According to Feoli-Fonseca (2001), in Quebec, the most frequent HPV types are 6, 16, 11, 31 and 18. In the Richardson (2002) study, also in Quebec, the most frequent HPV types were HPV 16 (7%), HPV 53 (4.3%) and HPV 84 (3.8%). In the previous Richardson study (2000), the most frequent types were HPV 16 (prevalence of 4.7% in the population studied) HPV 51 (2.2%), HPV MM8 (2.0%), HPV 66 (1.6%), HPV 6, 11, 31, 33, 58 (1.1% each) and HPV 18 and 53 with a prevalence of 0.8% each. This study considered only cervical HPV, unlike other studies that included HPV infections of the whole genital region. The prevalence of multiple HPV infections varies between 2.2% and 17.5% (Peyton 2001, Herrero 2000, Richardson 2000, Franco 1999, Kotloff 1998).

1.1.5 Epidemiology of lesions caused by HPV

Epidemiology of condylomata

The prevalence of genital warts is highest among young people around the age of 20 (McCowan 1999, Oriel 1971). Also, Joffe (1992) identified a condyloma prevalence of 5.2% in a population of American students aged 19 to 22. After this age, the prevalence diminished, regardless of sexual behaviour, possibly due to the development of an immune resistance to the infection (McCowan 1999). In a population of women 15 to 49 years old, the prevalence of condylomata was 1.1% (Sellors 2000). In 1987, roughly 2% of the sexually active population had condylomata or other visible forms of HPV infection (Ferenczy 1995). The lifetime risk of developing condylomata is approximately 10% (Franco 1997, Tortolero-Luna).

Epidemiology of cervical intraepithelial lesions

The prevalence of cervical lesions varies greatly – between 0.4% and 24% (Table 4, Appendix 1), depending on the population studied and the classification system used (Figure 1). The majority of clinics report a prevalence of around 2%, highest among sexually active women between the ages of 18 and 35 (Kiviat 1999).

Figure 1   Terminology for precancerous lesions of the uterine cervix

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│                        ┌─────────────────────────────────────┐                         │
│                        │  Precursors to uterine cervix carcinoma │                     │
│                        └─────────────────────────────────────┘                         │
│                                                                                        │
│  ┌──────────┐ ┌──────────┐ ┌──────────┐ ┌──────────┐ ┌──────────┐        ┌──────────┐  │
│  │ Atypical │ │ Mild     │ │ Moderate │ │ Severe   │ │ Carcinoma│ ───────▶│ Invasive │  │
│  │koilocytosis│ │dysplasia │ │dysplasia │ │dysplasia │ │ in situ  │        │ cancer   │  │
│  └──────────┘ └──────────┘ └──────────┘ └──────────┘ └──────────┘        └──────────┘  │
│                                                                                        │
│  ┌──────────┐    ┌──────────┐ ┌──────────┐    ┌──────────┐               ┌──────────┐  │
│  │Koilocytosis│    │ CIN  I   │ │ CIN II   │    │ CIN III  │ ───────────▶ │ Invasive │  │
│  └──────────┘    └──────────┘ └──────────┘    └──────────┘               │ cancer   │  │
│                                                                          └──────────┘  │
│     ┌─────────────────┐          ┌─────────────────┐                     ┌──────────┐  │
│     │  Low-grade SIL  │          │  High-grade SIL │ ──────────────────▶ │ Invasive │  │
│     └─────────────────┘          └─────────────────┘                     │ cancer   │  │
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Source: Parkin, The epidemiological basis for evaluating screening policies, 1997.

This terminology classifies the different types of observed lesions. Squamous intraepithelial lesions (SIL), also called cervical intraepithelial neoplasia (CIN), represent precancerous cellular changes in the squamous epithelium of the uterine cervix (Suris 1999). The LSIL/HSIL denominations are used mainly to express cytological results[1], while CIN 1-3 represent histological diagnostics.

Cytological lesions are classified as low- and high-grade lesions (LSIL and HSIL), which correspond to histological diagnoses of CIN 1 (LSIL) and CIN 2 and 3 (HSIL) (Fig. 1), reflecting the increasingly abnormal maturation of the affected epithelium (Suris 1999).

However, a Pap smear may not always be able to correctly identify a lesion and classify it according to this terminology. Such smears are classified as ASCUS or "atypical squamous cells of undetermined significance." The proportion of smears classified in this way (Table 4, Appendix 1) varies greatly depending on the population, country, region and even laboratory, ranging from 2.2% (Dalstein 2001, France) to 20% (Koumans 2002, sexually active Black adolescents, USA). In Montreal, a study of university students (Richardson 2000) reported 7.2% ASCUS.

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[1]   The Bethesda system classifies cytological squamous lesions in four categories: atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions and squamous cell epitheliomas (Drouin 1998).

Prevalence of cervical intraepithelial lesions

The prevalence of cervical intraepithelial lesions is 3.2% in the United States, 1% in Taiwan, 0.7% in Egypt, 3.6% in Australia and 0.9% in Norway (Suris 1999). At the end of the 1970s, the proportion of Canadian women with precancerous cervical lesions was 1.69% (Johnson 1994). In Canada, the prevalence of squamous intraepithelial lesions is 6.9% in British Columbia (Suris 1999), 6.7% in Ontario (Sellors 2000), 9.2% in Newfoundland (Ratnam 2000) and 6.9% in Nunavut (Healey 2001).

In a group of Montreal students, the prevalence of cytological abnormalities was 11.5% (Richardson 2000). These values are difficult to compare since they include a variable proportion of ASCUS results (Table 4, Appendix 1).

According to Herrero (2000), the average age of women with **low-grade squamous intraepithelial lesions** was 29 (maximum prevalence of 5.2%, among women under 25), that of women with **high-grade squamous intraepithelial lesions** was 34 (maximum of 2% at age 30 and another spike after age 65) and the average age of women with **invasive cancer** was 39.

In British Columbia in 1988, the highest prevalence of moderate or severe cervical intraepithelial lesions was among women aged 20 to 35 (Benedet 1992).

Incidence of cervical intraepithelial lesions

In the study by Woodman (2001), among a group of sexually active British women aged 15 to 19, the cumulative risk of developing an abnormal cytology was 28% over 3 years.

In a cohort of 128 805 American women, the incidence of high-grade intraepithelial lesions (HSIL) was 60/10 000 among women under 30, 22/10 000 among women 30-49, 15/10 000 among women 50-64 and 10/10 000 among women over 65 (CDC 2000). The incidence of all lesions diminishes with age (CDC 2000). The same tendency was seen in a study by Kibur (2000), according to which the incidence of high-grade cervical intraepithelial lesions (CIN 3) was highest among women aged 18-19 (56.5/10 000), falling to 18.3/10 000 among 25-28-year-old women.

In Washington D.C., in 1987-1991, the incidence of carcinoma in situ (CIS) was 62.4 /100 000, while that of invasive cancer was 7.9 /100 000. Between 1980 and 1990, the incidence of CIS increased, particularly among young women. In 1989-1991, the adjusted incidence of CIS was 196/100 000 among women aged 18-24 and 212/100 000 among women aged 25-34 (Kiviat 1999).

One woman in 10 will have an abnormal Pap test in her lifetime (O'Mahony 1996). Similarly, 13.1% of Canadian women 15 to 49 have had at least one colposcopy due to an abnormal Pap test (Sellors 2000).

Mathematical model

According to Myers' mathematical simulation (2000), the maximum prevalence of HPV infection occurs at 21 years (24.7%). Regarding intraepithelial lesions, the maximum prevalence occurs at 28 years (8.3%) for low-grade lesions (LSIL) and at 42 years (2.6%) for high-grade lesions (HSIL). The maximum incidence of cervical cancer occurs at 48 years (81/100 000), with 46.4% at stage I, 27% at stage II, 18.1% at stage III and 8.5% at stage IV. The total risk of cervical cancer without screening was 3.7% in the base model (between 2% and 6% based on relative risk of HPV infection). In the absence of any HPV infection, the risk of cervical cancer among women over 50 is less than 0.5%, even in the absence of screening. According to the sensitivity analysis, the risk of cervical cancer is influenced mostly by the incidence of HPV infection, the proportion of HPV infections that progress directly to a high-grade intraepithelial lesion and finally, by the level of progression of the low-grade lesions.

1.1.6   Epidemiology of cervical cancer

Worldwide, there are an estimated 465 000 new cases and 200 000 deaths per year, with 80% occuring in developing countries (Haverkos 2000). The incidence of cervical cancer varies between 3.8 (Israel) and 48.2 (Colombia) per 100 000 women (Haverkos 2000). In the United States, 14 000 new cases are reported yearly, with roughly 5000 deaths (Douglas 2000).

In Canada, cervical cancer is ranked 12th among diagnosed cancers in women of all ages, but 3rd among women aged 20 to 34 and 35 to 49 (Health Canada, 2002). Among women under 20, the incidence of cervical cancer is very low, namely 2 per million (O'Mahony 1996).

The estimated incidence of cervical cancer in Canada was 10.2/100 000 women in 2000 and 8.0/100 000 in 2001, with a mortality rate of 2.7/100 000 women in 2000 and 2.1/100 000 in 2001 (National Cancer Institute of Canada 2001), corresponding to 1608 new cases and 650 deaths (Ferlay 2001). In Canada, it is estimated that in 2002, 1400 women will be diagnosed with invasive cervical cancer and that 410 of them will die (Health Canada 2002).

The Quebec cervical cancer rate (estimated at 7.0/100 000 in 2001 by the National Cancer Institute of Canada) is the lowest in Canada. According to the most recent official data, in 1996, the rate of incidence of cervical cancer was 8.0/100 000 in Quebec, while the rate for Canada was 9.2/100 000 (Health Canada).

Evolution of the incidence of cervical cancer

The historical trend indicates a significant reduction in the incidence of cervical cancer in the nineties, mostly among women 25 to 54, but little change among women over 55 (Sasieni 2001, Hemminki 2002). At the same time, in recent years in countries like Great Britain, Canada, Australia and New Zealand, the incidence of mortality due to cervical cancer has increased among women younger than 40. This increase appears to be linked to the increasing prevalence of HPV infection (Kiviat 1999). The lifetime risk of developing cervical cancer is 0.5% among women born in 1938, 0.9% among women born in 1948 and 1.8% among those born in 1958 (Peto 2001).

Between 1958 and 1996, the incidence of invasive squamous cell cervical cancer fell in Sweden, particularly in the 40-44 age group. However, during the same period, the incidence of in situ and invasive adenocarcinoma steadily increased, particularly in the 40-44 and 30-39 age groups. The increase in adenocarcinoma incidence appears to be determined by the increased prevalence of HPV. It is the efficient cervical cancer screening programme that countered this effect and blocked a possible increase of squamous cell carcinoma (Hemminki 2002).

In Canada, the age-adjusted incidence of cervical cancer fell from 13.4/100 000 women in 1970-72 to 9.1/100 000 in 1996 (Liu 2001). The incidence was more than 21/100 000 in 1969 (Health Canada, SOGC 1998) and 8.0/100 000 in 2001 (National Cancer Institute of Canada 2001). Mortality due to cervical cancer fell from 7.4/100 000 in 1969 to 2.4/100 000 in 1992 (Health Canada, SOGC 1998) and to 2.1/100 000 in 2001 (National Cancer Institute of Canada 2001).

Between 1972 and 1996, the incidence of adenocarcinoma and adenosquamous carcinoma increased respectively from 1.3 to 1.8 per 100 000 and from 0.15 to 0.4 per 100 000, particularly among women aged 20 to 49 (Liu 2001).

In British Columbia, the incidence fell from 28.4/100 000 to 4.2/100 000 between 1955 and 1988, representing a reduction of 85%. During the same period, the mortality rate fell by 80%, from 11.4/100 000 to 2.3/100 000 (Suris 1999).

In Quebec, the incidence of cervical cancer in all age groups decreased by 46%, from 13/100 000 women in 1984 to 7.0/100 000 in 2001.

1.1.7   Epidemiology of anal HPV infection

Anal HPV infection is found mainly in men who have sex with men (MSM) and in women who have receptive anal sex. Perianal and anorectal junction abnormalities have been detected in 50-75% of asymptomatic MSM and 84% of symptomatic MSM (Lawee 1990).

HPV infection is virtually universal among HIV-positive MSM and its prevalence is higher than the prevalence of cervical HPV infection among HIV-positive women (Palefsky 2001).

In a group of MSM, the prevalence of anal HPV infection, tested with PCR, was 93% among HIV-positive subjects and 61% among HIV-negative subjects. The most common type was HPV 16, detected respectively in 38% and 19% of specimens. More than one type of HPV was detected in 73% of HIV-positive subjects and in 23% of HIV-negative subjects. Many MSM were having multiple infections: the average number of types detected per positive specimen ranged from 3.3 to 3.9 among HIV-positive subjects and 1.9 among HIV-negative subjects (Palefsky 1998).

According to a study using Hybrid Capture, the prevalence of HPV was 87% among HIV-positive subjects and 37% among HIV-negative subjects. HPV 16 was detected among 35% of HIV-positive subjects and among 9% of HIV-negative subjects (Palefsky 1998).

Among women, 76% of HIV-positive women and 42% of HIV-negative women had an anal HPV infection. Twenty-eight percent of the HIV positive women were having multiple infections, compared to 8% in the HIV-negative (Palefsky 2001).

The incidence of anal cancer is 9/100 000 among women, 7/100 000 among men and 35/100 000 among MSM who had receptive anal sex (Palefsky 1996).

1.1.8 Epidemiology of HPV infection and cervical lesions among HIV-positive subjects

The prevalence of HPV infections is greatest among persons infected with HIV, ranging from 40% to 93% (Table 5, Appendix 1). According to a study by Hankins (1999), the prevalence of HPV infection was 67% among women living with HIV. The anal HPV viral load was also highest among HIV-positive men (2.4 for low-risk HPV and 4.0 for high-risk HPV, compared to HIV-negative men) (Palefsky 1998). According to Chritchlow (1998), the cumulative incidence of HPV infection was 40% at year 1 and 54% at year 2 for HIV-negative subjects and 45% and 78% respectively for HIV-positive subjects.

In Lillo's study (2001), 24.5% of HIV-positive women tested positive for HPV 16, 1.8% for HPV 18, and 33% for HPV 31, 33, 35 or 45. Also, 24.6% were infected with multiple types, while 16% had undetermined types (Lillo 2001). The viral load was highest among HIV-positive subjects (Chritchlow 1998). According to Rezza (1997), the most frequent types were HPV 18 (27.6%), 16 (26.3%) and 31 (9.2%), with no difference in the proportion of oncogenic types among the HIV-positive and negative individuals. The prevalence of cervical lesions among HIV-positive women ranges from 9.9% to 35.6% (Ellerbrock 2000, Hankins 1999, Petry 1999, Rezza 1997), with 6.2% to 12.3% high-grade lesions (Lillo 2001, Petry 1999, Rezza 1997).

According to a study by Petry (1999), the incidence of severe cervical lesions was 4659/100 000/year, or 4.7/100 persons per year. In the prospective study by Ellerbrock (2000), the incidence of squamous intraepithelial lesions was 8.3 cases/100/year in HIV-positive women and 1.8/100/year in HIV-negative women.

Vulvovaginal and perianal condylomata and intraepithelial neoplasia were most common among HIV-positive women – 9% compared to 1% among HIV-negative women (Conley 2002). The relative risk (hazard ratio) of vulvovaginal and perianal lesions is 17.0 in the presence of HIV infection (Conley 2002). The recurrence rate for external genital warts is also highest among HIV-positive individuals – 66.4% versus 26.8% among HIV-negative individuals who received identical treatments (de Panfilis 2002).

1.1.9 Surveillance of the HPV infections

In most countries, there is no surveillance system for HPV infection. To date, the most viable approach for the surveillance of genital HPV infections is the study of their prevalence and the application of sentinel surveillance programmes (DSTDP-CDC 1999). However, a systematic, structured surveillance of carcinoma in situ within the population would be extremely useful. Given that this pathology is mostly diagnosed and treated in ambulatory settings, a cancer registry based on hospital reports would not be a reliable source of information for surveillance purposes (DSTDP-CDC 1999).

1.1.10 Modes of transmission of HPV infection

HPV is essentially sexually transmitted (McCowan 1999, Ferenczy 1995, Lawee 1990, Oriel 1971). The mean incubation period is estimated to be 2 to 3 months, ranging from a few weeks to eight months (Handsfield 1997, Oriel 1971). The rate of transmission to partners of infected individuals is estimated to be 50-70% (Lawee 1990, Oriel 1971).

Among partners of patients with genital warts, 64% likewise developed warts. According to Verdon (1997), the probability of genital wart transmission through a single sex act is 60%. The infectiousness of condylomata appears to diminish over time (McCowan 1999, Handsfield 1997, Oriel 1971). Individuals who transmitted the infection had condylomata for an average of 3.5 months, while individuals who did not transmit the infection had condylomata for an average 12 months (Oriel 1971). Besides sexual transmission, autoinoculation and heteroinoculation through cutaneous warts is also possible, as is maternofetal transmission (Ferenczy 1995, Fairley 1993). Other ways of transmission, though rare and anecdotal, include intimate non-sexual contact (baths, for instance) and non-penetrative sexual activities (Fairley 1993).

Kjaer et al (2001) looked at the transmission of HPV infection among a group of young women who were either monogamous or without sexual experience and who changed their behaviour during the follow-up. The results support the importance of the sexual transmission of HPV infection: the prevalence of HPV infection was 0% among the virgins, but increased to 35.4% after they became sexually active. Likewise, the HPV prevalence of HPV in monogamous women increased from 14.8% to 34.6% after sexual activity with a new partner.

According to Franco (1995), high-risk HPV infection of cervix has the characteristics of a sexually transmitted infection (STI); Low-risk HPV infection, however, does not. The number of sexual partners and age of first sexual contact appear to be associated only with high-risk HPV.

One controversial area is the question of vertical transmission. According to Fairley (1993), perinatal transmission was demonstrated through a link between laryngeal papillomatosis in children and vaginal birth and the presence of the virus and even lesions at the time of birth. Some studies have shown a high prevalence among newborns of infected mothers (Tseng 1998), but in others (Castellsagué 2000), there was no significant difference between newborns of infected or uninfected mothers.

According to some authors, the prevalence of high-risk HPV in newborns may vary between 20 and 38% (Rice 1999, Cason 1998). While the presence of HPV in newborns is considered by some to be a transitory contamination (Tenti 1999), others consider that, in the majority of cases, the virus persists for several months (Rice 1999). According to Rice (1999), the long-term effects of HPV infection in newborns is not known and might eventually interfere with immunisation programs against HPV.

According to Cason, even if maternofetal transmission is a real possibility, the consequences of such infections do not appear to be dramatic and do not justify either the routine testing of infected children or preventive cesarian sections (Cason 1998).

In Denmark, the prevalence of HPV among a group of randomly selected children was 1.6% in the anal region and 0.25% in the oral cavity; all viruses detected were of unknown type (Koch 1997). Besides perinatal transmission, the most frequent causes of genital warts in children are autoinoculation from cutaneous warts (presence of HPV type 2, typically detected in cutaneous warts) or sexual abuse (de Jesus 2001, Handley 1997). The type of HPV might suggest the probable source of infection (Handley 1997). Cason (1998) mentioned that HPV infection in children might be connected to sharing baths with parents or caused by horizontal transmission, possibly through contaminated objects. Transmission through breast milk, blood or gamete infection seems not probable (Cason 1998).

1.1.11   Risk factors for HPV infection

The main factors associated with HPV infection are sex, age, race, sociodemographic characteristics, prior sexually transmitted infections, parity, contraceptive methods and smoking.

It is difficult to make a connection between HPV infection and gender since the majority of studies look at women only. Within the framework of NHANES III, the seroprevalence of HPV 16 was higher in women than in men (17.9%, C.I. of 15.8-20.3%, versus 12.5%, C.I. of 10.7-14.5%) (Stone 2000). Another study of seroprevalence, Slavinsky (2001), identified a positive link between gender and the presence of antibodies against HPV 6/11 and HPV 16.

HPV infection is most common in people aged 20-29 (Stone 2000, Ross 1996, Clavell 2001, Sellors 2000). After the age of 30, the prevalence of HPV diminishes rapidly (Franco 1997, Sellors 2000). The majority of studies show an inverse association between age and HPV infection, except in those that look at highly homogenous populations in terms of age (Table 6, Appendix 1). The reduction in HPV prevalence with age appears to be independent of sexual activity (Franco 1997).

African-american ethnicity is associated with higher HPV prevalence, according to Stone (2000) and Morrison (1998).Also, Peyton (2001) demonstrated an increased risk of high-risk HPV infection among women of Hispanic ethnicity, while Ho (1998) identified a lower risk for HPV infection among Caucasian students.

Socioeconomic status, particularly occupation and income, are often associated with the presence of HPV (Peyton 2001, Wen 1999, Muñoz 1996). A link with education is less consistent (Table 6, Appendix 1). Marital status appears to be a factor associated with HPV infection, with single or

divorced women more often infected than married women (Peyton 2001, Sellors 2000, Wen 1999), probably due to the number of sexual partners.

The most significant risk factor for HPV infection is sexual behaviour (Franco 1997). The total number of sexual partners and the number of recent partners appear to be the most consistent factors, particularly for infections with carcinogenic HPVs (Table 6, Appendix 1). Age at the time of the first sexual contact is a less constant factor of HPV infection.

Other factors, such as STI history, hormonal factors (oral contraceptives or pregnancy), condom use, and smoking are occasionally associated with HPV infection (Table 6, Appendix 1).

Participating in cervical cancer screening through Pap tests is linked with a lower prevalence of HPV (Kataja 1993, Rousseau 2000). It is not surprising, however, that having a previous abnormal Pap test is associated with an increased risk of HPV positivity, more specifically with oncogenic HPV (Peyton 2001, Sellors 2000, Kataja 1993, Kjaer 1990).

Among men, HPV infection is associated with Hispanic origin, with high frequency of sexual activity, and previous history of gonorrhea or genital warts (Baldwin 2002). Education level, monogamy, absence of anal sexual contact, circumcision, and condom use are inversely associated with the presence of HPV (Baldwin 2002). The IARC study reinforces that circumcision appears to be a protecting factor against HPV infection (Castellsagué 2002).

Risk factors for anal HPV infection

The main risk factors associated with anal HPV infection are HIV infection (Palefski 2001b) and the number of CD4 lymphocytes (Palefsky 2001b, Palefsky 1998).

Among HIV-positive women, the risk factors for anal HPV infection are young age, Caucasian race, and previous antiretroviral treatment (namely zidovudine). In a multivariate model, independent factors for anal HPV infection were the number of CD4 (<200 cell/mm³), the presence of cervical HPV, age and Caucasian race (Palefsky 2001b). The absence of association with sexual behaviour and with other STIs suggests other, non-sexual ways of transmission, biological differences in anal HPV infection (Palefsky 2001b) or lack of validity of the questionnaires used (Coutlée, personal communication).

Factors linked to HPV positivity among men infected with HIV were the use of "poppers", a history of rectal discharge and the frequency of receptive anal sex (Palefsky 1998). This study could not determine the risk factors for HIV-positive men because of to the extremely high prevalence of HPV infection (Palefsky 1998).

Risk factors for HPV infection and HIV infection

The risk factors for HPV infection among HIV-positive individuals are:

- CD4 count under 200/ml (Lillo 2001, Palefsky 2001b, Spinillo 2001, Hankins 1999, Chritchlow 1998). However, according to Ellerbrock (2000), there was no association between the incidence of intraepithelial lesions and the number of CD4;

- advanced stage of HIV infection (Spinillo 2001);

- high HIV viral load (Spinillo 2001);

- race other than Caucasian (Hankins 1999);

- high number of sexual partners since the last visit (Chritchlow 1998);

- unprotected receptive anal sex (Chritchlow 1998);

- inconsistent condom use (Hankins 1999), regular condom use has been associated with reduced risk of 70% (OR of 0.29) (Spinillo 2001);

- use of oral contraceptives (Rezza 1997);

- age under 30 (Hankins 1999).

Antiretroviral treatment has not been associated with a reduction of the risk of high-risk HPV infection (Lillo 2001). On the other hand, incidental HPV 16 and 18 infections were more rare among women who had received highly active antiretroviral therapy (HAART), with an odds ratio of 0.3 (Lillo 2001). An ASCUS diagnosis at the time of recruitment was associated with the appearance of intraepithelial lesions: 39% of HIV-positive women with ASCUS had an intraepithelial lesion during follow-up compared to 25% of HIV-positive women without ASCUS (Ellerbrock 2000). A cohort study is under way in Quebec, looking at risk factors and the evolution of anal lesions caused by HPV among MSM receiving HAART (Coutlée, personal communication).

Risk factors for developing squamous intraepithelial lesions among HIV-positive individuals are:

- the stage of HIV infection: intraepithelial lesions were present among 45% of women in stage A, 68.2% in stage B and 76.2% in stage C, p = 0.001 (Spinillo 2001);

- CD4 count (Lillo 2001, Spinillo 2001), however Ellerbrock (2000) did not find any type of association;

- HPV infection (Ellerbrock 2000, Petry 1999) and the persistence of HPV infection (Ellerbrock 2000);

- HIV-HPV interaction (RR adjusted to 2.7) (Ellerbrock 2000);

- young age (Ellerbrock 2000);

- early start of sexual activity (Ellerbrock 2000);

- treatment with HAART, OR of 3.54 (Lillo 2001).

In Chritchlow's study (1998), the factors associated with the persistence of anal HPV infection were HIV serpositivity, HPV type other than 6/11, viral load, and the presence of HIV DNA in the anal canal.

1.2   NATURAL HISTORY OF HPV INFECTION

1.2.1   Pathogenesis

To date, more than 85 HPV types have been identified and sequenced, and more than 120 new types are partially characterized (zur Hausen 2000). Approximately 40 HPV types infect the anogenital region (zur Hausen 2000). HPVs may be grouped in two main categories, based on their oncogenetic risk level: high risk (types 16, 18, 31, 33, 39, 45, 52, 58 and 69) and no- or low-risk (types 6, 11, 42-44, 53, etc.) (zur Hausen 2000, Beutner 1998, Ferenczy 1995). The major difference between the two virus categories is represented by the exclusive capacity of the high-risk HPVs to integrate the host cell's chromosomes (Ferenczy and Franco 2002).

After penetrating the epithelium, facilitated by preexisting micro-lesions, HPV may induce a productive infection, with the appearance of koilocytes and the development of exophytic warts (condylomata acuminata and flat condylomata). Another alternative is the induction of cellular transformations, causing the appearance of dyskaryotic cells and eventually the development of intraepithelial squamous lesions (Syrjänen 1998). The infected unit is the whole virion, produced only in productive infections (Richart 2001).

1.2.2   Condylomata or genital warts

Aspects of the lesion

Condylomata are benign lesions, caused by low-risk HPV oncogenes, particularly types 6 and 11 (von Krogh 2000, Ferenczy 1995). According to von Krogh (2000), HPV 6 and 11 cause more than 90% of condylomata acuminata. Greer (1995) determined that 94% of condylomata acuminata have the DNA of HPV 6 and 8% of HPV 11 and that, in these condylomata, infections with multiple types are common (Greer 1995).

Condylomata may have variable aspects depending on their location. For instance, they may be keratinised, non-keratinised, pigmented or not.

Condylomata may manifest themselves as genital warts or macular condylomata. Genital warts are also called condylomata acuminata, most often detected on mucous surfaces, and papular condylomata, mostly detected on the keratinised epithelium. Macular or flat condylomata are subclinical lesions usually invisible during standard examinations (Von Krogh 2000, Handsfield 1997). These lesions (flat condylomata) are visible through visual enlargement and/or with the application of 5% acetic acid (Verdon 1997, Ferenczy 1995).

Localization

Lesions are most frequently detected in regions exposed to trauma during sexual act and may be single or multiple, measuring 1 to 10 mm. Condylomata appear most often on the prepuce of uncircumcised men, on the shaft of the penis of circumcised men and on the vulvar, perianal, anal, vaginal and exocervical region of women (Von Krogh 2000, Verdon 1997, Ferenczy 1995, Oriel 1971).

Incubation

In a prospective study, the average incubation period for acuminate condylomata was 2.8 months, varying between 3 weeks and 8 months (Oriel 1971).

Symptoms

The symptoms associated with genital warts are inconsistent and variable. They can be represented by fissures, itching, burning, dyspareunia or bleeding. Symptoms are more severe in pregnant women (Von Krogh 2000, Ferenczy 1995).

Clinical evolution

The natural history of condylomata acuminata and flat condylomata is not well known. Several condylomata acuminata regress spontaneously after several months, sometimes after years (Oriel 1971). Subclinical infections (flat condylomata) can persist for life. The persistence of HPV infection probably depends in cellular immunity (Handsfield 1997). A pre-existing HPV infection does not appear to protect against reinfection (Kotloff 1998).

The disappearance or spontaneous reduction of clinical lesions is well documented, but predicting individual evolution is impossible and delaying treatment may result in growth of the lesions and more difficult, costlier and lenghtier treatment (Ferenczy 1995).

Condylomata and pregnancy

During pregnancy, condylomata may grow, but they generally regress after delivery (Lawee 1990, Oriel, 1971). Warts may be transmitted to the newborn and cause laryngotracheal lesions. Recurrent laryngeal papillomas are very rare and are caused by the maternofetal transmission of HPV 6 and 11 (McCowan 1999, Verdon 1997, Ferenczy 1995, Lawee 1990).

