HUMAN PAPILLOMAVIRUS INFECTION AND CERVICAL DYSPLASIA IN NUNAVUT

by

Sylvia M. Healey

A thesis submitted to the

Department of Community Health and Epidemiology

in conformity with the requirements for the

Degree of Master of Science

Queen's University

Kingston, Ontario

June 2000

ABSTRACT

The high rate of cervical cancer in the aboriginal population of the Northwest Territories has led to concerns about current screening methods. Recent reports in the literature have indicated that although it is the best tool we have now, the Pap test is less than ideal for screening for cancer of the cervix, and this has generated interest in the potential of incorporating Human Papillomavirus (HPV) testing into the present screening program. As a prelude to this process, this study's objective was to determine the prevalence of high-risk HPV types in Nunavut and to explore the association between high-risk HPV and cervical dysplasia.

A cross-sectional study was done from May 1st 1999 to December 31st 1999 and women from 19 communities in Nunavut who had a routine Pap test were invited to participate. Testing for 13 high-risk HPV types was done on the same sample as the Pap test. HPV testing was done using the Hybrid II capture method. Age, ethnicity, health region, highest level of education in the household and smoking were controlled for as potential confounders.

The prevalence of high-risk HPV types in the participating communities in Nunavut, was 26% and of cervical dysplasia was 7.2%. The odds ratio between high-risk HPV and cervical dysplasia was 28.6 after adjusting for age, ethnicity, region, education and smoking. This study can contribute to the strategy for cervical cancer prevention in Nunavut. With knowledge of prevalence in specific age groups the effectiveness of including HPV testing in the screening program can now be examined.

ACKNOWLEDGEMENTS

There were many people whose support was invaluable through this challenging period of returning to university after many years of absence from the world of academia. I would like to thank the following people for their support:

- Dr. Kristan Aronson, Dr. Yang Mao and Dr. Eduardo Franco for their mentorship, expertise and dedication that made this an exciting learning experience
- The Baffin and Keewatin Health Boards for their collaboration
- Health Canada for funding the project
- The dedicated physicians and nurses who took time in their busy schedules to be involved in this study
- The women who participated in this study
- Dr. Alex Ferenczy who provided expert advice on HPV testing and screening
- Les Mery and Nicolas Schlecht who taught me the two statistical analysis software systems and helped me with the analysis
- Juliette Robitaille and Christy Woolcott for their technical assistance
- Dr. Andre Corriveau and Dr. Elizabeth MacNamarra who encouraged me to pursue my goal to become a research scientist
- My school colleagues who were always there to lend an ear or a shoulder

Most of all I would like to thank my husband Greg and my two daughters Gwen and Colleen for their love and support during my absence from home for the time it took to get this degree.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ASCUS	Atypical Squamous Cells of Undetermined Significance
BCCA	British Columbia Cancer Agency
CHC	Community Health Center
CHN	Community Health Nurses
CIN	Cervical Intra-epithelial Neoplasia
FDA	Federal Drug Agency (US)
HC-II	Hybrid Capture II
HPV	Human Papillomavirus
HSIL	High-grade Squamous Intra-epithelial Lesion
JGH	Jewish General Hospital
LSIL	Low-grade Squamous Intra-epithelial Lesion
MA	Maryland
NCI	National Cancer Institute
NWT	Northwest Territories
OR	Odds Ratio
PCR	Polymerase Chain Reaction
RPHO	Regional Public Health Office
SIL	Squamous Intra-epithelial Neoplasia
STD	Sexually Transmitted Diseases
TBS	The Bethesda System
US	Unites States of America

INTRODUCTION

Cervical cancer is the most common cancer occurring among women in the Northwest Territories (NWT), and represents about 35% of all cancers diagnosed among women between 1991 and 1996 [1]. Elsewhere in North America, cervical cancer has fallen from second among cancers in women prior to the 1950's to seventh place in 1996 [2].

Invasive cervical cancer is a disease that can be prevented by early detection and treatment. Recognizable precursor lesions generally precede it. The Papanicolaou (Pap) test, which detects cervical dysplasia, is the primary screen for cervical cancer. The introduction of Pap screening programs has accelerated the decline in mortality due to cervical cancer in the past 45 years[3]. Although this indicates a successful screening program, a recent meta-analysis of 939 bibliographic references, revealed the sensitivity of the Pap smear to be only 51% [4] and an unacceptable number of women who have been cytologically screened develop invasive cervical cancer [5 6].

The NWT has had a comprehensive cervical screening program since 1990 and has done this in concert with the British Columbia Cancer Agency (BCCA). In spite of having in excess of 48% of eligible women screened from Jan 1991 to Dec 1994 [7], the NWT had the highest rate of cervical cancer in Canada for that period. Nunavut was part of the NWT at that time and became a separate territory on April 1st 1999.

As awareness of the low sensitivity of Pap testing has increased over the past few years, the historical desire to avoid over-diagnosis has been outweighed by the need to avoid any possibility of being held responsible for missed cases [8]. This has resulted in escalation of the monetary and psychological costs of the cervical screening program.

Additionally, it has been demonstrated that up to 50% of women of all ages with minor cytological abnormality can harbor a high-grade cervical lesion[9]. These minor-grade abnormalities incur high costs as these women are managed by colposcopy. These costs are especially felt in Nunavut where women have to be flown to a hospital setting for a colposcopy at an average cost of $2200 per trip. In addition, this experience can be associated with significant anxiety for the women.

Pap testing is considered to be the best tool for screening for cervical cancer but there is currently great interest in the possible application of Human Papilloma virus (HPV) testing to supplement Pap screening for cervical cancer. Many epidemiological studies provide evidence that persistent infection with specific types of HPV is a strong independent risk factor for the development of cervical intraepithelial neoplasia (CIN) and cervical cancer[10 11]. Additionally, it appears that the predictive value of a negative HPV result together with a repeat Pap smear in women with an initial low grade Pap result is greater than 96 % (82.8-99.4%)[12]. A four-year study done in Montreal combining HPV testing in the cytology screening strategy has reduced unnecessary colposcopies by 35%. In

that study, over 90% of high-grade squamous intra-epithelial lesions (HSIL) were detected[13].

The prevalence of HPV in Nunavut and the NWT has not been previously determined. As part of a necessary first step in developing screening programs, this study plans to determine the prevalence of high-risk HPV types in Nunavut and explore the association of HPV with cervical dysplasia. This information can then be used by public health officials to evaluate the use of HPV testing in combination with the Pap smear for developing a more effective cancer-screening program.

LITERATURE REVIEW

Cervical Cancer in North American Aboriginal Communities

In the NWT, 61% of the population is Aboriginal [14] and in Nunavut, aboriginal people make up 85% of the population. Cervical cancer rates are higher in the NWT (which included Nunavut until April 1999), than in the other provinces and territory in Canada [15]. In particular, the rates are higher in the aboriginal populations [7]. This pattern of high rates of cervical cancer is also seen in other Canadian [16] and United States (U.S.) aboriginal populations [17]. A meta-analysis of cancer incidence in United States and Canadian native populations indicated that although native women had significantly lower incidence of cancers of other sites, they had significantly elevated incidence of cancers of the cervix, gallbladder and kidney [18]. In British Columbia (BC), the mortality from cervical cancer has remained high in BC native women compared to non-native women (24.3 versus 3.7/100,000 for 1973 to 1984) [19]. Among Alaskan Native women, the incidence of invasive cervical cancer was four to five times higher than that for non-natives from 1980 to 1987 [20]. Outside of North America, in Greenland, where there is also a large population of Inuit, the incidence of cervical cancer is six times higher than among Danish women [21].

Cervical dysplasia in the NWT

Cervical dysplasia is a broad term describing the precursor lesions that are considered to be indicators of the progression to cervical cancer. These lesions

were classified as cervical intra-epithelial neoplasia (CIN). Increasingly progressive gradations were classed as CIN I, II or III. The Bethesda System (TBS) for reporting cervical/vaginal cytological diagnoses was initially developed in 1988 at a workshop sponsored by the National Cancer Institute [22] and is a widely accepted format for reporting gynecological cytology. With this classification, terms such as mild dysplasia (CIN I)and condyloma effect (kiolocytic atypia) were combined into one category called Low-grade Squamous Intra-epithelial Lesion (LSIL) and moderate dysplasia (CIN II), severe dysplasia and carcinoma in situ(CIN III) were categorized as High-grade Squamous Intra-epithelial Lesion (HSIL). Atypical Squamous-epithelial Cells of Undetermined Significance (ASCUS) refers to those changes that are more marked than 'reactive' but fall short of demonstrating a squamous intra-epithelial lesion (SIL).

A review of the NWT cytology database from 1991 to 1996[23] showed a much higher prevalence (14%) of cervical cancer precursor lesions, CIN I, II and III, than the average prevalence seen in all samples processed by the BCCA in 1993 (7%). The highest prevalence occurred among the Inuit and Dene (16.1%). Of particular concern was the high rate of pre-clinical disease in the 15-19 year-old Aboriginal population, where 15% of the Inuit and Dene were classified as CIN I. That study also found 20 cases of 15-19 year-olds who had CIN III[23].

Risk factors for cervical cancer

The American College of Obstetricians and Gynecologists describes the

high-risk factors associated with development of CIN [24] to include:

- Women with current or prior HPV infection (including condylomata)
- Women who begin sexual intercourse at an early age
- Women who have multiple sexual partners or whose male sexual partners have had multiple sexual partners
- Women who have a history of cervical dysplasia
- Smokers and abusers of other substances
- Women of low socioeconomic status

Numerous studies have consistently reported the association between sexual behavior and cervical cancer [25-27], and since the 1980's attempts have been made to try to understand the role of HPV as the sexually transmitted agent responsible. The poor sensitivity and specificity of the methods used for HPV testing have led to varying estimates of the relationship between HPV infection and cervical neoplasia [28-30] and this variability had led to considerable skepticism about the clinical role of HPV. A new generation of HPV testing has shown more consistent associations, and HPV DNA has been detected in over 99.7% of tumors from patients with invasive cervical cancer. HPV- negative cancers are virtually non-existent [31].

In examining indicators of socio-economic status, one study used low educational achievement and found it associated with increased odds ratios (OR's) of 3.4 (1.2-10.1) for CIN [30]. Bosch et al [32] also found a low level of education to be associated with cervical cancer.

The role of smoking is controversial. Some studies have shown a significant association between smoking and invasive cervical cancer [33,34]; however, there has been uncertainty about whether the reported association was a causal or a confounding phenomenon reflecting such factors as sexual habits and infection with an unidentified infectious sexually transmitted agent. Kjaer and colleagues found crude estimates showing a weak association between smoking and invasive cervical cancer that disappeared when controlling for active sexual behavior [35].

Other risk factors that have been examined in the literature are oral and barrier contraceptives. Studies on oral contraceptives have shown protective [36], null, or weak associations [37,38] with cervical neoplasia. Most recent studies have shown no association with OC use[39]. Barrier contraceptives have been shown to have a protective effect against cervical cancer: vaginal spermicides (OR = 0.28) [36], diaphragms (OR =0.67) and condoms (OR = 0.53) [25].

Role of HPV

There are more than 70 HPV types defined on the basis of DNA homology, of which more than 30 infect the anogenital tract[40]. Specific HPV types [41] cause genital warts, also known as condylomata acuminata, and probably most malignant lesions of the anogenital tract. The association between specific HPV types and cervical cancer is strong and consistent with OR's over 15 in case-control studies[42]. The low-risk group includes HPV types 6,11 and 42 to

44. Low-risk types are present in some low-grade lesions but are absent in cervical cancers. Types 16,18,31,33,35,39,45,51,52,56,58,59 and 68, referred to as the 'cancer-associated types', account for nearly 90% of HPV types detected in HSIL and cancer [43]. Recent studies have revealed that a unique feature of HPV testing is the ability to predict the subsequent development of cervical cancer precursors among cytologically negative women [44]. A prospective study done in the Netherlands recently reported that the cumulative six-year incidence of clinical progression to CIN III was 40% (95% CI: 21-59) among women who had persistent high-risk HPV from baseline. No clinical progression was documented among women who were negative for high-risk HPV DNA [45].

Risk factors for HPV infection

Cervical HPV infection detected by DNA hybridization techniques is found among 15% to 40% of sexually active women [41]. Molecular epidemiology surveys have revealed a sexually transmitted profile of cervical HPV infection. Although not all studies have uniformly confirmed this profile, recent studies have shown high risk types to be strongly and independently associated with both multiple partners (P=0.009, trend) and age at first intercourse (P=0.007, trend) in all age groups [46]. In a Swedish study, Karlsson and colleagues [47]found that the prevalence of HPV among sexually active women was 22% compared to 4% among virgins.

The most important determinant of HPV infection is age, with the highest

prevalence (60-80%) between the ages of 15 and 19 [48]. Infection in these individuals, however, appears to be transient and prevalence decreases to about 10% by age 30 and 3% by age 50. Persistence of HPV appears to be associated with progression to SIL [45].

The high birth rate in Nunavut [14 49] and the high rates of sexually transmitted diseases (STD) [50] imply that a potentially large number of women in Nunavut are at high risk for development of cervical cancer. Early detection could mean earlier treatment and a reduction of the number of women at risk for progression to invasive cancer.

The Conventional Pap Test

Cancer of the cervix is a preventable disease and, theoretically, with regular screening dysplasia can be detected early and invasive disease can be prevented. The Pap test is a cytological examination of a sample of cells taken from the cervix to determine the presence of disease-associated abnormal cells, which are reported using the Bethesda System[22]. The protective effect of cervical cytological screening (relative risks of 0.25-0.37) among women who have been screened cytologically compared to those who have never been screened increases with an increased number of screening smears and decreases with the increased length of interval since the last smear [8]. Although these results establish that the cytological screening program is successful, an unacceptable number of women who have been cytologically screened develop invasive

cervical cancer because of too many false negatives. Dysplasia is often missed in a cervical sample either because of human error in screening and interpretation or because of suboptimal quality of Pap smear[51-53]. Meta-analyses of Pap test accuracy showed an average false negative rate of 51% [4 51]. In Geneva, 14% of women with high grade CIN received a false negative cytology result in the two years before diagnosis[54]. This was also seen in a retrospective study of cancer cases in Alaskan women in 1988 where it was found that the Pap test had a sensitivity of 51% to render a diagnosis of dysplasia up to one year before the confirmation of invasive cancer. The comparable sensitivity of the Pap smear to detect dysplasia up to 36 months before a diagnosis of invasive cancer was 35% [6].

Pap Test Using Liquid Cytology

Recent developments in screening for cervical cancer include a new 'thin-layer liquid based cytology'. This technology (ThinPrep™) is designed to reduce sampling and reading errors by providing an improved quality of specimens that facilitates easier detection of abnormal cells in the cytological specimens[55].

Samples collected from the cervix with a cervical brush or broom are rinsed into a liquid medium (PreservCyt) that preserves the cells. The advantage of this technique is that most of the sample is available for analysis. With the traditional slide preparation, a large portion of the sample was left on the brush that was discarded.

In the laboratory, the samples are placed in an automated device that

standardizes the concentration of the cells and prepares a thin layer of cells on the slide. This thin layer allows a more consistent uptake of cytological stains and provides superior quality specimens for microscopic analysis.

Large-scale prospective studies have evaluated the accuracy of the ThinPrep Pap test and found sensitivities of 73% to 94% and specificities of 58% to 76% compared to a reference histological standard[38]. Conventional cytology by contrast has yielded sensitivities of 29% to 56% and specificities of 58% to 100% [4 56].

Management of Cervical Dysplasia

Among patients with an abnormal Pap smear, women with HSIL require immediate colposcopy and histologic diagnosis. For patients with ASCUS or LSIL, women can be followed by either performing colposcopy immediately or by repeating the smears every six months for two years, and then performing colposcopy if LSIL persists [57]. The literature suggests that one third to 50% of women with low grade cytological abnormalities have a high risk for cervical cancer[58 59], so the preferred option for managing these women is early referral for colposcopy [60] which means unnecessary investigation for some women. This approach is neither efficient nor cost-effective and causes unnecessary psychological trauma to many women.

HPV Testing

Early clinical methods for HPV testing such as filter in-situ hybridization and dot blot hybridization were insensitive and relatively non-specific. Their application in earlier epidemiological studies had led to inconsistent results [61 62] and this has resulted in significant skepticism in the literature as to the clinical utility of HPV testing. Two types of tests now dominate the field of HPV testing: Polymerase chain reaction (PCR) technology and the HPV DNA hybrid capture.

Hybrid Capture-II (HC-II, Digene Corp., MD, US) is the only HPV test approved by the US Federal Drug Administration (FDA) for clinical use. It uses signal amplification in cervical specimens to detect 13 high-risk HPV types (16,18,31,33,35,39,51,52,53,56,58,59,68). The HPV DNA from the sample is hybridized with a specific HPV RNA cocktail and the hybrids are captured using an enzyme-linked immunosorbent assay (ELISA) that uses chemiluminescent detection. Population-based studies have shown HPV DNA testing with HC-II to be more sensitive for detecting precancerous lesions (90 to 100%) than the conventional cytology counterpart [12]. Although it has a lower specificity compared to the histology gold standard, it has been shown that HPV DNA detection precedes and predicts the first cytological detection of SIL. In a prospective study, nested in a five-year follow-up of 17, 654 women who were initially cytologically normal, the women who were positive for HPV DNA at enrollment were 3.8 times more likely than women who were HPV negative to have LSIL diagnosed for the first time during the follow-up, and 12.7 times more

likely to develop HSIL [44].

Incorporation of HPV testing into the present Pap screening program has the potential to make screening for cervical cancer more effective, and a necessary prelude to assessing this, is determining the prevalence of the high-risk types in Nunavut.

OBJECTIVES

A collaborative study was done with the Baffin and Keewatin Regional Health Boards and Queen's University: The primary objectives of the study were:

1) To determine the prevalence of high-risk HPV types and of cervical dysplasia in the screened population in two of the three health regions in Nunavut.
2) To explore the association between high-risk HPV types and cervical dysplasia.

METHODS

Study Design

In order to achieve the objectives, a cross-sectional study was conducted in the Baffin and Keewatin regions of Nunavut. All women in these two regions who attended routine clinic for a Pap test from May 1 1999 to March 31st 2000, were invited to participate.

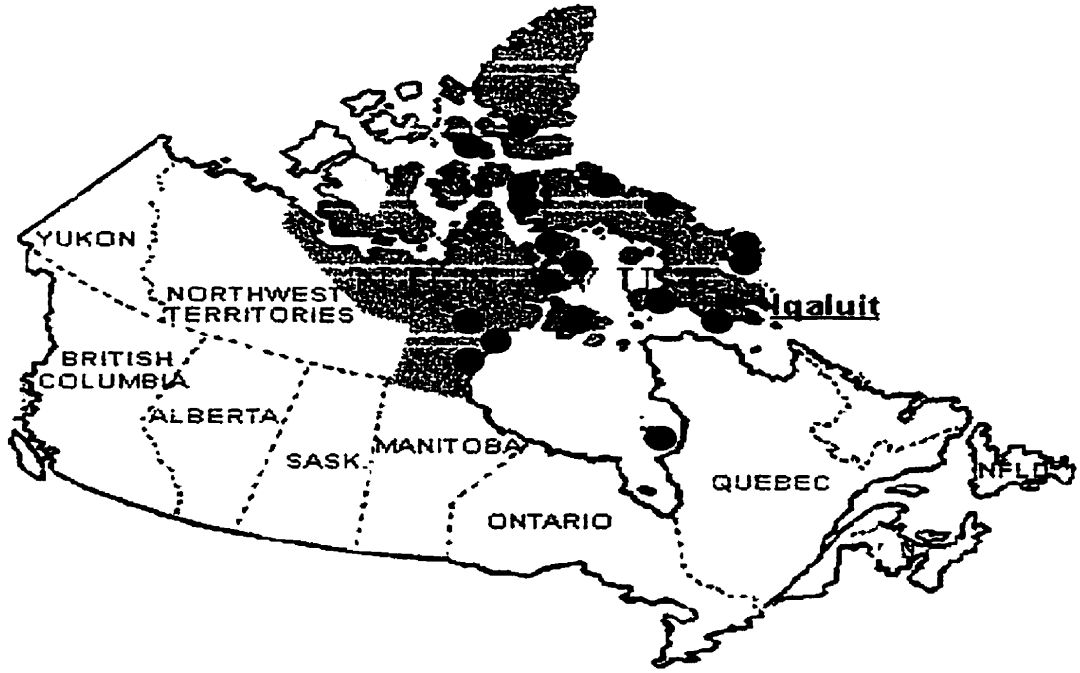
Setting

This study was conducted in 19 communities of Nunavut, which are spread out over a geographic area of over 2 million square miles. Nunavut is the eastern section of what used to be the NWT (See Figure 1). On April 1st 1999, Nunavut officially became a separate Territory. There are three regions in Nunavut: Baffin, Keewatin and Kiteokmeot. The population in the Baffin and the Keewatin constitutes 80% of the population of Nunavut. The participating communities are: Iqaluit, Cape Dorset, Clyde River, Kimmirut, Pangnirtung, Qiqiktarjuak, Pond Inlet, Arctic Bay, Nanisivik, Igloolik, Hall Beach, Resolute Bay, Grise Fiord, Rankin Inlet, Arviat, Baker Lake, Repulse Bay, Sanikiluaq and Coral Harbour. The ethnic distribution of this new Territory is 85% Inuit and 15% other ethnic groups[49].

There is only one hospital in Nunavut, located in Iqaluit. In all other communities, primary care is provided by Community Health Nurses (CHN). Routine Pap smears are made by physicians or CHNs. The Baffin region has nine

physician clinics and twelve community clinics, and the Keewatin has eight community clinics. The Kiteokmeot was not included in the study because their Pap smears are interpreted in a different center from the other two regions.

Figure 1. Participating Communities in Nunavut



Dark circles mark participating communities

Study Population

All women who attended routine clinics for a Pap test in the Baffin and Keewatin regions of Nunavut during the period from May 1st 1999 to March 31st 2000 were invited to participate in the study. Although diverse by geographic location, the 19 centers are quite similar in demographic composition, lifestyle and provision of health services (except Iqaluit, which has a higher population of non-Inuit, is more city-like, and has more economic opportunities).

Approximately 2200 Pap tests had been taken in a twelve-month period in 1997-98. Based on other Canadian experience[63], we anticipated a 75% acceptance rate. When the study was presented to the nurse practitioners, they expressed concern that they would not have the time to monitor non-acceptance. It was therefore decided that non-participation would be determined by comparison to the information collected in the cytology database. The Chief Medical Health Officer agreed to provide access to data from the database on the number of women who had Pap tests submitted, by age and ethnicity. The limitation of using this method to determine non-participation is that it is not possible to differentiate true non-participation from non-recruitment into the study (the latter presumably related to staffing shortages).

Ethics

The study protocol was submitted to the Queen's University Health Sciences and Affiliated Teaching Hospitals' Research Ethics Board for review and approval. Approval was received February 1st 1999 (See Appendix 1). The Director of Health Protection and the Chief Medical Health Officer also wrote letters of support indicating the need for such a study to help inform the practice of clinical management of cervical screening.

Written, informed consent was obtained from the women being screened. Subjects were assured that their participation was voluntary and that their regular medical care would not be affected if they declined to participate. All

questionnaires were kept confidential and stored in a locked cabinet until ready for processing by the researcher. All computerized patient data was password-protected with access restricted to the researchers. When all data were entered and checked, names were removed from the data set prior to analysis. Access back to the patient names is by a coded key, restricted to the researcher.

Research License

The Northwest Territories Scientists Act requires that all research conducted in Nunavut be licensed by the Nunavut Research Institute (NRI). The study protocol was submitted to the NRI for a license to conduct the study in Nunavut. Since this was a multi-centered study, the process of getting licensed involved getting approval from each Community Council, each Health Board, and the Chief Medical Health Officer. This study was licensed to proceed in 14 of the 21 communities on March 3rd 1999 and in another five communities on May 11th 1999 (See Appendix 2). Two communities did not respond by the deadline.

It was initially expected that all the data would be collected in 1999, however due to delays in start-up a request was made to the NRI for an extension to collect samples up to March 31st 2000 and this was approved.

Study Variables

Based on the literature, we chose to assess age, ethnicity, region, highest level of education in the household and smoking. The socio-demographic

variables examined are essentially surrogate confounders for relevant exposures. *Age* in this instance was a surrogate for both behavioral changes associated with aging and immunologic changes associated with aging. ***Ethnicity*** was examined as a surrogate for potential genetic factors that may independently be risk factors for susceptibility to HPV infection or cervical dysplasia. We were not aware of any differences by ***region*** that would contribute to confounding but we decided to investigate since large geographic distances may contribute to differences we were not aware of. ***'Highest level of education in the household'*** was used as an attempt to get a cursory indicator of socio-economic status (SES). It is difficult to know how well it represents socio-economic status in this population of primarily hunter-gathers; however, discussion with other health-care professionals in Nunavut seemed to indicate that it was probably the best one. Income is not considered a good measure of SES in a hunter-gatherer society [32].

Determinants of HPV and cervical dysplasia not assessed in this study

Numerous studies have established the role of sexual activity as an important determinant of HPV infection [46 64 65] as well as of cervical neoplasia[28 66]. In this study, we did not collect information on sexual activity. We were concerned that because of the sensitive nature of this information, the participation rate would decrease significantly and jeopardize the validity of the study.

Staff Training and Subject Recruitment

Recruitment of subjects was done by the physicians or the CHN's who saw patients for routine visits. Collaboration with the Health Board was vital and the Chief Executive Officer sent a letter to the staff informing them of the Health Board's commitment to the study and the expectations of the different personnel (See Appendix 3).

A complete package of all the items needed for the study was sent to each Community Health Center (CHC). It included:

- summary sheet with instructions
- general information on HPV for health professionals including answers to questions commonly asked by patients
- information for participants in English and Inuktitut (Appendices 4a & 4b)
- consent forms in English and Inuktitut (Appendices 5a & 5b)
- questionnaires in English and Inuktitut (Appendices 6a & 6b)
- return-addressed envelopes
- sample collection brushes
- sample transport containers
- instructions on collecting a sample for a Pap test

Presentations on the study were done for the medical, nursing and laboratory staff in Iqaluit and Rankin Inlet. Presentations for the other Community Health Centers were done by regional teleconferences, first in the Baffin and then in the Keewatin. At these sessions, all procedural issues were discussed and any concerns were addressed. After this, individual CHC teleconferences were held for nurses in each center to confirm procedures and deal with community-specific issues.

During the data collection period, there were numerous staff changes.

Nurses passing through Iqaluit were given a half-hour instructional session on the study. Others were trained by telephone. A toll-free telephone number with an answering machine allowed participants, nurses, laboratory personnel and physicians to contact the researcher at any time. The answering machine was checked at least once a day and the phone was answered from 11 a.m. to 2 p.m. on weekdays. The researcher could also be contacted by Fax or e-mail. All supplies were stored in Iqaluit and after the initial shipment, additional supplies were forwarded to the communities as needed. The communities were contacted every month to ensure adequate supplies and to monitor progress of the study.

It must be stressed that Health Board support was invaluable to this study. They provided the high quality translation needed when translating medical terminology. Most issues requiring translation were dealt with at the health center even though it would have been available had the participants phoned directly. The cost of teleconferencing is very high (approximately $1300 per teleconference) and had not been anticipated in the planning of this study. The Health Boards were very supportive and allowed the researcher time to present during their regular teleconferences.

Sample Collection

The procedure for sample collection for HPV testing was incorporated into routine Pap testing. Women who attended a clinic to have a Pap test were invited by the physician or CHN to participate in the study. They were given

prepared information on the study in both English and Inuktitut (Appendix 4a and 4b), asked to sign a consent form (Appendix 5a and 5b) and complete a questionnaire (Appendix 6a and 6b). The participants were assured that refusal to participate in the study would not affect their care. The health professionals assisted with directing the participant to the researcher when they had additional questions. Participants were able to contact the researcher by calling a designated phone number and reversing the charges.

Pap samples were collected in a liquid based medium, ThinPrep (Preservcyt; Cytyc Corp., Boxborough, MA, USA), which allowed both cytological diagnosis and HPV testing to be done on the same sample. Samples were stored in the regional laboratories either in Iqaluit or Rankin Inlet and shipped to the Jewish General Hospital (JGH), in Montreal three times a week together with routine laboratory samples. The questionnaires were put into pre-addressed envelopes and sent to the Regional Public Health Office (RPHO), or transported with the lab samples to the Regional Laboratory. Once there, they were retrieved by the lab staff and sent to the RPHO. The Health Board had approved the use of the RPHO as a central collection and interim storage place for this confidential material. The questionnaires were stored in a locked cabinet in the RPHO, which had a restricted key entry. The key to the cabinet was kept safe by the researcher.

Questionnaire to Assess Smoking Status

A questionnaire with six questions to assess smoking status was used (See Appendix 6). It asked respondents if they ever smoked and how much, if they currently smoked and how much, and when they started and stopped smoking. A question on 'highest level of education in the household' was included in the questionnaire as a cursory measure of socio-economic status (SES). The questionnaire was translated into Inuktitut by a professional translator who has many years of experience with translating educational and health materials. The design of the questions used, was from a larger questionnaire on a Nutrition study done by Health Canada (198). Researchers who had assessed smoking habits during a recently completed contaminants study in Nunavut also reviewed and approved of our questionnaire.