Condylomata and cancer

Cervical lesions with HPV 6 and 11 have a very low carcinogenic risk since these viruses do not integrate the chromosomes of the infected cell. The cancer risk of women with condylomata is the same as that of women without condylomata or the general population (Griffiths 2002, Verdon 1997, McCowan 1999, Koutsky 1992). On the other hand, in a study by Howard (2002), 39% of women with genital warts had intraepithelial lesions of the cervix, and Coker (2001a) too identified a positive link between genital warts and cervical lesions. Patients with condylomata may be infected simultaneously with high-risk HPVs, which may cause subclinical lesions associated with intraepithelial neoplasia and anogenital cancers (Von Krogh 2000). However, according to Ferenczy (1995), the majority of lesions associated with condylomata are low-grade lesions (CIN 1).

Intraepithelial neoplasia in the anogenital region are similar to flat or papular condylomata and are precancerous lesions caused by high-risk HPV (van Krogh 2000).

1.2.3   Cervical HPV infection

The majority of HPV infections are temporary, 70-90% regressing spontaneously in less than 4 to 5 years (Petry 2001, Richart 2001, Dillner 2000, Elfgren 2000, Ho 1998). In Richardson's study (2002), the average time for infection clearance was 25.3 months. In a group of more than 9000 Costa Rican women, the majority of HPV infections cleared after 5 years, except those that were associated with a prevalent or incident diagnosis of CIN 2 or worse (Shiffman 2001). Similarly, 70% of women followed by Moscicki (1998) had eliminated the HPV infection within 24 months. According to Nobbenhuis (2001), high-risk HPV infection disappeared in 23-50% of women within under 40 months, depending on the presence and severity of the cervical lesions.

In a study of Quebec women by Brisson (1996), the persistence rate of infection at 10 weeks was 50% for all HPV, including high-risk HPV. When only same types of viruses were considered, the persistence rate was 31.1% (Brisson 1996).

The average duration of HPV infection is 6-25 months (Nobbenhuis 1999, Ho 1998, Kotloff 1998). High-risk HPV infections persist on average 9.2 months, low-risk HPV infections on average 7 months (Kotloff). An infection that has persisted for more than 4 years has little chance of remission (Richart 2001).

Among women, 66-80% of HPV infections will regress, while 6.3-20% of women will develop intraepithelial lesions (SIL) (Meijer 2000, Syrjänen 1997). The risk of progression depends on the site of infection, especially the squamocolumnar junction. The squamous epithelium of the cervical transformation zone seems to be especially vulnerable. Micro-erosions allow HPV to access the basal cells where replication of the virus may cause the onset of precancerous lesions (Syrjänen 1998).

According to Peto (2001), the association of invasive cervical cancer and CIN 3 with early sexual activity and with a high number of partners, even over a long period, suggests the possibility that HPV infection is persistent but undetectable by current methods.

Risk factors for infection persistence

A number of factors have been associated with persistence of cervical HPV infection. The most significant are:

- infection with high-risk HPV (Richardson 2002, Ho 1998, Brisson 1996), more specifically, HPV 16 (Richardson 2002, Elfgren 2000, Ho 1998, Brisson 1996) and HPV 18 (Ho 1998, Brisson 1996), the viral load (van Duin 2002, Brisson 1996, Rousseau 2001b), continuous virus production (Richart 2001) and multiple infections (Ho 1998);

- older age (Ho 1998);

- the Arg/Arg genotype in the gene that codifies the p53 protein (Rousseau 2001b);

- a high number of sexual partners (Brisson 1996, Elfgren 2000);

- early first sexual contact (Elfgren 2000);

- a history of condyloma in the partner is associated with the persistence of the same virus type (Brisson 1996);

- the presence of vulvar condylomata (Moscicki 1998);

- the use of oral contraceptives for more than 2 years has been associated with an increased risk of persistent infection, according to Brisson (1996), but not according to Elfgren (2000);

- recent stress (Coker 2001);

- smoking was inversely associated with HPV persistence according to a study by Ho (1998), though other studies failed to make any correlation between smoking and viral persistence (Elfgren 2000).

1.2.4   Intraepithelial lesions of the uterine cervix

Intraepithelial lesions of the cervix are often caused by oncogenic HPVs and are precursors of cervical cancer (Syrjänen 1998, Kiviat 1999). However, the majority of intraepithelial lesions have a favorable clinical evolution with spontaneous regression (Syrjänen 1998). These lesions are considered to be the earliest morphological changes associated with cancer. Nonetheless, the natural history and the significance of these lesions are still insufficiently documented (Kiviat 1999).

Cervical intraepithelial lesions were long considered and are still often considered to be elements of a continuum (Suris 1999). However, according to a recent theory, low-grade lesions (LSIL or CIN 1) appear to be non-progressing manifestations of HPV infection, while the most severe lesions (HSIL or CIN 2-3) appear to be *de novo* precancerous lesions caused by high-risk HPV infection (Cox 2001, Kiviat 1999).

Detection of HPV in the cervix is followed quickly by the onset of cellular changes associated with intraepithelial lesions. High-grade lesions (CIN 3) may represent a precocious and relatively frequent manifestation of high-risk HPV infections, particularly with HPV 16 (Cox 2001, Kiviat 1999). Actually, detection of an HPV infection is a better predictor for CIN 2-3 than CIN 1. It seems that at least a part of CIN 2-3 do not develop from CIN 1, but establish themselves de novo, following an HPV infection. It is therefore possible that CIN 1 and CIN 3 are distinct manifestations of different

HPV infections. Another possibility is that CIN 1 and CIN 2-3 are coexisting lesions but with different localizations and growth characteristics and, as a result, with a different probability of cytological detection. It would be important to correctly understand of the actual significance of CIN 1 (marker for benign HPV infection or for precancerous lesion) for proper management of these lesions (Kiviat 1999).

According to Richart (2001), low-grade lesions (CIN 1) are caused by productive HPV infections, 20% by low-risk HPV and 80% by high-risk HPV. These lesions may be indistinguishable from flat condylomata, are temporary and result in atypical cytological results such as polyploid and multiclonal changes (Richart 2001). The possibility that the cervix could the site of two distinct types of lesions caused by HPV has already been considered by Meisels in 1977.

Risk factors associated with intraepithelial lesions

The most significant risk factor for the presence of intraepithelial lesions is HPV infection. The McGill-Ludwig cohort in Brazil showed that the incidence of intraepithelial lesions was 8.7/10 000 women-years among women without HPV infection and 104/10 000 among women with HPV 16 or 18 (Schlecht 2001). The presence of viral DNA was associated with a risk for CIN 3 to 44.3 times higher than among women without viral DNA (Koushik 2001, Woodman 2001, Herrero 2000, Nobbenhuis 1999, Ho 1998, Cox 1995). Considering only high-risk HPV, the relative risk for intraepithelial lesions varies between 5.2 and 110 (Hildesheim 2001, Herrero 2000, Shlay 2000, Ho 1998).

The HPV type with the highest risk of cervical lesions is HPV 16 (Hildesheim 2001, Schiffman 2001, Herrero 2000, Moscicki 2000, Kiviat 1999). According to Kiviat (1999) and Schiffman (2001), between 36 and 44% of women infected with HPV 16 will develop a high-grade cervical intraepithelial lesion during the first 2 years of infection. The non-European variant of HPV 16 is associated with an additional risk of intraepithelial lesion (Hildesheim 2001). Other HPV types associated with a high risk of intraepithelial lesion are HPV 18, 31, 33, 35, 39, 45, 58, 51, 52 (Schlecht 2001, Schiffman 2001, Herrero 2000, Moscicki 2000, Kiviat 1999, Suris 1999).

Besides the type of the HPV, the duration of the HPV infection (Moscicki 2001), the viral load (Woodman 2001, Bettinger 2000, Gravitt 2000, Josefsson 2000, Ylitalo 2000, Schiffman 2000, Swan 1999), multiple infections (Gravitt 2000, Swan 1999) and the persistence of infection (Cox 2001, Elfgren 2000, Moscicki 1998, Ho 1998) are associated with cervical lesions.

Other factors associated with intraepithelial lesions of the cervix are younger age (Kataya 1993), the host's genetic factors (HLA types) (Cox 2001), sexual behaviour (Peto 2001, Suris 1999, Kataya 1993, Koutsky 1992, Meisels 1977), reproductive history (Hildesheim, 2001, Suris 1999) and previous STI history (Coker 2001a, Suris 1999, Koutsky 1992). Also associated are smoking (Hildesheim 2001, Moscicki 2001, Suris 1999, Kataya 1993), folic acid and vitamin C deficiencies (van Eenwyk 1993) and non-participation in cervical cancer screening programs (Peto 2001, Suris 1999, Kataya 1993).

The use of hormonal contraceptives and IUDs is inconsitently associated with CIN: while Coker (2001a) and Hawkins (1999) failed to show an association, Hildesheim (2001) revealed an association with oral contraceptives among women with fewer than three pregnancies, and Meisels (1977)

identified an independent link between cervical lesions and the use of oral contraceptives. Barrier methods appear to have a certain protective effect against intraepithelial lesions (Coker 2001a, Hildesheim 2001, Suris 1999, Coker 1992), as may personal hygiene (Kataya 1993). The association with genital warts is controversial, as mentioned in Chapter 2.7.

Prevalence of HPV in cervical lesions

HPV DNA is present in 20-60% of ASCUS smears (atypical squamous cells of undetermined significance), in 45-83% of low-grade epithelial lesion smears (LSIL) and in 65-89% of high-grade lesions (HSIL) (Table 7, Appendix 1).

The prevalence of HPV in histological specimens with intraepithelial lesion (CIN) is similar: 29-95% in CIN 1, 33-98% in CIN 2 and 46-98% in CIN 3 (Table 8, Appendix 1). The lower values originate from a study by Matsuura (1998) and were obtained with the ViraPap test, which is less effective than tests used in other studies. The higher values come from studies by Nobbenhuis (1999) and Fait (2000). The latter described a definite change in the predominance of HPV types depending on the lesion degree: specimens without histological and CIN 1 lesions essentially contained low-risk oncogenic HPVs, while high-risk oncogenic HPVs were present in cases of CIN 2 or 3 (Fait 2000).

The prevalence of HPV infection in cervical lesions was dependent on age: in a group of women with ASCUS or minor cytological lesions, HPV was detected more often in women under 30 compared to those over 30 (Rebello 2001, Schlay 2000).

Evolution of cervical lesions

Precancerous lesions may have different evolutions: progression, regression or persistence. The majority of lesions are benign in their evolution, with rates of regression increasing over time (Syrjänen 1998, Meijer 2000).

Regression

In the absence of HPV, the median time for cervical lesion regression is 5 to 6 months, depending on the severity of the lesions. By contrast, if HPV is present, the regression time is 17 to 60 months. the regression of the lesions seems to be preceded by the disappearance of HPV infection, in average 3 months earlier (Nobbenhuis 2001). Approximately 68% of ASCUS lesions will eventually regress (Melnikow 1998).

The regression rate for low-grade lesions (LSIL, CIN 1) is between 37 and 88%, the mostly between 50 and 60% (Nobbenhuis 2001, Holowaty 1999, Matsuura 1998, Melnikow 1998, Walsh 1998, Syrjänen 1997). The lowest value of 37% was observed after a 1-year follow-up of women with persistent HPV infection (Nobbenhuis 2001), while the higher value of 88% was obtained after a 10 year follow-up (Holowaty 1999). Among adolescents and young women, Moscicki (2002) revealed a regression rate of 95% over 36 months, with a median regression time of 7 months.

There are few studies of the evolution of high-grade lesions. The regression rate for this type of lesion is estimated to 25-83%, with most authors reporting values around 33% (Holowaty 1999, Melnikow 1998, Matsuura 1998, Walsh 1998, Syrjänen 1997). The highest value in this group, of 83%, represented the regression rate of CIN 2 over a period of 10 years (Holowaty 1999).

Progression

The progression rate for intraepithelial lesions varies greatly in the literature: between 0 and 71% of intraepithelial lesions progress towards the development of invasive cancer (Kiviat 1999), although the majority of authors cite values of approximately 1% (National Institutes of Health, 1997, Melnikow 1998).

As for ASCUS, 7.2-9.3% progress towards more severe lesions (Nobbenhuis 1999, Melnikow 1998). The progression rate for ASCUS to invasive cancer is 0.06% at 6 months and 0.25% at 24 months (Melnikow 1998).

The progression of LSIL occurs in approximately 10% of cases, varying between 4.2 and 28.8% over follow-up periods of 1 to 10 years (Petry 2002, Nobbenhuis 2001, Holowaty 1999, Syrjänen 1997). Moscicki (2002), in a group of young women aged 13 to 22, found a rate of progression to high-grade lesions (HSIL) of 2% after 36 months. The progression to carcinoma in situ is estimated to 10-14% (Suris 1999, National Institutes of Health 1997).

Progression of HSIL occurs in 8-79% of cases (Peto 2001, Richart 2001, Holowaty 1999, Melnikow 1998, Syrjänen 1997). Also, according to Holowaty (1998), the progression of CIN 2 to carcinoma in situ is 8.1% over a 2-year period, while that of CIN 3 is 22.7%.

In a group of Ontario women, the relative risk of progression to carcinoma in situ (CIS) or worse over the first 2 years was 8.1 for CIN 2 and 22.6 for CIN 3 compared to CIN 1. After 2 years, the relative risk remained constant, 2.5 and 4.1 respectively for CIN 2 and 3. The risk of invasive cancer was 4.5 and 20.7 during the first 2 years and 2.1 and 5.6 after 2 years (Holowaty 1999).

Progression of high-grade lesions to invasive cancer occurred in 0.15% of cases at 6 months and 1.4% at 24 months (Melnikow 1998). The progression of severe lesions normally occurs during the first 2 years of follow-up (Holowaty 1999). According to Suris (1999), 36% of carcinoma in situ will progress to invasive cancer.

Meta-analysis

According to Melnikow's meta-analysis (1998), 47.4% of low-grade lesions regress, 6.6% progress to high-grade lesions within 6 months and 20.8% within 24 months. The progression rate to invasive cancer is 0.04% at 6 months and 0.15% at 24 months (Melnikow 1998).

As for high-grade lesions (HSIL), 35% regress, while 6.8% progress to carcinoma in situ within 6 months, 23.4% at 24 months.

Latency period

The minimum interval between HPV infection and invasive cancer is 7 years, while the average interval is 20-30 years (Petry 2001). HPV persistence may lead to the development of CIN 3 and, after a latency of approximately 13 years, the development of invasive cancer (Meijer 2000, Suris 1999). The viral load might influence the evolution towards cancer: the mean incubation period between the time of the first positive results for HPV 16 and a diagnosis of carcinoma in situ is estimated at 17 years for cases with a high viral load and more than 19 years for cases with an average viral load (Ylitalo 2000). The long latency period suggests other influencing factors, as well as modifications to the cellular genome (Meijer 2000).

The incidence of carcinoma in situ is highest between 25 and 40 years of age, while the incidence of invasive carcinoma peaks between 48 and 55 years (Haverkos 2000). The cumulative risk of CIN 3 is up to 10% between 50 and 60 years.

Factors associated with the progression of cervical lesions

Factors associated with the persistence and progression of cervical lesions are: the persistence of HPV infection (Meijer 2001, Nobbenhuis 2001, Ho 1995), the presence of HPV 16 or 18 (Syrjänen 1998), high viral load (van Duin 2002, Syrjänen 1998, Ho 1995), the presence of integrated viral DNA (Peitsaro, 2002), older age (Holowaty 1999, Syrjänen 1998) and the presence of high-grade cytological lesions (Nobbenhuis 2001, Holowaty 1999, Syrjänen 1998). In the study by Petry (2002), no HPV-negative low-grade lesion progressed during a 9-month follow-up. Markers associated with progression are the increased presence of E6 and E7 and the dysregulation of protein p16 (Richart 2001).

1.2.5   Cancer of the cervix

HPV-cancer causality

According to the International Agency for Research on Cancer's (IARC) monograph on HPVs, HPV 16 and 18 play a causal role in the development of cervical cancer. They are classified as confirmed carcinogenes to humans (Group 1). Types 31 and 33 are classified as probable carcinogenes to humans (Group 2A). Other HPV types are possible carcinogenic to humans (Group 2B), with limited evidence of their carcinogenic effects. Evidence suggests no carcinogenic effect for HPV 6 and 11 (IARC 1995).

Two recent case-control studies (Muñoz 2001, Bosch 2000) identified HPV prevalences of 90.4 and, respectively, 88.9% among patients with cervical cancer and 13.9 and 15.4% among the control groups. In the study by Riou (1990), the prevalence of HPV infection among cervical cancer patients was 81%. However, the test used (PCR) only detected a small number of HPV genotypes. In his case-control study, Lehtinen (1996) found that the only infectious factor associated with cervical cancer was HPV 16 infection.

In a retrospective study, the prevalence of HPV was 77% in archived biopsy specimens of women diagnosed with cervical cancer (84% for squamous cell carcinoma and 47% for adenocarcinoma). In this group, on the last normal smear prior to diagnosis the prevalence of HPV was 30%, compared to 3% among controls of the same age, without cancer (Wallin 1999).

The multinational IARC study investigating the causal relation between HPV and cervical cancer detected, in a first time, an HPV prevalence of 93% in the cancer biopsy specimens (Muñoz 2000). Analysis of the HPV-negative specimens with more sensitive methods and excluding the histological specimens without cancer led to a total prevalence of 99.7% (Muñoz 2000, Walboomers 1999). These figures suggest that HPV infection is virtually always present in cervical cancer and is a necessary cause of cervical cancer (Muñoz 2000, Walboomers 1999).

Another indication for the causal role of HPV is its similar prevalence in cancerous lesions in all countries included in the study, despite the fact HPV prevalence in the general population varies largely between these countries (from 5% in Spain to 20% in South America, Thailand and the Philippines) (Bosch 1995).

HPV types most often present in cervical cancer lesions are: HPV 16 in 49-59% of cases (Muñoz 2001, Muñoz 2000, Bosch 2000, Bosch 1995, Riou 1990) and HPV 18 in 12-38% of cases (Muñoz 2001, Muñoz 2000, Bosch 2000, Riou 1990). HPV 16 is most common in women under 40 and in well-differentiated tumors (Riou 1990), while types 33 and 35 are mostly present in older women (Riou 1990) and HPV 18 is usually detected in adenocarcinoma (Bosch 2000, Bosch 1995, Riou 1990).

Risk of cervical cancer associated with HPV infection

The risk of cervical cancer associated with HPV infection, expressed as an odds ratio, varies between 16.4 (Wallin 1999) and 70 (Muñoz 2000) for squamous cell carcinoma and is around 50 for adenocarcinoma (Muñoz 2000). Depending on the HPV type, the odds ratios were 69 to 710 for HPV 16 (Hildesheim 2001, Bosch 2000, Herrero 2000, Muñoz 2000, Ylitalo 2000), 179.5 to 231 for HPV 18 (Bosch 2000, Muñoz 2000), 60 for HPV 31 (Muñoz 2000), 41 to 148 for HPV 45 (Bosch 2000, Muñoz 2000) and 347 for HPV 59 (Muñoz 2000).

Besides the presence of HPV DNA in the cervix, the viral load (Josefsson 2000, Ylitalo 2000), the persistence of infection (Wallin 1999), non-European HPV 16 variants (Hildesheim 2001, Zehbe 1999) and HPV 16 seropositivity (Luostarinen 1999, Daling 1996) are associated with a high risk of cervical cancer.

HPV 6/11 seropositivity seems to have a protective effect against HPV 16-associated cervical, through an antagonistic mechanism, probably at antibody level (Luostarinen 1999, Silins 1999). According to Luostarinen (1999) the risk of cancer for individuals with antibodies against HPV 16 and HPV 6/11 appears to be similar to that of seronegative individuals (RR =1).

Other risk factors for cervical cancer

The fact that only a portion of women with HPV infections will develop cervical cancer suggests that HPV infection is not a sufficient condition for cervical cancer (Muñoz 2000, zur Hausen 2000). Numerous studies have sought to identify other factors associated with the development of cervical cancer.

The main factors associated with cervical carcinogenesis are host characteristics, as well as chemical and infectious factors. The first category includes genetic factors that increase the organism's susceptibility to HPV's carcinogenic effect (Ghaderi 2001, Hildesheim 2001, Maciag 2000). The tumour necrosis factor (TNF) variant TNFa-11 also increases the risk of cancer, particularly in the presence of HPV 16 infection (Ghaderi 2001). Another factor associated with carcinogenesis is the polymorphism of the p53 gene, namely the p53Arg genotype (Zehbe 2000, Zehbe 1999, Makni 2000).

Chemical factors that increase the risk of cervical cancer are smoking (Muñoz 2001, Kjelberg 2000, Burger 1996, Daling 1996), tar (Haverkos 2000) and oral contraceptives (Moreno 2002, Muñoz 2001, Haverkos 2000, Daling 1996). The role of hormonal factors is also supported by the association between parity and the risk of cervical cancer (Bayo 2002, Muñoz 2002, Muñoz 2001, Kjelberg 2000) as well as between first pregnancy at a young age and the risk of cervical cancer (Muñoz 2002). However, according to Kjelberg (2000), oral contraceptives are not linked to cervical cancer. Nutritive deficiencies (Muñoz 2000) and genital hygiene (Bayo 2002) could also play a role in carcinogenesis.

Other possible infectious cofactors for cervical cancer are genital *Chlamydia trachomatis* infection (Smith 2002, Muñoz 2001, Muñoz 2000) and HSV-2 infection (Muñoz 2001, DiPaolo 1999, Daling 1996). Homologous sequences of HSV-2 DNA have been detected in 10-30% of genital tumours. HSV-2 RNA and DNA are detected more often in intraepithelial lesions than in invasive cancers and are not present in normal cervical cells (Daling 1996). Some evidence suggests that HSV and HPV infections may occur simultaneously in the cervical cells and may be followed by malignant transformation (DiPaolo 1999, Daling 1996). On the other hand, other studies associate HSV-2 with cervical cancer only for HPV-negative cancers (Haverkos 2000, Daling 1996).

1.2.6   Cervical adenocarcinoma

The natural history of adenocarcinoma is little understood. It is possible that the model for squamous carcinoma does not apply to adenocarcinoma. Precancerous glandular lesions are rare and more difficult to test for using cytology (Sheets 2002).

In England, the incidence of adenocarcinoma increased sharply in the 1980s, only to stabilize starting in 1988 and diminish again in 1996-1997. This phenomenon was particularly seen among young women. According to the age-cohort model, women born around 1960 are at least 14 times more at risk of adenocarcinoma than women born prior to 1935. The actual magnitude of this phenomenon cannot yet be accurately evaluated due to the young age of women born after 1961 (Sasieni 2001).

The causes of the increase in adenocarcinoma incidence are not known. Hypotheses include changes in sexual practices, HPV 18 infection, use of oral contraceptives (contradictory results) and easier screening for cervical cancer among young women (among older women, the transformation zone is moved to the interior of the cervix and an eventual carcinoma in situ becomes inaccessible) (Sheets 2002, Sasieni 2001).

1.2.7   Anal squamous carcinoma

Generalities

Anal cancer is relatively rare, though incidence is on the rise, particularly among men who have sex with other men (MSM) and HIV-positive individuals (Palefsky 2001, DSTDP-CDC 1999).

The biological and anatomical similarities between the cervix and the anus suggest that the anal region may be the site of lesions caused by HPV such as anal intraepithelial lesions (ASIL) and invasive anal cancer. The relation between HPV, ASIL and invasive anal cancer is comparable to that between HPV and cervical cancer. The HPV types are the same in both sites. HPV 16 is the most frequent cause of both cervical and anal cancer. It is therefore reasonable to assume that high-grade anal intraepithelial lesions are precancerous lesions similar to high-grade cervical intraepithelial lesions (DSTDP-CDC 1999, Palefsky 1996).

There are no guidelines for screening anal intraepithelial neoplasia (AIN) and presently the incidence of these lesions in MSM is higher than the incidence of cervical cancer in women (Palefsky 2001).

Persons most at risk of developing anal cancer are HIV-positive women and men and those who have had receptive anal sex. Anal HPV infection is probably mostly sexually transmitted, although the possibility of transmission via fingers or contaminated objects has not been ruled out (Palefsky 1996).

Association of HPV infection with anogenital cancers other than cervical

The role of HPV infection in the onset of anal intraepithelial lesions and squamous neoplasia of the anus is not well known (Palefsky 2001b). According to a case-control study by Bjørge (1997), anogenital cancers (other than cervical) are associated with the presence of HPV 16 (OR of 3.1 for all cancers, 4.5 for vulvar and vaginal cancers and infinite for preinvasive lesions). The OR for anal and penile cancers is 4 but is not statistically significant. Vaginal cancers are more often associated with HPV infection than are vulval cancers (76% versus 30%). On the other hand, HPV is often detected in vulvar intraepithelial lesions (Bjørge 1997).

1.2.8   HPV infection and HIV infection

The association between the two infections is bidirectional. On one hand, the presence of well-vascularized and fragile squamous intraepithelial lesions may encourage the acquisition of HIV infection or reinfection with new strains of HIV (Palefsky 1996). On the other, it seems that HIV

infection alters the effect of HPV on the cervix, increasing the risk of developing intraepithelial lesions. The association of HPV with intraepithelial lesions is strongest among women with mild immunosuppression, suggesting that in cases of more severe immunosuppression, factors other than HPV infection may intervene or that there is a direct interaction between HPV infection and HIV infection (Rezza 1997).

The presence of HIV DNA might cause a local immunitary dysfunction and an inability to control HPV infection. Other studies have described the over-regulation of HPV by HIV (Chritchlow 1998). As well, HIV infection may be associated with an increased transcription activity of the first-stage HPV genes (Spinillo 2001). Furthermore, the role of immunity in preventing cervical cancer is well documented (Kiviate 1999). Globally, women infected with HIV have a higher risk of acquiring sexually transmitted infections (STI), including HPV infections (Palefsky 1996). HIV-positive women are more at risk of developing squamous intraepithelial lesions of the cervix (Hawes 2001, Ellerbrock 2000) and invasive cancer (Hawes 2001).

HIV is associated with a high prevalence of precancerous lesions and the persistence of HPV infection among HIV-positive women (Haverkos 2000, Palefsky 1996). Infection by multiple types is more common and HPV shedding is increased among those infected with HIV. HIV-positive women often have multifocal HPV lesions, including not only cervical lesions but also vulvar and anal lesions. Among HIV-positive women, invasive cervical cancers are more aggressive and treatment of intraepithelial lesions is more often unsuccessful (Palefsky 1996). HPV infection is modulated by the degree of immunosuppression, the HPV's viral replication increasing with the reduction of immunitary function (Palefsky 1996). Despite this association, the incidence of cervical cancer has not increased in women infected with HIV in recent years (Haverkos 2000, Palefsky 1996). It is possible that HIV-positive patients die of other causes before developing invasive cervical cancer (Kiviat 1999).

The introduction of highly active antiretroviral therapy and longer follow-up of HIV-positive women suggest that in the future more women might develop precancerous cervical lesions and that participation by women in screening programs is imperative (Ellerbrock 2000). Finally, the incidence of anal cancer has significantly increased among HIV-positive men and women (Palefsky 1996).

1.3 DETECTION OF HPV INFECTIONS

1.3.1 Testing methods for HPV detection

Until recently, the only means of diagnosing HPV infection was direct or enhanced visual inspection, a specific but not particularly sensitive method. Applying acetic acid increases the sensitivity of visual inspection for all HPV infections, but does not distinguish between benign and precancerous lesions (Johnson 1994). Likewise, colposcopy with acetic acid application is sensitive (66-96%, depending on the size of the lesion) but has a low specificity of approximately 80% (Denny 2002, Belinson 2001, Sankaranarayanan 2001, Johnson 1994). The past decades have witnessed the introduction of increasingly effective molecular diagnostic techniques for HPV infection.

The **Southern Blot** method, developed in 1975, is the foundation for all other specific HPV detection methods. In this method, DNA is extracted and enzymatically digested. The resulting fragments are then separated by electrophoresis according to their size. The isolated fragments are denatured and identified with the help of single-strand fragments of complementary DNA or RNA labelled with radioactive or calorimetric molecules. This method requires relatively large quantities of DNA, is tedious and is impossible to automate (Cuzick 1999a).

The **Dot Blot** method **(ViraPap, Viratype)** is a simplified version of the Southern Blot that avoids the enzymatic digestion and electrophoresis stages. It may be partially automated but requires large amounts of DNA and has lower sensitivity and specificity (Cuzick 1999a).

The **FISH** method (*filter in situ hybridisation*) is also derived from the Southern Blot but skips the DNA extraction step. The target cells are applied directly to a solid support and treated to DNA denaturation and identification. While the method is simple, it does not perform adequately in clinical use (Cuzick 1999a).

In situ **hybridization (ISH)** is used for directly analyzing biological tissues fixed to microscope slides. The permeability of cellular membranes is enhanced and nucleic DNA is denatured using either alkaline solutions or heat. The steps that follow are similar with those of the Southern Blot. Recent variants of this method have allowed for typing of all HPVs and have made automation possible (Cuzick 1999a). ISH detects HPV only in the presence of active synthesis of viral DNA, as opposed to other more sensitive methods (Nuovo 1998). According to the study by Euscher (2001), *in situ* hybridization appears to be the most effect method for ASCUS triage – more specific than HC II testing. According to Coutlée (personal communication), *in situ* hybridization is useful for doubtful biopsy results and for diagnosing HPV laryngeal papillomatosis wherein the viral replication is high.