Pap Testing and Assessment of Cervical Dysplasia

A cervical broom device (Papette; Wallach Surgical Devices, Milford, CT, USA) was used to collect cells from the endo-cervix. The brush was then swirled immediately into a 20-ml container of buffered fixative (PreservCyt) to dislodge the cells into the medium. The sample was transported to the cytology laboratory at the Jewish General Hospital in Montreal via the two Regional Laboratories. The Thin Prep Pap test slides were then prepared using a semi-automated processor (Thin Prep 2000; Cytyc Corporation) according to instructions provided by the manufacturer. The Pap test was always done first. Residual

samples in PreservCyt were forwarded to the HPV laboratory if patient consent was indicated and if the Pap result did not indicate that the sample was unsatisfactory. Pap smear reporting was based on the Bethesda System [22] and the results were forwarded to the researcher. The cytology results were organized by the following categories: Negative, Benign Cellular Changes (BCC), ASCUS, LSIL and HSIL. A pathologist routinely reviewed all abnormal Pap smears. All cyto-technologists at the JGH are certified by the Canadian Society of Medical Technologists. The laboratory is accredited by the Canadian Council on Health Services (personal communication with the chief technologist of the cytology laboratory) and observes guidelines for practice and quality assurance in cytopathology published by the Canadian Society of Cytology.

HPV assessment

HPV testing was done on the same sample as the Pap test using a second-generation molecular hybridization, sandwich capture assay (HCII) (Digene). A minimum of 4 ml of residual sample in PreservCyt was required for this test. The HCII assay for HPV DNA detects in a single assay, one or more of 13 cancer-associated HPV types: 16,18,31,33,35,39,45,51,52,56,58,59 and 68.

HPV testing was always performed after cytology testing and the technologist performing the HPV testing was blinded to the cytology results and clinical status of the patient. The technologist doing the HCII testing was trained to perform the assay by Digene in Maryland, USA.

The HCII assay uses unlabelled full genomic RNA probes that hybridize in solution with the denatured target HPV DNA from the specimen. The resulting RNA-DNA hybrids are captured on the surface of a well coated with antibodies that are specific for the RNA-DNA hybrids. These immobilized hybrids are then reacted with an anti-hybrid antibody conjugated to alkaline phosphatase and detected using a chemiluminescent substrate. As the substrate is cleaved by the bound alkaline phosphatase, light is emitted that is measured in relative light units (RLU) using a plate luminometer. The emitted light intensity is proportional to the amount of target DNA in the specimen. Results are expressed as a ratio of sample RLU to the RLU of the positive calibrator. A relative light unit measurement greater than or equal to the prospectively chosen cutoff value (equivalent to 1 pg/ml HPV DNA or approximately 5000 genomic equivalents of HPV DNA per test) indicates the presence of HPV DNA sequences in the specimen. A measurement less than the cutoff value indicates the specimen is negative for the 13 HPV DNA sequences included in the test or that the HPV DNA levels for these 13 types is below the detection threshold of this assay.

Semi-quantitation of viral load is possible with this method for HPV testing. The following cut-offs are used by the laboratory: 1+ = 1-50 RLU, 2+ = 51-500 RLU, 3+ = over 501 RLU. Digene reports a sensitivity of 95% to detect HSIL compared to colposcopy[67].

Reporting

All patient results were communicated directly to the primary physicians and CHNs. Subjects were informed of their results in the same manner that they were informed of their Pap tests, in keeping with routine clinical practice, i.e. phoned if they are positive and not called if negative. The health care professionals were able to consult with a gynecologist/pathologist at the JGH about management of patients with a positive HPV result.

Sample Size

The number of women eligible for Pap testing (usually age 15 years and over) is 3835 in the Baffin and 1570 in the Keewatin[49]. We estimated that with the sample size of 1000 samples we would have reasonably narrow 95% confidence intervals for a prevalence between 5 to 40% and have power in excess of 99% to detect the expected odds ratio for the HPV-cervical dysplasia association in excess of 15 [42].

Because of the time restriction for completion of this thesis, only the data collected up to December 31st 1999 was used in this report. In that time period, we recruited 1331 participants and had 1290 adequate samples.

DATA ANALYSIS

Definition of Variables

Cervical Dysplasia - A categorical variable reported in this format by the lab. It was dichotomized for logistic regression:

Negative	Cytology within normal limits
BCC	Benign Cellular Changes
ASCUS	Presence of Atypical Squamous Cells of Undetermined Significance
LSIL	Presence of Low-grade Squamous Intra-epithelial lesion
HSIL	Presence of High-grade Squamous Intra-epithelial lesion

Negative	Negative or BCC.
Positive	Positive for ASCUS, LSIL or HSIL.

HPV - A categorical variable reported as a semi-quantitative measure by the lab. It was dichotomized for logistic regression.

Negative	Negative or below detection threshold for all of the 13 high-risk types listed above.
1+	1-50 RLU
2+	51-500 RLU
3+	>500 RLU

Negative	Negative or below detection threshold for all of types 16,18,31,33,35,39,45,51,52,56,58,59 and 68.
Positive	Positive for one or more of types 16,18,31,33,35,39,45,51,52,56,58,59 and 68.

Age - (at mid point of the study, Oct 1 1999) Calculated from date of birth information provided on the laboratory requisition and categorized according to the format commonly reported in HPV literature.

1	Age 13-20
2	Age >20 to 30
3	Age >30 to 40
4	Age >40 to 79

Ethnicity– A dichotomous variable determined from the coding of the Healthcare Number provided on the laboratory requisition.

1	Inuit
2	Non-Inuit

Highest Level of Education in the Household – Grade level reported on the questionnaire categorized by standard schooling blocks.

Primary	None or up-to Grade 7
Secondary	Grades 8-12
Post-secondary	Grades 12 and greater

Smoking Status – Obtained from responses to the questionnaire. Two people who smoked before did not respond to whether they also smoked now and were included in the current smokers.

Never	Has never smoked or reported experimenting only
Current	Currently smoking
Former	Was a smoker but has quit

Pack-years – Information on lifetime cigarette consumption was obtained from responses to the questionnaire and was calculated by multiplying the number of cigarettes smoked per day by the duration of smoking. One pack-year was defined as smoking one pack of cigarettes per day for a year [68 69]. Categories were based on pack-year tertiles.

Negative	Non-smoker
>0-3	smoking up to 3 packs of cigarettes per day for a year
3-6	smoking 3 to 6 packs of cigarettes per day for a year
> 6	smoking >6 packs of cigarettes per day for a year

Data Confidentiality

Access to the data was limited to three researchers and was always password protected. After data cleaning, patient names were removed prior to analysis and only one investigator had access to the patient information and that was through a unique identity code.

Data cleaning

All data were entered into a Statistical Analysis Software (SAS) [70] database. An unanticipated challenge was the use of the unique identifier. The Healthcare Number was used to identify each unique patient. When Nunavut separated from the NWT, the Healthcare Number changed but the new numbers were not used consistently. The old Healthcare Numbers were used more frequently. Permission was obtained to access the Health Information Database to convert all the new numbers entered into the study back to the old numbers. This was necessary in order to eliminate duplicates.

Frequency distributions and descriptive statistics were generated to check for entry errors and out-of-range values. Logical comparisons were tested. For example, if the participant answered that they did not smoke now then the answer to the question on 'average number of cigarettes smoked now' should

have been left blank. These were checked on the original form. The data were then transferred to SPSS (statistical software program)[71] and cross-tabs were run as an additional check for errors. Duplicates were eliminated. It had been decided at the beginning of the study that if there were duplicate samples, only the first entry would be accepted.

Statistical estimation

Confidence intervals, (the least frequency with which the interval will contain the true parameter) do much more than assess the extent to which the null hypothesis is compatible with the data. They provide simultaneously an idea of the likely magnitude of the effect and random variability of the point estimate [72]. In this study 95% confidence intervals were used to assess statistical significance and random variability of the point estimate. Confidence intervals can also show that the data do not contain the information necessary for reassurance about an absence of effect. For a study to provide evidence of lack of an effect, the confidence limits must be near the null value [69]. P-values were reported when analysis of trends were done.

The distribution of the population was described by frequency of age, ethnicity, region, highest education in the household and smoking. The frequency distribution, by age group, of the participants was compared to the non-participants. Women who had a Pap test were also compared to the general base population in order to assess how representative the study population was

of the general population. Responders and non-responders to the questionnaire were compared by age and ethnicity as well as by the two indicators of health status (HPV and cervical dysplasia). The chi-square test for homogeneity of proportions was done to assess the significance of the differences.

To accomplish objective one, the prevalence of high-risk HPV types and of cervical dysplasia in this population was reported together with a 95% confidence interval around the estimates. Confidence intervals for prevalence estimates were obtained using CONFINT, which is part of the software program PEPI (Programs for Epidemiologists)[73]. The frequency of each cytology diagnosis was determined and the prevalence of these diagnoses in each age group was reported. The prevalence of HPV in those with positive cytology diagnoses was also examined.

To accomplish objective two, the main association of interest between HPV and cervical dysplasia was examined using a logistic regression model that contains all five other variables as potential confounders. Justification for use of these variables is based on findings reported in the literature, as explained in the literature review for this thesis. This is a biologic model and this approach is feasible because of the limited number of variables under study.

Non-responders to the questionnaire were classified as 'unknown' when analyzing the whole data set (N=1290). This analysis was repeated using the subset (N=755) population. The information from the questionnaire allowed us to calculate a smoking measure frequently reported in the literature: pack-

years[74]. Although our primary interest was in using current and former smoking status, we also investigated the effect using pack-years. Finally, the age-adjusted association between viral load and cervical dysplasia is examined using logistic regression. A 95% confidence interval is reported around all estimates of association.

RESULTS

In this section the study population and participation in the study are described. With regard to external validity, they are compared to the base population of the Baffin and Keewatin Regions of Nunavut. The differences between respondents and non-respondents to the smoking questionnaire are examined and then, to address objective one, the prevalence of HPV and cervical dysplasia are examined according to age, ethnicity, region and highest level of education in the household.

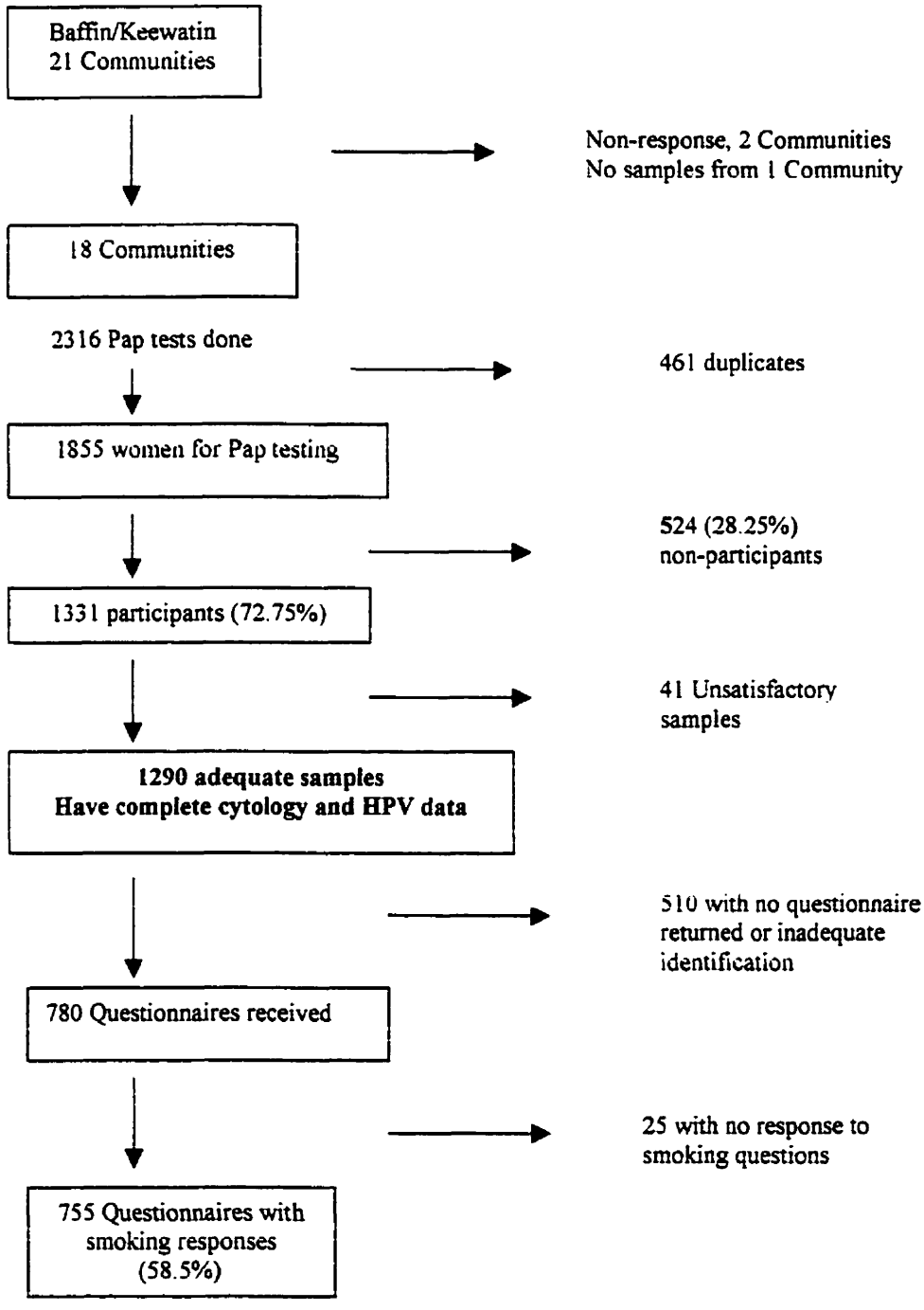
Associations with HPV are presented as descriptive information. For the second objective, cervical dysplasia is the outcome and odds ratios are presented for HPV as the main "exposure" of interest, with control for the other variables. These analysis are repeated and presented, using the subset (N=755) population that responded to the smoking questions. The data collected on the questionnaire allowed us to calculate a cumulative smoking measure as well as 'never current, former' status, and so these two are compared. This Chapter concludes with looking at a semi-quantitative measure of HPV to explore dose response with cervical dysplasia.

Participation in the Study

Figure 2 describes the participation in this study. Nineteen out of twenty-one communities responded positively and were included in the study. Of these,

samples were only received from 18 communities. In order to assure an adequate sample size of 1000 participants, the collection period was originally planned from May 1st 1999 to March 31st 2000; however, by December 31st 1999, we had in excess of the 1000 samples we had expected to need for this thesis. For this purpose, therefore, only these data were analyzed.

Figure 2 Study Population



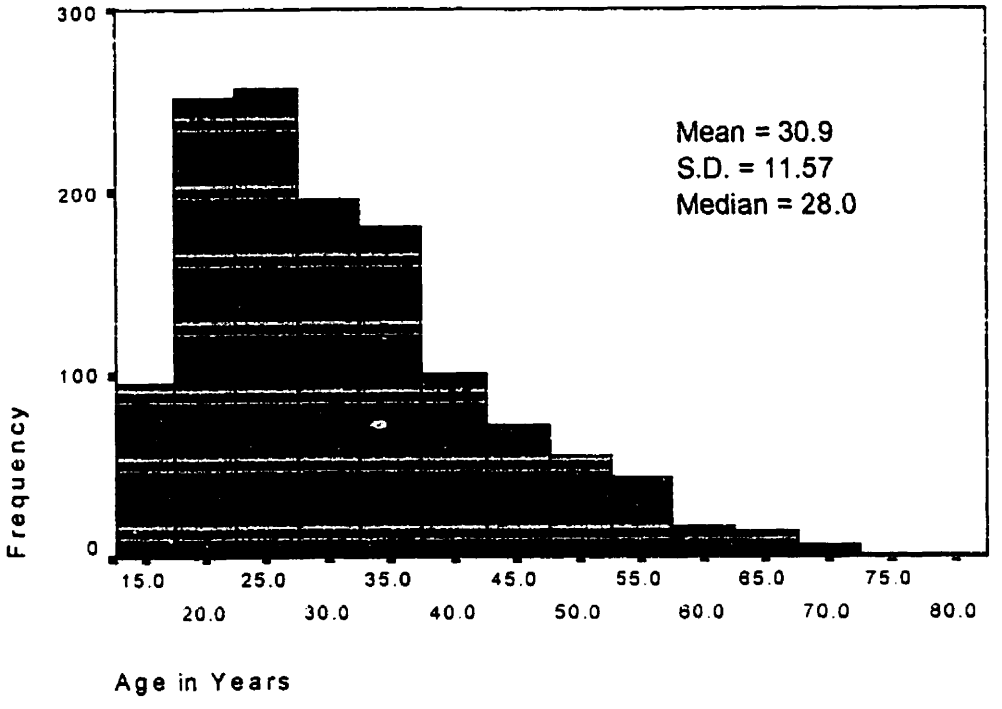
The total number of women in the two regions that were eligible for a Pap smear (i.e. over fifteen years old) was 5,405 based on the 1996 population statistics [4]. As seen in Figure 2, the number of Pap tests collected during this time period was 2316. Of these, 461 were repeat tests done for follow-up visits and, therefore, 1855/5405 (34%) women had a Pap test between May 1st and December 31 1999. Among those women who had a Pap test in this time period, 1331 (72%) participated in this study. Non-participation was either because women refused or because the nurse or physician was too busy to explain the details of the study and invite them to participate. Nurse or physician practitioners identified non-participants on the cytology lab requisition. 'Liquid Cytology' using the 'Thin Prep' method was to be offered to all women regardless of whether they participated in the study or not. Most non-participants' samples were collected using the conventional Pap method. Cytology was always done first so if the woman was a non-participant, her sample was not forwarded for HPV testing. In addition, 41 samples were unsatisfactory for cytological analysis and these were not forwarded for HPV testing.

A total of 1290 samples, referring to 1290 women, were adequate and processed for cytology and HPV. For these women, age and ethnicity is known from the information provided on the lab requisition. Of the 1290 participants, 510 did not return the questionnaire. Of those who did return the questionnaire, 25 did not answer the smoking questions, leaving 755 women (59%) with data on

smoking.

Description of Study Population

Figure 3 Frequency Distribution for Age (N=1290)

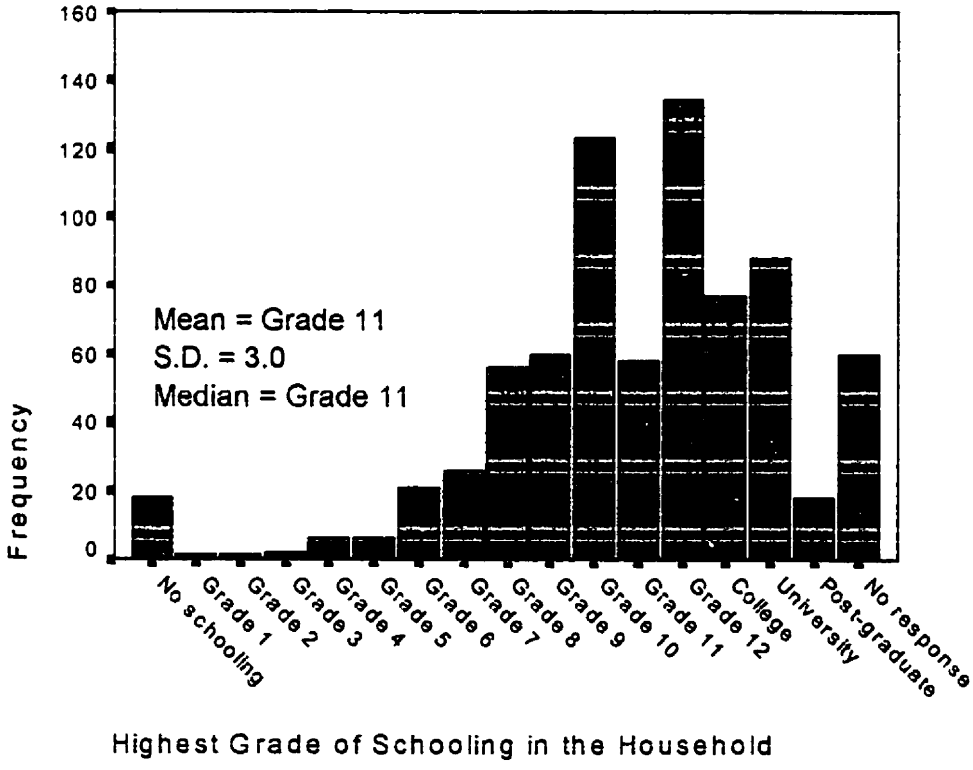


Figures 3 describes the participants (N=1290) by age. The mean age of the participants was 31 years, and 86% of them were Aboriginal. Since all the Aboriginal participants were Inuit, the participants are heretofore identified as Inuit or non-Inuit.

Figures 4 through 6 describe the 755 participants who provided information on region of residence and highest education level in the household and smoking.

Seventy-six percent of this subset population was from the Baffin and 24% were from the Keewatin. In Figure 4, the participants are shown by the level of 'highest grade of education in the household'. Sixty women who completed the questionnaire did not answer the question on education. The mean level of schooling was grade 11.

Figure 4 Highest Grade of Schooling in the Household (N=695)



The smoking status of the participants was examined using 'never', 'current' and 'former' categories as shown in Figure 5. Information was also collected on quantity smoked and Figure 6 shows the frequency of pack-years in

current and former smokers. One pack-year corresponds to smoking one pack of cigarettes per day for one year. The mean number of pack-years was 6.1.

Figure 5 **Frequency Distribution for Smoking (Never, Current, Former)**

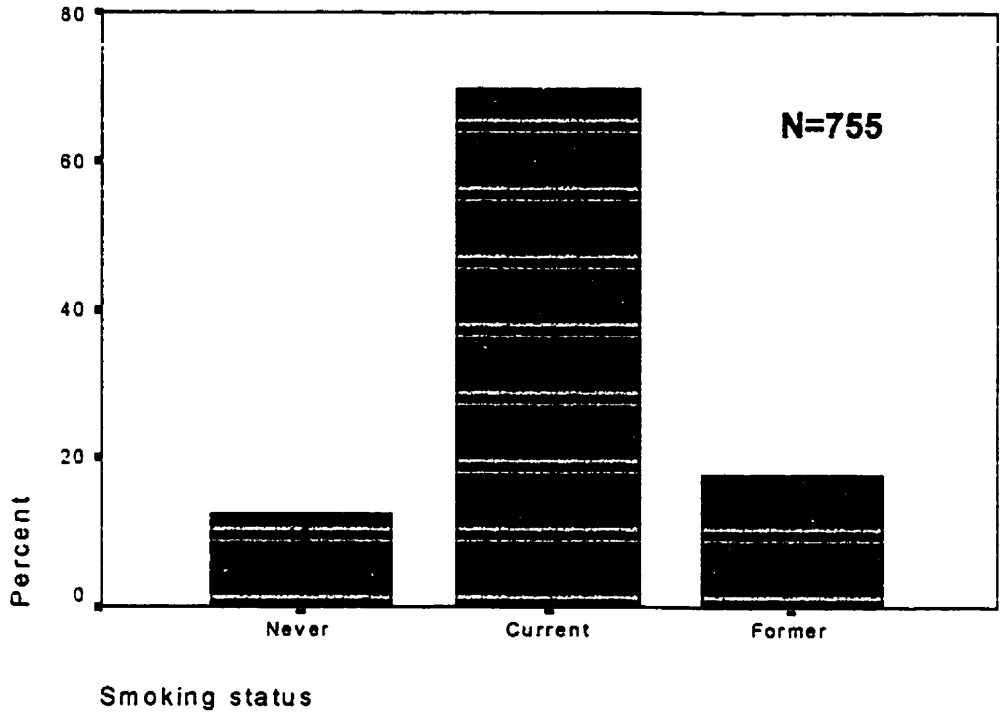
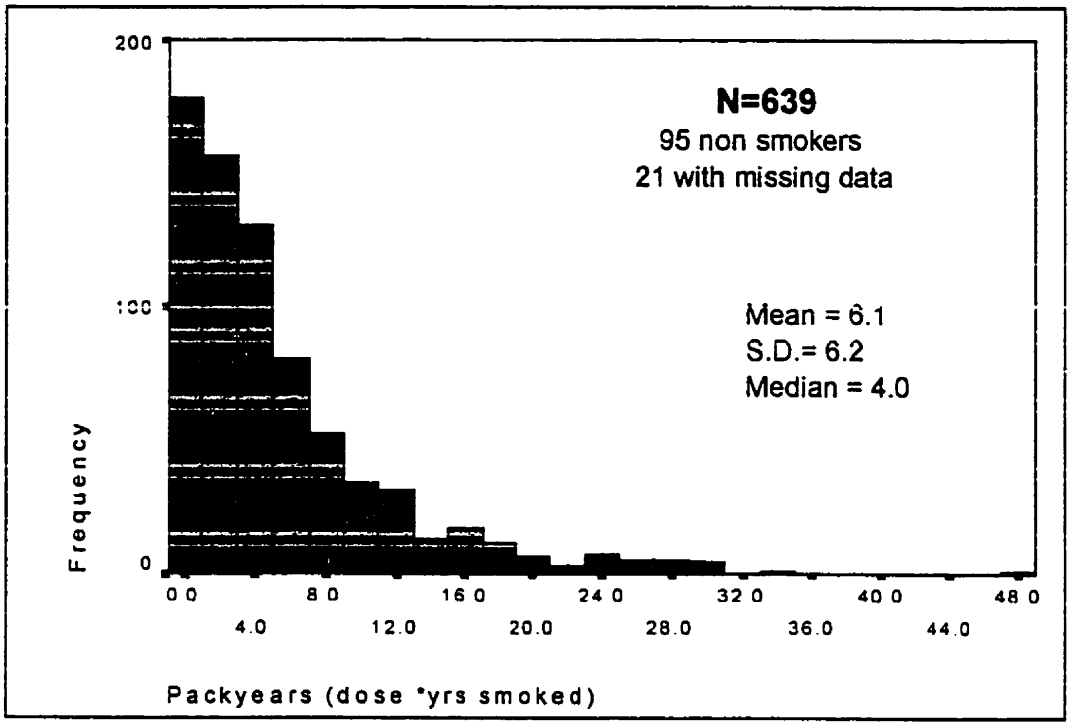


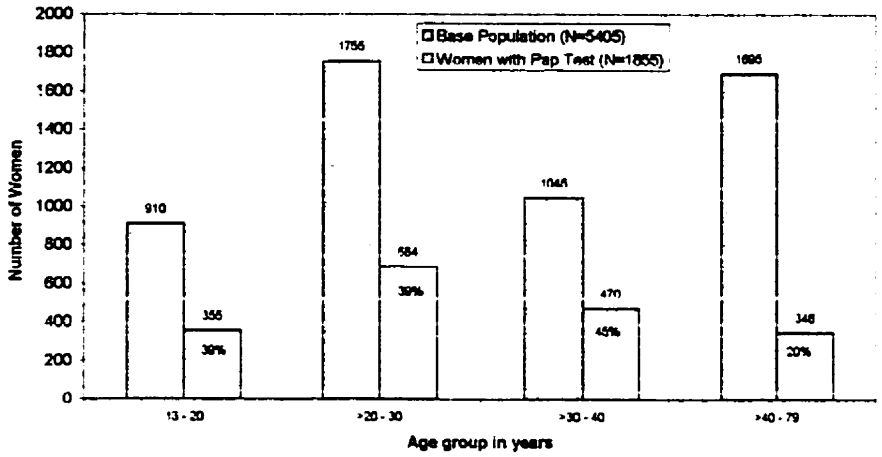
Figure 6 Frequency, Pack-years among Current and Former Smokers



Comparison of Participants to Reference Population

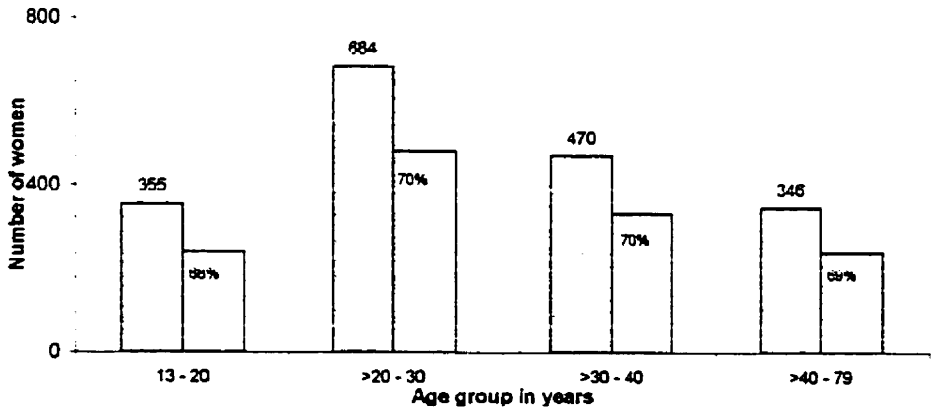
Figure 7 compares the women who obtained a Pap test during the study period to the total population of women in the two regions according to age groups. Between 20% and 45% of women in the different age groups were tested, with those in the 40-79 year age group being the least represented at 20%.