Hybrid Capture is based on hybridization in a homogenous solution of unmarked single-strand RNA probes that complement the targeted sequences. The kinetics of reassociation between the nucleic acid strands work best in a liquid solution, as opposed to the previos tests, which rely on heterogeneous reaction background. The cellular DNA is denatured and hybridized with complete specific RNA probes. The resulting molecular hybrids are then captured in a microplate well or in a tube by universal capture antibodies specific for the DNA-RNA hybrids. After washing, the captured DNA-RNA molecules are detected using multiple monoclonal antibodies conjugated with alkaline phosphatase. The addition of chemiluminescent dioxetane causes the emission of light that can be measured by a luminometer (Coutlée, personal communication). This reaction is expressed in relative light units (RLU) corresponding to a 1.0 pg/ml concentration of DNA (Cuzick 1999a). The threshold value recommended in the United States is 1 pg/ml. In other countries, the value varies between 0.5 and 5 pg/ml, depending on the prevalence of HPV infection (Terry 2001).

The first-generation Hybrid Capture (**HC I**) was difficult to automate and had a less than optimum sensitivity and specificity. The method was able to detect the presence of one of 9 high-risk HPV genotypes (16, 18, 31, 33, 35, 45, 51, 52 and 56) and one of 5 low-risk types (Cuzick 1999a), without identifying the specific type of the present HPV (Franco 2002).

Hybrid Capture II (**HC II**) detects more HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) and its sensitivity is similar to PCR. The format of the test is conducive to automation and large-scale use. The HC II is an effective test that requires less expertise than cytology (Terry 2001). Currently, the HC II test is the only HPV test available for commercial use (Cuzick 1999a). The method is also simple to learn and allows for easy quality control (Coutlée, personal communication).

The **PCR** (polymerase chain reaction) allows the replication (amplification) of the sample DNA, by using a repetitive technique of denaturation, hybridization with complementary primers and DNA synthesis. The method requires minimal amounts of DNA and has a high sensitivity and specificity. The PCRs for HPV infection use consensus primers that are capable of amplifying a large number of HPV genotypes. The most used consensus PCR protocols are MY09/MY11, GP5+/GP6+, SPF and PGMY. The MY09/MY11 PCR is less sensitive for HPV 35 and there are occasional variations between batches. A new variant of the method, PGMY09/11, is more sensitive, particularly for HPV 35, 52 and 56 (Coutlée 2002). The GP5+/GP6+ is better for detecting HPV 43, 35 and 44 (Bauer 1992) but is less sensitive for HPV 53 and 61, as well as for multiple infections. The PGMY and SPF PCR have a better reproducibility because they do not require the use of degenerated primers (van Doorn 2002) and are integrated in a nonisotopic typing format (line dot and line probe) according to a standardized protocol and using standardized reagents. Intralaboratory and interlaboratory reproducibility, along with the precision of these PCRs are excellent for HPV detection and typing (Coutlée, personal communication). Although they are more analytically sensitive than HC II, PGMY and SPF PCRs are possibly less specific (Coutlée, personal communication).

The detection of the amplifimers can be automated, allowing quick analysis of an important number of samples (Cuzick 1999a). The major problem with PCRs is the high risk of contamination, which may result in false positive results (Villa 2000, Cuzick 1999a) and the need for specialized laboratories (Cuzick 1999).

A new method for HPV detection and genotyping is the **DNA Chip**. This method, still under evaluation, uses PCR amplification products and is able to identify 22 HPV genotypes (Im 2001). Compared to the HC II, the sensitivity and specificity of the DNA Chip are 100% and 98% respectively, with a correspondence of 98.6% (Im 2001). Other future possibilities are the quantification of high-risk HPVs using real-time PCR, the detection of integrated HPV and the use of real-time PCR to measure the transcriptional activity level (RNAm) of high-risk HPVs (Coutlée, personal communication).

HPV detection is strongly affected by the quality of the samples, in terms of cell quantity. Only the PCRs include a control of the cells content of the sample (Coutlée, personal communication).

1.3.2   Methods of HPV typing

The presently existing methods for identifying HPV types include type-specific PCR, line blot methods and pyrosequencing.

Reverse line blot analysis is a quick and simple HPV typing procedure, based on GP5+/GP6+ PCR amplification products. This method can analyze 42 samples per day per membrane, with a concordance of 96.5% for both single and multiple infections (van Den Brule 2002).

Pyrosequencing is effective (100% concordance with type-specific PCR), easily automated (capacity of 96 samples simultaneously), quick, inexpensive and does not use radioactive material. Typing is done using PCR amplification products (Gharizadeh 2001) and can correctly identify the presence of high-risk HPV, even for multiple infections (Gharizadeh 2002). Eventual problems with the sequencer may increase costs and a panel of experts convened to discuss this matter concluded that sequencing might not be the future answer for typing. It may also lack sensitivity. On the other hand, sequencing is excellent for analyzing type variants (Coutlée, personal communication).

PGMY and SPF consensus PCR now use an inverse hybridization strip test, which allows for typing of up to 35 HPV types per single nonisotopic hybridization reaction. These tests allow for the detection of multiple infections. A microplate test using a generic HPV probe has been developed that, in a first step, determines which sample contains HPV DNA and eliminates the need to run typing tests on the HPV-negative samples (Kornegay 2001).

1.3.3   Serology

The detection of HPV antibodies is less used, due to the multitude of HPV genotypes and inconsistent immunological response. Roughly half of the cervical cancers are associated with HPV 16 and only half of these HPV 16 infections induce a seroconversion (Höpfl 2001, Shah 1997, Viscidi 1997) for unknown reasons (Höpfl 2001). According to Daling (1996), HPV seroprevalence is an unreliable measure of HPV exposure, its association with the presence of viral DNA demonstrating weak sensitivity. Among women with HPV 16 DNA detected, only 42.7-46% were seropositive (Daling 1996, Viscidi 1997).

The sensitivity of serology for detecting anti-HPV antibodies is approximately 50% in best case scenarios, maybe up to 65-75%. Specificity is difficult to measure but is estimated at more than 98% (Dillner 2000). HPV seropositivity is associated with the number of sexual partners, cytological lesions and previous HPV 16 infection (Castle 2002). According to Viscidi (1997), it is not associated with external genital warts, low-grade cytological lesions or condom use.

In a case-control study (women with cervical cancer and matched controls) to demonstrate the link between the presence of HPV antibodies and cervical cancer, 33.3% of women with cervical cancer were seropositive for HPV 16 and 33.3% for HPV 6. Cervical cancer was directly associated with HPV 16 seropositivity and with the level of HPV 16 antibodies, the adjusted odds ratios being 3.9 and 7.5 for the two measured antibody levels (Shah 1997).

1.4 TREATMENT

1.4.1 Treatment of genital warts

The goal of treating external condylomata or genital warts is the ablation of lesions. Conventional therapies may remove the majority of symptomatic warts but no single treatment is ideal for all patients (Beutner 1998). Treatment should be adjusted according to symptoms, the patient's needs and available resources (Beutner 1998). Available treatments can only deal with visible lesions and do not treat the HPV infection itself (Ferenczy 1995).

According to the American Medical Association (AMA) consensus conference, condylomata treatment may result in genital wart-free periods but does not necessarily eradicate the infection.

It cannot be determined whether eliminating genital warts reduces infectiousness since these lesions may represent only a portion of the viral burden (Beutner 1998). In other words, we do not know if visible condylomata are more infectious than latent or subclinical ones, nor do we understand the effect of condylomata ablation on transmission (Verdon 1997). The effect of treatment on the transmission of HPV infection is also little known. Theoretically, however, ablation of clinical lesions should reduce the viral load, and, consequently, transmission (Wilson 2002).

The disappearance or spontaneous reduction of clinical lesions is well documented, though it is impossible to predict individual evolution. On the other hand, delaying treatment may result in growth of the lesions and treatment becoming more difficult, costlier and lengthier (Ferenczy 1995). Van Krogh (2000) states that, considering the very real possibility of spontaneous regression, delaying treatment is an acceptable option for managing warts, regardless of their localization. Wilson (2002) also concluded that sometimes treatment provides little benefits, other than cosmetic and psychological, and that the patient should make the final decision. Verdon (1997) questioned the value of treatment for stable monogamous couples due to the benign nature of genital warts and the possibility of spontaneous remission. However, the majority of patients prefer treatment due to the psychological distress caused by the lesions (Verdon 1997).

The recurrence rate for genital warts does not change with the presence or absence of condylomata in the partner, nor with condom use. Recurrences seem to originate from the patient's own reservoir of infection rather than the partner's. Evaluating and treating the partner has no influence on the recurrence rate of condyloma acuminata, or on the time between recurrences (Krebs 1991). Also, in the study by Krebs (1990), treating the partner's warts did not influence the treatment results of women with cervical lesions. Thus, there is no justification for screening and treating stable and monogamous partner's subclinical lesions, due to the complications, high cost of treatment, and marginal expected benefits (Ferenczy 1995).

It is unlikely that the ablation of condylomata (genital warts) among women influences the development of cervical cancer (Verdon 1997).

Post-treatment follow-up is not absolutely necessary. It may be useful for patients worried about possible recurrences (Beutner 1998).

Treatment types

Therapies available for condylomatosis are surgery, cryotherapy, LEEP, laser vaporization, trichloroacetic acid, 5-fluoro-uracil, interferon, podophyllotoxin, podophilox and imiquimod. All these options, except the latter two, require application by a health-care professional. Podophilox and imiquimod are the only treatments available for self-administration. Usually treatment must be repeated several times, which contributes to its high cost (Ferenczy 1995).

Surgery (curettage, excision) is effective[2] (80 -93%) with infrequent sequelae. Recurrence, however, may occur in 20-30% of cases (Von Krogh 2000).

Cryotherapy is simple and inexpensive, with an effectiveness of 63-89%. Techniques, however, are difficult to standardize (Von Krogh 2000).

LEEP (electroexcision) is among the preferred treatments for vaginal condylomata and cervical lesions and is inexpensive (Ferenczy 1995), with an effectiveness of 72-90% (Alam 2001).

CO2 vaporization has an effectiveness of 80-90% but is expensive (Ferenczy 1995).

Trichloroacetic acid (concentrations of 50-80%) has an initial response rate of 70-81% and a recurrence rate of up to 36%. The risks of sequelae due to excessive application are quite high. This method may be used during pregnancy (Von Krogh 2000).

5-fluoro-uracil is used for condylomata of the meatus with an effectiveness of 60-90% (Ferenczy 1995).

The intralesional injection with **interferon** has an effectiveness of 80%. Systemic interferon has little effect in treating condylomata, but increases the recovery rate when it is administered in parallel with excision (Ferenczy 1995). Nonetheless, the side effects and the high cost of systemic interferon treatment have led to the abandonment of this therapy.

Podophylline (concentration of 20-25%) is inexpensive but offers only modest results (effectiveness of 38-79%) and seems to have mutagenetic effects (Von Krogh 2000).

Podophyllotoxin (concentrations of 0.5 and 0.15%) is a local treatment that can be applied by the patient at home. Treatment is normally 4 weeks long and leads to the disappearance of 70 to 90% of condylomata acuminata (French 2002, Von Krogh 2000, Beutner 1989) and the complete disappearance of condylomata in 45-68% of patients (Tyring 1998, Syed 1994, Kirby 1990, Beutner 1989). The rate of recurrence is 7-38% (Von Krogh 2000, Beutner 1989), but according to a study by Kirby (1990), all patients had recurrences over the long term (non-specified duration). The frequency of side effects is 50-65% (Von Krogh 2000). Side effects are temporary and usually of light or moderate intensity (Beutner 1989).

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[2] Effectivenss is defined as the capacity to induce disappearance or reduction of more than 50% of treated lesions.

Imiquimod 5% is an immune response modulator that triggers the local production of interferon α and γ and the recruitment of immune cells, including CD4. The length of treatment varies between 8 and 16 weeks. This procedure may induce wart regression and the reduction of HPV DNA. In the study by Fife (2001), 90% of warts regressed. The clearance rate (complete disappearance of warts) is 45-62% (French 2002, Golnick 2001, Von Krogh 2000), higher among women (77%) and circumcised men (40%) (Von Krogh 2000, Beutner 1998). As well, the clearance time is shorter in women (8 weeks versus 12 weeks). The recurrence rate is 13-19%; the proportion of patients with side effects is 67% (Von Krogh 2000, Beutner 1998).

According to the meta-analysis of Moore et al (2001), the effectiveness of imiquimod 5% was 47% for the complete clearance of warts (compared to 18% with imiquimod 1% and 2.4-7.3% with a placebo). Women saw a higher rate of disappearance than men (72% compared to 37% in men). The percentage of patients whose warts completely disappeared and had no recurrence was 37% with imiquimod 5%, 15% with imiquimod 1% and 4-5% with a placebo. The frequency of adverse reactions that forced the treatment to be terminated was 2.4% with imiquimod 5%. The most common side effect was local inflammation. In conclusion, imiquimod 5% is an, effective, patient-applied treatment that can result in some reversible side effects, primarily inflammatory reactions (Moore 2001).

Podophyllotoxin and imiquimod are not recommended for pregnant women (imiquimod has not been tested on pregnant women but has not demonstrated any teratogenic effect in animals) (Von Krogh 2000).

The use of more than one therapeutic method simultaneously is not recommended as a routine approach (Beutner 1998).

Side effects

The side effects of condylomata treatment vary, depending on the therapeutic approach. Ablative methods may cause chronic pain syndrome or hyperesthesia and scarring or persistent changes in pigmentation (Beutner 1998). Topical treatments may often cause inflammatory reactions (Edwards 1998). Cutaneous lesions caused by treatment may facilitate the transmission or acquisition of other STIs (Beutner 1998). Thus, the side effects of treatment may contribute significantly to the morbidity associated with genital warts (Verdon 1997).

1.4.2   Treatment of cervical lesions

The clinical management options for dealing with cervical intraepithelial lesions (SIL) include surveillance, selective treatment or routine treatment. The best approach appears to be selective treatment, but it is difficult to identify the selection criteria (Prendiville 2000). The choice of treatment should consider the following factors: the presence of high-risk HPV, the relative indication for treatment or surveillance, the probability of defaulting on follow-up, patient anxiety, colposcopic suspicion of intraepithelial lesion, the persistence of the abnormality over more than two years, age and smoking (Prendiville 2000, Ferenczy 1997).

The incidence of HPV infections and low-grade cervical lesions that spontaneously regress is very high among young women. Thus, screening these women reveals the clinical manifestations of these infections but does not necessarily identify those women that will develop cervical cancer. A post-screening biopsy may therefore reveal intraepithelial lesions that were treated in an invasive manner, sometimes unnecessarily (O'Mahony 1996).

Treatment options for cervical lesions are cryotherapy, the loop electrosurgical excision procedure (LEEP), laser therapy and cold-knife conization (Ferenczy 1997). The preferred treatment method for cervical lesions is the LEEP, which eliminates the risk of overlooking invasive cancers and has little risk of complications (Ferenczy 1997). As well, the cost of equipment is reasonable and 90% of patients are treated in a single session (Ferenczy 1995). In the study by Ferenczy (1996) on using LEEP in a "see and treat" approach, 14% of excised specimens did not have any histological lesions and the clearance rate was 92% (95% after a second LEEP), with complications seen in 7% of patients.

Other non-surgical treatments are in development. In a series of 14 patients with vulvar, vaginal or cervical dysplasia (6 CIN3, 2 VaIN3 and 6 VIN3) treated with imiquimod 5% 3 times a week for 16 weeks, the regression rate for lesions was 71%, while the rate of recurrence was 21% after an average follow-up of 19 months. The proportion of patients with light side effects was 28%, with none presenting signs of severe side effects. A phase IIb trial is under way to evaluate the effectiveness of imiquimod to treat genital intraepithelial lesions (Diaz-Arrastia 2001). Cidofovir is an anti-viral agent with antiproliferative effects that offers promising results in the treatment of intraepithelial neoplasia (Abdulkarim 2001).

Among women treated with laser vaporization or conization for cervical intraepithelial lesions, 90% tested negative for HPV, 6 to 12 months after treatment; only one of the 30 treated women showed persistence of cytological lesions in a follow-up Pap test (Strand 1997). In the study by Dalstein (2001), 9 months after treatment for cervical lesions, 84.5% of women tested negative for HPV and 85.7% had normal cytologies. The link between HPV positivity and the presence of cytological lesions on post-treatment follow-up suggested that HPV testing is an invaluable tool for evaluating the effectiveness of treatment, with HPV disappearance being a sign of success, while persistence suggests incomplete excision (Dalstein 2001). Also, in the Bettinger study (2000), after treatment for cervical lesions, 85% of patients had undetectable or reduced HPV DNA viral load. An increased viral load following treatment was an indicator of therapeutic failure or of a recurrence (Bettinger 2000). According to Ferenczy (1995), the risk of recurrence of cervical HPV infections is low (4.1-6.7/1000), even without treatment of the partner. Treatment failure for cervical intraepithelial neoplasia is associated only with the persistence of HPV infection and with smoking (Acladious 2002).

1.4.3   Follow-up of cytological abnormalities

The management procedure for women with cytological abnormalities should take into consideration the temporary nature of the majority of low-grade and ASCUS lesions. A repeat Pap test or using an HPV test are two possible approaches to identify the women who really need an intervention. HPV testing has greater value in women aged 30 to 35 with an ASCUS cytology and in women over 35 with an ASCUS cytology or with low-grade lesions. For women under 35, a positive HPV test calls

for a repeat Pap test within a year, because of often transitory nature of these infections and the associated lesions. Among women over 35, a positive HPV test, in the presence of minor atypia in the transformation zone, justifies, according to some authors, treatment by excision because a high-grade lesion may be present (Miller 2000).

In Canada and the Netherlands, low-grade lesions (LSIL) and ASCUS are followed up with additional Pap tests every 4 to 6 months for 2 years; in persistent cases, colposcopy is recommended. After three normal Pap tests, the normal time between screenings (every 3 years) may resume. In the United States, most gynecologists recommend an immediate colposcopy and biopsy, followed by ablative treatment or excision. Considering that the majority of lesions regress, a follow-up with Pap tests or even colposcopy reduces costs, stress and therapeutic complications. The disadvantages of the monitoring are anxiety, frequent visits, the cost of frequent colposcopies and the risk of dropout (Walsh 1998)

The management procedure in the case of high-grade lesion is immediate colposcopy with endocervical curettage and biopsy (Walsh 1998).

1.4.4   Therapeutic vaccines

Therapeutic vaccinations for infected individuals must target the antigen-specific T cell immunity. The antigens used to develop therapeutic vaccines are E6 and E7. These proteins are always present on the surface of the infected cells, therefore it is most unlikely that cancerous cells could evade the immune response (Ling 2000). Vaccines tested to date demonstrated a good immunogenicity. Their efficacity, however, is not yet known (Stanley 2002).

It is not yet known to what extent these vaccines are capable to induce an effective immune response among individuals with persistent infections, mostly people with a constitutional inability of their immune system to identify and fight the main viral antigenes (Wheeler 1997).

1.5   PSYCHOLOGICAL IMPACTS

Being diagnosed with a genital HPV infection has a considerable psychosocial impact. The psychological impacts are essentially related to the sexual way of transmission and worries about possible complications, specifically the fear of progression to cancer (Mast 2001). According to Crum and Berkowitz (2002), the success of HPV screening depends largely on the success of the education of the target population.

Having an STI is generally associated with shame and stigma, particularly in the context of limited knowledge (Harper 2001, Alexander 2000). More precisely, the psychological effects related to the diagnosis of HPV infection include negative emotions at the time of diagnosis – anger, shame, depression, isolation, fear of rejection (66%), guilt (60-78% of patients), worry about transmitting the infection (73%) and fear of negative judgement (73%) (Clarke 1996).

In a group of university students, emotional reactions were intense following a hypothetical disclosure of a positive HPV test; these including anxiety and regrets. Negatives emotions were not associated with knowledge. But anxiety and preoccupation were associated with higher levels of knowledge, while distress was associated with a low level of knowledge (Ramirez 1997).

Refusing to undergo an HPV test was associated with negative emotions, with those who did refuse expressing greater negative emotions. Regret and low self-esteem were particularly strongly associated with refusal of the test (Ramirez 1997).

The psychological impact seems to be long lasting, not improving significantly over time (Neil 1998). The majority of women diagnosed with an HPV infection are in long-term relationships or married. Thus, the repercussions of these psychosexual perturbations are even more important for the couple (Campion 1988).

The impact on sexuality manifests itself through reduced sexual pleasure (68%), low perceived desirability (72%), fear of sexual rejection (19%), difficulty in approaching a new sexual partner, reduced spontaneity (86% and 73%) and fewer sexual relations (72%). These negative impacts diminish over time but persist at significant levels even years after diagnosis (Clarke 1996).

More specifically, the psychosexual effects of a diagnosis of a cervical HPV infection are:

- a high percentage of pathological test scores for anxiety (Mast 2001, Neil 1998, Filiberti 1993) and depression (Mast 2001, Filiberti 1993). By contrast, Neil (1998) and Zarcone (1998) did not demonstrate excessive depression compared to the general population.

- guilt (Philips 2000).

- negative impact on sexual activity in roughly half of patients (Zarcone1998, Filiberti 1993, Campion 1988) or even complete abstinence (Zarcone1998, Filiberti 1993). Women identify sexuality as cause of their illness, resulting in the loss of sexual desire and the turning sexuality into an unpleasant and emotionally hurting experience (Zarcone 1998).

- deterioration of the emotional relations with the partner (Zarcone1998, Filiberti 1993, Campion 1988).

- reduced libido (suggesting profound changes in self-esteem and body image), less frequent sexual contacts and a reduced response to sexual stimuli (Campion 1998).

- fear of cancer (Philips 2000, Filiberti 1993).

Detected barriers to the resolution of fears and uncertainties are linked to the health care system (paternalistic attitude of health professionals, information material poorly adapted to patients' specific needs), but also to the individual (fear of asking questions or wasting the doctor's time, etc.) (Harper 2001). In an ASHA investigation, the majority of individuals with HPV infection were not satisfied with the medical services they received. The least satisfactory aspects were emotional counseling, questions about sexual practices and references to other sources of information. One third of patients changed healthcare provider and were more satisfied with the new one. However, inadequacies remained in terms emotional counseling and questions about sexual practices (Clarke 1996).

When interpreting the results of studies on psychological aspects, it is important to note that some lack scientific rigour.

1.5.1 Impact of condyloma diagnosis

Anogenital warts have a distinctive psychosexual impact due to their visual aspect – anxiety, guilt, anger, loss of self-esteem, as well as worries about future fertility and risk of cancer (Van Krogh 2000). The majority of patients consider treatment for warts difficult, embarrassing, painful and uncomfortable (Maw 1998).

The Maw study compared the impact of condyloma diagnosis in several populations and demonstrated a stronger concern among Canadians, particularly in terms of the need for information on risk of transmission, on recurrence and on association with cervical cancer. Among Canadians, 40% expressed a desire for additional information on condylomata (versus 6% of Germans, 13% of Britons), a need for clear communication and appropriate counseling, including information on treatment options and on lifestyle changes necessary to reduce the risk of transmission (Maw 1998).

1.5.2 Impact of diagnosis and treatment of cervical lesions on psychosocial and sexual life

HPV screening identifies a large number of infected women, but only a minority will eventually develop cancer. Thus, significant proportions of women worry needlessly and feel stigmatized about having a sexually transmitted infection. This fact may discourage participation in screening, mostly for some of the women who are at higher risk (Cuzick 1999a).

The difference in emotional reaction following disclosure of an HPV infection compared to an abnormal Pap test is not known. Routine follow-up of a Pap test reassures women, while the introduction of a new test that is associated with an STI might change the existing equilibrium in the women's attitude and might reduce the willingness to undergo screening (Harper 2001).

Annual cervical cancer screening programs may cause feelings of embarrassment and self-consciousness. Follow-up procedures, diagnosis and treatment, in the case of cytological abnormalities, generate considerable fear and anxiety (Mast 2001). Colposcopies also generate considerable anxiety specially the see-and-treat approach. The anxiety generated appears to be higher than anxiety felt prior to some surgical interventions (non-specified) or after detection of high levels of alpha-fetroprotein (score of 56.6 versus 41.2 and 47.7) (Freeman-Wang 2001). However, according to a randomized trial by Freeman-Wang (2001), distributing information material prior to the procedure significantly reduces anxiety. The psychosexual trauma caused by repeated smears and colposcopies appears to be that much greater among adolescents who have just become sexually active (O'Mahony 1996).

1.6 PREVENTING HPV INFECTION

In public health, it is generally admitted that preventive interventions must occur on three levels: primary prevention, secondary prevention and tertiary prevention.

Primary prevention is defined as any measure that blocks the onset of problems (STIs) (pro-active action). Secondary prevention consists of measures to detect STIs as early as possible. Tertiary prevention is any measure aimed at treating infection to prevent further transmission and complications[3].

STI progression is determined by three factors[4]:

1. *the mean exposure rate of susceptible individuals;*
2. *the average probability that an exposed individual will contract the infections (average effective transmission rate);*
3. *the mean duration during which the recently infected individual remains infectious and can transmit the infection to another person.*

Interventions that can prevent the spread of STIs in a population must therefore attempt to*:*

- *reduce the exposure rate by lowering the number of sexual partners;*
- *lower the efficacy of transmission during exposure;*
- *reduce the duration of STI infectiousness.*

Primary prevention

Considering that viral STIs such as HPV infection are often asymptomatic and undiagnosed, that they may be sexually transmissible even in the absence of symptoms, that treatment does not necessarily eradicate infection, that they may progress to serious complications and that they may contribute to HIV transmission, primary prevention is an essential strategy. Primary prevention of STIs must therefore encourage delaying of sexual activity, adopting lower risk sexual behaviours and vaccination. The main primary prevention strategies are information, education and communication (IEC), the use of barrier methods and prophylactic vaccination.

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[3] MSSS. Stratégie québécoise de lutte contre les MTS. Orientations 2000-2002. 2000.
[4] Institute of Medecine, Division of Health Promotion and Disease Prevention, Committee on Prevention and Control of Sexually Transmitted Diseases, *The Hidden Epidemic* (Thomas R. Eng and William T. Butler, editors, National Academy Press, 1997, 432 pages), ch. 4, *Prevention of STDs*, pp. 118-164.

1.6.1   Information, education and communication

A number of studies have investigated the HPV knowledge level among young people. The majority of young people with an acceptable understanding of STIs in general have few specific notions about the HPV infection and about its associated pathology (Lambert 2001). If young people seem to be relatively well informed about external condylomata and genital warts, they are less knowledgeable about the prevalence of infection, infections of the cervix and penis, ways of transmission, risk factors, the utility of the Pap test and association with cervical cancer (Baer 2000, Mays 2000, Ramirez 1997).

In a group of adolescent and adult women, only 35% of adolescents and 40% of adults understood the goal of the Pap test and none of the women associated it with HPV infection. Only six participants mentioned that the results of the Pap test indicate the presence or absence of lesions linked with cancer. The majority of women considered the Pap test to be a general exam for reproductive health, including fertility and detecting pregnancy and infections (Mays 2000).

The perceived risk related to HPV infection seems very low (Baer 2000, Ramirez 1997). Many young people acknowledged being more concerned with relatively rare infections (such as HIV infection) than with contracting more common STIs, such as genital Chlamydia or HPV infection (Baer 2000). Risk perception is a complex notion and is influenced by many different factors. While it is recognized that knowledge alone is not sufficient for appropriate risk perception, it is a significant element. Improving understanding of the HPV infection is therefore an objective of primary prevention interventions. Such interventions may target the general population, target groups (teenagers, STI patients, MSM, etc.) or individuals (counseling) (Meheus 1997). Improving public understanding about HPVs appears to be beneficial, though difficult to achieve. According to the CDC (2000), the optimal approach would be the ongoing information of the population on scientific progress, in order to reduce stigmatisation and increase compassion.

Information sources

The main information sources for young people concerning HPV infection are health education programs (29-87% of participants), magazines (23-43.7%, particularly for women), television (17-33%), health care professionals (30-31%), friends (22%), parents (22%) and clinics (23%) (Baer 2000, Mays 2000, Ramirez 1997). In a multinational study (European countries and Canada), the primary source of information on condylomata, reported by 85% of participants, was the medical doctor (Maw 1998).

Promoting safe sexual behaviour

Considering the factors associated with a high prevalence, it is logical to assume that postponing initial sexual activity, reducing the number of sexual partners and choosing "low-risk" partners might reduce the prevalence of HPV infection (DSTDP-CDC 1999). Given the frequency of exposure to HPV during early sexual activity, some authors estimate that education programs that have proven to be effective in STI preventing might be even more effective in preventing HPV infection (Lambert 2001). In a study by Lambert (2001), educational intervention increased the knowledge level on HPV infection, a prerequisite for eventual behavioral changes that could prevent infection.

According to the Cochrane Review (Shepherd 2001, Shepherd 2000), intervention strategies that promote safe sexual behaviour are usually effective, particularly if several strategies are used simultaneously (information, group discussions, role-playing, practical exercises, media, peer educators). Educating women about HPV should be planned in a culturally and age-appropriate manner, without alarming or labelling them. According to the experience of the breast cancer prevention programmes, peer education would be a promising approach (Alexander 2000).

1.6.2   Barrier methods

Several studies have demonstrated the protective effect of barrier methods against cervical lesions (Coker 1992, Coker 2001a, Suris 1999, Hildesheim 2001). The inverse association between barrier methods and cervical lesions reveals a dose-effect association: the protection offered increasing with the duration of use (Coker 2001a, Coker 1992, Parazzini 1989). The reduction of the risk of cervical lesions is, after controlling for confounding factors, between 30 and 70% (Coker 1992, Parazzini 1989), possibly higher for invasive cancer (Parazzini 1989). According to Coker (1992), a diaphragm might offer better protection than a condom, possibly due to simultaneous spermicide use. Recent data concerning the effect of Nonoxynol 9 on genital mucous membranes may raise doubts about this hypothesis.

According to Verdon (1997), condom use may reduce the risk the transmission of condylomata (genital warts), less so for scrotal or vulvar warts. According to Ferenczy (1995), the recurrence rate for condylomata is not affected by condom use.

1.6.3   Training of health care professionals

Health professionals themselves often lag behind in their understanding of HPV, excepting, maybe, gynecologists (Kerr 2000). Education of health care professionals is therefore a prerequisite for implementing measures within the population (Kerr 2000). Many health care professionals are reluctant to speak about the association between HPV and cancer. These discussions require time, special skills, competence and feeling comfortable with intimate sexual health matters (Alexander 2000).

As well, health care professionals need training on the role of HPV in the pathogenesis of cervical cancer and on developing counseling skills, particularly with female patients (Alexander 2000). According to Suris, health care professionals must be aware that, if women did not smoke, had a single sexual partner and had not used oral contraceptives for an extended period, the incidence of cervical dysplasia would be reduced by 72% (Suris 1999).

Because of the success of existing Pap test-based screening programs, health care providers are reluctant to accept changes to the screening strategies. Detecting HPV requires new technologies and information and revised patient counseling.

1.6.4 Prophylactic vaccines

A number of trials on vaccines against HPV are under way (Stanley 2002, Ling 2000). Prophylactic vaccines are based on the L1 capsid protein, integrated in virus-like particles (Stanley 2002, Ling 2000).

Animal research reveals that virus-neutralizing antibodies may protect the host from infection. Immunity to VLP (virus-like particles with expression of L1, the major capsid protein) is specific and free of cross-reactivity between HPV types. It is not yet clear if humoral immunity effectively protects against natural HPV transmission. In humans, these vaccines are safe and immunogenic, but there is not yet data on their effectiveness (Stanley 2002). Phase III clinical trials using this type of vaccine are currently under way in Costa Rica (Ling 2000).

One problem that is preventing the development of an HPV vaccine is insufficient understanding of immune responses to specific HPV proteins (Wheeler 1997).

The main target of the vaccines in development is HPV 16, which causes the majority of cervical cancers. Geographical variations in types and virus variants pose additional challenges for vaccination strategies (Wheeler 1997). The major challenges for developing vaccines are:

- the impact of the vaccine on the dynamic and prevalence of HPV (Wheeler 1997);

- identifying success indicators and appropriate target populations (utility of PCR and serology to detect HPV infection, the need or not of having negative HPV results, the acceptability of the absence of lesions as success criterion, age and target groups) (Wheeler 1997);

- understanding the natural history of the disease (Frazer 1996);

- virus variability – an effective vaccine should contain 20 different L1 proteins (repeated exposure produces sequential infections, starting with the most common, followed by rarer and unknown types) (Frazer 1996);

- the potential for infection in the case of a massive virus dose (Ling 2000);

- the possibility that the virus is transmitted while being integrated into squamous cells; in this case the host cell would protect the virus from an immune response (Ling 2000);

- the development of antigen presentation systems that would trigger the appropriate immune response (Wheeler 1997);

- understanding the protective effect of the anti-HPV antibodies (Wheeler 1997);

- tests for virus neutralisation – it is not possible to conduct preliminary tests in vitro (Frazer 1996);

- the cost-benefit ratio for vaccines and their affordability for developing countries (Wheeler 1997).

The questions that need to be answered before launching an eventual vaccination program are linked to the epidemiology of HPV infection, acceptance of an HPV vaccine, which groups to target, the cost-benefit ratio, possible alternative routes of administration, the effectiveness of a vaccine in other populations and the effect of a vaccine on sexual behaviour (DSTDP-CDC 1999). According to a study by Boehner (2002), 74% of young people would accept an anti-HPV vaccine. Associated factors would include cost, the universality of the vaccination program and the belief that friends and partners would recommend the vaccine.

Prophylactic vaccines against HPV infection would have to be tested on youth under 20, even under 18, without sexual experience prior to vaccination, which poses some ethical problems (Frazer 1996). A prophylactic vaccination to prevent cervical lesions would have to be aimed at young women who are sexually active but HPV-negative and would have to be accompanied by an effective screening program (Tyring 2002). The goal would be the absence of any incident CIN 1 (infectious or dysplastic LSIL) (Frazer 1996). As well, it is still to be determined what effects such a vaccine would have on the incidence of cervical cancer and on the distribution of HPV types.

According to the randomized trial by Koutsky[5] (2002), a vaccine against VPH 16 L-1, tested on young women with neither prior HPV 16 infection nor cervical intraepithelial lesions, was 100% effective in preventing persistent HPV 16 infection and intraepithelial lesions associated with this particular type of virus. The proportion of women with seroconversion to HPV 16 following vaccination was 99.7%.

Nonetheless, if the vaccinated women did not have epithelial lesions associated with HPV 16, the number of vaccinated women with cervical intraepithelial neoplasia not associated with HPV 16 was the same as in a group of non-vaccinated women. This raises the question of the real effectiveness of a vaccine that targets a single HPV type in preventing cervical cancer.

Secondary and tertiary prevention

Secondary prevention consists of any measure meant to detect STIs as soon as possible. Tertiary prevention includes any measure that treats the infection to stem transmission and complications[6]. Considering the lack or insufficiency of data concerning the effectiveness of proposed treatments for reducing transmission, secondary and tertiary prevention of HPV infection consists essentially of early detection of the infection in order to prevent complications. Secondary prevention focuses on early screening for precancerous lesions, on improvement of detection methods, and expanding services to those who are not receiving them presently. It also includes developing effective antiviral treatments and therapeutic vaccines (NIH 1997).

1.7 CYTOLOGY SCREENING FOR CERVICAL CANCER

The Papanicolaou test (Pap test), despite a lack of rigorous randomized trials, is usually considered to be the most effective test for cervical cancer screening (Shaw 2000, Health Canada 1998a). Numerous studies have established a link between the existence of structured screening programs for cervical cancer and the decline in cervical cancer incidence and mortality associated with the disease. The relative risk of cancer among participants in various screening programs ranges from 0.1 to 0.5, compared to non-participants (Health Canada and SOGC 1998). Even 10 years after their last screening, the risk of cancer is very low among women with normal cytologies. These results demonstrate the effectiveness of a structured cervical cancer screening program (Viikki, 1999). In Quebec, despite the lack of such a program, the incidence of cervical cancer is among the lowest in the world, suggesting that wide accessibility, itself, to the test plays a significant role in preventing cervical cancer.

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5   Study published after the final stage of expert consultation.
6   MSSS, *Stratégie québécoise de lutte contre les MTS, Orientations 2000-2002*, 2000.

However, it is important to note that properly used Pap tests may reduce the incidence of cervical cancer by roughly 60-70%, but no more. The majority of developed countries have already attained this level (Cuzick et al 2000).

1.7.1 Cervical cancer screening: targeted populations

In the United States, screening for cervical cancer is recommended to start at the age of 18 or when sexual activity begins (DSTDP – CDC 1999, NIH 1997). Screenings are yearly at first, then less frequent (every 2 or 3 years) following 3 successive negative tests and if there are no risk factors (NIH 1997). Even if the majority of screened lesions are benign and will regress, the CDC (DSTDP – CDC 1999) continues to recommend that women begin screening at a young age but that follow-up should be conservative (repeated Pap tests) when dealing with minor cytological abnormalities.

In the study by Clavel (2001), 45% of women who developed high-grade lesions were younger than 30, a phenomenon that reinforces the justification for recommending cervical cancer screening prior to that age. Similar results were obtained by Schiffman (2000), who reported that 31% of high-grade lesions were detected in women under 30. However, considering that the incidence of cervical cancer among women under 20 is only 2 per million, that the prevalence of lesions detected by Pap tests is very high and that the majority of lesions regress spontaneously, some authors (O'Mahony 1996) propose that cervical cancer screening not begin prior to age 20, while some (Dillner 2001) even propose that screening begin after age 30. The majority of high-grade lesions (CIN 3) develop before the age of 45; consequently, regular screening between the ages of 20 and 45 would prevent the majority of cancer cases. According to Peto (2001), screening starting after the age of 20 might miss a portion of cases, while after the age of 50 the profitability (cost-benefit) of screening is questionable.

In the United States, more than 50 million Pap tests are performed each year, with approximately 5% of them revealing abnormalities. While the management of high-grade lesions is relatively clear, treating low-grade lesions is controversial due to the frequent spontaneous regression of the lesions.

1.7.2 Participation in screening programs

Half of the women with invasive cervical cancer never had a Pap test, while another 10% had not had one in the previous 5 years. There is still a significant segment of the population, particularly older, less educated and immigrant women, who do not participate in cervical cancer screening (Suris 1999). These groups correspond with those most at risk of developing cervical cancer, namely older, poor women of ethnic minority and women in rural regions (NIH 1997).

In a group of Swedish women who had not participated in the cervical cancer screening program the most significant factor associated with non-participation was their pattern of health services use. The role of health care professionals in raising awareness among women is essential. Socioeconomic status and sexual behaviour had little effect on cervical cancer screening (Eaker 2001).

Other factors associated with failing to participate in screening were (Eaker 2001):

- living in a scarcely populated region (OR of 1.54);

- use of non-oral contraceptives (OR of 3.4 for barrier contraceptives, 2.7 for others and 6.8 for none);

- irregular gynecology visits (OR of 1.9 for seeing different gynecologists and 2.35 for not seeing one at all);

- regular condom use (OR of 1.9);

- lack of intention of having a mammography (OR of 2);

- more than 5 doctor visits per year (OR of 3.1) or none in the previous 5 years (OR of 1.8);

- the belief that the recommended screening interval between 2 Pap tests was greater than 3 years (OR of 2.2).

At the same time, the presence of genital symptoms in the previous 5 years (OR of 0.56) and personal initiative to undergo a Pap test (OR of 0.43) were protective factors, inversely associated with non-participation (Eaker 2001).

In a group of women who had sex with other women, 36% mentioned at least one reason for not having undergone a Pap test for more than 2 years. The most common reasons were lack of health insurance, previous negative experiences and the belief that Pap tests were not necessary in the absence of heterosexual contact. Nine women (4%) reported that their doctor had told them that Pap tests were unnecessary for them. HPV infection was present among women who have never had sexual relations with men or who had had solely homosexual relations for long periods. In conclusion, women who have sexual relations with women should also participate in screening programs for cervical cancer (Marazzo 2001).

Approximately 50% of invasive cervical cancers occur in women who were not screened according to the recommandations. The other cases are linked to false negative test results, inadequate sampling and inappropriate follow-up of abnormal cytologies (Shaw 2000). No methods have been proved to be effective in recruiting non-participating women, but it is possible to improve test performance, sampling techniques and follow-up procedures for women with abnormal cytologies.

1.7.3   The situation in Canada

Cervical cancer screening began in Canada in 1949 in British Columbia and spread during the 1950s, once the Canadian and American Cancer Societies officially recognized the Pap test. The introduction of oral contraceptives in the following decade led to the development of cervical cancer screening programs connected with family planning services. According to current recommendations included in Health Canada's Canadian Guide to Clinical Preventive Health Care, annual screening should begin once sexual activity is initiated or at the age of 18. The screening interval may increase to 3 years up to the age of 69 following two consecutive normal smears. Annual screening throughout this period (35 smears) appears to reduce incidence of cancer by 93.3%, while the proposed formula (14 smears) reduces incidence by 90.1%, with significantly lower costs and inconvenience. After a gap of 5 years

or more, the triennial interval begins again following two normal smears a year apart (Health Canada and SOGC 1998). Despite these recommendations, many clinicians continue to perform annual screening, increasing the burden for cytology labs and the screening costs (Shaw 2000). According to a study that included 128 805 women who participated in cervical cancer screening, annual screening might have negative health impacts due to the high number of abnormal test results (usually ASCUS and LSIL) that required repeat procedures or more invasive investigation (i.e. colposcopy), contributing to morbidity and anxiety among women with minor abnormal cytologies. The risk of HSIL and squamous carcinoma was not reduced as a result of screening intervals of less than 3 years, reinforcing the absence of substantial benefits for annual screening (CDC 2000). Moreover, a screening interval of less than 3 years had a cost-benefit ratio of more than $50 000 per life-year saved (Nanda 2000).

The recommended screening interval for immuno-depressed women was yearly following two normal smears at 6-month intervals and if the results remained normal (Health Canada and SOGC 1998).

A survey conducted in 1998-1999 through a self-administered questionnaire revealed that 79% of women had undergone a Pap test in the previous 3 years, with minor variations by province (Health Canada 2002). There is no centralized data on cervical screening participation, although actual participation appears to be lower than what the women declared. In Quebec, participation in screening appears to be similar to that of the rest of Canada (Health Canada 2002).

According to a Health Canada study (1998b), in 1994, the proportion of Canadian women who had had a Pap test in the previous year was 45.7%, while 68.1% had it in the previous 3 years. After adjustment for women who had undergone a hysterectomy, the proportions respectively were 54.6% and 81.3%. Almost 100% of Canadian non-hysterectomized women aged 45 to 54 had a Pap test in the previous 3 years (Health Canada 1998b).

However, there is a trend towards a decrease in the proportion of women who undergo screening for cervical cancer, particularly among women 15 to 24 and 55 to 64 years old. In 1990, 41% of women 15-24 had never undergone a Pap test, compared to 35% in 1985. Similarly, 11% of women 25-34 and 11% of women 55-64 had never had a Pap test, compared respectively to 5% and 7% in 1985. In 1990, the proportion of women who had never undergone screening was 8% for women 35-44 and 7% for women 45-54 (Health Canada and SOGC 1998).

Factors associated with non-participation were older age, recent immigration, low education level and mother-tongue other than English or French (Health Canada and SOGC 1998).

The proportion of women who had at least one Pap test in the previous three years was associated with income (adjusted rate of 70% for those with incomes under $20 000, compared to 91.8% for those with family income over $80 000) and level of education (64.7% among those with less than high-school versus 86.5% among women who completed their post-secondary education) (Health Canada 1998b). Other factors associated with no screening were limited access to tests, lack of awareness concerning the advantages of screening and fear of the procedure (Health Canada 1998a).

In 1976, a committee on cervical cancer screening, presided by R. J. Walton, recommended establishing central or regional registries for recruiting and recalling women for screening. Since then, British Columbia, Nova Scotia and Prince Edward Island have introduced cytology registries (Shaw 2000, Health Canada and SOGC 1998). More recently, Manitoba and Ontario have also introduced organized programs for cervical cancer screening (Health Canada 2002).

1.7.4   Traditional Pap test performance

Sensitivity and specificity of Pap tests:

Its sensitivity for detecting precancerous lesions varies depending on the selected threshold: it is higher when ASCUS is included, lesser with low-grade lesions (LSIL) as treshold and very low if high-grade lesions (HSIL) are the treshold. Inversely, specificity is less for the ASCUS threshold, an important number of ASCUS results being actually false positives. The performance of the Pap test is modest, but frequent repetition reduces screening errors (Sawaya 2001, Nanda 2000).

According to the meta-analyses by Nanda (2002) and the AHCPR (1999), at the LSIL threshold, the sensitivity of the Pap test for detecting anycervical intraepithelial lesions is 47-51%, while the specificity is 95-98%. At the ASCUS threshold, the sensitivity for all lesions varies between 18% and 98%, while specificity ranges between 17% and 99% (Nanda 2002).

In a recent Canadian retrospective study, among 64 young women from Ontario, the sensitivity of cytology at the ASCUS threshold was 39% for detecting all intraepithelial lesions and the specificity was 68% (Howard 2002). For detecting higher-grade lesions (CIN 2-3), sensitivity and specificity were 80% and 69%.

In the study by Sellors (2000), also in Ontario, the sensitivity and specificity of the Pap test (unspecified threshold) were 77.6% and 81% for detecting high-grade lesions (HSIL).

In the studies we surveyed, Pap test sensitivity for detecting lesions from high-grade to ASCUS thresholds varied between 26% and 94%, while specificity was 41% to 95% (Tables 9 and 10, Appendix 1).

The reproducibility of the Pap test is low, especially for ASCUS results (Sherman 1994). False negative results are caused primarily by human error during preparation or while reading smears and by glandular abnormalities. Just as most screening tools, the test in itself is not infallible and it appears to be impossible to reduce the percentage of false negatives below 5-10% (Shaw 2000).

The less than optimal sensitivity and specificity of traditional cytology limits the number of cervical cancer cases averted by this method, not to mention the economic burden and excessive psychological trauma caused by the number of false positives (Cuzick et al 2000).

1.7.5   New cytology technologies

New screening tests for cervical cancer include liquid-based cytology, computerized re-evaluation of the slides and HPV detection (Sawaya 2001, Walsh 1998).

Thin-layer cytology is based on the suspension of sampled material to avoid cervical cell loss and spreading a uniform thin layer on the slide (Velasco 2001, Walsh 1998). With conventional cytology, only 20% of collected cells are transferred to the smear (Velasco 2001). Thin-layer (liquid) cytology and electronic re-evaluation are more sensitive compared to conventional cytology, although their specificity appears to be diminished (Sawaya 2001). Liquid cytology (ThinPrep) is better at detecting intraepithelial lesions, particularly low-grade lesions. As well, ASCUS results are less frequent than with conventional cytology (Ferrecio 2001, Vassilakos 2000, Bolick 1998).

However, according to the study by Monsonego (2001), thin-layer cytology increases the number of ASCUS results. As for intraepithelial lesions, thin-layer cytology was particularly sensitive for screening low-grade lesions. Finally, the number of satisfactory smears was slightly reduced compared to conventional cytology, due to the absence of endocervical cells (Monsonego 2001).

According to Velasco (2001), the sensitivity and specificity of thin-layer cytology was generally better than that of conventional cytology. Other advantages of this method include reduced reading time and the possibility of complementary tests (HPV) on the same sample (Velasco 2001). Liquid cytology and automated systems reduce the impact of human error during preparation and interpretation of the smears (Shaw 2000). Automated re-evaluation methods identify the smears that are more susceptible of having abnormalities and retest them preferentially. These methods could also be used to evaluate the smears with ASCUS (Walsh 1998).

The disadvantages are increased cost and the alteration of cellular morphology (Velasco 2001). This test is particularly useful in populations with a low prevalence of cervical lesions (Walsh 1998). The costs of screening appear to be possibly higher with thin-layer cytology, although its use becomes more cost-efficient in regions where Pap tests are less sensitive and if screening is done at 3-year intervals (Sawaya 2001).

1.8   CERVICAL CANCER SCREENING USING HPV DETECTION TESTS

HPV infection is the most common STI among women, with roughly 5.5 million new cases per year in the United States (ASHA 1998). In most cases, HPV infection regresses spontaneously, although persistent infection appears to be more common in the cases of high-risk HPVs and among women over 30. Persistent HPV infection may cause precancerous changes in the cellular morphology. On the other hand, the absence of HPV strongly reduces the probability of a cervical lesion progressing to cancer (Petry 2002).

In addition, HPV persistence following treatment of lesions is a good predictor of recurrence. That is why it is increasingly believed that follow-up for patients with abnormal cytological results should include screening for high-risk HPV (Ledger 2000).

Because there is no data suggesting that the type of virus (within the group of high-risk HPV) is significant for predicting the potential for developing precancerous lesions, screening tests should only detect the presence of HPV belonging to a high-risk group. However, HPV testing without typing cannot distinguish between persistent infection and reinfections.

The causal association between HPV and cervical cancer is well established and current tests available for HPV are effective enough to consider this approach for cervical cancer screening (Cuzick et al 2000, Walsh 1998).

1.8.1   Sensitivity and specificity of HPV detection for screening for cervical lesions

The **sensitivity** of current HPV tests for screening for CIN varies between 65.2% and 100% using PCR and between 68.1% and 100% using HC II (Tables 9 and 10, Appendix 1). The majority of studies reveal a sensitivity of approximately 85-95% for the two tests. Their predictive negative value is 92.2-100% (PCR) and 94-100% (HC II) (Tables 9 and 10, Appendix 1).

In a transversal comparative study on the performance of HC II and PCR tests, HC II proved to be highly reproducible and its concordance with PCR was high (kappa of 0.8). The rate of false negative results was 8.1% compared to PCR (Terry 2001). The recommended threshold value for the HC II test in the United States is 1 pg/ml, corresponding to approximately 5000 copies of DNA per test (Terry 2001, Cuzick 1999a). In other countries, this value varies between 0.5 and 5 pg/ml, depending on the prevalence of HPV infection (Terry 2001).

According to Cuzick, HPV screening identifies more than 90% of severe lesions, compared with the Pap test, which, under ideal conditions, identifies 50-66% of lesions. According to Meijer (1998), both PCR and HC II are sensitive enough for use in cervical cancer screening. Quality control is another essential aspect and should be strictly regulated, due to the repercussions of false-negative results (Meijer 1998).

The **specificity** is 59-93.9% for PCR and 50.6-97.1% for HC II (Tables 9 and 10, Appendix 1), with median values of 70-80%. According to Schiffman (2000), the HC II test's overall performance is similar to the PCR's, despite its specificity reduced by the cross-detection of nononcogenic HPV types (false-positive results given by several low-risk HPVs such as HPV 53 and 66). In a comparative study between PCR and HC II, the latter demonstrated a sensitivity of 96% but a specificity of 57% due to the cross reaction with HPV 53, a low-risk type that was particularly common in the studies population, present in approximately 6% of subjects (Depuydt 2001). The positive predictive value for HPV detection varied largely, between 11% and 79% for PCR and between 10% and 54% for HC II, depending on the prevalence of HPV infection in the studied population (Tables 9 and 10, Appendix 1). In the study by Terry (2001), the rate of false-positive results was 8.3% using PCR as the reference test and 6.4% if the reference was the histology.

While it is clear that HPV detection improves sensitivity and offers a very good negative predictive value (Cuzick et al 2000), its drawback is that it has a generally lower specificity than that of cytology (Nobbenhuis 2001). Moreover, there is little understanding of the evolution of CIN detected only through HPV testing and confirmed by histology. Also, there is little information on the evolution of histological lesions detected by cytology that are HPV-negative (Cuzick et al 2000, Schneider 2000, Walsh 1998).

1.8.2 Pertinence of using HPV detection in cervical cancer screening

An ideal screening program for cervical cancer would use the most sensitive test at the longest intervals possible. Variation in sensitivity should be minimal to ensure good performance under any circumstances. Because the HPV test satisfies these conditions, its utilization would seem logical (Holmes 2001). The HPV test might reduce the amount of time required for consultations and for laboratory analysis (Cuzick 2000). Actually, a better screening test could improve the management of minor lesions and lengthen the intervals between screenings. Even more, sequential cytology and HPV detection using the same specimen, when the cytology is abnormal, circumvents the need for a second visit. If cytology requires more technical time than an HPV test, the fewer number of cytologies might also reduce the time for laboratory analysis (in terms of human resources). These saved resources could then be used to recruit women who do not participate – a major problem with cervical cancer screening programs (Kinney 2001).

The percentage of women referred for colposcopy following an HPV test depends largely on the prevalence of HPV infection in the population. It is therefore necessary to carefully plan the introduction of an HPV testing program into the cervical cancer screening protocol (Schiffman 2000).

The probability of the presence of histological CIN 3 is lower when the HPV test is negative. Furthermore, the clearing of the HPV infection predicts cytological regression, while persistent infection indicates a high risk of neoplastic lesions (Nobbenhuis 2001). Therefore, the use (eventually repeat use) of an HPV test might reduce the need for treatment of women with cytological lesions and with no HPV or with transitory infection. In fact, in these cases, the evolution of the lesions is benign, normally regressing spontaneously (Cuzick 2000, Schneider 2000).

The social acceptability of a screening program depends on many factors, including cost, how well the procedures are understood, the goals and the significance of the results, as well as the associated or perceived negative effects (pain caused by testing or treatment, associated morbidity) (Harper 2001). Repercussions on quality of life (the impact of being diagnosed with an STI and the inconveniences caused by examination and follow-up testing) might act as barriers to introducing HPV detection as part of cervical cancer screening (Harper 2001). Some recent studies addressed the public acceptability of such a test. They have shown that the majority of women thought that including an HPV test in cervical cancer screening routine was acceptable (Philips 2002, Svare 2002, Tristram 2002[7]). However, some women were less comfortable with the test (Svare 2002) and the nature of the infection was often poorly understood (Philips 2002). Study participants underscored the importance of their doctor's recommendation (Svare 2002) as well as the importance of receiving some written information prior to testing (Tristram 2002).

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[7]   Study published after the final stage of expert consultation.

In a group of 4761 German women, patients were more likely to comply with treatment follow-up if they tested positive for HPV (80%) than if they had an abnormal cytology (62%) or a positive colposcopy (52%) (Schneider 2000).

Besides its performance, HPV testing can use specimens obtained by selfsampling (Cuzick 2000). This method is particularly useful in countries with a poorly developed screening network and for women who cannot or do not want to go to a clinic (Cuzick 2000). Tests using samples of vaginal secretions collected by the patient herself perform as well as those using clinically obtained samples (Harper 2002) or slightly less well. Specifically, according to the study by Sellors (2000), HPV detection (HC II) has a sensitivity and specificity of 98.3% and 52.1% using cervical specimens collected by the clinician and 86.2% and 53.5% using self-collected vaginal specimens. However, according to the study by Lorenzato (2002), self-collected specimens for HPV tests are less reliable for detecting intraepithelial lesions or invasive cancer. Their sensitivity is half of that of specimens collected by the physician (Lorenzato 2002). For the majority of women, self-sampling is more acceptable than Pap tests (Dzuba 2002, Harper 2002, Sellors 2000), although they wished to continue their annual medical visits (Harper 2002).

To date, there is no data on reducing cervical cancer morbidity and mortality as a result of the introduction of HPV testing as a screening method for cervical cancer (Apgar 1999, Kaufman 1999).

Possible uses for HPV detection within the framework of cervical cancer screening and management

HPV testing may be used in the following situations:

1. Triage of ASCUS or AGUS cytological abnormalities (Dillner 2001, Holmes 2001, Cuzick 2000, Meijer 2000, Cuzick 1999a, Walsh 1998), tested in several large-scale studies, reducing costs in regions with high percentage of equivocal cytological results (Dillner 2001) due to a reduction in the number of needless colposcopies (Walsh 1998).

2. Identifying minimal or moderate histological lesions that are susceptible to progression (Meijer 2000).

3. Primary cervical cancer screening, in parallel with cytology (Dillner 2001, Ledger 2000, Meijer 2000) or alone (Holmes 2001, Cuzick 2000) represents the most interesting potential for HPV detection. The concomitant use of the two tests would allow screening intervals to be extended to 5 years in Great Britain and 3 years in the United States, particularly in older women (Dillner 2001, Cuzick 2000). HPV testing also allows self-collection (Cuzick 2000).

4. Monitoring the laboratory performance of cytology, due to the strong correlation between the prevalence of HR-HPVs and the severity of cytological lesions: 85% of SIL and 2% of normal cytologies are positive for HR-HPV (Sherman 1994).

5. Quality control for the treatment of precancerous lesions (Dillner 2001), in order to detect residual or recurrent lesions (Dalstein 2001, Cuzick 2000, Meijer 2000) and to reduce postoperative surveillance (Cuzick 2000). HPV persistence appears to be an excellent indicator of lesion persistence, the reappearance of HPV infection suggesting a recurrence (Cuzick 2000, Meijer 2000). According to Kinley (2001), a single HPV-negative result and a normal cytology

following treatment of intraepithelial lesions are sufficient to revert to the normal screening interval.

Besides virus detection, other more specific tests may eventually help in diagnosis and management:

1. Determining the viral load is one of the current challenges, the risk of cancerous lesions being proportional to the number of viral copies. Tests used to date have not, however, been sufficiently precise to be used in clinical practice (Villa 2000).

2. HPV typing to identify high-risk HPV may be useful for screening, although available studies didn't manage to demonstrate satisfactory performances (Walsh 1998).

3. Identifying the different variants of HPV 16, in order to distinguish viral persistence from reinfection (Mayrand 2000).

4. A possible future test would demonstrate the presence of integrated HPV genomes in the host cell chromosomes, associated with the severity of cervical lesions (Klaes 2001).

The conclusions in the review by Cuzick (2000, 1999a) are as follows:

- Current information supports the limited introduction of HPV testing for the triage of low-grade cytological abnormalities (ASCUS and LSIL), particularly in women over 30. Three modalities are proposed: using cytology test residues, an immediate repeat consultation or a second consultation after 6 months.

- Concomitant HPV testing and cytology would be useful in certain situations, particularly if there is reason to believe that the patient may not return for a follow-up appointment.

- The specificity of HPV testing is generally lower than that of cytology. The false-positive rates are 3-10% among women over 35 and 20-25% among women under 35. The false-positive rate for cytologies is less than 5%.

- HPV testing could become the only test for primary screening, particularly for older women, though it is necessary to confirm its sensitivity for high-grade lesions.

- There is not sufficient information on the duration of protection in negative tests, nor on the reduction of the incidence of cervical cancer.

- The role of HPV testing in post-treatment surveillance of high-grade CIN requires additional study.

- The cost-benefit ratio of HPV testing in primary screening is not sufficiently evaluated.

- HPV testing using self-collected specimens seems to be an interesting approach to recruit women who are reluctant to seek consultation, although this requires additional study.

- The Hybrid Capture is a performant test if it is automated.

- When evaluating the pertinence and effectiveness of introducing HPV testing in cervical cancer screening, advances in cytology must also be considered.

The report of the March 2000 International Consensus Conference of the International Academy of Cytology (IAC) on HPV-related genital lesions in women concluded that all ASCUS results should be followed by HPV detection and typing (Feichter and Meisels 2002). In industrialized countries, the use of HPV testing in parallel with cytology should reduce screening costs by allowing for longer screening intervals, namely from 3 to 5 years (Feichter and Meisels 2002).