Figure 7 Women with Pap Test Compared to Base Population



Of the women who did get a Pap test, participants were equally represented at about 70% in every age group as shown in Figure 8.

Figure 8 Study Participants Compared to all Women who had a Pap Test



The population distribution of women in the two regions is 3340 (35%) in the Keewatin and 6195 (65%) in the Baffin [4]. The distribution of the study population (1290) was 24 % from the Keewatin and 76% from the Baffin, so the

Keewatin is slightly underrepresented compared to the base population.

Comparison of Respondents and Non-respondents to the Smoking Questions

Table 1 presents the frequency distribution by age and ethnicity of the study population who answered the questions on smoking habits (N=755) and those who did not (N=535). There was no significant difference in the two groups by age; however, more non-Inuit than Inuit answered the questionnaire.

Table 1 Comparison of women who did and did not provide smoking information by age and ethnicity

Variable	Category	Frequency (%)		p-value ‡
		Respondents N = 755*	Non-respondents N = 535†	
Age group				
	0-20	17.7	19.8	0.377
	>20 to30	37.7	36.4	0.676
	>30 to 40	25.7	25.6	0.980
	>40	18.8	18.1	0.805
Ethnic group				
	Inuit	83.2	89.5	0.001
	Non-Inuit	16.8	10.5	

* Study participants who provided personal smoking information (N=735)
† Study participants who did not provide personal smoking information (N=535)
‡ 2-sided p-value comparing proportions

Table 2 Frequency (%) for HPV and cervical dysplasia comparing the subset populations that did and did not provide smoking information

Variable	Category	Frequency (%)		p-values‡
		Respondents N = 755*	Non-respondents N = 535†	
HPV status				
	Negative	73.4	75.3	0.481
	Positive	26.6	24.7	
Cervical dysplasia				
	Negative	92.8	92.7	0.967
	Positive	7.2	7.3	

* Study participants who provided personal smoking information (N=735)
† Study participants who did not provide personal smoking information (N=535)
‡ 2-sided p-value comparing proportions

Table 2 presents the frequency distribution of these same two groups by HPV status and cervical dysplasia. The distributions of responders and non-responders to the questionnaire for these variables were virtually identical.

Prevalence of HPV Infection

Table 3 addresses objective 1 and shows the prevalence and 95% confidence intervals of HPV infection in the whole study population (N =1290) during the period from May 1st to December 31st 1999.

Table 3 Prevalence of HPV infection (N=1290) according to selected socio-demographic characteristics in 18 Nunavut communities from May 1st 1999 to December 31st 1999.

Variable	Category	Number of subjects (%)	HPV prevalence (%)	95%CI
Age group				
	13-20	240 (18.6)	42.1	32.6, 51.8
	>20 to30	480 (37.2)	31.3	22.5, 40.6
	>30 to 40	331 (25.7)	13.9	10.5, 17.9
	>40 to 79	239 (18.5)	15.1	10.9, 20.0
Ethnic group				
	Inuit	1107 (85.8)	26.2	23.7, 28.8
	Non-Inuit	183 (14.2)	23.5	17.8, 30.0
Region				
	Baffin	582 (45.1)	28.2	24.6, 31.9
	Keewatin	198 (15.3)	22.7	17.3, 28.9
	Unknown	510 (39.5)	24.3	20.7, 28.2
Education				
	None/Primary	55 (4.3)	29.1	18.3, 42.1
	Secondary	457 (35.4)	26.9	23.0, 31.1
	Post-secondary	183 (14.2)	25.7	19.7, 32.4
	Unknown	595 (46.1)	24.7	21.4, 28.3

The overall prevalence of HPV was 25.8% (95%CI: 23.8 - 27.9%) HPV prevalence differs significantly in the three age groups up to age 40. It was highest in the 13 to 20 year-olds and was successively lower as age increases. There was somewhat of a leveling effect after age 40.

There was no significant difference in HPV prevalence by ethnic group, comparing Inuit to non-Inuit, even though the number of non-Inuit was only 183. Prevalence of HPV by region did not differ significantly between the Baffin the Keewatin. Regional residence was not known for about 40% of the

participants and prevalence in that group was at a level in between that for the Baffin and Keewatin regions.

HPV prevalence also did not differ significantly by education level in the household. Information on education was not completed by 46% of the study population and prevalence in this group was about the same as for those with known education.

Prevalence of Cervical Dysplasia

Table 4 shows the prevalence and 95% confidence intervals of cervical dysplasia in the whole study population (N =1290) during the period from May 1st 1999 to December 31st 1999.

Table 4 Prevalence of Cervical dysplasia (N=1290) according to selected socio-demographic characteristics in 18 Nunavut communities from May 1st 1999 to December 31st 1999.

Variable	Category	Number of subjects (%)	Prevalence (%) of Cervical Dysplasia	95%CI
Age group				
	13-20	240 (18.6)	9.2	6.3, 13.8
	>20 to30	480 (37.2)	9.8	7.4, 12.7
	>30 to 40	331 (25.7)	4.5	2.7, 7.2
	>40 to 79	239 (18.5)	3.3	1.6, 6.3
Ethnic group				
	Inuit	1107 (85.8)	7.2	5.8, 8.9
	Non-Inuit	183 (14.2)	7.1	4.0, 11.6
Region				
	Baffin	582 (45.1)	7.2	5.3, 9.5
	Keewatin	198 (15.3)	6.6	3.7, 10.7
	Unknown	510 (39.5)	7.5	5.4, 10.0
Education				
	None/Primary	55 (4.3)	5.5	1.4, 14.1
	Secondary	457 (35.4)	7.2	5.1, 9.9
	Post-secondary	183 (14.2)	8.7	5.3, 13.5
	Unknown	595 (46.1)	6.9	5.1, 9.1

The overall prevalence of cervical dysplasia was 7.2% (95% CI: 5.9 – 8.7%). The prevalence of cervical dysplasia was highest in the age groups up to age 30. At age >30-40, the prevalence was half of that at the younger ages, and dropped even lower among those over 40. There was no significant difference in prevalence of cervical dysplasia by ethnic group. Prevalence by region was also not significantly different. Regional residence was not known for about 40% of the participants and prevalence in this group was the highest at 7.5%, but not statistically different from the other groups.

Although not statistically different, prevalence of cervical dysplasia was

slightly higher among those with secondary education in the household than in those with no or primary education, and higher again among those with a post-secondary education. Highest level of education in the household was not known for 46% of the study population and prevalence in that group was similar to those with a secondary education.

Prevalence of Cervical Dysplasia by Cytology Diagnosis

Figure 9 shows the frequency distribution of cervical dysplasia (N=1290) by cytology diagnosis. The prevalence of abnormal cytology was 7.2%, most of which were low-grade SIL. Benign cellular changes are not regarded as positive changes related to the development of cervical cancer and are displayed here only for informational purposes.

Figure 9 Distribution of Cervical Dysplasia by Diagnosis (N=1290)

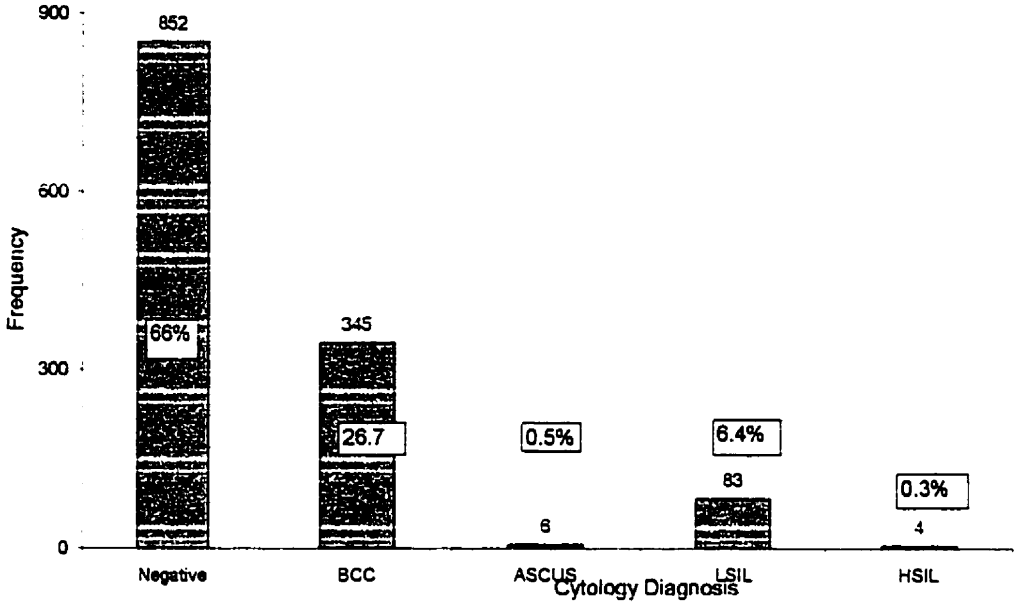


Figure 10 shows the cytology diagnosis in each age group. ASCUS was seen in approximately the same frequency in all age groups. LSIL was most frequent in the under 30 year-olds and decreases gradually after age 30. HSIL was only present in the 20-40 year-olds.

Figure 10 Frequency of Positive Cytology Diagnosis by Age-group (N=93)

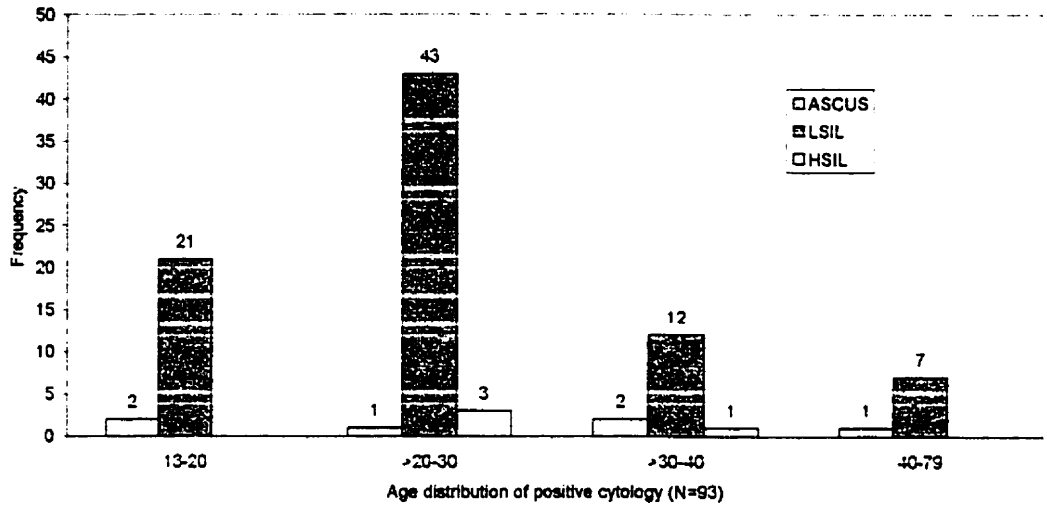


Figure 11 HPV Prevalence (%) and 95% CI among those with positive cytology (N=93)

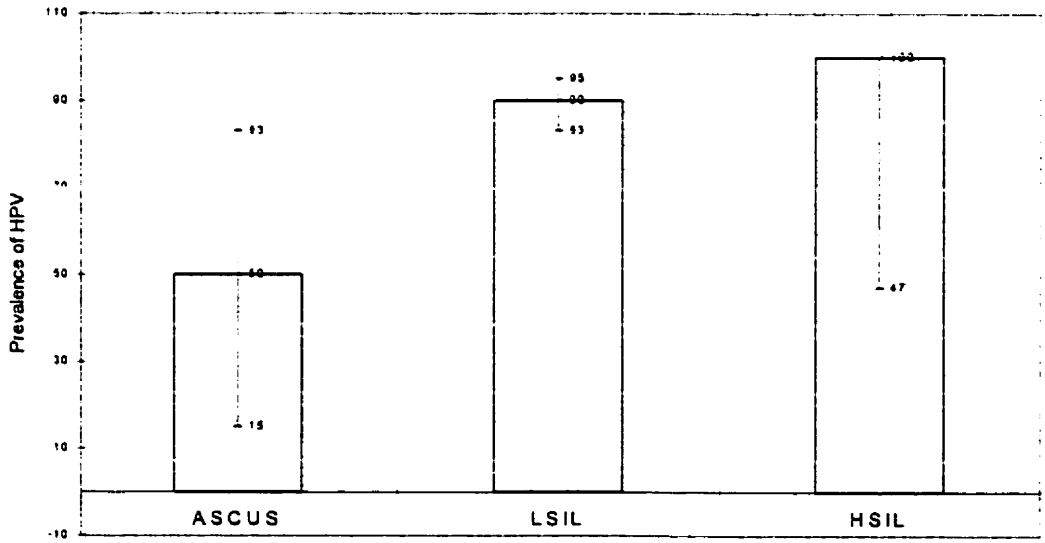


Figure 11 shows the prevalence of HPV (N=93) in those women with abnormal cytology. In women with the cytological diagnosis of SIL, over 90% had HPV. Twenty-one percent of the women who were negative for cervical

dysplasia (including BCC) were positive for HPV.