The American guidelines for managing ASCUS cytologies (Wright 2002) recommend the use of HC II testing for HPV detection as a convenient alternative to immediate colposcopy or repeat cytology. The reflex HPV test, using a cytology specimen, is considered the preferred alternative when liquid-based cytology is used (Wright 2002).

However, according to the 1994 Canadian Guide to Clinical Preventive Health Care, HPV screening would not contribute greatly to reducing the incidence of cervical cancer but it would considerably increase costs and have a negative impact on the quality of life of the screened women (Johnson 1994).

HPV detection is not yet very widespread. According to the national study by McCree (2002), around 22% of American doctors who treat STIs recommend an HPV test for their patients. Gynecologists and female doctors are more likely to use HPV screening tests.

1.8.3   HPV detection as a primary screening method for cervical cancer

Given that HPV is found in a vast majority of cervical cancers and precancerous intraepithelial lesions, HPV detection could prove to be a useful alternative in screening for cervical intraepithelial lesions, either replacing cytology or completing it.

According to some authors, HPV screening is more sensitive than the Pap test and could safely replace it as the main method for cervical cancer screening, particularly for older women (Cuzick 2000, Meijer 2000). HPV is normally identified in histologically confirmed cytological lesions and often absent when the lesions are not confirmed (Dillner 2001). Because of the few HPV-negative CIN 3 cases (false negatives), the concomitant use of the two tests is being evaluated. It seems, however, that those few cases of HPV-negative CIN 3, are lesions that will regress (Meijer 2000).

HPV testing may improve the quality of screening programs for women over 30 by identifying HPV-negative women with no risk of cancer for the following 5 to 10 years (Petry 2001). In this age group, the presence of HPV in cervical specimens is associated an increased risk of acquiring intraepithelial lesions or cancer, the relative risk varying between 50 and 1000 (Dillner 2001).

Because of the lower specificity of HPV detection, the number of colposcopy referrals following such a test could be higher than using cytology (Schiffman 2000, Ratnam 2000). Nevertheless, an important percentage of women over 35 with a positive HPV test will eventually develop cancer. So, the higher number of women referred for colposcopy following HPV testing does not necessarily signify a low specificity but may imply higher costs. In fact, according to Dillner (2001), the risk of cervical cancer is 2% without any screening intervention, while the prevalence of HPV infection is 1-8% among women over 35.

Performance studies on HPV testing as a primary screening method and comparative studies

To date, there have been no randomized studies on the performance of HPV detection as a primary screening method for cervical cancer. In addition, the majority of existing studies are hindered by verification bias, due primarily to the lack of verified negative results. The effect of this bias is an artificial increase in the sensitivity of tests and decrease of their specificity. Prospective studies published to date (Table 9, Appendix 1) are based on short-term follow-up, so they do not allow for evaluating the effectiveness of HPV-based primary screening in reducing the incidence of cervical cancer or the associated mortality (Franco 2002).

Several large randomized trials are currently under way. A number of randomized trials to evaluate the performance of HPV detection as a primary screening method for cervical cancer are conducted (Dillner 2001, Cuzick 1999a) in eight countries (Dillner 2001), including Canada (Franco, personal communication). One such trial is conducted in Great Britain, examining the concomitant use of cytology and HPV detection by HC II. The protocol includes a follow-up at 6 months for HPV-positive women with normal cytology (Cuzick 2001). In another study, taking place in Quebec and Newfoundland, participants undergo a cytology and HPV test in random succession. Women with positive results on either test and a random sample of women with negative results will be referred for colposcopy and biopsy (Franco 2002).

Transversal studies

Many transversal studies examined the use of HPV detection in primary cervical cancer screening. The results of the major studies are summarized in Table 9 (Appendix 1).

Arby (2001) compared the performance of HPV detection (HC II) as a primary screening method (in conjunction with liquid-based cytology) to its use for the triage of ASCUS and low-grade intraepithelial lesions in a group of 3000 Belgian women. The use of HPV detection in primary screening identified 27% more high-grade lesions (CIN 2-3) than triage, but it required 22 times as many HPV tests.

In a French study on the performance of the HC II test in a group of 2979 women, the sensitivity of HPV detection was 92.3% with a specificity of 78.9%. In comparison, the sensitivity of cytology for identifying intraepithelial lesions (SIL) was 72.2% (79.4% for ASCUS threshold), with a specificity of 96.2% (Dalstein 2001).

In the study by Schiffman (2000), the sensitivity of HC II at a threshold of 1 pg/ml was 88.4%, the specificity 89%, with 12.3% of participating women referred for colposcopy – the best performance in this study compared to other detection thresholds tested. The rate of referral for colposcopy was 21% among women 18-30 years old, 11.2% for those 31-40 and 7.1% for those over 40 (Schiffman 2000). The sensitivity of the traditional Pap test using the ASCUS threshold was 77.7%, the specificity 94.2%, with 6.9% of screened women being referred for colposcopy (Schiffman 2000).

In his study, Schneider (2000) compared cytology, HPV detection (PCR) and colposcopy as primary screening methods for cervical cancer in a group of German women. The women with Pap tests or a positive test for high-risk HPV and those with negative results were examined by colposcopy, with biopsies taken even in the absence of visible lesions in order to identify false-negative results. The sensitivity of cytology for detecting moderate lesions or worse (CIN 2 or worse) was 18.4% at the SIL threshold and 26.3% at the ASCUS threshold, that of colposcopy alone 13.2% and that of HPV detection 94.7%. The specificity of cytology was 99%, as was that of colposcopy, compared to 93.9% for HPV detection. The rate of false-positive results for HPV detection was 19 times higher that that of cytology, with a PPV of 29% versus 50%.

In a group of 1415 black women with no previous cervical cancer screening, HPV detection (HC II) had a sensitivity of 83.9% and specificity of 84.5% versus 67.9% and 87.7% for Pap tests with an ASCUS threshold (Wright 2000). Based on positive HPV detection or a cytology that identified a low-grade lesion (LSIL) or worse, 39% of women were referred for colposcopy and 7% were diagnosed with intraepithelial lesions or invasive cancer. The rate of false-positive results was 15.5% for HPV detection, 12.3% for cytology with an ASCUS threshold and 3.2% for cytology with a threshold identifying low-grade lesions (LSIL). There was no difference in test performance according to age.

In the study by Cuzick (1999b) on the performance of high-risk HPV oncogene detection as a screening method for cervical lesions among women over 35, the sensitivity of PCR was 79.4% for CIN 3 and 73.8% for CIN 2 and worse. The PPV was 17.4% for CIN 2 lesions and worse. The sensitivity of HC II test was 100% for CIN 3 and 95.2% for CIN 2 and worse. The PPV was 17%, 27% and 28% at thresholds 1, 2 and 4 pg/ml. The sensitivity of cytology was 62% at the threshold of HSIL, 79% at the threshold of LSIL and 83% for the ASCUS threshold. The corresponding positive predictive values were 63%, 47% and 22% (Cuzick 1999b).

Longitudinal studies

Among the prospective studies on using HPV testing as a primary screening method for cervical cancer, the most important for our review are those by Clavell (2001) and Ratnam (2000).

In the Clavell study (2001), which took place in France, sensitivity was 100% with the HC II test, 87.8% for liquid-based cytology (ThinPrep) and 68.1% for traditional cytology. The sensitivity for women over 30 was highest with the HC II test and lowest with the two cytology techniques (statistical significance not calculated).

Specificity was best for traditional cytology and lowest for HC II (95.3% versus 87%), that of the HC II test being slightly higher among women over 30 (Clavell 2001). The predictive positive values were 23.5% for cytology and 14.2% for HPV detection. The predictive negative value of 100% for HPV detection would be particularly useful for increasing screening intervals (Clavell 2001).

The authors propose using simultaneous HPV detection and liquid cytology in developing countries to maximize the sensitivity and specificity of screening programs (Clavell 2001). In a previous study by the same team, the sensitivity of HPV detection (HC I) was 64%, the specificity 92.6%. Cytology revealed a sensitivity of 84% and a specificity of 99.7%. The positive predictive values were

91.3% for cytology and 17.8% for HC I. The combination of the two tests obtained a sensitivity of 96% (Clavell 1998).

In the cohort study conducted in Newfoundland (Ratnam 2000) to determine the utility of adding HPV detection to a cervical cancer screening program, sensitivity and specificity of HPV detection were 62.1% and 66.1% for all lesions and 85.3 % and 58% for high-grade lesions (HSIL). After adjustment for verification bias, sensitivity and specificity of the HPV test were 20.8% and 93.3% for detecting all intraepithelial lesions and 68.1% and 90.6% for high-grade lesions (HSIL). Adjusted sensitivity for the Pap test in detecting all intraepithelial lesions was 14.4% (at ASCUS threshold), 8.3% (at LSIL treshold) and 1.9% (at HSIL threshold). For detecting high-grade lesions (HSIL), the adjusted sensitivity was 41.2%, 28.3% and 11.6%. The adjusted specificity was 97.3% and 96.2% at the threshold for identifying low-grade lesions (LSIL) and 99.1% and 99.1% at the threshold for identifying high-grade lesions (Ratnam 2000). In order to avoid verification bias, women with negative results were also referred for colposcopy.

The parallel use of two screening tests increased sensitivity for all CIN to 82.7% and for high-grade CIN to 100%, if the cytology threshold was LSIL. The specificity remained at 51% for all CIN and at 41% for CIN 2-3. Values corrected for verification bias were: sensitivity of 23% for all CIN and of 76.3% for CIN 2 and CIN 3 and a specificity of 92% and 89% respectively (Ratnam 2000). According to the cytology, 9.2% of women were referred for colposcopy, with the percentage increasing to 12.3% for the two tests combined (Ratnam 2000).

The advantages of using HPV detection in the primary screening of cervical cancer

The majority of studies on using HPV detection in primary screening have demonstrated a sensitivity that is clearly superior to cytology, although specificity is lesser (Table 9, Appendix 1). In fact, the sensitivity of HPV detection varies between 62.1% and 100% (HC II or PCR), while that of cytology at ASCUS threshold is 26.3-83%. In addition, according to Meijer (2000), HPV-negative intraepithelial lesions are most probably lesions that will regress rather than false-negative cases. Specificity of HPV detection is 52.1-97.1%, while that of cytology is 81-99% (Table 9, Appendix 1). Among women aged 30 to 35, the specificity of HPV detection is improved due to the low prevalence of HPV infections at that age, temporary infections being particularly rare (Franco 2002).

Sensitivity of HPV detection is approximately 95% for cervical cancer, and specificity is high enough to allow this test to be used as a primary screening method. The effects of HPV detection on long-term morbidity are still not known well enough. However, at least theoretically, a negative result predicts a very low risk of developing invasive cancer within the next 6 years (Dillner 2001). Women with negative Pap tests should not develop invasive cancer within the following 3 years or die of cervical cancer within the following 5 years. Considering that HPV infection precedes the lesions, it seems logical that a longer interval before repeating a negative HPV test **might** turn out to be adequate (Dillner 2001).

The major argument for HPV-based primary screening is the possibility to decrease the frequency of the screening visits. Eventually this would resulting a lesser use of resources and the possibility to increase screening participation rates, due to a lower number of lifetime visits (Dillner 2001)

In countries where colposcopy is recommended for all abnormal cytologies, including ASCUS, using cytology and HPV together could lead to more exact screening, fewer gynecological referrals, reduced over-treatment and possibly a better cost-benefit ratio for screening. Women with normal cytologies and negative HPV tests might require follow-up at every 8-10 years rather than 3 years (Meijer 2000).

The disadvantages of using HPV detection in the primary screening of cervical cancer

According to Sigurdsson (1999), the Hybrid Capture test as a primary screening method for cervical cancer has a limited value in countries with a well-structured Pap screening system. This test would be more useful as a supplement for the triage of cases with repeat low-grade and inconclusive cytologies, in order to identify women at risk of evolution to high-grade lesions. The lower specificity would be a major disadvantage of HPV testing.

Current situation of primary screening using HPV testing

Primary screening and post-treatment surveillance require more study in parallel with new cytology technologies that allow cytology and HPV detection using the same sample (Cuzick 2000). European Community nations are preparing a joint cervical cancer screening program, possibly based on HPV detection, either alone or in conjunction with cytology (Kjaer 2001, personal communication). In the United States, the FDA has approved use of the Hybrid Capture II test as a primary screening method for cervical cancer.

Scenarios for the application of primary screening for cervical cancer using HPV detection

The group that would benefit the most from HPV detection as a primary screening tool is women over 30. The most economical approach would be a single HPV test sometime between ages 30 and 40 – after the high prevalence age but prior to increased risk of cervical cancer. In Sweden, the prevalence of HPV infection is around 20% among young women and 1% among older women with normal cytology. The majority of infections disappear within 1-2 years. In contrast, women who develop a CIN or cancer have persistent HPV infection. Therefore, one method for determining the persistence of the infection and predicting evolution is a repeat HPV test within a year's time. Approximately half of women over 35 infected with HPV have a persistent infection and a high risk of cancer (Dillner 2001).

Other possible approaches for identifying women at high risk are measuring the viral load, identifying genetically susceptible women (those with haplotypes DQw3 and DR15/DQ6) and identifying integrated or episomal HPV forms (Dillner 2001).

Screening for HPV infection using PCR migh be useful for sexually active young women (concomitant with their first Pap test), particularly for those with multiple sexual partners. Women whose HPV results are positive should have more frequent follow-ups (Ledger 2000).

Follow-up for women with an HPV infection should continue until the spontaneous clearing of the infection or HPV-negativity following treatment for CIN. The majority of infections disappear within 40 months or progress to CIN. The possibility of regression has the potential of considerably reduce negative effects and costs (Dillner 2001).

If HPV detection is used in parallel with cytology, it is important to avoid needlessly increasing colposcopy referrals. One solution for women with a positive HPV result and a negative cytology would be to determine viral persistence (2 positive HPV results 6 months apart). Another possible approach would be to consider factors associated with persistence such as high viral load, age or the presence of HPV 16 (Cuzick 1999b).

1.8.4 Use of HPV detection for ASCUS triage

According to Cuzick (2000), ASCUS results represent approximately 5% of all cytology results. In the United States, approximately 3.5 million women are diagnosed each year with cytological abnormalities, of which 2 million are ASCUS (Wright 2002). In addition, among all cytology results, ASCUS is the largest source of histological diagnoses of high-grade cervical intraepithelial neoplasia (Monsonego 2000). Histopathological exams identify between 6.7% and 25% of women with ASCUS as having a CIN 2 lesion or worse (Fait 2000, Shlay 2000, Mans 1999). As well, according to the study by Lytwyn (2000), in Ontario, 10.1% of ASCUS and 12% of LSIL are identified by histology to be CIN 2 or worse.

The suboptimal sensitivity of cytology and the difficulties in reaching an important percentage of women are obstacles to further reducing the incidence of cervical cancer. In order to improve screening sensitivity, ASCUS should be followed up with either colposcopy, HPV detection or repeat cytology (Monsonego 2000, Apgar 1999).

Colposcopy is the most sensible option, but it is a costly and invasive procedure, with a low acceptability among women with minor abnormalities, most of which are exempt from precancerous lesions. Also, this technique must be performed by specially trained professionals (Monsonego 2000, Apgar 1999).

Repeat cytology for ASCUS triage is less costly and easier, but there is a risk of failing to identify up to 30% of high-grade lesions. In addition, many women would eventually undergo colposcopy due to repeat ASCUS diagnoses. Considering the resulting needless treatments, this method becomes costly.

HPV detection increases the sensitivity for screening, with minor changes in specificity (Apgar 1999). HPV testing detects more than 90% of histological high-grade lesions. Following a Pap test with ASCUS results, HPV detection has a sensitivity (93%) similar to that of colposcopy, higher than that of cytology, while its specificity is higher than that of both colposcopy and cytology. The high viral load might distinguish between patients with underlying high-grade lesions and those without (Monsonego 2000).

There are also a few studies that do not support using HPV testing for ASCUS triage. For example, Kaufman et al (1999) reported that a repeat Pap test for triage of cytological lesions offers similar results as HPV testing. Looking at the cost-benefit ratio of HPV detection, the authors concluded that such a test would double the cost of the follow-up.

The performance of the test used for follow-up is a significant criterion for women with ASCUS. This was the conclusion of the study by Ferris (1997), which looked at women's preferences for follow-up of ASCUS and low-grade lesions. Other factors that would influence the choice of the test were personal and family history of cervical neoplasia, education, income, age and knowledge of the proposed tests (Ferris 1997).

Performance studies of HPV testing for ASCUS triage and comparative studies

According to the studies surveyed, using HPV testing for ASCUS triage would result in 16.9-56% of women with ASCUS requiring a colposcopy (Table 10, Appendix 1). This proportion is lower among older women than among younger women. In addition, the proportion of women referred for colposcopy following a second cytology with ASCUS results or worse is 31-42%. The sensitivity of HPV testing varied between 55% and 97%, while that of cytology was 55-85.9% at ASCUS threshold and 38-59% at the threshold of SIL (Table 10, Appendix 1).

The centerpiece for all recommendations concerning ASCUS triage using HPV testing is the randomized ALTS study (2000). Two other studies are also particularly interesting for us. The first is a small randomized study, conducted in Canada by Lytwyn, which also included a cost-benefit analysis. The other is a case-control study by Morin (2001), conducted in Quebec, which compared several ASCUS triage strategies.

Transversal studies

In a Quebec case-control study to evaluate the performance of various ASCUS triage strategies, the best results were obtained by combining HC I and Pap tests, HC II and Pap tests and HC II alone (Morin 2001).

A repeat Pap test alone had a sensitivity of 73.7% and a specificity of 62.9% at the ASCUS threshold, while at the threshold of LSIL, sensitivity was 42%. With the repeat Pap test strategy, 39% of women had to be referred for colposcopy. The sensitivity of HPV detection (HC I, HC II, PCR) depending on the test used were respectively 68.4%, 89.5%, 89.5%, while specificity was 85.9%, 74.1% and 59%. The proportion of women referred for colposcopy following HPV detection was respectively 16.9%, 29.2% and 44%. Managing ASCUS with a combination of Pap test and HPV detection (HC I, HC II, PCR) had a sensitivity of 89.5%, 94.7 % and 94.7% depending on the test and a specificity of 83.5%, 73.2% and 57.6%. Based on this approach, respectively 20.3%, 30.4% and 45% of women would have been referred for colposcopy (Morin 2001).

The Pap test, at a threshold of LSIL, failed to identify 60% of high-grade lesions (CIN 2-3), while the HC I missed 30% of CIN 2-3 and the HC II and PCR missed 10% each. The PCR, on the other hand, had a very low specificity, with a high number of referrals for colposcopy (Morin 2001).

In the study by Rebello (2001) of a group of 333 women with minor persistent cytological lesions, sensitivity of HPV detection (HC II at a threshold of 1 pg/ml) was 93%, while specificity was 55%. Specificity was higher among older women (72% versus 33% among younger women). Increasing the detection threshold to 2 and 4 pg/ml reduced sensitivity to 91% and 85% respectively and increased specificity to 57% and 62% (Rebello 2001).

In a group of 195 high-risk women (history of abnormal cytologies, low socio-economic status) with ASCUS or AGCUS, sensitivity and specificity of HC II testing were 93.3% and 73.9% (100% and 57.4% among women under 30 and 85.7% and 83.9% among women over 30). HPV detection would have allowed limiting colposcopy referrals to only 31% of patients. The higher risk in HPV-positive women determined a better adherence to follow-up (Shlay 2000).

In a transversal study on the performance of HPV detection (using HPV Profile – an older test with quite low performance) in a group of women with 2 consecutive ASCUS or LSIL cytologies, sensitivity and specificity of HPV testing for detecting high-grade lesions (CIN 2-3) were 67.2% and 65.8%, while corresponding values for repeat Pap testing were 62.7% and 61.5%. Using a Pap test with an ASCUS threshold, 41.9% of women were referred for colposcopy versus 38.9% using HPV testing. Simultaneous use of repeat cytology and HPV detection had a sensitivity and specificity of 82.1% and 48.9%, with 55.6% of women referred for colposcopy (Kaufman 1997).

In a group of 217 young American women with ASCUS (average age was 21), the sensitivity of a repeat Pap test was 38% at the threshold identifying an intraepithelial lesion (SIL), with a specificity of 96%. At ASCUS threshold, sensitivity was 60% and specificity 77%, with 31% referred for colposcopy. The sensitivity and specificity of HPV detection (HC I) were 88% and 69%, with 42% referred for colposcopy. The repeat cytology/HPV test combination revealed a sensitivity and specificity of 90% and 58%, with 53% of women referred for colposcopy (Cox 1995).

Prospective studies

In a cohort of 278 Dutch women with minor cytological lesions, the sensitivity of high-risk HPV detection (HC II) for identifying underlying CIN 2-3 was 96.3%, with a specificity of 60.2%. The positive predictive value was 20.6% and the negative predictive value was 99.3%. HPV testing reduced the number of colposcopies by 55%. In this group, only one woman with CIN 2 was HPV-negative (Meijer 2001).

According to the study by Fait (2000), the sensitivity and specificity of high-risk HPV detection (HC) for triage of women with two consecutive ASCUS results were 85.7% and 97% with PPV and NPV of 90.5% and 93.4% respectively. Among those with LSIL, the sensitivity and specificity of high-risk HPV detection were 88.2% and 94.7%, with PPV and NPV of 84.5% and 96.1%. HPV triage reduced the need for colposcopy by 24.6%.

In a cohort of 995 women with ASCUS, the sensitivity of HPV detection to identify histologic HSIL lesions or cancer was 89.2%, while its specificity was 64.1% (PPV of 15.1% and NPV of 98.8%). The sensitivity of a repeat liquid-based cytology (with ASCUS threshold) to detect HSIL was 76.2% (PPV of 12.9% and NPV of 97.4%) (Manos 1999). There was no significant difference between the two tests. The combination of immediate HPV testing and repeat cytology among HPV-negative women had a sensitivity of 96.9% with a minor increase in colposcopy referrals. According to the authors, the optimal approach would be using liquid cytology, which would detect HPV without an additional consultation (reflex HPV testing). In addition, liquid-based cytology would be more sensitive and result in fewer ASCUS readings, thus limiting the group needing HPV testing. Using HPV detection, 39.5% of women were referred for colposcopy, compared to 38.9% with repeat cytology (Manos 1999).

In the study by Manos, the HPV test's sensitivity was 100% for women under 30 and 80% for women over 30. Using HPV detection eliminated ASCUS diagnoses (HPV-negative cytologies would be reclassified as benign lesions, while HPV positives would be classified as low-grade intraepithelial lesions), thereby reducing costs and patient anxiety. Delivering results should be reassuring and nonjudgmental (Cox 1999).

In a cohort study of 265 participants with ASCUS or low-grade intraepithelial lesions (LSIL), the sensitivity of HC II testing for detecting all intraepithelial lesions (CIN) varied between 86% (0.2 pg/ml) and 55% (10 pg/ml), while specificity was 39-71%. At 0.2 pg/ml, the test identified 93% of high-grade lesions (CIN 2 and CIN 3). The sensitivity of the tube HC test (at 10 pg/ml) was 62% with a specificity of 65%. There was no difference in sensitivity whether the initial diagnosis was ASCUS or low-grade lesions, although the specificity was lower among women with low-grade lesions. Acceptable thresholds would be 0.2 pg/ml and 0.5 pg/ml (specificity of 42% and 52% among women with ASCUS and sensitivity of over 90%). The method would be optimal for screening women over 30 (Wright 1998).

In a cohort of 353 women with ASCUS, the sensitivity of HPV detection (PCR) for detecting high-grade lesions (CIN 3) was 96% at recruitment, 97% at 6 and 12 months and 95% at 18 months. The specificity was 50% at recruitment, 65% at 6 months and 71% at 12 and 18 months. The sensitivity of a repeat cytology was 70 to 79% between 6 to 18 months after recruitment, with a specificity of 61% to 84% (Nobbenhuis 1999). The authors recommended testing for HPV among women with moderate and minor lesions and, in the case of infection persisting after 6 months, referring them to a gynecologist. For women who were HPV-negative in the first test and who became positive at 6 months, they recommended repeat Pap and HPV tests after another 6 months (Nobbenhuis 1999).

In a prospective study of 1007 women with cytological lesions (high-grade lesions or two ASCUS/low-grade lesions), the sensitivity of HPV detection (PCR) was 65%, while its specificity was 60%. The corresponding values for cytology were 62% and 62%. A repeat Pap test for women with ASCUS or low-grade intraepithelial lesions was negative among 58.6%, identical to the first Pap test among 33.9% and detected a high-grade lesion among 7.5%. Among the women with high-grade lesions, repeat Pap tests (at 2-12 months) were negative among 41%, showing ASCUS/low-grade lesions among 32.5% and high-grade lesions (HSIL) among 26.4% (Adam 1998).

In the study by Euscher (2001), comparing *in situ* hybridization (ISH, Ventana) with HC II, the former was more accurate for predicting the progress of ASCUS: 81% of women who tested HPV-positive using this test developed intraepithelial lesions, versus 15% of women who tested HPV-positive using HC II. In addition, among women with normal cytology, 60% of women persistent HPV-positive using ISH and 24% of women who tested HPV-positive using HC II developed intraepithelial lesions during follow-up. The sensitivity of ISH for detecting SIL was similar to that of HC II testing (86% versus 79%).

Randomized trials

According to the ALTS Group's randomized trial, the prevalence of HPV among women with LSIL was too high to use HPV detection for triage, with colposcopies reduced by only 20-27%, at excessive costs (ALTS 2000). By contrast, for the triage of 3488 ASCUS to identify high-grade lesions (CIN 3 and worse), HPV detection (HC II) had a sensitivity of 96.3%, the Pap test with ASCUS threshold a sensitivity of 85.3% and 44.1% at LSIL treshold. The percentage of women referred for colposcopy was respectively 56.1%, 6.9% and 58.6%.

Results were similar for CIN 2+ (Solomon 2001). A significant limitation of the study is represented by the fact that 11.7% of results identified by the HC II as positive for high-risk HPV turned out to be low-risk HPVs that had not been targeted (cross reaction) (ALTS 2000).

According to the ALTS study, HPV detection for ASCUS triage is most accurate for women over 29. In this group, only 31.2% of women were referred for colposcopy (19.5% among women over 40) (Sherman 2002). Specificity was best at the threshold value of 10 pg/ml, with a small decrease in sensitivity. Thin-layer cytology was less accurate than the HC II test. The study did not find any effective strategies for the triage of low-grade intraepithelial lesions (Sherman 2002).

In a randomized trial (Lytwyn 2000) on 212 women with cytological abnormalities (ASCUS and low-grade intraepithelial lesions), HC II detected 87.5% of high-grade lesions (CIN 2-3), versus 55.6% using a second Pap test at ASCUS threshold (and 11% at HSIL threshold) carried out at 6 months. Specificities were similar for both tests (data not presented). Women in the cytology arm were more likely not to show up for colposcopy than those in the HPV arm (32.7% versus 17.1%). Thus, reflex HPV detection would contribute to a substantial decrease in the dropout of women who require follow-up and eventual treatment of cervical lesions (Lytwyn 2000).

Scenarios for the application of HPV testing in secondary cervical cancer screening

All studies using last-generation HPV tests (HC II and PCR) have shown that HPV detection is preferable to other existing possibilities (cytology or immediate colposcopy) for triage of ASCUS cytology results.

While the evidence is clear concerning the utility of HPV detection to reduce the number of colposcopies while detecting the immense majority of high-grade lesions, there are no studies on the effect of HPV detection on cervical cancer morbidity and mortality. As well, there are no studies on

the profitability of this approach, except in certain mathematical models. The use of HPV detection for ASCUS triage would be particularly useful in some countries where all ASCUS are referred for colposcopy (i.e. United States).

Several triage strategies using HPV detection are possible. One option is HPV detection for women with ASCUS or AGUS results (Meijer 2000, Jin 1999, Sigurdsson 1999). The sensitivity of this approach is high but specificity is lower (Meiher 2000). HPV detection could be the only follow-up test or could be used in parallel with repeat cytology (Cox 1995). Among women with AGUS, HPV testing identifies the majority of adenocarcinoma *in situ* (AIS) and may reduce the number of unnecessary colposcopies and cone biopsies (Meijer 2000).

According to the chart proposed by Apgar (1999), all women with ASCUS and positive for HR-HPVs would be referred for colposcopy, those with low-risk HPV would undergo 2 repeat cytologies at 6-month intervals, while HPV-negative patients would undergo a repeat cytology at 6 months, then annually if the results were negative. A second positive cytology (ASCUS or worse) would justify colposcopy. At the same time, according to Cuzick (2000), the presence of HPV in women with ASCUS is enough of an indicator to require immediate colposcopy.

Another possibility is selecting the women with moderate lesions (LSIL) who should be referred to colposcopy: those with two HPV-positive tests at a 6 months interval would be referred to colposcopy. The negative predictive value of a second test is 99% compared to 87% for a second Pap test; specificities are similar (Meijer 2000).

Among women with low-grade intraepithelial lesions (LSIL) a single positive HPV result has little value due to the high prevalence of HPV infection (ALTS 2000, Sherman 2002). According to Monsonego (2000), the management of low-grade intraepithelial lesions (LSIL) using HPV detection remains controversial but would be useful in regions where HPV prevalence is low or where the diagnosis of low-grade lesions (LSIL) is more prevalent than ASCUS (Monsonego 2000). On the other hand, according to the study by Gamzu (2002), high-risk HPV detection among women with low-grade lesions would have a positive predictive value of 97% and a negative predictive value of 100% for the existence of underlying high-grade intraepithelial lesions (CIN 2-3).

Women over 30, who have a lower prevalence of HPV infection, could benefit from HPV detection for triage of low-grade intraepithelial lesions. Among these women, high-risk HPV detection, based on the association between HPV persistence and the persistence of lesions, identifies 2 sub-groups: HR-HPV-positive women, with a high risk of developing high-grade lesions (CIN 3) and HR-HPV-negative women, not likely to develop high-grade intraepithelial lesions in the next 4 years (NPV of 99.3%) (Meijer 2001b). Besides identifying women with evolutive low-grade intraepithelial lesions, it is more important that this approach identifies those with low-grade lesions that will regress (Meijer 2001b). Currently, the standard procedure for managing low-grade intraepithelial lesions (LSIL) is a repeat Pap test after 6 months and referral for colposcopy if the lesion persists. This approach seems unnecessarilly expensive and stress-generating in patients (Meijer 2001b).

Among women over 35, HPV positivity and atypia of the transformation zone justifies excision, according to some authors, as there is a high risk of a subjacent high-grade lesion (Miller 2000).

According to Monsonego (2000), the most economical method for detecting HPV is using the HC II test on residual cells from a liquid-based cytology (reflex detection, which does not require the patient to return for HPV sampling). However, according to Meijer (2000), using liquid cytology is questionable due to its higher cost.

The Hybrid Capture test appears to be the best option for HPV screening, as PCR is more easily inhibited by various substances and more easily contaminated. For the HC test, it is essential to have an adequate specimen to avoid false-negatives. Another option is PCR with HPV typing to identify intermediate- or high-risk types (Jin 1999).

According to the guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP), immediate colposcopy, repeat cytology and HPV detection are equally useful for monitoring women with ASCUS, except if using liquid cytology, when HPV reflex testing is the optimal strategy (Wright 2002). Given that 3-10% of women who undergo Pap tests in the United States have an ASCUS result, the use of HPV detection to minimize colposcopy referrals appears to be an interesting possibility. The most promising approaches for triage are repeat Pap test with an HPV test or HPV detection alone with an adequately sensitive test. Reflex testing, using residue from the liquid cytology specimen, offers the major advantage of testing without additional clinic visits, (Cox 1995).

1.8.5 HPV screening among HIV-positive individuals

The utility of screening for HPV infection among individuals infected with HIV is controversial. On one side are those who believe that this population segment would greatly benefit from HPV screening (Harper 2001, Lillo 2001, Petry 1999), while on the other side are those who find that the high prevalence of HPV renders the test useless, with a very low positive predictive value (for evolution towards cancer) (Hankins 1999).

The performance of cytology is also uncertain among HIV-positive individuals (Petry 1999, Palefsky 1996), due to the high prevalence of inflammatory lesions (Petry 1999). In fact, sensitivity and specificity of the Pap test with an ASCUS threshold were 94% and 58.7% and 64.7% and 97.5% with a CIN 2 treshold for prevalent lesions. HPV detection (HC I) in the same population had a sensitivity and specificity of 94% and 70.3%. In the follow-up of this population, the sensitivity of the Pap tests for incident cases was 84.6 % at ASCUS threshold and 23 % at CIN 2 threshold. The corresponding specificity was 44.4 % and 9.3 %. The sensitivity and specificity values for HPV detection for incidental cases were 100% and 66.7%. The Pap test missed 3 out of 30 women with advanced lesions, while 57.3% of all women were referred for colposcopy. The Hybrid Capture test identified 29 out of 30 severe lesions (Petry 1999).

Nonetheless, cytology is recommended as a preventive means for all HPV-associated anogenital cancers (Lillo 2001, Hankins 1999, Palefsky 1996). Among HIV-positive women, the CDC recommends repeat cytologies at 6 months, then annually if results are normal. Cytological lesions of any degree (including ASCUS) should be referred to colposcopy. Besides the cervix, the vulvar and anal regions should also be examined (Palefsky 1996).

According to Goldie's (2001) mathematical model for cervical cancer screening for women infected with HIV, an aggressive, targeted screening strategy would be the most economical. The variable that most influenced the simulation results was the global incidence of high-grade intraepithelial lesions and the rate of progression of high-grade intraepithelial lesions to cancer.

1.9   SCREENING FOR ANAL CANCERS

There is little information on the screening and treatment of anal lesions in terms of effectiveness, side effects, costs, effect on quality of life, etc. More research is necessary on the natural history of anal HPV infection, its risk factors, the effects of treatment, the performance of anal Pap tests and the performance of HPV detection for primary screening and triage of anal cytological lesions (DSTDP-CDC 1999)

The main obstacles for introducing a screening program for anal intraepithelial lesions (ASIL) are a lack of trained clinicians able to diagnose and treat anal lesions (Palefsky 2001, Goldie 1999) and the limited therapeutic options (Palefsky 2001). In addition, there are no studies on the effectiveness of anal cancer prevention through screening and treatment of anal intraepithelial neoplasia (AIN) (Palefsky 2001).

According to the mathematical model on effectiveness and the cost-effectiveness ratio of routine screening for anal cancer among HIV-positive MSM, screening initiated at the onset of HIV infection and repeated every 2 years or annually would obtain the best results. Beginning screening at more advanced stages of the HIV infection reduces gains and increases costs, while screening at 6-month intervals provides no significant additional benefits (Goldie 1999). According to Palefsky (1996), the target groups for anal cancer screening would be those who have had receptive anal sex (HIV-negative and HIV-positive), those with perianal or intra-anal condylomata and HIV-positive men with immunosuppression. Anal cytology appears to be the appropriate test for screening, followed by anuscopy and biopsy in the case of cytological lesions (Palefsky 1996).

A study of HPV testing for anal cancer screening in HIV-positive persons, with an emphasis on the dimensions of the HPV infection, is under way in Montreal (Coutlée 2001).

1.10   ECONOMIC IMPACT OF HPV INFECTION

The financial burden of genital HPV infection in the United States is estimated at $1.6-6 billion a year, not counting indirect costs or the social and psychological burden of infection. The real costs are much higher than those calculated solely based on treatments related to cervical cancer. In fact, HPV is the most costly STI after HIV infection (Douglas 2000, DSTDP-CDC 1999).

Canadian data on the financial burden of HPV genital infection are incomplete and do not present an overall picture of the total costs.

In 1993, the incidence of cervical cancer in Canada was of 1300 cases, with approximately 400 estimated deaths and related costs of between $180 million and $240 million (Johnson 1994). In 2002, it is estimated that 1400 women will be diagnosed with invasive cancer of the uterine cervix, with an estimated 410 fatalities (Health Canada 2002).

More than 4 million cervical smears are collected each year in Canada, of which more than 8% (325 000) are abnormal (SOGC 1998). Ontario laboratories read approximately 2 million smears a year, of which 20 000 to 40 000 are high-grade lesions (Shaw 2000).

In the study by Sellors (2000) on Canadian women 15 to 49 years old, 13.1% of participants had already been referred at least once for colposcopy. In Quebec in 2000, 46,736 initial colposcopies (as opposed to follow-up colposcopies) were conducted (representing 2.4% of total surgical procedures), costing $2,299,455 or 1.1% of surgery-related expenses. Among the surgical procedures, initial colposcopies ranked seventh in terms of frequency and eighth in terms of cost. In addition, 28,350 follow-up colposcopies were performed (1.4% of surgical interventions), at a cost of $809,990 or 0.4% of surgery-related expenses (RAMQ 2001).

1.10.1 Cost-effectiveness of new means of cervical cancer screening

The cost-effectiveness ratio of technologies that are improving cytology sensitivity (automated techniques, liquid-based cytologies) is directly linked to the frequency of screening (prolonged intervals improving the ratio and reducing costs). The cost-effectiveness ratio of new technologies is difficult to estimate, due to their uncertain sensitivity and specificity (AHCPR 1999). Other variables, such as the natural history of the disease, the cost of technologies, and age at the onset of screening, have little influence on the cost-effectiveness ratio (AHCPR 1999).

Liquid-based cytology

According to Montz, liquid-based cytology has the potential to further reduce the incidence of cervical cancer by a minimum of 30%, with a cost-effectiveness ratio of approximately US$11 000/life-year saved. The cost per life-year saved is inversely proportional to the predictive value of liquid-based cytology.

Primary HPV screening

There is little information on the cost-effectiveness ratio of adding HPV testing to the cervical cancer primary screening protocol. According to mathematical models, HPV screening with or replacing a Pap test appears to be feasible and economical (Harper 2001).

An HPV detection test added to the cervical cancer screening programs could potentially improve the cost-effectiveness ratio of screening compared to current strategies (Holmes 2001). For instance, in Great Britain, the concomitant use of cytology and HPV testing among women over 20 reduced the number of inadequate smears from 7.9% to 1% and would allow for prolonged, 5 year, screening interval. The most cost-effective model, without negatively affecting the reduction in mortality, is

using both tests every 10 years (Holmes 2001). Primary screening using the Pap test and HPV detection every 5 years is slightly more expensive than using a Pap test alone every 3 years (analysis based solely on mortality, without considering morbidity). If the analysis was based on the number of years gained, adjusted for quality of life, including anxiety and time spent on repeat testing, the cost-effectiveness ratio appears to be much more favorable (Holmes 2001).

In a group of 4761 German women, the cost-benefit analysis, based on the number of lesions identified as CIN 2 or worse, resulted in costs of 1088 Euros per identified case using an HPV test (PCR and EIA), 2587 Euros for cytology and 6483 Euros for colposcopy (costs include follow-up for positive cases). After adjustment for follow-up bias, the costs per case were reduced respectively to 927, 1871 and 4999 Euros (Schneider 2000).

According to the mathematical model by Myers (2000) which looked at variations in sensitivity and specificity and in screening intervals of 1, 2 and 3 years, only the 3-year screening interval was able to maintain a cost-effectiveness ratio under $25,000 with reasonable sensitivity and specificity. New technologies will be more economical only if the added sensitivity is associated with improved specificity, if the frequency of screening can be reduced or if the follow-up treatment is less costly. New HPV screening tests may meet these conditions. Based on a constant specificity of 97%, variations in screening sensitivity led to increased costs for each life-year saved. When screening was every 5 years, the cost per life-year saved varied between $2853 and $2919, every 3 years between $14,483 and $41,881, and with annual screening it was between $107,631 and $381,928. The optimal strategy would be screening at 5 years intervals, if the HPV tests were highly sensitive (Myers 2000).

Used every 3 years, the two tests would generate a cost of $16,000 per life-year saved, which in the United States is considered a reasonable investment. At a screening interval of 3 years, the combination of liquid cytology / HC II is more economical than conventional Pap cytology ($21 000 per life-year saved) (Myers 2001). Cuzick and Sasieni (1995) have estimated the impact of introducing HPV testing as part of primary cervical cancer screening. According to them, the concomitant use of cytology and HPV testing significantly reduces screening costs, with annual savings of £30 million, or more than a quarter of current costs, due mainly to the prolonged screening interval, in the same time increasing the number of prevented cancer cases by approximately 40%. The benefits of less frequent screening for women were not considered.

HPV screening: ASCUS triage

Currently in the United States, follow-up for women with ASCUS causes expenses of $3.6 billion out of the $5-6 billion spent annually on cervical cancer screening. Women with ASCUS and AGUS represent more than half the cases of histologic HSIL, which cannot be overlooked (Kinney 2001). Using HPV detection for ASCUS triage would reduce the number of subsequent Pap tests and colposcopies and would substantially reduce the cost of follow-up compared to the current strategy in use in the United States, consisting of colposcopy for all ASCUS cases (Holmes 2001).

In a randomized trial in Ontario, comparing the effectiveness of HPV detection with the effctiveness of a repeat Pap test among women with ASCUS or LSIL, HPV detection created an additional cost per detected case of C$ 3003, compared to repeat cytology, including the costs of confirmation and treatment, a cost that could be considered acceptable. In this study, HPV testing required an additional visit for specimen collection, avoidable if liquid-based cytology were used.

In Canada, cost comparisons for various strategies may differ significantly from those in the United States, mainly due to different costs for medical procedures. As well, Canadian guidelines recommend cytology for the follow-up (as opposed to routine colposcopy in the United States) of women with ASCUS or LSIL (SOGC 1998).

In Lytwyn's study, the calculated costs for diagnostic and therapeutic procedures were C$59.63 for HPV detection (HC II), C$49.78 for a repeat Pap test, C$121.33 for a colposcopy, and C$32.01 for a biopsy. As for treatment interventions, the costs were C$57 for an endocervical curettage, C$437.81 for a LEEP, C$87.03 for a laser ablation, C$977.53 for a cone excision. A gynecology clinic visit was C$85.83 and a visit with a general practitioner was C$40.20 (Lytwyn 2000).

According to the mathematical model by Lytwyn (1998), applied to an imaginary cohort of 10 000 women with ASCUS or LSIL, repeat Pap test identified 1125 CIN 2-3 at a cost of $1,490,000 or $1324 per identified case, while HC testing identified 1350 cases at a cost of $1,980,000 or $1466 per identified case. The HC test identified 225 more cases than the Pap test at a cost of $2178 per additional identified case. The reference test was immediate colposcopy which identified all 1482 lesions (at a cost of $2 420 000 or $1633/case, or $3333 per additional case identified).

Even if only 10% of unidentified and untreated CIN 2-3 evolve to invasive cancer, the costs for the additional identified cases are clearly lower than the cost of treating the cancers the women would have developed if their lesions would be missed at screening (Lytwyn 1998). The cost-effectiveness ratio was dependent on the sensitivity and specificity of the tests. If the sensitivity of Pap testing were less than 58%, it would become more expensive than HC testing, while identifying fewer CIN 2-3 cases. If the specificity of HC testing were less than 33%, its cost would become higher than immediate colposcopy, with fewer numbers of cases identified (Lytwyn 1998).

Triage by HPV detection using specimens collected at the time of the initial cytology would eliminate the need for an additional visit. Considering that 5% of Pap tests are ASCUS or LSIL, using the preserving solution should cost less than $1.45/specimen for this approach to be less expensive than supplementary visits for the HPV detection (Lytwyn 1998).

In a transversal study on the performance of HPV detection among women with 2 consecutive ASCUS and/or LSIL results, the cost of triage for colposcopy was $692/case with cytology (identifying 42 cases out of 67), $1267/case with HPV detection (Virapap, 45 identified cases) and $1246/case with both methods (55 identified cases). At a sensitivity of 100%, the cost of triage based on HPV detection would be $1074/indentified case (Kaufman 1997).

In another study of a group of high-risk women with ASCUS or AGUS results, the cost of each CIN 2-3 detected by colposcopy was $4875. Using conventional Pap test and HPV detection slightly reduced this cost, to $4809 (with a sensitivity of 93%). If the sensitivity of follow-up visits increased to 100%, the cost per identified case became $4488. The cost per identified case using liquid cytology and HPV detection was $4307 if the sensitivity was 93% and $4020 if the sensitivity was 100% (Shlay 2000).

Kinney (2001) developed a mathematical model for using HPV detection (reflex HC II) for triage, considering that using a repeat Pap test for ASCUS triage has a sensitivity of 89.2% for HSIL (94.2% for AGUS triage),. The study concluded that reflex HPV detection could reduce the number of follow-up Pap tests by 49% and colposcopies by 28%. Considering that a second Pap test would not be necessary for triage using HPV detection, the reduction in follow-up Pap tests would be of 85%. In fact, even using ThinPrep, HPV triage would be less expensive than the current approach, if a second Pap test was not necessary (Kinney 2001). The same author estimated the cost of conventional follow-up for 1000 ASCUS cases at $366,596. The follow-up with a conventional Pap test and reflex HC II test on a separate specimen would cost $293,626 for 1000 ASCUS, while using ThinPrep for all cytologies and HC II on the same specimen in TP solution would cost $439,352 for 1000 ASCUS, if Pap tests were added for follow-up (Kinney 2001).

According to Myers's mathematical model, the combination of liquid-based cytology and HPV detection using HC II is more effective and less costly than liquid cytology alone, for ASCUS triage at any screening intervals. The results of the study were robust for a variety of costs and probability suppositions (Myers 2001).

Similarly, Kim's (2002) mathematical model identified reflex triage (HPV detection using a specimen obtained for liquid-based cytology) as the strategy with the best cost-effectiveness ratio, more sensitive than repeat cytology (total reduction of cancer incidence of 86% versus 84% with cytology) and less costly than immediate colposcopy ($24,700 per life-year saved versus $411,500 for colposcopy).

Currently, there is no effective triage strategy for low-grade lesions. However, such a strategy would be desirable, given that, according to Walsh (1998), colposcopic evaluation and treatment of all LSIL would cost US$6 billion per year in the United States.

1.10.2   Cost-effectiveness of screening for HIV-positive individuals

According to Goldie's (2001) mathematical model on cervical cancer screening for HIV-positive women, a targeted and aggressive screening strategy was most economical, with a cost-effectiveness ratio of $11,400 per quality-adjusted life-year saved, for women with CD4 counts of 200-500 and on HAART, $13,100 for those with <200 CD4/mm³ on HAART, and $20,300 for those with < 200 CD4/mm³ and without HAART. The results of the simulation using PRC or HC II test were similar.

The variables that influenced most the results of the simulation were the global incidence of HSIL and the progression rate of HSIL to cancer. All other variables appeared to have little influence (including the cost of tests and treatments and relative risks as well as the prevalence of HPV infection). Reducing the HSIL incidence by 75% increased the cost-effectiveness ratio from $11,500 to $50,000 per quality-adjusted life-year saved,. Persistence of the infection did not influence the cost-effectiveness ratio (Goldie 2001).

1.10.3   Cost-effectiveness of anal cancer screening

According to a mathematical model on effectiveness and the cost-effectiveness ratio of routine screening for anal cancer among HIV-positive MSM, screening introduced at the onset of HIV infection and repeated every 2 years or each year would offer the best results (gain of 2.7 and 3 months respectively, with a cost-effectiveness of $13,000 and $16,600 respectively per life-year saved, quality-of-life-adjusted, which is comparable to other accepted prevention measures). Initiating screening at more advanced stages of HIV infection reduces gains and increases costs, up to more than $50,000 per life-year saved, quality-of-life-adjusted. Screening at 6-month intervals did not provide any significant benefits but did increase the cost-effectiveness ratio to $49,600. The most significant factors influencing the cost-effectiveness ratio were the progression rate for high-grade ASIL to carcinoma and the effectiveness of ASIL treatment (Goldie 1999).

1.10.4   Cost of condyloma treatment

According to the model by Langley (1999a) on various treatment modalities for external condylomata, the cost per case cured (without recurrence during the 12 subsequent weeks) was $1150 with imiquimod and $990 with podophyllotoxine (effectiveness of 44% and 19.6% respectively). After adding additional costs for patients with therapeutic failure, the cost increased to $1263 for imiquimod and $1304 for podofilox (calculated using an average success rate of 30% for surgical procedures). If the success rate for ablative interventions is lower, imiquimod is even more cost-effective. Repeating initial treatment (imiquimod or podofilox) increases the cost per case cured to $1158 for imiquimod and $1304 for podofilox (with a cure rate of 76.4% and 47.9% respectively). The cost per case cured for doctor-administered treatment varied between $1120 (laser) and $2508 (podophylline). The cost of laser ablation may be artificially low due to the lack of CPT coding for this procedure performed on women. In conclusion, according to Langley, and on the assumption that his estimates on the effectiveness of treatments are accurate, ablative therapies are more costly than self-administered treatments, with imiquimod appearing to be more cost-effective than podofilox (Langley 1999a). The study, financed by the pharmaceutical company 3M (manufacturer of imiquimod), used only two studies for its effectiveness parameters, one on podophyllotoxine and one on imiquimod. A cost-effectiveness analysis with effectiveness parameters based on several randomized studies might offer different results.

In a subsequent study, Langley (1999b) used more recent medication costs and obtained similar results. This study again revealed a good cost-effectiveness ratio for imiquimod for women ($719 per confirmed cure), with much more modest results for men ($1655). The presented calculations did not consider quality of life and indirect costs (pain, side effects, lost time). The same observations applied concerning estimation parameters for treatment effectiveness.

1.11 SUMMARY OF LITERATURE SURVEY

Our analysis of the literature review allowed us to identify the following summary highlights:

1.11.1 Epidemiology

- The prevalence of HPV infection is high throughout the world, with significant regional variations: from 5.4% of the general population in Spain to 39% of women under 40 in the United States.

- The situation in Canada and Quebec appears to be similar to that of the United States. In a study of university students conducted in Montreal, the prevalence of HPV infection was 22-29%, with an increasing trend.

- The incidence of HPV infection is particularly high among young people.

- There are no Canadian data on the prevalence of genital warts (condylomata) caused by HPV.

- Cytological abnormalities of the cervix seem to be slightly more common in Quebec than elsewhere (11.5%, of which 7.2% are ASCUS), although this difference might be explained by the choice of the study population (the only Quebec study was conducted on young university students) and the large proportion of ASCUS smears. On the other hand, the incidence of invasive cancer and associated mortality in Quebec are relatively low.

- The incidence of invasive cancer of the uterine cervix has diminished abruptly since the introduction of cervical cancer screening using cytology. However, the incidence of carcinoma *in situ* has increased slightly, especially among young women, while some countries have seen an increase in the incidence of cervical adenocarcinoma.

- HIV-positive individuals are at increased risk of acquiring HPV infection and HPV-caused lesions.

- Anal HPV infection and associated lesions are more common in MSM and HPV-positive individuals. Among MSM, the incidence of anal cancer is similar to the incidence of cervical cancer among women prior to the introduction of cytological screening.

- HPV infection is transmitted primarily through sexual contact. Vertical transmission is possible and may cause recurrent laryngeal papillomatosis. The frequency and significance of HPV vertical transmission is controversial.

- The presence of genital warts in children may be related to autoinoculation or other rare means of transmission but can also be an indicator of sexual abuse.

- Risk factors for HPV infection are age, race and sexual behaviour. Smoking, condom use and oral contraceptives are occasionally associated with HPV infection. Participating in a screening program is inversely associated with HPV infection.

1.11.2   Natural history of HPV infection

- The HPV family includes numerous genotypes, some of which are associated with cervical carcinoma and other carcinoma of the anogenital region. Other genotypes may cause condylomata, usually benign lesions that may take on various morphological aspects.

- The link between condylomata and precancerous lesions is controversial.

- Cervical dysplasia (cervical intraepithelial neoplasia, squamous intraepithelial lesions) are precancerous lesions associated with certain HPV genotypes, more precisely with persistent HPV infection.

- The majority of HPV infections and low-grade SIL regress. Only a minority of lesions persist or progress. A significant proportion of high-grade lesions also seem to regress.

- The minimum interval between HPV infection and the development of invasive cancer is 7 years, with an average interval of 20 to 30 years.

- HPV infection is a necessary but not sufficient factor for developing cervical cancer. Other possible associated factors are immune response modulators of the host, chemical factors (smoking, oral contraceptives, and nutritional deficiencies) and infectious factors (Chlamydia, HSV-2).

- Anal cancer is associated with HPV infection and seems to have an evolution that is similar to cervical cancer.

- HIV infection increases the risk of intraepithelial lesions and anal cancer. At the same time, the incidence of cervical cancer has not increased in HIV-positive women. There is little data on the effect of HAART on the incidence of lesions.

1.11.3   Detection of HPV infection

- Visual inspection, acetic acid application and the Pap test perform poorly in detecting HPV infection.

- Accurate tests for detecting HPV antigens are currently available, including PCR and Hybrid Capture tests. However, to date, only the HC II test is appropriate for clinical use.

- The DNA chip may some day lead to a valuable technique for HPV detection.

- Serology has little utility for detecting HPV infection.

1.11.4   Treatment

- There are numerous means of treating genital warts, none of which is ideal.

- Imiquimod does not appear to be more effective than other available treatments.

- Under certain circumstances, withholding treatment is also an acceptable option.

- The success rate for treating genital warts varies between 40% and 90%, with a recurrence rate of 10-40%.

- Treatment should be chosen according to the patient's preferences and existing possibilities.

- The effect of condyloma treatment on transmission of infection is not well known.

- The procedures following a diagnosis of cervical lesions include follow-up and immediate treatment. Women with low-grade lesions have little risk of developing invasive cancer and may be followed without immediate treatment.

- In Canada, HSIL are referred for immediate colposcopy, while LSIL and ASCUS are followed by repeat cytologies at 4-6 months. In the event of a second ASCUS or LSIL smear, colposcopy is recommended.

- Treatment of cervical lesions is effective and diverse therapeutic options have similar values. The preferred method is LEEP due to its effectiveness and the possibility of histological analysis of the obtained specimen.

1.11.5   Psychological impacts

- HPV infection is a source of negative emotions that appear to be long-lasting.

- Patients with an HPV infection sometimes consider that medical services are inadequate, particularly when it comes to psychological support.

- Patients diagnosed with an HPV infection express an increased need for information and effective communication.

- Screening itself is a possible source of distress, while follow-up procedures and treatment generate considerable anxiety, particularly among adolescents.

- The effect of detecting HPV infection on the acceptability and participation rates in cervical cancer screening programs is insufficiently understood.

- Reducing the number of colposcopies to a minimum could have a positive impact on the acceptability of cervical cancer screening.

- Genital warts are associated with negative feelings and fear of cancer.

- Treatment of warts is considered painful and embarrassing.

1.11.6   Prevention

Primary prevention

- Most young people and adults have little knowledge of HPV infection and cervical cancer screening.

- The perceived risk of HPV infection is considerably low.

- Health care professionals are sometimes insufficiently trained for treating and counseling patients with HPV infection.

- Interventions that includes promoting safe behaviour seem to be somewhat effective.

- Condoms provide a certain protective effect against cervical infection and against cervical intraepithelial lesions. There is little data on the effectiveness of condoms in preventing genital warts.

- Several prophylactic vaccines are in development.

Cervical cancer screening using cytology

- While Pap tests under-perform, their regular use demonstrated the capability to reduce cervical cancer incidence by 60 to 70%. Nonetheless, screening using conventional cytology has currently reached a plateau for reducing incidence.

- The Pap test was introduced in Canada in 1949 and helped reduce the incidence of cervical cancer to 9.1/100 000 in 1996.

- According to Health Canada, there is a trend towards reduced participation in screening programs, especially among women 15 to 24 and 55 to 64.

- The risk factors for non-participation are low income, low level of education, lack of accessibility and fear of the intervention.

- Quebec's participation rate is comparable to the Canadian average. Specifically, 79% of women have undergone screening in the past 3 years.

- Despite recommendations by the Walton Committee, Quebec does not have a cytology registry, neither a structured screening program.

- Annual screening does not provide any advantages over less frequent screening intervals; Canadian guidelines recommend an interval of 3 years between two cytologies. However, the application of these guidelines is insufficiently documented and it seems that many low-risk women have annual cytologies despite their low utility.

- New cytology techniques perform better, though at higher cost.

Cervical cancer screening using HPV detection

- Current HPV detection tests are more sensitive than Pap testing for screening cervical lesions but less specific. There is no data on the effectiveness of HPV testing in reducing the incidence of cervical cancer, nor the associated mortality.

- HPV detection tests have a negative predictive value of nearly 100%, which helps identify the women with very low risk of developing cervical cancer.

- The use of HPV detection tests allows longer intervals between screenings for cervical cancer.

- HPV testing might be useful for primary screening, for triage of ASCUS and LSIL, monitoring cytology laboratory performance and follow up after treatment of precancerous lesions.

HPV testing as a primary screening method

- The use of HPV detection combined with cytology increases screening sensitivity but risks to reduce its specificity. Repeat HPV testing to identify persistent infections may increase screening specificity.

- A major advantage of HPV detection as a primary screening method is the possibility of increasing screening intervals.

- HPV detection using self-collected specimens is an interesting approach for countries without an adequate system for cytology and for women who refuse to have a Pap test.

- One proposed strategy is to use HPV detection for women over 35. Another option would be to use HPV screening simultaneously with the first Pap test of young women around the age of 20.

- Numerous randomized studies on the performance of HPV detection in the primary screening of cervical cancer are under way.

- There is little information on the acceptability of HPV testing in the population and on the impact of such a test on screening participation. Data from some studies suggest that this strategy appears to be generally acceptable.

HPV testing for ASCUS triage

- ASCUS, due to its high frequency, represents a public health problem.

- The majority of ASCUS correspond to benign lesions, although biopsy finds moderate or severe CIN in 6.7-25% of cases.

- The management options for women with ASCUS are colposcopy, repeat cytology or HPV detection.

- Immediate colposcopy for all ASCUS is an expensive strategy.

- Repeat cytology is simple to perform and inexpensive but may overlook up to 30% of high-grade lesions.

- HPV detection may be used alone or with cytology for ASCUS and AGUS triage.

- Randomized trials demonstrated that the performance of HPV detection for ASCUS triage has been significantly effective. This has also been demonstrated in prospective and transversal studies.

- HPV testing instead of immediate colposcopy following an ASCUS diagnosis reduces the number of colposcopies by 30 to 59%.

- Compared to repeat cytology following an ASCUS diagnosis, HPV detection is more sensitive and, depending on the prevalence of infection in the population studied, may reduce the number of colposcopies.

CHAPTER 2: EXPERT CONSULTATION

Analyzing the literature survey helped identify material to answer questions of public health interest. Our analysis was submitted to a group of experts for validation and comments.

As planned, the expert consultation using the Delphi method was made up of 2 stages.

The first stage consisted of asking the experts to complete a questionnaire based on the highlights of our literature survey: 16 questions on specific aspects of the literature survey and 2 questions intended to garner general comments or suggestions. The preliminary report on the literature survey was submitted as a reference document, however, the experts were invited to comment on it if they so desired. A summary document presenting the highlights was also submitted as reference material.