Odds Ratios for Selected Variables and HPV Infection

Table 5 examines associations between the selected variables and HPV infection adjusted first for age and then for age, ethnicity, region and highest level of education in the household (which will be referred to as 'education')

Table 5 Odds ratios (OR) and 95% confidence intervals (95%CI) for HPV infection (N=1290) in 18 Nunavut communities from May 1st 1999 to December 31st 1999

Variable	Category	Number of Cases / Total	Unadjusted*		Age Adjusted†		Fully Adjusted‡	
			OR	95% CI	OR	95% CI	OR	95% CI
Age group (years)								
	0-20	101/240	1.0	Referent			1.0	Referent
	>20 to30	150/480	0.63	0.5, 0.9			0.60	0.4, 0.8
	>30 to 40	46/331	0.22	0.1, 0.3			0.21	0.1, 0.3
	>40	36/239	0.24	0.2, 0.4			0.21	0.1, 0.3
Ethnic group								
	Inuit	290/1107	1.0	Referent	1.0	Referent	1.0	Referent
	Non-Inuit	43/183	0.87	0.6, 1.2	1.18	0.8, 1.7	1.06	0.7, 1.7
Region								
	Baffin	164/582	1.0	Referent	1.0	Referent	1.0	Referent
	Keewatin	45/198	0.75	0.5, 1.1	0.72	0.5, 1.1	0.70	0.5, 1.0
	Unknown	124/510	0.82	0.6, 1.1	0.78	0.6, 1.0	0.47	0.2, 1.2
Education								
	None/Trimary	16/55	1.0	Referent	1.0	Referent	1.0	Referent
	Secondary	123/457	0.90	0.5, 1.7	0.56	0.3, 1.1	0.57	0.3, 1.1
	Post-secondary	47/183	0.84	0.4, 1.6	0.71	0.4, 1.4	0.65	0.3, 1.4
	Unknown	147/595	0.80	0.4, 1.5	0.56	0.3, 1.1	0.62	0.3, 1.5
Smoking status								
	Never	27/95	1.0	Referent	1.0	Referent	1.0	Referent
	Current	143/527	0.94	0.6, 1.5	0.79	0.5, 1.3	0.82	0.5, 1.5
	Former	31/133	0.77	0.4, 1.4	0.91	0.5, 1.7	0.92	0.5, 1.8
	Unknown	132/535	0.83	0.5, 1.3	0.73	0.4, 1.2	1.45	0.4, 4.7

* Unadjusted logistic models † Separate logistic models adjusted for age
‡ Multivariate model adjusted for all other variables in the table

Women aged 13 - 20 years had the highest OR for HPV infection. The OR was significantly lower (0.63) in the 20-30 year-old group and dropped even lower (0.22) in those over age 30. This difference was still significant after adjusting for ethnicity, region, education and smoking status.

There was no significant difference in OR for HPV infection (1.1) by ethnic group when comparing Inuit or non-Inuit. When comparing the OR's by regional residence however, there appeared to be a lower OR (0.70) for those from the Keewatin and this was barely insignificant as the confidence intervals bordered 1.0. The OR for HPV infection in the group for whom there was no regional residence information was about the same as that in the Keewatin region.

When comparing the OR for HPV infection in the groups by education, the lowest association (fully adjusted) was for the group with secondary education and those with no or only primary education had the strongest association with HPV. Those with unknown education had the same OR as those with secondary education.

In the group who provided smoking information there appeared to be decreasing OR's for HPV infection with the highest OR in those who never smoked. This seemed to decrease (0.92) in those who were former smokers and was lower still (0.82) in those who were current smokers. None of these differences were statistically significant. The people who did not provide information on smoking had age-adjusted OR's similar to the current smokers.

Table 6 Odds ratios (OR) and 95% confidence intervals (95%CI) for cervical dysplasia in 18 Nunavut communities (N=1290) from May 1999 to December 31st 1999

Variable	Category	Number of Cases / Total	Crude*		Age Adjusted†		Fully Adjusted‡	
			OR	95% CI	OR	95% CI	OR	95% CI
HPV status								
	Negative	11/957	1.0	Referent	1.0	Referent	1.0	Referent
	Positive	82/333	28.1	14.7, 53.5	27.63	14.3, 57.4	28.57	14.7, 55.5
Age group (years)								
	0-20	23/240	1.0	Referent			1.0	(ref)
	>20 to30	47/480	1.02	0.6, 1.7			1.50	0.8, 2.7
	>30 to 40	15/331	0.45	0.2, 0.9			1.30	0.6, 2.8
	>40	8/239	0.33	0.1, 0.7			0.86	0.3, 2.2
Ethnic group								
	Inuit	80/1107	1.0	Referent	1.0	Referent	1.0	(ref)
	Non-Inuit	13/183	0.98	0.5, 1.8	1.21	0.7, 2.3	0.82	0.3, 1.9
Region								
	Baffin	42/582	1.0	Referent	1.0	Referent	1.0	(ref)
	Keewatin	13/198	0.90	0.5, 1.7	0.86	0.5, 1.6	1.07	0.5, 2.2
	Unknown	38/510	1.03	0.7, 1.6	1.01	0.6, 1.6	2.94	0.3, 25.5
Education								
	None/Primary	3/55	1.0	Referent	1.0	Referent	1.0	(ref)
	Secondary	33/457	1.35	0.4, 4.5	0.93	0.3, 3.2	1.36	0.4, 5.2
	Post-secondary	16/183	1.66	0.5, 5.9	1.42	0.4, 5.1	1.74	0.4, 7.5
	Unknown	41/595	1.28	0.4, 4.3	0.97	0.3, 3.3	0.53	0.1, 3.7
Smoking status								
	Never	10/95	1.0	Referent	1.0	Referent	1.0	(ref)
	Current	36/527	0.62	0.3, 1.3	0.55	0.3, 1.2	0.62	0.2, 1.6
	Former	8/133	0.54	0.2, 1.4	0.65	0.2, 1.7	0.70	0.2, 2.2
	Unknown	39/535	0.67	0.3, 1.4	0.63	0.3, 1.3	0.70	0.1, 10.0

* Unadjusted logistic models † Separate logistic models adjusted for age
‡ Multivariate model adjusted for all other variables in the table

Odds Ratio's for Selected Variables and Cervical Dysplasia

Table 6 shows the OR's and 95% CI for the selected variables and cervical dysplasia adjusted first for age and then for all the other variables. HPV was very strongly associated with cervical dysplasia (OR: 28.6) even after having adjusted for age, ethnicity, region, education and smoking status. Even though the confidence intervals were large (95%CI: 12-76), it was evident that HPV was significantly associated with cervical dysplasia.

Women aged 30 and younger had the highest OR for cervical dysplasia and it was less than half for the women over 30. This OR with age became insignificant in the fully adjusted model and in fact it was HPV that most influenced this change as is seen Table 7 which shows the OR's with age after adjusting for all the other variables first and then additionally adjusting for HPV.

Table 7 Odds ratios (OR) and 95% confidence intervals (95%CI) for cervical dysplasia and age, adjusting for the other variables and then additionally adjusting for HPV

Variable	Category	Number of Cases / Total	Crude*		Fully Adjusted†		HPV adjusted‡	
			OR	95% CI	OR	95% CI	OR	95% CI
Age group (years)	0-20	23/240	1.0	Referent	1.0	Referent	1.0	(ref)
	>20 to30	47/480	1.02	0.6, 1.7	1.03	0.6, 1.7	1.50	0.8, 2.7
	>30 to 40	15/331	0.45	0.2, 0.9	0.43	0.2, 0.9	1.30	0.6, 2.8
	>40	8/239	0.33	0.1, 0.7	0.32	0.1, 0.8	0.86	0.3, 2.2

*Unadjusted logistic models

† Separate logistic models adjusted for age, ethnicity, region, education and smoking

‡ Multivariate model additionally adjusted for HPV

The OR estimate for cervical dysplasia was lower for the non-Inuit than the Inuit (0.82) but this was not statistically significant. There was no significant difference in the OR's for cervical dysplasia when comparing by region.

While the highest OR was seen for those with post-secondary education, there was no significant difference in the OR's for cervical dysplasia when comparing the groups by highest education in the household. The OR for those who highest level of education in the household was not known, was similar to those of who had a secondary education.

There seemed to be a pattern of decreasing OR estimates for cervical dysplasia in smokers with those who were former smokers having a lower OR (0.70) and current smokers having an even lesser OR (0.62), however, none of these were statistically significant.

Analysis Using the Subset who Provided Smoking Data (N=755)

Table 8 Odds ratios (OR) and 95% confidence intervals (95%CI) for cervical dysplasia in those who provided smoking data (N=755)

Variable	Category	Number of Cases / Total	Crude*		Age Adjusted†		Fully Adjusted‡	
			OR	95% CI	OR	95% CI	OR	95% CI
HPV status								
	Negative	6/554	1.0	Referent	1.0	Referent	1.0	Referent
	Positive	48/201	28.6	12.0, 68.2	28.4	11.7, 69.1	30.7	12.4, 76.0
Age group (years)								
	0-20	13/134	1.0	Referent			1.0	Referent
	>20 to30	27/285	0.97	0.49, 2.0			1.29	0.6, 2.8
	>30 to 40	8/194	0.40	0.2, 1.0			1.35	0.5, 3.9
	>40	6/142	0.41	0.2, 1.1			1.10	0.3, 3.7
Ethnic group								
	Inuit	45/628	1.0	Referent	1.0	Referent	1.0	Referent
	Non-Inuit	9/127	1.01	0.5, 2.1	1.23	0.6, 2.7	0.47	0.2, 1.4
Region								
	Baffin	42/573	1.0	Referent	1.0	Referent	1.0	Referent
	Keewatin	12/182	0.89	0.5, 1.7	0.86	0.4, 1.7	1.0	0.5, 2.1
Education								
	None/Primary	3/55	1.0	Referent	1.0	Referent	1.0	Referent
	Secondary	33/457	1.35	0.4, 4.6	1.0	0.3, 3.5	1.5	0.4, 6.0
	Post-secondary	16/183	1.66	0.5, 5.9	1.50	0.4, 5.4	2.3	0.5, 10.3
	Unknown	2/60	0.60	0.1, 3.7	0.51	0.1, 3.2	0.6	0.1, 4.1
Smoking status								
	Never	10/95	1.0	Referent	1.0	Referent	1.0	Referent
	Current	36/527	0.62	0.3, 1.3	0.56	0.3, 1.2	0.50	0.2, 1.4
	Former	8/133	0.54	0.2, 1.4	0.63	0.2, 1.7	0.56	0.2, 1.8

* Unadjusted logistic models † Separate logistic models adjusted for age
‡ Multivariate model adjusted for all other variables in the table

Table 8 examines the association between the selected variables and cervical dysplasia using only the subset (N=755) who provided smoking information. The results were similar to the N=1290 population, showing HPV as having the strongest association with cervical dysplasia. The decreasing pattern with increasing age was similar to the 1290 population, however here the confidence intervals overlapped 1.0, obviously reflecting the difference in sample size. In the smaller subset, the difference in odds of acquiring cervical dysplasia were 50% lower in the non-Inuit than the Inuit but this was not statistically

significant. OR's for region, education and smoking were comparable in both the 1290 and the 755.

Comparison of Smoking Measures

Table 9 compares the OR's between cervical dysplasia and the four socio-demographic variables as well as HPV (N=755), after adjusting for smoking using 'never, current, former' and 'pack-years'. There was also no significant difference in adjusted OR's for cervical dysplasia and HPV using the two different measures for smoking.

Table 9 Comparison of the adjusted values of two different smoking measures on the odds ratios (OR) for cervical dysplasia after having adjusting for the other variables

Variable	Category	# with Cervical Dysplasia/ Total	Adjusted for all and Smoking Never, Current, Former†		Adjusted for all and Smoking pack-years‡	
			OR	95% CI	OR	95% CI
HPV Outcome						
	Negative	11/957	1.0	Referent	1.0	Referent
	Positive	82/333	30.7	12.4, 76.0	32.6	13.1, 81.2
Age group (years)						
	0-20	13/134	1.0	Referent	1.0	Referent
	>20 to30	27/285	1.29	0.6, 2.8	1.57	0.7, 3.5
	>30 to 40	8/194	1.35	0.5, 3.9	1.89	0.6, 5.9
	>40	6/142	1.10	0.3, 3.7	1.66	0.5, 6.0
Ethnic group						
	Inuit	45/268	1.0	Referent	1.0	Referent
	Non-Inuit	9/127	0.47	0.2, 1.4	0.48	0.2, 1.5
Region						
	BaffIn	42/573	1.0	Referent	1.0	Referent
	Keewatin	12/182	1.0	0.5, 2.1	1.02	0.5, 2.2
Education						
	None/Primary	3/55	1.0	Referent	1.0	Referent
	Secondary	33/457	1.5	0.4, 6.0	1.38	0.3, 5.6
	Post-secondary	16/183	2.3	0.5, 10.3	2.01	0.4, 9.1
	Unknown	2/60	0.6	0.1, 4.1	0.57	0.1, 4.2

† Separate logistic models adjusted for all variables in the table and smoking status (Never Current, Former).
‡ Separate logistic models adjusted for all variables in the table and smoking (Pack-years).

Odds Ratios for HPV Viral Load and Cervical Dysplasia

Table 10 shows the association between HPV viral load and cervical dysplasia controlling for age and then additionally controlling for all the other variables. The age-adjusted odds of having cervical dysplasia increased significantly and dramatically with increasing viral load. The p-value for this trend is <0.0001.

Table 10 Odds ratios (OR) and 95% confidence intervals (95%CI) for cervical dysplasia (N=1290) and HPV Viral Load

Variable	Category	Number of Cases	Crude*		Age adjusted†		Full Adjusted‡	
			OR	95% CI	OR	95% CI	OR	95% CI
HPV viral load (relative light units)	Negative	8	1.0	(ref)	1.0	(ref)	1.0	(ref)
	1 – 50	18	13.05	5.6, 30.5	13.70	5.8, 32.4	14.43	6.1, 34.2
	51 – 500	26	55.86	24.2, 129.1	58.38	24.7, 138.2	64.37	26.8, 154.7
	> 500	35	125.33	54.0, 291.1	152.52	62.3, 373.4	162.1	65.0, 403.9

* Unadjusted univariate model
† Separate logistic models adjusted for age
‡ Multivariate model adjusted for age, ethnicity, region, education and smoking (never, current, former)

DISCUSSION

This study was undertaken because of the high rates of cervical cancer in Nunavut and the growing evidence about the potential role of certain HPV types in the development of cervical cancer. In the five-year period from 1991 to 1996, there were 146 reported cases of cancer of the cervix in the NWT and these represented 34.8% of the incident cancer cases in women for that period, reported to the NWT cancer registry [1]. Increasing concerns in the literature about the lack of sensitivity of the Pap smear [19] and the possible potential for incorporating HPV testing to increase the effectiveness of screening programs for cervical cancer in Nunavut fuelled interest in the Public Health Community. A necessary prelude to planning the screening program was to determine the prevalence of the high-risk strains of HPV in Nunavut and the primary objective of this study was to do just that. There have been no other studies published on the prevalence of high-risk types of HPV in the Inuit in Canada.

Studies of prevalence are seldom of value in etiologic research since they yield associations that reflect determinants of survival with disease just as much as they do the causes of disease [9]. This study explores the association between high-risk HPV types and cervical dysplasia. However, the purpose of this is not to attempt to establish an etiologic role for HPV, but to confirm that associations seen in other groups are similar in the Nunavut population.

Summary of Results

This study population represented about 70% of all women who had a Pap test in these two regions and they were equally represented in all four age groups. They also represented the reference population equally by ethnicity i.e. 86 % Inuit compared to 85% in the base population. Respondents to the questionnaire did not differ significantly by age or by frequency of either HPV or cervical dysplasia outcome, but fewer Inuit responded to the questionnaire than non-Inuit.