Consensus was reached on most of the questions in this first round. Additional suggestions, as well as questions that had generated dissimilar opinions, were included in the second round of the questionnaire, which was sent to the experts along with the results of the first round. These questions focused on epidemiology (target groups for prevalence studies), natural history (research approaches proposed by the experts) and screening (liquid-based cytology for ASCUS triage and measures to reduce the incidence of cervical cancer).

The questionnaires used in the two rounds of consultation are presented in the appendices.

Out of 18 experts approached, 10 (56%) agreed to participate and responded to both consultation questionnaires. The participants included 2 pathologists, 1 microbiologist, 3 epidemiologists and/or public health experts, 2 non-medical researchers and 2 general practitioners.

The levels of consensus were categorized as follows:

- Unanimous: All experts in agreement.
- Consensus: Agreement among at least 7 experts and no more than 1 clearly expressed opposing view.
- Lack of consensus: Agreement among fewer than 7 experts or more than 1 clearly expressed opposing view.

The results of the expert consultation are presented according to main theme, namely epidemiology, natural history, HPV detection and surveillance of those infected, and prevention.

Each theme section includes the questions asked of the experts and the elements from the literature survey analysis submitted for consultation, followed by a compilation of the experts' responses.

The intervention approaches recommended at the conclusion of the consultation are presented at the end of this chapter.

2.1 OVERVIEW OF THE CONSULTATION FINDINGS

2.1.1 Epidemiology

Question 1: What would be the most appropriate approach for HPV surveillance?

Question 2: Would it be useful to undertake epidemiological studies on HPV infection or on the lesions it causes? If so, which ones?

Question 3: Would there be any value in establishing a surveillance system for carcinoma *in situ*? If yes, what would be the best strategy?

Elements from the literature survey analysis

Including HPV infection among mandatory reportable diseases is not judicious. The most realistic approach for HPV surveillance is conducting studies on prevalence and establishing sentinel projects. As well, systematic and structured surveillance of carcinoma *in situ* would be extremely useful. A study of its prevalence in the general population would be relatively useless. However, prevalence studies would be useful for certain target groups (women aged 20 to 35, women 35 to 45, HIV-positive individuals, MSM, etc.). Studies of the prevalence of cervical intraepithelial lesions and the evolution of the incidence of cervical adenocarcinoma would be moderately to very useful.

Results of the first round of questions

Concerning surveillance, the experts unanimously agreed that there is no need to include HPV infection among mandatory reportable diseases (MRD) and that undertaking sentinel surveillance projects could be beneficial. They were less in favour of undertaking prevalence studies for HPV surveillance: based on the available data from existing studies, the consensus of the experts was that HPV prevalence studies in the general population were of no or little value. Concerning the need for HPV prevalence studies in certain population groups, expert consensus could not be established on the relevance of such studies or on the groups to be targeted. Regarding the question of surveillance of epithelial lesions caused by HPV, there was expert consensus that the surveillance of high-grade lesions be made a priority. The systematic structured surveillance of carcinoma *in situ* was also considered to be a generally appropriate option, although the framework for such surveillance must be specified (public health program or research activity), as well as its modalities (target group, technology used, collection method and data analysis). When it came to the incidence of cervical adenocarcinoma, a large majority of experts agreed on the lack of information and on the importance of studying the evolution of cervical adenocarcinoma incidence.

Results of the second round of questions

Faced with varying opinions on the value of conducting studies on HPV prevalence within target populations, we asked the experts to clarify their position on this issue. Consensus was reached that people living with HIV and, to a lesser degree, women over 35 were the groups most likely to benefit from prevalence studies. There was little interest in HPV prevalence studies among young women, men and MSM.

2.1.2 Natural history of HPV infection

Question 4: To what extent should studies be developed on the natural history of HPV infection?

Elements from the literature survey analysis

Aspects of the natural history of HPV infection that should be better understood and that would justify new studies are the link between condyloma and precancerous lesions, incriminating cofactors in infection persistence and the development of cervical cancer, the evolution of anal HPV infection, and the effect of new antiretroviral therapies on the incidence of cervical epithelial lesions among HIV-positive women.

Results of the first round of questions

The vast majority of experts (consensus) felt it would be worthwhile to better document incriminating cofactors in HPV persistence and the development of cervical cancer, the evolution of anal HPV infection and the effect of new antiretroviral therapies on the incidence and evolution of HPV infection among HIV-positive individuals. At the same time, the experts' consensus was that the link between condyloma and precancerous genital lesions was not a research priority. A new study (in the process of being published) on the benefit of colposcopy among women diagnosed with condyloma acuminata is investigating the link between condyloma and precancerous lesions. Some experts suggested other research approaches concerning the natural history of HPV infection: natural evolution of infections among women infected in adolescence (cohort in place at Sainte-Justine Hospital); availability and application of guidelines for monitoring women infected with HIV and HPV; the need to treat partners of patients with cervical/anal lesions; and the clinical evolution of adenocarcinoma *in situ*.

Results of the second round of questions

The experts were consulted concerning new research approaches suggested in the first consultation stage. Two additional aspects of the natural history of HPV infection secured the interest and consensus among our experts: natural evolution of infections among women infected in adolescence and the availability and application of guidelines for monitoring women infected with HIV and HPV. As well, several experts stressed the need for clear guidelines for monitoring all HPV infections. There

was no consensus on the need to treat partners of patients with cervical/anal lesions or on the clinical evolution of adenocarcinoma *in situ*.

2.1.3   HPV detection and follow-up of infected individuals

Question 5:   Among HPV detection tests available, which is most appropriate for clinical use and what would be the main indicators for using it?

Question 6:   Are there currently therapeutic options that would be effective in reducing the impact of HPV infection on public health?

Question 7:   What role does counselling play and what types of tools would be helpful in counselling patients with HPV infection?

Question 8:   What type of training do health care professionals need?

Elements from the literature survey analysis

The HC II test is currently the best option for clinical detection of HPV.

There is little information on what impact treating HPV infection has on transmission. A study in this regard would be useful. As well, a study on what impact evaluating and treating partners has on HPV recurrence would be particularly informative. As for genital warts, a more complete analysis of the cost-benefit ratio of imiquimod use would be appropriate. Counselling patients with HPV infection should be a key aspect of medical intervention. Consultation should include the distribution of documents adapted to the infected person's needs. In this sense, it would be useful to provide professionals with additional training in counselling and regarding the psychological aspects of HPV infection.

Consultation results

HPV diagnosis

A consensus was established that HC II is currently the best option for detecting HPV in the cervix, although the high cost of such a test was often mentioned as a negative factor. Other experts recommended waiting for new tests to become available or using PCR, which, while more complicated, costs about the same and performs better. One interesting mention was the possibility of automating PCR for clinical use. When PCR was considered, the importance of establishing quality-control measures was stressed. As well, PCR was suggested as the test of choice for cases of doubtful diagnoses or for sperm donors.

Treatment of HPV lesions

Concerning the treatment of HPV lesions, virtually all of the experts spoke of a lack of information on the impact treatment has on infection transmission, and of the need for a study documenting the effectiveness of treatment in reducing transmission. There was also consensus on there being insufficient data on the cost-benefit ratio of imiquimod and on the need for studies in this regard. As well, there was consensus that better documentation was needed on what impact evaluation and treatment of partners have on HPV recurrence. However, the feasibility of such studies was questioned several times.

There was consensus that counselling patients with HPV infections is a key aspect of medical intervention. The proposed tools to assist in counselling included distributing documents adapted to identified needs, developing support groups, reinforcing telephone help lines, and making appropriate and up-to-date information available on recognized, legitimate Web sites.

2.1.4   Primary prevention

Question 9:   What would be the pertinence of developing HPV awareness/information activities? What would be the target groups?

Question 10:   Should condom use for preventing HPV infection be promoted? If so, would some groups benefit more than others?

Elements from the literature survey analysis

Educating patients and the general population is key in preventing HPV infection. Condom use should be promoted. It appears to be particularly effective in preventing infections of the uterine cervix.

Results of the first round of questions

The experts unanimously agreed that educating patients and the general population was an important means of preventing HPV infection and cervical cancer. It would be particularly important to include education and awareness in a structured screening program. Proposed target groups included the general public, young people and older women. While young women were mentioned by more than one expert, there was no clear consensus on prioritizing one group over the other. Still in the context of primary prevention, the majority of experts were in favour of promoting condom use, even if it appears to have limited effect. According to the expert consensus, health care professionals require additional training in the area of counselling. Several experts suggested more extensive training on HPV than is currently offered, as well as introducing incentives for doctors to intensify their involvement in the recommended interventions (counselling, screening).

Results of the second round of questions

The second consultation stage for this theme attempted to clarify the value of sensitizing and educational activities specifically targeting young women, who were identified as target clients by some experts in the initial consultation round. Despite this process, a clear consensus could not be established: half the experts felt this option would be very useful or somewhat useful, while the other half thought the measure would have little value.

2.1.5   Screening

Question 11:   Would there be any value in creating a cytology registry? If yes, how feasible would this be?

Question 12:   Is it appropriate and affordable to make liquid-based cytology a routine cytology test?

Question 13:   What would be the optimum strategies for reducing the incidence of cervical cancer?

Question 14:   Should HPV detection be integrated in systematic cervical cancer screening? If yes, what would be the optimum strategy?

Question 15:   What would be the relevance of studying the impact of introducing HPV detection on the level of participation in cervical cancer screening?

Question 16:   Would an evaluation study on the actual costs of screening and treatment of cervical cancer be useful?

Question 17:   If the procedures for cervical cancer screening were to change, what is the best way to encourage the application of new guidelines concerning the introduction of a new test (HPV detection) and modifications to screening intervals?

Elements from the literature survey analysis

Creating a cytology registry and an organized screening program would be essential. Introducing liquid-based cytology would increase screening performance. However, there is insufficient data on the cost-benefit ratio of liquid-based cytology. The best interventions for reducing the incidence of cervical cancer would be recruiting women who do not participate in screening and using a more sensitive test than traditional Pap tests. As for the role of HPV detection in cervical cancer screening programs, using it for ASCUS triage would be useful. The ideal strategy would be to implement a pilot project using HPV detection for ASCUS triage. On the other hand, it would be prudent to wait for the results of studies currently under way before implementing a cervical cancer screening program based on the systematic detection of cervical HPV. A study on what impact HPV detection would have on participation in cervical cancer screening would be important. A study of the actual costs of

screening and treatment for cervical cancer would be moderately beneficial to the provincial screening program.

Results of the first round of questions

<u>Cervical cancer screening</u>

Within the framework of cervical cancer screening, the experts were unanimous that creating a cytology registry and implementing an organized screening program would be of major importance and quite feasible. Such a registry would provide for the surveillance of intraepithelial lesions. Despite reservations concerning the high cost of an evaluation study on the actual costs of cervical cancer screening, most experts felt it would be useful. The suggested formulas include a calculation based on existing data or a mathematical study based on the Markov model.

<u>Liquid-based cytology</u>

Opinions on liquid-based cytology were contradictory and it was not possible to form a clear consensus. Some experts recommended replacing conventional cytology with this test, while others recommended it be used solely for evaluating women with abnormal cytologies in conjunction with HC II testing for HPV screening. Finally, one group of experts questioned the appropriateness of introducing liquid cytology considering it performs just as well as conventional cytology but costs more. A new study is expected to support this latter position (Moseley and Paget 2002). The majority of experts agreed on the lack of data concerning liquid-based cytology's cost-benefit ratio. The formulas proposed for evaluating this cost-benefit ratio include theoretical estimation, clinical studies or a pilot project.

<u>HPV detection</u>

There was consensus on the value of HPV detection for ASCUS triage. The proposed methods essentially include the use of a single sample for cytology and HPV testing. There was also a reference to using PCR on biopsy specimens. The vast majority of experts agreed that the ideal strategy would be implementing a pilot project using HPV detection for ASCUS triage. Almost all of the experts declared that it would be prudent to wait for the results of studies currently under way before implementing a cervical cancer screening program based on the systematic detection of cervical HPV infection (primary screening). No consensus could be reached on the value of studying what impact introducing HPV detection would have on participation in cervical cancer screening. Those experts who were opposed to such a study felt that it should be conducted as needed only after the introduction of new technologies and that, generally, a well-conceived information/education program would be more beneficial. Based on these remarks, we decided not to recommend this type of study in the current context.

Proposed strategies for reducing the incidence of cervical cancer

The experts were unanimous that recruiting women who do not participate in screening was necessary to reduce the incidence of cervical cancer. As well, there was consensus on the value of introducing a more sensitive screening test than conventional cytology. Other suggestions included intensifying primary prevention in young women, improving quality control for conventional cytology and improving follow-up for women with cytological abnormalities.

Other avenues worth considering

Other suggestions looked at the value of studies on anal cancer, educating groups at risk (HIV+, MSM, etc.) and the link between aerodigestive cancers and HPV.

Second round of questions

Due to the lack of consensus on the use of liquid-based cytology, we sought opinions from the experts on the possibility of using this technique specifically for the triage of ASCUS smears, as suggested by one of the experts in the first round. Despite this second consultation, a consensus could not be reached; 1 expert abstained from stating an opinion, 4 stated it would have little or no value and 4 said it would be highly valuable. According to 1 of the experts, the method would be ineffective if used on its own, but very useful if used in concert with HPV detection tests.

There was also a question raised in the first round of consultations about improving quality control for conventional cytology and follow-up for women with cytological abnormalities.

The experts were unanimous in recognizing the need for improving quality control for conventional cytology and follow-up for women with cytological abnormalities (patient disappearance, access to colposcopy).

CHAPTER 3: RECOMMENDED APPROACHES

Based on the literature survey and expert consultation, we recommend the following approaches:

3.1   EPIDEMIOLOGY

- HPV surveillance would be useful from a public health point of view, although its inclusion in the MRD group would not be judicious.

- The best approach for HPV surveillance would be establishing sentinel projects. More specifically, there should be systematic, structured surveillance for high-grade cervical lesions.

- A study on HPV prevalence in the general population is not considered a priority. Studies of prevalence in young women, men and MSM are thought to be of little value.

- On the other hand, the experts support studies of prevalence among older women and people living with HIV.

3.2   NATURAL HISTORY

- It was deemed relevant to undertake studies focusing on the following aspects:
  - incriminating cofactors in HPV persistence and the development of cervical cancer;
  - the evolution of anal HPV infection;
  - the effect of new antiretroviral therapies on the incidence and evolution of HPV infections in HIV-positive individuals;
  - the natural evolution of HPV infection among women infected during adolescence.

3.3   HPV DETECTION AND FOLLOW-UP OF INFECTED INDIVIDUALS

- The Hybrid Capture II test is currently the best option for detecting cervical HPV infection despite its relatively high cost. One might also consider waiting for new, more responsive tests to become available. Using PCR is also an avenue worth considering. Quality control must be a major preoccupation in choosing any technology.

- Better documentation is needed on the impact treating HPV lesions has on infection transmission.

- Concerning the treatment of genital warts, there is insufficient information to determine the cost-benefit ratio for imiquimod use and to promote it over other available options.

- There is insufficient documentation on the impact that treating partners has on reducing the recurrence of HPV infection. While there is consensus on the value of studying this aspect, there is doubt about its feasibility.

- It would be appropriate to distribute guidelines on preventing cervical cancer in HIV-positive women (screening intervals, screening methods, follow-up for HPV infection) and to confirm their application.

- Counselling is an essential intervention activity in treating people infected with HPV. Proposed tools to assist in counselling include distributing written material, developing support groups, reinforcing telephone help lines, and making appropriate information available on the Web.

3.4   PRIMARY PREVENTION

- Educating patients and the general population may help prevent HPV infection and play an important role in a structured cervical cancer prevention program. Proposed target groups are the general population, youth and older women.

- *There is value in promoting condom use, even though this appears to have limited effect.*

- Health care professionals require additional training on HPV, particularly when it comes to counselling infected patients. There is insufficient scientific knowledge to determine the value of intensifying prevention programs aimed at young women.

- The most effective means of prevention appears to be prophylactic vaccination. Several vaccines are currently being studied, although several questions need to be answered before a vaccination program can be implemented.

3.5   CERVICAL CANCER SCREENING

- The creation of a cytology registry and an organized screening program is considered to be of major importance and quite feasible. Such a registry would allow for the surveillance of intraepithelial lesions, particularly high-grade lesions.

- Quality control for conventional cytology or any other screening technology should be an integral part of a good screening program.

- Distributing and applying guidelines for follow-up of women with cytological abnormalities is critical to the success of any cervical cancer screening program.

- Despite reservations concerning the high cost of an evaluation study on the real costs of cervical cancer screening, the majority of experts felt it would be useful. The suggested formulas include calculations based on existing data or a mathematical study based on the Markov model.

- There is not sufficient scientific evidence to evaluate the appropriateness and affordability of replacing conventional cytology with liquid-based cytology.

Cervical cancer screening using HPV detection

- Scientific evidence supports introducing HPV detection for ASCUS triage.

- The ideal strategy would be implementing a pilot project using HPV detection for ASCUS triage.

- There is not yet sufficient scientific evidence to justify implementing a primary screening program for cervical cancer based on the systematic detection of cervical HPV infection. Several randomized studies are under way and should be considered in any future discussions.

To summarize, the proposed strategies for cervical cancer prevention are as follows:

- Establish a structured cervical cancer screening program, including the creation of a central registry to promote monitoring and program evaluation.

- Establish screening program parameters based on clear consensus, which could eventually be established by the creation of a permanent committee of experts, concerning:
  - screening interval;
  - technology used;
  - referral and follow-up of women identified within the program framework.

- Establish measures encouraging participation by women most at risk: access, methods that respect the concerns of the target client, program visibility, etc.

- Train health care professionals.

- Educate the population.

LIMITATIONS OF THIS PROCESS

The literature survey was meant to be as exhaustive as possible in a field where documentation is particularly abundant. The rapid evolution of knowledge in the field of HPV infection obliged us to continuously update the literature survey, even after the final expert consultation. Nonetheless, content accuracy declines very quickly and any intervention concerning HPV should be preceded by an updated survey.

The consultative approach used in this project is limited by several elements, mainly concerning the experts' participation. Only 10 out of the 18 solicited experts agreed to participate. Unfortunately, this did not include any gynecologists, which limits the validity of the results. We cannot deduce the reaction of gynecologists should the recommendations of this report be implemented.

As well, even though a clear consensus was not obtained for all of our questions, we halted the consultation process after the second round because the positions taken seemed quite firm; we therefore estimated that a third round would not provide any substantial benefits. However, we cannot fully exclude the possibility that further consultation could have resulted in a consensus on these questions.

Finally, several experts expressed the need for a face-to-face meeting to debate the major issues related to cervical cancer screening. Such a meeting could not be organized within the framework of the project but would be essential in continuing the work of cervical cancer prevention.

CONCLUSION

Controlling sexually transmitted infections is recognized around the world as a public health priority. In Quebec, government orientations (strategies, provincial priorities, provincial public health program) call for concerted effort on the part of the public health network and its partners, namely the health care network, the education system, the public security milieu and the community.

As a result, several courses of action have been implemented (or are in the course of being implemented) throughout Quebec:

- surveillance of sexually transmitted infections within the framework of mandatory reportable diseases;

- promoting safe sexual behaviour, particularly among high-risk individuals;

- introduction of screening services and prevention programs for sexually transmitted and blood-borne diseases aimed specifically at vulnerable populations;

- free treatment program for sexually transmitted diseases (confirmed cases or syndromes compatible with genital chlmaydiosis, gonococcic infection, syphilis, chancroid, lymphogranuloma venerium and granuloma inguinale);

- preventive intervention program for partners of individuals infected with genital chlmaydiosis, gonococcic infection and syphilis.

Where does HPV prevention fit into this scheme? Can established courses of action for bacterial STI prevention be applied to HPV infection and its complications?

The approach taken within the framework of this project was aimed at responding to these questions and was, at least in part, successful. Basically, despite the abundance of publications on HPV infection, the recurring theme was, unfortunately, that data is too often insufficient to support the appropriateness of particular interventions.

For example, from a public health perspective, it is difficult to justify including HPV treatment in a free program for treating STIs considering the insufficient data on the effectiveness of treatment in preventing transmission. As well, again from a public health perspective, the relevance of preventive intervention among partners of individuals infected by HPV cannot be determined by scientific evidence.

On the other hand, several strategies currently used to control STI could very easily be adapted for viral infections such as HPV infection: promoting safe behaviour, training for health care professionals, public education.

The literature survey, as well as the expert consultation, justifies the establishment of a structured cervical cancer screening program. Even if we do not have the answers to all of the questions that planning such a program would raise, there are sufficient scientific grounds and consensus among the experts to move forward with such a project. More specifically, the value of HPV testing for triage of ASCUS smears has been demonstrated by international research, while the majority of experts consulted agreed on the expediency of introducing such a program in Quebec.

As well, considering the number of questions without sufficient answers, this process has helped prioritize research approaches. We therefore hope that this document will be a first step in a structured approach to the prevention of HPV and its complications, particularly cervical cancer.

APPENDIX 1

TABLES

Table 1   **Prevalence of HPV infection**

Author	Year	Country	Test used	Number	Population	HR HPV Prevalence	LR HPV Prevalence	Total HPV Prevalence
Baldwin, 2002	N/A	US	PCR	349	Male STI patients	12.0%	13.8%	31.8%
Peyton, 2001	1996-2000	US	PCR MY09/11	3863	Women, 18-40 years, white and Hispanic	26.0%	14.7%	39.2%
Ho, 1998	N/A	US	PCR Southern blot	608	University students			26.0%
Kotloff, 1998	1992-1993	US	PCR MY09/11	414	University students, 18-40 years	22.2%	5.0%	35.0%
Forslund, 2002	N/A	Sweden	PCR GP5+/6+	6123	Women, 32-38 years	6.0%		
Forslund, 2000	N/A	Sweden	PCR GP5+/6+	2587	General, women 32-38 years	7.0%		
Kjaer, 1990	1986	Denmark Greenland	Hybridization	661 586	General Women, 20-39 years	13.0%[1] 8.8%[1]	7.5%[2] 6.7%[2]	14.7% 10.9%
Schneider, 2000	1996-1998	Germany	PCR GP	4761	General, women	7.8%		

Clavell, 2001	1997-2001	France	HC II	7932	General, women
					  <20
					  21-30
					  31-40
					  41-50
					  51-60
					  >60
						15.3%
						20.1%
						23.6%
						13.9%
						12.2%
						10.8%
						9.3%		

Clavell, 1998	1996-1997	France	HC I	1028	General, women	8.8%	1.8%	10.5%
Tenti, 1999	1995-1996	Italy	PCR MY09/11	711	Pregnant women	1.3%[1]		5.2%
De Sanjosé, 2000	N/A	Spain	HC II (1 pg/ml)	741	General			5.4%
Castellsagué, 2000	N/A	Spain	PCR MY09/11	943	Pregnant women			8.7%
Munoz, 1996	1985-1998 1990-1991	Spain Colombia Brazil	PCR GP5/6	1184	Middle-aged women			4.9% 12.6% 17.1%

[1] Types 16 and 18   [2] Type 16   [3] Types 6 and 11

Table 1   Prevalence of HPV infection (continued)

Author	Year	Country	Test used	Number	Population	HR HPV Prevalence	LR HPV Prevalence	Total HPV Prevalence
Franco, 1999	1993-1997	Brazil	PCR MY09/11	1425	Disadvantaged women	8.4%	7.0%	13.8%
Herrero, 2000b	N/A	Costa Rica	PCR MY09/11	3024	General and high-risk women <25 35-54 >65	7.6%	6.7%	16.0% 20.0% 5.0% 20.0%
Muñoz, 2001	N/A	multinational	PCR	2500	General			13.9%
Tseng, 1998	1994-1995	Taiwan	PCR consensus	301	Pregnant women	22.6%[1]		
Healy, 2001		Canada, Nunavut	HC II	1290	Inuit women, 13-79 years	26.0%		
Sellors, 2000	1998-1999	Canada, Ontario	HC II PCR consensus HC II	909	General, women from 15-49 years 15-19 20-24 25-29 30-34 35-39 40-44 45-49	9.6% 12.7% 13.8%(PCR) 23.1% 11.9% 8.1% 5.9% 2.5% 8.0%		13.3% 20.0% (PCR) 23.1% 14.7% 11.8% 11.0% 3.3% 13.0%
Rohan, 1991	1990	Canada, Ontario	PCR consensus	105	University students	10.4%[2]	2.8%[3]	18.1%
Ratnam, 2000	1996-1998	Canada, Newfoundland	HC I HC II	2098	General, women	10.8%		
Richardson, 2002	1996-1999	Canada, Montreal	PCR MY09/11	621	University students	21.8%	14.8%	29.0%
Richardson, 2000	1992-1993	Canada, Montreal	PCR MY09/11	489	University students	11.8%	6.2%	22.7%

[1] Types 16 and 18   [2] Type 16   [3] Types 6 and 11

Table 2 Seroprevalence of HPV infection

Author	Year	Country	Test used	Number	Population	Prevalence HPV 16	Prevalence HPV 6/11
Stone, 2000	1991-1994	US	ELISA	7218	General	13.0%	
Xu, 2002	1988-1994	US	ELISA	4528 83	General, men MSM	8.0% 38.0%	
Daling, 1996	1986-1992	US	ELISA	672	General, women	22.2%	
Slavinsky, 2001	1993-1995	US	ELISA	109	STI clinic	36.1%	31.6%
Kibur, 2000	1983-1984 1990-1991	Finland	ELISA L1 and L2	1260 3432	Primaparous pregnant women	24.0%[1] 24.0%[1]	
Viscidi, 1997	1992-1993	US	ELISA	376	University students	24.0%	

[1] Seroprevalence adjusted according to age

Table 3   Incidence of HPV infection

Author	Year	Country	Test used	Number	Population	Incidence
Moscicki, 2001	1990-	US	HPV Profile PCR generic	105	13-20 years, FP clinic	55.0% over 3 years
Kotloff, 1998	1992-1993	US	PCR MY09/11	414	University students	24.0% per year
Ho, 2001	N/A	US	PCR Southern blot	608	University students	14.0% per year 43.0% over 3 years
Kibur, 2000a	1983-1991	Finland	ELISA	1279	Women under 25 years	4.5%[1] per year (HPV 16 only)
Woodman, 2001	1988-1992	Great Britain	PCR GP5+/GP6+	1075	Women, 15-19 years	44.0% over 3 years 60.0% over 6 years
Collins, 2002	1988-1997	Great Britain	PCR GP5+/GP6+	242	Women, 15-19 years with a single partner	46.0% over 3 years
Franco, 1999	1993-1997	Brazil	PCR MY09/11	1425	Disadvantaged women	23.6% over 18 months
Richardson, 2002	1996-1999	Canada, Montreal	PCR MY09/11	621	University students	36.4% over 2 years (29.2% HR HPV 23.9% LR HPV)

Table 4   Prevalence of cervical cytological lesions

Author	Year	Country	Number	Population	ASCUS	LSIL	HSIL	Total
Richardson, 2000	1992-1993	Canada, Montreal	375	University students	7.2%	3.4%	0.8%	11.,5%
Sellors, 2000a	1998-1999	Canada, Ontario	941	General population, 15-49 years	4.04%	2.3%	0.32%	6.7%
Ratnam, 2000	1996-1998	Canada, Newfoundland	2098	General population, 18-69 years				9.2%
Suris, 1999	N/A	Canada, British Columbia	N/A	N/A	69.6%[1]	24.7%[1]	5.7%[1]	6.9%
Benedet, 1992	1988	Canada, British Columbia	490 985	General, >15 years	52.2%[1]	18.5%[1]	4.3%[1] (0.2% CI[2])	9.2%
Fonn, 2002	N/A	South Africa	20 603	General, >20 years		2.42%	1.8% (0.47% CI[2])	
Dalstein, 2001	N/A	France	2979	General, primary and secondary screening	2.2%	7.1%	5.3% (0.2% CI[2])	15.9%
Koumans, 2002	N/A	US	313	Black, sexually active adolescents	20.0%	15.0%	1.0%	

[1] Mild, moderate, respectively severe dyskaryosis, percentages compared to total cytological abnormalities
[2] Invasive cancer

Table 5   **Prevalence of HPV infection in HIV-infected individuals**

Author	Year	Country	Test used	Number	Prevalence of LSIL	Prevalence of HSIL	Prevalence of SIL	Prevalence of HR HPV	Total prevalence of HPV	Total prevalence of HPV HIV neg.
Petry, 1999	1990-1998	Germany	HC I	138		12.3%	26.8%	28.99%		
Hankins, 1999	1993-	Canada	PCR MY09/11	375			9.9%	49.1%	67.2%	
Rezza, 1997	1994-1995	Italy	PCR MY09/11	236		11.2%	35.6%		40.0%	32.0%
Palefsky, 2001b	1995-1997	US	PCR MY09/11						53.0%	24.0%
Ellerbrock, 2000	1991-1996	US	PCR L1 and E6	653	18.2%		20.0%		54.0%	32.0%
Spinillo, 2001	1998-1999	Italy	PCR MY09/11	124					63.7%	
Lillo, 2001	1995-1997	Italy	PCR MY09/11	163	20.2%	6.2%			65.0%	
Chritchlow, 1998	1989-1997	US	PCR MY09/11	609					91.6%[1]	
Palefsky, 1998	1991-1994	US	PCR HC	608 men					93.0%[1] 87.0%[1]	

[1] Anal HPV

Table 6   Risk factors for HPV infection

	Munk, 1997 DK	Wen, 1999 Australia	Ross, 1996 US	Muñoz, 1996 multin	Morrison, 1998 US		Kjaer, 1990 Denmark, Greenland			Richardson, 2000 Canada, Montreal			Moscicki, 2001 US	Rousseau, 2000 Brazil	
Population studied	11 088 F, 20-29 years	12 496, general	429 F cases, 418 F control	895 F, middle-aged	608 students		DK: 661 F, age 20-39 GL: 586 F, age 20-39			489 F, students			644 F, 13-20 years	1425 F, 18-60 years	
Diagnosis and test used	Condyl. Exam	Condyl. Exam	Condyl. Exam	VPH+ PCR GP	VPH+ PCR MY		VPH+ Hybridization			VPH+ PCR MY			VPH+ PCR GP	VPH+ PCR MY	
					HR	LR	6/11	16/18	HPV	HR	LR	All		HR	LR
Age	No	Yes (inv)[8]	Yes (inv)	No	No	No				No	No	No	No	Yes inv	No
Race					Yes (Black)	Yes (Black)								No	Yes
Sociodemographic factors															
1. education		Yes women		No										No	Yes
2. occupation/income		Yes women		Yes (inv)										No	No
3. marital status															
Sexual behaviour					Yes	Yes									
1. age of initial sexual act	No			Yes			No	No	No	No	No	No	No[2]	Yes	No
2. no. years since first act	Yes	Yes men											No		
3. total no. of sexual partners	Yes			Yes			Yes inv	Yes inv	Yes inv	No	No	No	Yes	Yes	Yes
4. no. of recent sexual partners										No	No	No	Yes	Yes	Yes
5. frequency of sexual acts				No						Yes	No	Yes			
6. no. of long-term partners			Yes (inv)							Yes	No	Yes			
Previous STD															
1. chlamydia															
2. genital herpes	Yes	Yes (inv)	Yes (inv)							No	No	No			
3. other STD	No	Yes (inv)		Yes									No		
4. partner with condyloma	No			No			Yes	No	Yes				Yes / Yes gw[3]		
Previous obstetrics	No														
Pap test															
1. participated in CC screening	Yes			Yes	No	No	Yes	No	No				No	No	No
2. abnormal Pap test		Yes (neg)					Yes DK	Yes	Yes					Yes neg	Yes neg[2]
Contraceptive method				Yes (neg)			No	No	No	Yes neg	Yes	No	No		
1. condom	No		Yes		No	No	No	No	No	No	No	No	Yes neg	Yes	
2. oral contraceptive	No			No	No	No	No	No	No	No	No	No	Yes	Yes	Yes
Smoking	Yes	Yes men													

[8] Inverse association
[2] Significant at the limit
[3] Genital warts

Table 6   Risk factors for HPV infection (continued)

	Peyton, 2001 US			Kataja, 1993 Finland	Kotloff, 1998 US	Franco, 1995 Brazil			Rohan, 1991 Canada		Sellors, 2000 Canada	Ho, 1998 US	Elfgren, 2000	Kjaer, 2001 Denmark
Population studied	3863 F, 18-40 years			691 F, cyt les, 706 F cyt norm	414 F, 18-40, students	718 F, middle-aged			105 F, students		909 F, 14-49 years	608 F, students	44 VPH+, 46 VPH-	8654 F, 20-29 years
Diagnosis and test used	HPV+ PCR MY			Abnormal cytology	VPH+ PCR MY	VPH+ PCR MY			VPH+ PCR		VPH HR+ PCR L1	VPH+ inc. PCR	VPH+ PCR MY	VPH+ PCR GP
	HR	LR	All			HR	LR	All	VPH 16	All				
Age	Yes neg	Yes neg	Yes neg	Yes neg	No						Yes neg	Yes neg		No
Race	Yes (Hisp)	No	No		No							Yes		
Sociodemographic factors														
1. education	No	No	No											
2. occupation/income	Yes	Yes[1]	Yes[1]											
3. marital status	Yes	Yes	Yes								Yes			
Sexual behaviour									Yes[4]	Yes[4]		Yes[5]		
1. age of initial sexual act				Yes	No	Yes	No	No	No	No	Yes		Yes	No
2. no. years since first act						No	No	No						
3. total no. of sexual partners	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes		Yes	Yes
4. no. of recent sexual partners	Yes	Yes	Yes	Yes	No				No	No	Yes	Yes	Yes	Yes
5. frequency of sexual acts				Yes		No	No	No				Yes		
6. no. of long-term partners														
Previous STD				Yes	No									
1. Chlamydia	Yes[3]	No	No									No		
2. genital herpes	No	No	No											
3. other STD				Yes gw[2]		Yes[3]	No	No						
4. partner with condyloma	No	Yes	Yes	Yes										
Previous obstetrics	No	Yes neg	No	Yes neg	No						Yes inv			
Pap test														
1. participated in CC screening				Yes neg										
2. abnormal Pap test	Yes	No		Yes							Yes			
				Yes neg	Yes neg[3]									
				Yes										
Contraceptive method	No	No	No	No	No				--	No	Yes		No	
	No	No	No											No
1. condom				Yes neg										
2. oral contraceptive	No	No	No	Yes	No				Yes	Yes	Yes		No	No
Smoking														

1: Association with refusal to declare income   2: Genital warts   3: Significant to the limit   4: Sexual activity during menstruation   5: Partner's sexual behaviour

Table 7   Prevalence of HPV based on cervical cytological lesions

Author	Year	Country	Test used	Number	Population	Prevalence without lesions	Prevalence of ASCUS	Prevalence of LSIL	Prevalence of HSIL
Herrero, 2000	N/A	Costa Rica	PCR MY09/11	2974	General, 18-94 years	11.0%	20.0%	73.0%	89.0% (88.0% IC)
Nobbenhuis, 1999	1990-1992	Netherlands	PCR GP5+/6+	353	Women with abnormal Pap test		66.0%		
Cox, 1995	1991-1992	US	HC	217	Women with ASCUS		41.9% 37.3%[1]		
Cruishank, 1999	N/A	Great Britain	PCR type-specific	304	Women with mild dyskariosis			51.0% HPV16 18.0% HPV18	
Nouvo, 1998	N/A	US	PCR MY09/11	82	Archived Pap tests	5.0%	40.0%		78.0%
ALTS, 2000	1997	US	HC II		Women with ASCUS/LSIL			82.9%	
Solomon, 2001	1996-1998	US	HC II	3488	Women with ASCUS		50.6%		
Coker, 2001	1995-1998	US	HC I	376 427	FP clients, SIL and controls	18.3%		44.9%	65.0%
Koumans, 2002	N/A	US	PCR	313	Sexually active Black adolescents	54.4%	66.7%	91.0%	
Vassilakos, 2002	2000-2002	Switzerland	HC II	8676	General, low-risk	7.6%[1]	35.9%[1]	83.9%[1]	95.5%[1]

[1] Types of high-risk HPV

Table 8   Prevalence of HPV based on cervical histological lesions

Author	Year	Country	Test used	Number	Population	Normal prevalence	Prevalence of CIN 1	Prevalence of CIN 2	Prevalence of CIN 3	Prevalence of cancer
Matsuura, 1998	1989	US	ViraPap	148	LCIN		29.0%	33.0%	46.0%	
Cox, 1995	1991-1992	US	HC	217	ASCUS	25.8% HR 8.4% LR	68.6% HR 22.9% LR	93.3% HR 13.3% LR		
Feoli-Fonseca, 2001	N/A	Canada	PCR GP5+/6+ MY09/11	554	CIN/CCI		74.0%	88.0%	95.0%	100%
Ferenczy, 1996	N/A	Canada	HC II	364	Colpo	23.0%	60.0%	77.0%		50.0%
Schiffman, 2001	1993	Costa Rica	PCR MY09/11	9130	general	22.0%	80.0%		94.0%	
Shlay, 2000	1997-1999	US	HC II	195	ASCUS	21.6%	36.4%	93.3%		
Fait, 2000	1996-1997	Israel	HC	503	ASCUS LSIL	8.4% LR 0% HR 12.9% LR 3.2% HR	88.0% LR 6.7% HR 87.8% LR 6.1% HR	12.5% LR 85.7% HR 7.4% LR 88.2% HR		
Munoz, 2000	1985-1997	Multinat	PCR	2288 2513	CIC control	 13.7%				91.0%
Bosch, 2000		Multinat				15.4%				88.9%
Munoz, 2001	N/A	Multinat	ND	2430 2500	CIC control	 13.9%				90.4%
Riou, 1990	1984-1988	France	PCR	106	CIC specimens					81.0%
Burger, 1996	1988-1993	Netherlands	PCR GP	265	Cytol. abnormalities		47.0%	69.0%	86.0%	
Nobbenhuis, 1999	1990-1992	Netherlands	PCR GP5+/6+	353	Cytol. abnormalities				97.1%	

Table 9   Studies of test performance for primary cervical cancer screening

Author	Year	N°	Test used	Target	Sensitivity for HSIL Cyto	HPV	Cyto+HPV	Specificity for HSIL Cyto	HPV	Cyto+HPV	PPV Cyto	HPV	Cyto+HPV	NPV Cyto	HPV	Cyto+HPV	Colpo referral Cyto	HPV	Cyto+HPV
Transversal studies																			
Dalstein, 2001, Fr	ND	2979	HC II	HG SIL	79.4%[1] 72.2%[2]	92.3%		96.2%	78.9%										
Arbyn, 2001, B	2000	3000	HC II Cyt liq	CIN 2+	47.4%[3]	94.7%		99.9%[3]	97.1%										
Shiffman, 2000, CR	1993 1995	8554	HCT HC II	HG SIL	77.7%[1]	74.8% 88.4%		94.2%[1]	93.4% 89.0%								6.9%	7.7% 12.3%	
Schneider, 2000, Ger	1996 1998	4761	PCR GP	CIN 2+	26.3%[1] 18.4%[2]	94.7%		99.0%[2]	93.4%		50.0%[2]	29.1%		97.5%	99.6%				
Cuzick, 1999b, GB	N/A	2988	PCR HC II HC	CIN 2+	83%[1] 79%[2] 62%[3]	79.4%[4] 73.8%[5] 100%[4] 95.2%[5] 87.5%[4]					22.0%[1] 47.0%[2] 63.0%[3]	17.4% 17%[4] 27%[4]							
Wright, 2000, SAfr	1998 1999	1415	HC II	CIN 2-3	67.9%	83.9% 66.1%*		87.7%[1]	84.5% 82.9%								39.0%		
Ferenczy, 1996, Can	N/A	364	HC II TPrep	HG SIL+	87.5%[5] 78.0%[6]	75.3%[5] 66.3%[6]	95.1% 87.7%	57.0%[5] 73.6%[6]	63.7% 77.5%	47.2% 64.6%	36.0%[5] 75.0%[6]	37.0%[5] 75.0%[6]	34.0% 72.0%	94.0%[5] 76.0%[6]	90%[5] 69%[6]	97.0% 83.0%			
Prospective studies																			
Clavel, 2001, Fr	1997 2001	7932	HC II	HG SIL	87.8%[1]° 68.1%[1]	100%	100%° 100%	93.1%° 95.3%	87.0%	38.1% 24.5%	15.7% 23.5%	14.2%		99.8% 99.3%	100%				
Ratnam, 2000, Can	1996 1998	2098	HC I HC II	CIN 2+	40.2%[1] 26.8%[2] 14.2%[3]	68.1%	76.3% 76.3% 72.0%	91.6% 96.2% 99.1%	90.6%	85.9% 89.3% 90.3%	10.7% 15.0% 28.1%	15.4%	98.4% 98.1% 97.9%	99.1%			9.2%		12.0%
Petry**, 1999, Ger	1990 1998	138	HC I	CIN 2+	94.0%[1] 64.7%[2]	94%		58.7%[1] 97.5%[2]	70.3%		24.2% 68.8%	40.0%		98.6% 95.9%	98.8%		57.3%[1] 29.0%[2]	29.0%	

[1] ASCUS threshold [2] SIL threshold [3] HSIL threshold [4] CIN 3+ [5] CIN 2+ [6] LGSIL+ * Self-sampled ** HIV positive ° liquid-based cytology

Table 10   Studies of test performance for ASCUS triage

Author	Year	N°	Test used	Target	Sensitivity for HSIL			Specificity for HSIL			PPV			NPV			Colpo referral		
					Cyto	HPV	Cyto+HPV	Cyto	HPV	Cyto+HPV	Cyto	HPV	Cyto+HPV	Cyto	HPV	Cyto HPV	Cyto	HPV	Cyto HPV
Transversal studies																			
Morin, 2001, Can, Qc	N/A	3600	HC II PCR HC I	CIN 2-3	73.7%[1] 42.0%[2]	89.5% 89.5% 68.4%	94.7% 94.7% 89.5%	62.9%[1] 93.5%[2]	74.1% 59.0% 85.9%	73.2% 57.6% 83.5%	10.0%[1] 26.7%[2]	16.0% 11.0% 21.0%	16.5% 11.5% 23.3%	97.7%[1] 96.7%[2]	99.0% 99.0% 98.0%	99.6% 99.5% 99.3%	39.0% 8.4%	29.0% 44.0% 17.0%	30%[2] 45%[2] 20%[2]
Rebello, 2001, US	N/A	333	HC II 1pg/ml 4pg/ml	CIN 2-3		 93% 85%			 55% 62%			 52% 54%			 94% 89%			 52% 54%	
Shlay, 2000, US	1997 1999	195	HC II	CIN 2-3		93.3%			73.9%			23.0%			99.0%			31.0%	
Kaufman, 1997, US	N/A	462	HPV Profile	CIN 2-3	62.7%[1]	67.2%	82.1%	61.5%[1]	65.8%	48.9%	21.6%	25.0%	21.4%	90.7%	92.0%	94.1%	42.0%	39.0%	56.0%
Cox, 1995, US	1991 1992	217	HC I	CIN 1-3	60.0%[1] 38.0%[2]	86.0%	90.0%[1] 88.0%[2]	77.0%[1] 96.0%[2]	71.0%	58.0%[1] 69.0%[2]	44.0%[1] 73.0%[2]	47.0%	39.0%[1] 46.0%[2]	87.0%[1] 84.0%[2]	94.0%	95.0%[1] 95.0%[2]	31%[1] 12%[2]	42.0%	53.0%
Prospective studies																			
Meijer, 2001, HL	N/A	278	HC II	CIN 2-3		96.3%			60.2%			21.0%			99.0%			45.0%	
Fait, 2000[4], Israel	1996 1997	503	HC (I ?)	CIN 2-3		85.7%			97.0%			90.0%			93.0%			25.0%	
Nobbenhuis, 1999, HL	1990 1992	353	PCR GP5/6	CIN	70%	97%		61%	65%		36%	46%		87%	99%				
Manos, 1999, US	1995 1996	995	HC II ThinPr	HG SIL	76.2%	89.2%	96.9%		64.1%		12.9%	15.0%		97.0%	99.0%				
Wright, 1998, US	N/A	265	HC I[5] HC I[6]	CIN 1-3		86% 55%			39% 71%										
Adam, 1998, US	N/A	454	PCR HPV Profile	CIN 2-3	62.5%[1] 70.6%[3]	65.2% 56.1%		41.5%[1] 23.5%[3]	60.1% 67.8%		16.5%[1] 48.0%[3]	22.0% 23.0%							

[1] ASCUS threshold   [2] SIL N/A   [3] HSIL N/A   [4] ASCUS and LSIL   [5] 0.2 pg/ml   [6] 10 pg/ml

Table 10   Studies of test performance for ASCUS triage (continued)

Author	Year	N°	Test used	Target	Sensitivity for HSIL			Specificity for HSIL			PPV			NPV			Colpo referral		
					Cyto	HPV	Cyto+ HPV	Cyto	HPV	Cyto+ HPV	Cyto	HPV	Cyto+ HPV	Cyto	HPV	Cyto+ HPV	Cyto	HPV	Cyto HPV
Randomized study																			
Lytwyn, 2000, Can	1995 1998	159	HC II	CIN 2-3	55.6%[1] 11.1%[3]	87.5%		55.6%[1] 95.2%[3]	50.6%		15.2%[1] 25.0%[3]	15.0%		89.7%[1] 88.2%[3]	98.0%				
ALTS, 2000, US	1996 1998	3488	HC II	CIN 3+ CIN 2+	85.3%[1] 64.0%[2] 44.1%[3] 85.9%[1] 59.2%[2] 34.8%[3]	96.3% 95.9%					8.5%[1] 14.3%[2] 37.5%[3] 16.7%[1] 25.9%[2] 58.1%[3]	10.0% 20.0%		97.9%[1] 97.1%[2] 96.5%[3] 95.8%[1] 93.6%[2] 92.0%[3]	99.0% 99.0%		59%[1] 26%[2] 7.0%[3]	56.0%	
Cruickshank, 1999, GB	N/A	304	PCR (16-18)	CIN 2-3	77%	41%	94%	63%	88%	26%		79%	71%		57%	71%			

[1] ASCUS threshold   [4] ASCUS and LSIL
[2] SIL threshold   [5] 0.2 pg/ml
[3] HSIL threshold   [6] 10 pg/ml

APPENDIX 2

QUESTIONNAIRES SENT TO EXPERTS

First questionnaire
Results of first round and second questionnaire

FIRST QUESTIONNAIRE

Question 1   What would be the most appropriate approach for HPV surveillance?

Our recommendations:

- At this time, the most realistic approach for HPV surveillance is conducting studies on prevalence and establishing sentinel projects (target population and frequency to be determined).

- Including HPV infection among mandatory reportable diseases is not pertinent.

Your opinion:

Question 2   Would it be useful to undertake epidemiological studies on HPV infection or on the lesions it causes? If so, which ones?

Our recommendations:

- A study of prevalence in the general population would be relatively useless from a public health point of view.

- However, prevalence studies would be useful for certain target groups such as women 20 to 35 years old (for the surveillance of prevalence and to evaluate the effectiveness of prevention measures), women 35 to 45 (for planning the implementation of screening programs), persons living with HIV, MSM, etc.

- A study of the prevalence of SIL would be moderately useful.

- A study of the evolution of the incidence of cervical adenocarcinoma would be moderately to very useful.

Your opinion:

Question 3   **Would there be any value in establishing a surveillance system for carcinoma *in situ*? If yes, what would be the best strategy?**

Our recommendation:

- The systematic and structured surveillance of carcinoma *in situ* would be extremely useful (feasibility to be determined).

Your opinion:

Question 4   **To what extent should studies be developed on the natural history of HPV infection?**

Our recommendations:

It would be beneficial to better document the following aspects:

- The link between condyloma and precancerous genital lesions.
- Incriminating cofactors of infection persistence and the development of cervical cancer.
- The evolution of anal HPV infection.
- The effect of new antiretroviral therapies on the incidence of cervical epithelial lesions among HIV-positive women.

Your opinion:

Question 5   **Among HPV detection tests available, which is most appropriate for clinical use and what would be the determining factors?**

Our recommendation:

- The HC II test is currently the best option.

Your opinion:

Question 6   **Are there currently therapeutic options that would be effective in reducing the impact of HPV infection on public health?**

Our recommendations:

- There is currently insufficient information on what impact treating HPV infection has on transmission. A study in this regard would be useful.

- A more complete analysis of the cost-benefit ratio of imiquimod use in treating genital warts would be useful.

- A study on what impact evaluating and treating partners has on HPV recurrence would be particularly useful.

Your opinion:

Question 7   **What role does counselling play and what types of tools would be helpful in counselling patients with HPV infection?**

Our recommendations:

- Counselling patients with HPV infection should be a key aspect of medical intervention.

- Consultation should include the distribution of information material.

Your opinion:

Question 8   **What are the training needs of health care professionals?**

Our recommendation:

- It would be useful to provide professionals with additional training in counselling and the psychological aspects of HPV infection.

Your opinion:

Question 9   **What would be the pertinence of organizing HPV awareness/information activities? What would be the target groups?**

Our recommendation:

• Educating patients and the general population is key in preventing HPV infection.

Your opinion:

Question 10   **Should condom use for preventing HPV infection be promoted? If so, would some groups benefit more than others?**

Our recommendation:

• Condom use should be promoted. It appears to be particularly effective in preventing infections of the uterine cervix.

Your opinion:

Question 11   **Would there be any value in creating a cytology registry? If yes, how feasible would this be?**

Our recommendation:

• Creating a cytology registry and an organized screening program would be extremely useful.

Your opinion:

Question 12   **Is it appropriate and affordable to make liquid-based cytology a routine cytology test?**

Our recommendations:

- Introducing liquid-based cytology would increase screening performance.
- There is insufficient data on the cost-benefit ratio of liquid-based cytology.

Your opinion:

Question 13   **What would be the optimum strategies for reducing the incidence of cervical cancer?**

Our recommendation:

- Reducing the incidence of cervical cancer means recruiting women who do not participate in screening and using a more sensitive test than traditional Pap tests.

Your opinion:

Question 14   **Should HPV detection be integrated in systematic cervical cancer screening? If yes, what would be the optimum strategy?**

Our recommendations:

- HPV detection for ASCUS triage would be an appropriate strategy for Quebec, due to the high prevalence of ASCUS results.
- The ideal strategy would be to implement a pilot project using HPV detection for ASCUS triage.
- It would be prudent to wait for the results of studies currently under way before implementing a cervical cancer screening program based on the systematic detection of cervical HPV.

Your opinion:

Question 15   **What would be the value of studying the impact introducing HPV detection would have on the level of participation in cervical cancer screening?**

Our recommendation:

•   A study on the impact HPV detection would have on participation in cervical cancer screening would be important.

Your opinion:

Question 16   **Would an evaluation study on the actual costs of screening and treatment of cervical cancer be useful?**

Our recommendation:

•   A study of the actual costs of screening and treatment for cervical cancer would be moderately beneficial for the provincial screening program.

Your opinion:

Question 17   **If the procedures for cervical cancer screening were to change, what is the best way to encourage the application of new guidelines concerning the introduction of a new test (HPV detection) and of modifications to screening intervals?**

Your opinion:

Question 18   **Other suggestions or recommendations.**

RESULTS OF THE FIRST ROUND AND SECOND QUESTIONNAIRE

RESULTS OF THE FIRST CONSULTATION ROUND

Epidemiology

Summary of consultation results

The first of our questions dealt with the epidemiology of HPV infection and its associated lesions: surveillance, prevalence studies, target populations.

The experts unanimously agreed that there is no need to include HPV infection among mandatory reportable diseases (MRD). For several experts, establishing sentinel surveillance projects was considered the best option for the surveillance of HPV infection. Based on available data from existing studies, the experts felt that HPV prevalence studies in the general population are of little or no value. Concerning the need for HPV prevalence studies in certain population groups, opinions varied on the value of such studies as well as on which groups should be targeted. As for what were the identified needs in terms of surveillance of epithelial lesions caused by HPV, the experts generally agreed on making the surveillance of high-grade lesions the priority. The systematic, structured surveillance of carcinoma *in situ* was also generally considered to be an appropriate option, although the framework of such surveillance must be specified (public health program or research activity) as well as its modalities (target group, technology used, collection method and data analysis).

When it came to incidence of cervical adenocarcinoma, the vast majority of experts agreed on the lack of information and on the importance of studying the evolution of cervical adenocarcinoma incidence.
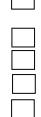
Follow-up question #1

Faced with varying opinions on the value of conducting prevalence studies and, more specifically, on populations to be targeted, we would like to know the general opinion of the experts consulted concerning a number of suggestions that were raised.

We therefore ask your opinion on the usefulness of targeted prevalence studies for the following groups:

	1 (Not useful) to 4 (very useful)
a. women under 35 (for the surveillance of prevalence and to evaluate the effectiveness of prevention measures)	☐
b. women 35 to 50 (for planning the introduction of screening programs)	☐
c. men in general	☐
d. MSM	☐
e. persons living with HIV	☐

Comments on the consultation summary or the follow-up question:

Natural history

Summary of consultation results

Results of the first round of questions

In the second section, the questions looked at the natural history of HPV infection: the evolution of HPV infection, co-factors in the occurrence of cervical cancer, anal HPV infection, influence of HPV and HIV co-infection, etc.

The vast majority of experts feel it would be worthwhile to better document incriminating cofactors in HPV persistence and the development of cervical cancer, the evolution of anal HPV infection and the effect of new antiretroviral therapies on the incidence and evolution of HPV infection among HIV-positive individuals. At the same time, the link between condyloma and precancerous genital lesions is not considered to be a research priority. A new study (in the process of being published) on the benefit of colposcopy among women diagnosed with condyloma acuminata is investigating the link between condyloma and precancerous lesions.

Follow-up question # 2

Other research approaches having to do with the natural history of HPV infection were suggested by certain experts. We would like to know the opinion of all participants on the usefulness of these research approaches.

	1 (Not useful) to 4 (very useful)
a. natural evolution of infections among women infected in adolescence (cohort formed at Ste-Justine)	☐
b. availability and application of follow-up guidelines for monitoring women infected with HPV	☐
c. the need to treat partners of patients with cervical/anal lesions	☐
d. the clinical evolution of adenocarcinoma *in situ*	☐

Comments on the consultation summary or the follow-up question:

Follow-up for persons infected with HPV

Summary of consultation results

HPV diagnosis

The majority of experts agree that HC II is currently the best option for detecting HPV in the cervix, although the high cost of such a test was often mentioned as a negative factor. Other experts recommend waiting for new tests to become available or using PCR, which, while more complicated, costs about the same and performs better. One interesting mention is the possibility of automating PCR for clinical use. As well, PCR was suggested as the test of choice for cases of doubtful diagnoses or for sperm donors.

Treatment of HPV lesions

Concerning the treatment of HPV lesions, virtually all of the experts refer to a lack of information on what impact treatment has on infection transmission and on the need for a study documenting the effectiveness of treatment in reducing transmission. Opinions converge that there is insufficient data on the cost-benefit ratio of imiquimod and that there is a need for studies in this regard. As well, the experts agree that a study on the impact of evaluation and treatment of partners on HPV recurrence would be particularly useful. However, the feasibility of such studies was questioned several times.

The experts generally agree that counselling patients with HPV infections should be a key aspect of medical intervention. The proposed tools to assist in counselling include written material, support groups, telephone help lines and Web sites.

Comments on the consultation summary:

Prevention

Summary of consultation results

An important means of preventing HPV infection and cervical cancer is educating patients and the general population, a statement that all experts espouse. Education and sensitization would be particularly important to integrate into a structured screening program. Proposed target groups were the general public, young people and older women.

Still in the context of primary prevention, the majority of experts are in favour of promoting condom use, even if it appears to have a limited effect.

According to the experts, health care professionals require additional training in the area of counselling. Several experts suggest broader training on HPV than is currently offered, as well as introducing incentives for doctors to intensify their involvement in the recommended interventions (counselling, screening).

Comments on the consultation summary:

Screening

Summary of consultation results

Within the framework of cervical cancer screening, creating a cytology registry and an organized screening program is considered of major importance and quite feasible. Such a registry would allow the surveillance of intraepithelial lesions.

Despite reservations concerning the high cost of an evaluation study on the actual costs of cervical cancer screening, the majority of experts feel it would be useful. The suggested formulas include a calculation based on existing data or a mathematical study based on the Markov model.

Liquid-based cytology

Opinions on liquid-based cytology are contradictory. Some experts recommend the general use of the test to replace conventional cytology, while others recommend it be used solely for evaluating women with abnormal cytologies in conjunction with HC II testing for HPV screening. Finally, one group of experts questions the appropriateness of introducing liquid cytology considering it performs just as well as conventional cytology but costs more. A new study is expected to support this latter position (Moseley and Paget 2002). The majority of experts agree on the lack of data concerning liquid-based cytology's cost-benefit ratio. The formulas proposed for evaluating this cost-benefit ratio include theoretical estimation, clinical studies or a pilot project.

HPV detection

The value of HPV detection for ASCUS triage is recognized by the vast majority of experts. The proposed method essentially includes the use of a single sample for cytology and HPV testing. There was also a reference to using PCR on biopsy specimens. The vast majority of experts agreed that the ideal strategy would be implementing a pilot project using HPV detection for ASCUS triage.

The vast majority of experts declare that it would be prudent to wait for the results of studies currently under way before implementing a cervical cancer screening program based on the systematic detection of cervical HPV infection.

Opinions are mixed concerning the value of studying what impact introducing HPV detection would have on participation in cervical cancer screening. Those experts who are opposed to such a study feel that it should be conducted as needed only after the introduction of new technologies and that, generally, a well-conceived information/education program would be more beneficial. Based on these remarks, we have decided to reject the recommendation that this type of study be conducted given the current context.

Proposed strategies to encourage the application of new screening guidelines

The experts' recommendations on encouraging the introduction of eventual changes to screening procedures include:

- Establish a structured cervical cancer screening program, including a central registry, monitoring, and program evaluation.

- Establish program parameters in terms of:
  - screening intervals and methods to use, based on study results;
  - establishing a clear consensus, eventual creation of a permanent committee of experts;
  - program accessibility.

- Provide training for health care professionals.

- Educate the population.

Follow-up question #3

The experts were unable to declare whether liquid-based cytology improves cervical cancer screening performance. However, we submit for your opinion a suggestion to recommend this technique for the triage of conventional cytologies (ASCUS):

	1 (Not useful) to 4 (very useful)
According to you, how useful would liquid-based cytology be for ASCUS triage?	☐

Follow-up question #4

The experts suggested other interventions for further reducing the incidence of cervical cancer. Please specify, according to you, to what degree the following interventions would be effective in further reducing the incidence of cervical cancer.

	1 (Not useful) to 4 (very useful)
a) intensifying primary prevention in young women	☐
b) quality control of conventional cytology and follow-up for women with cytological abnormalities (patient disappearance, access to colposcopy)	☐

Comments on the screening consultation summary:

Other suggestions

Other suggestions focused on:

1. the value of anal cancer studies

2. educating risk groups (HIV+, MSM, etc)

3. the link between aerodigestive cancers and HPV

Comments on the consultation summary

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