The prevalence of high-risk HPV types in the two regions was about 25% and did not differ significantly by ethnicity, region or highest level of education in the household. However, it did differ significantly by age showing a dramatic decrease in prevalence from 42.1% in the 13-20 year-olds to 14% in the over 40 year-olds.

Prevalence of cervical dysplasia was about 7.2% and did not differ significantly by ethnicity region or highest level of education in the household. It too differed significantly by age between under thirty (9.7%) and over thirty year-olds (3.9%). Over 90% of women with a cytological diagnosis of SIL had high-risk HPV types. It was interesting to note that the prevalence of ASCUS in this study is only 0.5%. This is much lower than the 3 to 3.5% rates reported with conventional Pap testing[75] and is probably reflective of the reduction of the number of smears giving rise to interpretive difficulties.

Crude and age adjusted OR's between HPV and the five selected variables

showed age as the only variable significantly associated with HPV. Age was also significantly associated with cervical dysplasia but the OR estimates shifted toward the null when controlling for HPV and the association changed to become insignificant after that adjustment.

HPV was strongly associated with cervical dysplasia with a fully adjusted OR of 28.6 (14.7, 55.5). The association between cervical dysplasia increased markedly with increasing viral load (P<0.0001; trend). There were no differences in adjusted odds ratios whether using 'pack-years' or 'never, current, former' as smoking measures

Study Precision

Precision in measurement and estimation corresponds to the reduction of random error [20]. The primary method for increasing precision is to have a study sample that is sufficiently large. Prior to commencing the study it was estimated that a sample size of 1000 would be required to provide reasonable precision. The confidence intervals obtained in this study, for estimates of both prevalence and association provide us with reasonable confidence that the sample size was sufficiently adequate to significantly assess the role of chance.

Validity

Validity or lack of systematic error is usually separated into two components: *Internal validity* (the validity of the inferences drawn as they pertain

to the members of the source population) and *External Validity or Generalizibility* (the validity of the inferences as they pertain to the people outside that population)[20]. Internal validity is a prerequisite for external validity.

Internal validity

Various types of bias can detract from internal validity. Bias is defined as any systematic error in an epidemiological study that results in an incorrect estimate of association between exposure and risk of disease[76 77]. There are two general classes of systematic error. The first, selection bias, refers to any error that arises in the process of identifying the study populations. The second is observation or information bias and includes any systematic error in the measurement of information on exposure or outcome[26].

Selection Bias

In this cross-sectional study, the women had no prior knowledge of their HPV status. HPV testing is not done routinely and this test was not available as an option to physician management of patient care.

All women who attended clinic for a Pap test were invited and 72% participated. In teleconferences with the health centers, it became apparent that to a large extent, non-participation was related to staffing shortages and nurses having insufficient time to explain the study goals and invite women to participate. This shortage was universal and affected all the communities at some point in the study period.

Information Bias

Information bias can occur whenever there are errors in the measurement of subjects but the consequences of the errors are different, depending on whether the distribution of errors for one variable (exposure or disease) depends on the actual value of other variable [20].

Misclassification

In this study, both the assessments of HPV status and cervical dysplasia are susceptible to classification errors. Both are complex lab measures requiring numerous processes by humans and machines and there was therefore a potential for subjects to be erroneously categorized with respect to either exposure or disease status. All the testing was done at the Cytology Laboratories of Jewish General Hospital in Montreal, which is a nationally accredited facility.

In this study the proportion of subjects misclassified on HPV status does not depend on presence of cervical dysplasia and the proportion of subjects misclassified for cervical dysplasia does not depend on HPV status. The misclassification therefore is non-differential and will only serve to underestimate the true effects.

The limits of accuracy and precision are defined as follows: The sensitivity of a measurement method is the probability that someone who is truly exposed will be classified as exposed by that method. The false negative rate of that method is the probability that someone who is truly exposed will be classified as unexposed. It equals one minus the sensitivity. The specificity of the method is

the probability that someone who is truly unexposed will be classified as unexposed by that method. The false positive rate is the probability that someone who is truly unexposed will be classified as exposed. It equals one minus the specificity.

The manufacturer of the HPV test reported a sensitivity of 95% to detect HSIL[67]. A recent report that compared the Hybrid Capture II method and conventional Pap smears with their ability to detect HSIL, as determined by colposcopy, reported a sensitivity and specificity of 37.9% and 76.5% for the Pap test and 86.2% and 57.1% for the HPV test[12].

The utility of colposcopy as the 'gold standard' in assessing the specificity of HPV testing has been challenged in the literature, [44 78] and it has been shown in prospective studies[44] that rather than being a false positive result, it is predictive of future lesions. In that study, women who were HPV positive and initially cytology negative were 4 to 13 times more likely to have an SIL within a five-year follow-up period. In a retrospective assessment of Pap smears, Cox indicates that 16 out of 18 patients with negative Pap smears preceding a diagnosis of cervical cancer were subsequently shown to test positive for high-risk HPV types in these negative Paps for up to six years before the diagnosis of cancer[78].

Confounding

Confounding may be considered a confusion of effects where the

apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect (which may be null)[79]. In this study, as explained in the methods section, the socio-demographic variables examined were essentially surrogate confounders. Smoking was also examined as a potential confounder. Since the number of variables being analyzed was small, it was decided a priori to keep all the variables in the model. The association between HPV cervical dysplasia was very strong and was relatively unaffected by adjusting for all the other five variables.

We did not collect information on sexual activity because the subject was sensitive and we were concerned that a resulting drop in participation rate would jeopardize the internal validity of the study. The sexually transmitted profile of HPV has already been established and it is possible that the sexual activity correlates of cervical cancer are in reality determinants of risk for acquiring HPV infection.

External Validity

This is a cross-sectional study, where both HPV and cervical dysplasia are tested at the same point in time and therefore, no assumptions can be made about the temporal or etiologic relationship. If, however, there is a biologic role for HPV in inducing cervical dysplasia, then the results could be generalized to the rest of the population.

Age was the most significant determinant of both HPV and cervical

dysplasia and since the study population equally represented each age group, these results could probably be generalized to the women who did not participate. When considering the general population of Nunavut though, only 20% of the over forty year-olds attended clinic for a pap test. If as shown in other studies, this group is at high risk for development of cervical cancer then their under-representation will underestimate the OR for this age group.

Comparison of Results in This Study With Other Findings

The overall prevalence of HPV in the women in these two regions of Nunavut is 25% and decreases by age from 42% in the 13-20 year-olds to 15% in the 40-79 year-olds. It is difficult to compare prevalence in other aboriginal groups cited in the literature because most studies screened for a combination of low and high-risk types [65 80-82]. They also used different methods than those used in this study (Virapap™ Life Technologies Inc) or Polymerase Chain Reaction (PCR) methods) and report prevalence that ranges from 8% to 33%. A study on the Alaskan Native population examined 6 high risk-types and reported a prevalence of 21% using a PCR method [19].

Differences in HPV prevalence have been observed in different racial groups [64], and although we saw a lower estimate in the non-Inuit, this was not statistically significant. The number of non-Inuit in this study was only 183. A study in Winnipeg, Canada [34], found no difference in HPV prevalence between Aboriginal and non-aboriginal women. Kjaer et al [48] also found no difference in

prevalence between the Danish population and the Greenlandic Inuit.

The borderline differences in prevalence between the Baffin and Keewatin could possibly be a reflection of lifestyle differences in Iqaluit, which comprises about 35% of the Baffin population. It has more of an 'inner-city' lifestyle whereas the other communities are more traditional.

This study found a strong association (OR: 28) between high-risk HPV types and cervical dysplasia. Comparison with other studies has been difficult because of the different techniques used for detection and the different combinations of strains being tested for, nonetheless, OR's of over 15 have been reported in a review of case-control studies that used reliable methods for HPV DNA detection [2].

Cigarette smoking has been described as an independent risk factor for cervical neoplasia [32 33], however this was not evident in this study. The OR estimates were actually lower in smokers but these were not statistically significant.

In this study, we also had the opportunity to observe the association of viral load with cervical dysplasia. A marked increase in odds was observed with increasing viral load with the OR increasing from 11 for 1+ HPV to 116 for 3+ HPV ($P<0.0001$; trend).

Strengths and Limitations

The main strength of this study was the opportunity to determine HPV

prevalence in a predominantly Aboriginal population in Canada. It utilized improved technology for Pap testing (liquid cytology) which allowed for a more reliable assessment of cervical dysplasia. The opportunity to assess HPV screening as a better predictor of cervical lesions presents new options for the cervical cancer prevention program.

The researcher has long-term experience in the Nunavut communities and health system and was therefore able to facilitate resolutions to many obstacles that arise from coordinating a multi-center study in these remote locations. Inuktitut is the first language of the people of Nunavut and by conducting the study in collaboration with the health boards, the participants have had access to translators who are specifically trained to interpret medical terminology.

The small population of Nunavut (25,000) is scattered over a very large landmass with the farthest participating communities being farther apart than the distance between Montreal and Mexico City. Coordinating this project was a challenge and the success of the study depended on keeping the numerous physicians and Community Health Nurses educated and motivated in a system of heavy workload and constant transiency. The success is evident in the high rate of screening 34% compared to 12% reported in the 1998 study.

CONCLUSION

Findings and Application

In a 1995 report[83], the Canadian Task Force on the Periodic Health Examination identified research priorities regarding screening for Human Papilloma Viruses and this study partly addresses one of those priorities regarding defining HPV infection in the general population.

As suspected prior to undertaking this study, the prevalence of HPV is high in the Nunavut population and the association between HPV and cervical dysplasia is very strong. This study provides a basis upon which some decisions on a new screening strategy, which can supplement the present Pap screening, can be developed. The cost-effectiveness of testing with both Pap and HPV in certain age groups can be examined. Switching to Liquid Cytology is another possibility that can be examined. Overall, this report can contribute significantly to the cervical cancer prevention strategies of the Nunavut Ministry of Health.

REFERENCE LIST

1. Corriveau A. Cancer incidence and mortality in the NWT 1991 to1996. Epi-North 1997; 9(2):5.

2. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics. A Cancer Journal for Clinicians 1996; 46(1):5-27.

3. Gustafsson L, Ponten J, Zack M, Adami HO. International incidence rates of invasive cervical cancer after introduction of cytological screening. Cancer Causes and Control 1997; 8(5):755-63.

4. Agency for Healthcare Policy and Research. Evaluation of Cervical Cytology Summary Evidence report. Technology assessment: Number 5. January 1999. http://www.ahcpr.gov/clinic/cervsumm.htm. 2000.

5. NWT Health Protection Unit. Cervical screening for cancer: Why is cervical screening important. Epi-North 1996; 8(5):6-7.

6. Davidson M, Bulkow L, Lanier A *et al.* Incidence of cervical cancer preceeded by negative screening in high-risk Alaska native women. International Journal of Cancer 1994; 23(2):238-45.

7. Kelsey JL, Whittemore AS, Evans A.S., Thomson WD. Methods of sampling and estimation of sample size. Second edition edition. New York: Oxford University Press, 1996: 312-40.

8. Cox JT. Clinical role of HPV testing. Obstetrics and Gynecology Clinics of North America 1996; 23(4):811-45.

9. Bavin P, Giles J, Derry A, et al. Use of semi-quantitative PCR for human papillomavirus DNA type 16 to identify women with high-grade cervical disease in a population presenting with a mild dyskaryotic report. British Journal of Cancer 1993; 67:602-5.

10. HPV Summit 1998. Greater protection against cervical cancer. European HPV Clinical Summit Meeting Report. 1998: 1-16.

11. IAC Task Force Summary. Human Papillomavirus. Acta Cytologica 1998; 42(1):50-8.

12. Ratnam S, Ghatage P, Franco EL, Ferenczy A. Utility of HPV testing in combination with papanicolaou smear in primary cancer screening. 17th International Papillomavirus Conference (USA). 1999: 44.

13. Ferenczy A. HPV testing can reduce the number of colposcopies performed. European HPV Clinical Summit Meeting. 1998: 14-5.

14. Statistics Canada. 1996 NWT Census Data. www.gov.nt.ca/strategy 2010/strat_94.htm.

15. NCIC 1995. National Cancer Institute of Canada. Canadian Cancer Statistics 1995. National Cancer Institute of Canada 1995.

16. Mao Y, Morrison H, Semenciw R, et al. Mortality on Canadian Indian reserves. Canadian Journal of Public Health 1986; 77:263-8.

17. Mahoney M, Michalek A, Cummings K, Nasca P, Emrich L. Cancer mortality in a northeastern Native American population. Cancer 1989; 64:187-90.

18. Mahoney M, Michalek A. A meta analysis of cancer incidence in United States and Canadian Native populations. International Journal of Epidemiology 1991; 20(2):323-7.

19. Band P, Gallagher R, Threfall WJ, et al. Rate of death from cervical cancer among Native Indian women in British Columbia. Canadian Medical Association Journal 1992; 147:1802-4.

20. Nutting P, Freeman W, Risser D, et al. Cancer incidence among American Indians and Alaska Natives 1980 through 1987. American Journal of Public Health 1993; 83:1589-98.

21. Kjaer S, de Villiers E, Haugaard B *et al.* Human papillomavirus, Herpes simplex and cervical cancer incidence in Greenland and denmark. A population-based cross-sectional study. International Journal of Cancer 1988; 41:518-24.

22. Isacson C, Kurman RJ. The Bethesda System: a new classification for managing pap smears. Contemporary OB/GYN 1995; 67-74.

23. Carr C. Cervical cancer screening (Part 2). Epi-North 1996; 8(6):4-5.

24. ACOG 1995. March 1995 committee opinion. High risk factors associated with the development of CIN and cervical cancer. The American College of Obstetricians and Gynecologists 1995.

25. Slattery M, Overall J, Abbott T, French T, Robison L, Geyer JW. Sexual activity, contraception, genital infections and cervical cancer: Support for a sexually transmitted disease hypothesis. American

Journal of Epidemiology 1989; 130(2):248-57.

26. Brinton L, Fraumeni J. Epidemiology of uterine cervical cancer. Journal of Chronic Disease 1986; 39:1051-65.

27. Kjaer S, Dahl C, Engholm G, Bock J, Lynge E, Jensen O. Case-control study of risk factors for cervical neoplasia in Denmark. II. Role of sexual activity, reproductive factors, and venereal infections. Cancer Causes and Control 1992; 3:339-48.

28. Kjaer S, Engholm G, Teisen C *et al.* Risk factors for cervical HPV and Herpes Simplex virus infectiona in Greenland and Denmark: A population-based study. American Journal of Epidemiology 1990; 131(4):669-82.

29. Reeves WC, Brinton LA, Garcia M *et al.* Human papillomavirus infection and cervical cancer in Latin America. The New England Journal of Medicine 1989; 320:1437-41.

30. Morrison E, Ho G, Vermund S *et al.* HPV infection and other risk factors for cervical neoplasia: A case-control study. International Journal of Cancer 1991; 49:6-13.

31. Walboomers J, Jacobs M, Manos MM, Bosch FX, et al. Human papillomavirus is a necessary cause of invasive cervical cancer. Journal of Pathology 1999; 189(1):12-9.

32. Bosch FX, Munoz N, de Sanjose S, et al. Risk factors for cervical cancer in Columbia and Spain. International Journal of Cancer 1992; 52:750-8.

33. Winkelstein Jr W. Smoking and cervical cancer - current status. American Journal of Epidemiology 1990; 131:945-57.

34. Burger M, Hollema H, Gouw A, Pieters W, Quint W. Cigarette smoking and human papillomavirus in patients with reported cervical cytological abnormality. British Medical Journal 1993; 306:749-52.

35. Kjaer S, Engholm G, Bock J. Case-control study of risk factors for cervical squamous-cell neoplasia in Denmark. IV: role of smoking habits. European Journal of Cancer 1996; 5:359-65.

36. Celentano D, Klassen A, Weisman C, Rosenshein N. The role of contraceptive use in cervical cancer: The Maryland cervical cancer case-control study. Obstetrics and Gynecology 1987.

37. Boyce J, Lu T, Nelson J, Fructer R. Oral contraceptives and cervical carcinoma. American Journal of Obstetrics and Gynecology 1977; 128:761-6.

38. Worth A, Botes D. A case-control study into the possible effects of birth control pills on pre-clinical carcinoma of the cervix. J Obstet Gynaecol Br Commonw 1972; 79:673-9.

39. Davidson M, Schnitzer P, Bulkow L *et al.* The prevalence of cervical infection with HPV and cervical dysplasia in Alaska Native Women. The Journal of Infectious Diseases 1994; 169:792-800.

40. zur hausen H, de Villiers EM. Human papillomaviruses (Review 123 references). Annual Review of Microbiology 1994; 48:427-47.

41. Franco EL. Epidemiology of anogenial warts and cancer. Human Papillomavirus 1996; 23(3):597-623.

42. Munoz N, Xavier Bosch F. Cervical cancer and human papillomavirus: epidemiological evidence and perspectives for prevention. Salud Publica De Mexico 1997; 39(4):274-82.

43. IARC monographs on the evaluation of carcinogenic risks to humans. IARC working group on the evaluaton of carcinogenic risks to humans. Human papillomaviruses. WHO, 1995; 64.

44. Liaw K, Glass A, Manos MM *et al.* Detection of human papillomavirus DNA in cytologically normal women and subsequent cervical squamous intraepithelial lesions. Journal of the National Cancer Institute 1999; 9(11):954-60.

45. Nobbenhuis M, Walboomers JM, Helmerhorst T *et al.* Relation of HPV status to cervical lesions and consequences for cervical screening: a prospective study. The Lancet 1999; 354:20-5.

46. Franco EL, Villa LL, Ruiz A. Transmission of cervical human papillomavirus infection by sexual activity: Differences between low and high oncogenic types. Journal of Infectious Diseases 1995; 172:756-63.

47. Karlsson R, Jonsson M, Edlund K *et al.* Lifetime number of partners as the only independent risk factor for Human papillomavirus infection: A population-based study. Sexually Transmitted Diseases 1995; 119-27.

48. Koutsky LA, Galloway D, Holmes KK. Epidemiology of genital human papillomavirus infection. Epidemiological Reviews 1988; 10:122-63.

49. Statistics Canada. Nunavut regions and communities: July1,1996 population by age, ethnicity and fertility rates. www.stats.gov.nu.ca/demographics/vital. NWT Bureau of Statistics 1999.

50. Corriveau A. 1998 Review of gonococcal & chlamydial infections. Epi-North 1999; 11(1):14-5.

51. Fahey M, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. American Journal of Epidemiology 1995; 141(7):680-9.

52. Koss LG. Cervical (Pap) smear: New directions. CANCER Supplement 1993; 71(4):1406-12.

53. Confortini M, Ciatto S, Bonardi L *et al.* Analysis of false negative and underreported smears in the Florence district screening program for cervical carcinoma. Tumori 1997; 83(6):880-3.

54. Vassilakos P. Screening for cervical cancer. European HPV Clinical Summit Meeting Report 1998; 10-1.

55. Inhorn S, Wilbur D, Zahniser D, Linder J. Validation of the ThinPrep pap test for cervical cancer diagnosis. Journal of Lower Genital Tract Disease 1998; 2(4):208-12.

56. Austin R, Ramsey I. Increased detection of epithelial cell abnormalities by liquid-based gynecologic cytology preparations: a review of accumulated data. Acta Cytologica 1998; 42:178-84.

57. Ferenczy A, Jenson AB. Tissue effects and host response. the key to the rational triage of cervical neoplasia. Obstetrics and Gynecology 1996; 23(4):759-82.

58. Wright TC, Sun XW, Koulos J. Comparison of management algorithms for the evaluation of women with low-grade cytologic abnormalities. Obstetrics and Gynecology 1995; 85(2):202-10.

59. The ALTS group. Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions: Baseline data from a randomized clinical trial. Journal of the National Cancer Institute 2000; 92(5):397-402.

60. Ferenczy A. Human papillomavirus infections: Current concepts, new developments. Journal of the Society of Gynecology of Canada 1997; 19:369-81.

61. Franco EL. Cancer causes revisited: Human papillomavirus and cervical neoplasis. Journal of the National Cancer Institute 1995; 87(11):779-80.

62. Franco E. The sexually-transmitted model for cervical cancer: incoherent epidemiologic findings and the role of misclassification of human papillomavirus infection. Epidemiology 1991; 2:98-106.

63. Ratnam S, Franco EL, Ferenczy A, Ghatage P. Title: Efficacy of the combination papanicolaou smear and human papillomavirus testing in primary cervical screening: A prospective cohort study in Newfoundland
. Unpublished Study 1997; 1-19.

64. Ley C, Bauer HM, Reingold A *et al.* Determinants of genital human papillomavirus in young women. Journal of the National Cancer Institute 1991; 83:997-1003.

65. Young T, McNicol P, Beauvais J. Factors associated with human papillomavirus infection detected by polymerase chain reaction among urban Canadian Aboriginal and non-Aboriginal women. Sexually Transmitted Diseases 1993; 24(5):293-8.

66. Villa LL, Franco EL. Epidemiological correlates of cervical neoplasia and risk of human papillomavirus infection in asymptomatic women in Brazil. Journal of the National Cancer Institute 1989; 81:332-40.

67. Meilzynska I, Mclachlin MC, Lurincz A. Digene HPV test featuring hubrid capture technology: a new highly sensitive test for detecting HPV DNA in clinical specimens. McLachlin MC LA. Digene Corporation and Dept of Pathology, Victoria Hosp.London, Ont. 1-11.

68. Schlecht N, Franco E, Pintos J, Kowalski L. Effect of smoking cessation and tobacco type on the risk of cancers of the upper aero-digestive tract in Brazil. Epidemiology 1999; 10(4):412-8.

69. Kjaer S, Teisen C, Birthe J, et al. Risk factors for cervical cancer in Greenland and Denmark: A population-based cross-sectional study. International Journal of Cancer 1989; 44:40-7.

70. SAS Institute Inc. Proprietary Software Release 6.12 TS055 . Cary, NC, USA: 1989.

71. SPSS Inc. Proprietary Software Release 10.05. Copyright SPSS Inc. 1999.

72. Gardener M, Altman D. Statistics in medicine. Confidence intervals rather than P values: estimation rather than hypothesis testing. Brithish Medical Journal 1986; 292:746-50.

73. Abramson J, Cahlinger P. USD Inc., Computer Programs for epidemiologists. PEPI version 3. Stone Mountain, Georgia: 1999.

74. Mills C, Stephens T, Wilkins K. Summary report of the workshop on data for monitoring tobbaco use. Chronic Diseases in Canada 1994; 15(3):105-10.

75. Inscyte Corporation. CytoBase Annual Report. Cervical Cytology Database Statistics 1999; 3(2):1-15.

76. ACOG Committee Opinion. Routine cancer screening. American College of Obstetrics and Gynecology, Report 1997; 185, pgs1-5.

77. Hennekens C, Buring J. Analysis of Epidemiologic studies: Evaluating the role of bias. Epidemiology in Medicine. 1 edition. Boston: Little, Brown and Company, 1987: 272-86.

78. HPV Summit 1999. New approaches to the detection and elimination of cervical cancer. Chamonix, France: 1999.

79. Modern Epidemiology. Greenland S, Rothman K. Measures of effect and measures of association. 2 edition. Vol. 3. Boston: Lippincott-Raven, 1998: 29-46.

80. Wheeler C, parmenter C, Hunt W *et al.* Determinants of genital human papillomavirus infection among cytologically normal women attending the university of New Mexico student health centre. Sexually Transmitted Diseases 1993; 20(5):286-9.

81. Becker TM, Wheeler C, McGough N, Jordan S, Dorin M, Miller J. Cervical Papillomavirus infection and cervical dysplasia in Hispanic, Native American and non-Hispanic white women in New Mexico. American Journal of Public Health 1991; 81(5):582-6.

82. Kjaer S, de Villiers EM, Caglayan H, Svare E, et al. Human papillomavirus, Herpes simplex virus and other potential risk

factors for cervical cancer in a high-risk area (Greenland) and a low-risk area (Denmark) - a second look. British Journal of Cancer 1993; 67:830-7.

83. Johnson K, Canadian Task Force on Periodic Health Examination. Periodic Health Examination, 1995 Update: 1. Screening for human papillomavirus infection in asymptomatic women. Canadian Medical Association Journal 1995; 152(4):483-90.

APPENDICES

Appendix 1 – Queens University Ethics Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD REVIEW APPROVAL

Queen's University, in accordance with the "Guidelines on Research Involving Human Subjects, 1987," prepared by the Medical Research Council, requires that research projects involving human subjects be reviewed annually to determine their acceptability on ethical grounds.

A Research Ethics Board composed of:

Dr. A.F. Clark	Head and Professor, Department of Biochemistry, Professor, Department of Pathology, Faculty of Health Sciences, Queen's University (Chair)
Dr. B. Appleby	Departmental Assistant, Bioethics, Kingston General Hospital Instructor, Department of Family Medicine, Queen's University
Dr. M. Godwin	Associate Professor, Department of Family Medicine, Queen's University Associate Professor, Department of Community Health & Epidemiology Research Director, Department of Family Medicine, Queen's University
Dr. S. Irving	Psychologist, St. Mary's of the Lake Hospital
Ms. S. Laschinger	Assistant Professor, School of Nursing, Queen's University
Dr. J. Low	Professor, Department of Obstetrics and Gynaecology, Queen's University and Kingston General Hospital
Ms. F. O'Heare	Director, Risk Management Services, Kingston General Hospital Assistant Professor (Adjunct) School of Nursing, Queen's University
Dr. J. Parlow	Associate Professor, Department of Anaesthesia Assistant Professor, Department of Pharmacology & Toxicology, Queen's University
Dr. W. Racz	Professor, Department of Pharmacology & Toxicology, Queen's University
Dr. J. Rapin	Assistant Professor, Department of Emergency Medicine, Queen's University
Dr. M. Schumaker	Professor, Department of Religious Studies, Queen's University
Dr. L. Seymour	Co-Director, IND Program, NCIC Clinical Trials Group Associate Professor, Department of Oncology, Queen's University
Dr. S.J. Taylor	Bioethicist, Faculty of Health Sciences, Queen's University and Kingston General Hospital; Assistant Professor, Department of Family Medicine, Queen's University
Dr. G. Torrible	Community Member

has examined the protocol and revised consent form for the project entitled **"Human papilloma virus and cervical dysplasia in Nunavut"** as proposed by Dr. K. Aronson and Ms. S. Healey of the Department of Community Health and Epidemiology at Queen's University and considers it to be ethically acceptable. This approval is valid for one year. If there are any amendments or changes to the protocol affecting the subjects in this study, it is the responsibility of the principal investigator to notify the Research Ethics Board. Any adverse events must be reported to the Chair within 48 hours.

Albert F. Clark — Chair, Research Ethics Board

Feb 1, 1999 — Date

ORIGINAL TO INVESTIGATOR - COPY TO DEPARTMENT HEAD- COPY TO HOSPITAL(S) - PAT - FILE COPY

EPID-067-99
99-01-18

Appendix 2—Research License

Nunavummi Qaujisaqtulirijikkut / Nunavut Research Institute
Box 1720, Iqaluit, NT X0A 0H0 phone:(867) 979-4108 fax: (867) 979-4681 e-mail: slcnri@nunanet.com

SCIENTIFIC RESEARCH LICENCE

LICENCE # 0500499N-M AMENDED

ISSUED TO: Sylvia Healey
Community Health Department
Queens University
Abramsky Hall, Queen's University
Kingston, Ontario
K7L 3N6 Canada
613-533-8116

TEAM MEMBERS: Dr. Kristan Aronson, Dr. Yang Mao

AFFILIATION: Queens University

TITLE: Study on Human Papilloma Virus (HPV) and Abnormal Pap Tests in NT.

OBJECTIVES OF RESEARCH:
Cervical Cancer is the most common occurring femal cancer in the Baffin Region and there are indications that cervical cancer rates are higher in the NWT than elsewhere. During a study period from 1991 to 1994, when approximately 30,000 pap tests were done in the NWT a much higher proportion of "Abnormal" tests were found, than was expected. In particular, the most abnormal results were found in the Inuit and Dene. The Baffin Regional Health and Social Services Board in collaboration with Queens University is conducting a study to research the presence of certain strains of a virus that is thought to have some involvement with the development of cancer of the cervix, in the women in Nunavut, and whether this virus is present when there are abnormal pap test results. If we find that this virus is present in most of the abnormal pap tests, then consideration could be given to include HPV screening into the Cervical Cancer Screening program.

DATA COLLECTION IN NT:
DATES: February 01, 1999 - December 31, 1999
LOCATION: Arctic Bay, Broughton Island, Cape Dorset, Clyde River, Grise Fiord, Hall Beach, Igloolik, Iqaluit, Pangnirtung, Resolute Bay, Sanikiluaq, Arviat, Baker Lake, Repulse Bay, Resolute Bay, Pond Inlet, Kimmirut, Nanisivik, Coral Harbour, Rankin Inlet

Scientific Research Licence 0500499N-M AMENDED expires on December 31, 1999
Issued at Iqaluit, NT on May 11, 1999

Sharon Troke
Science Advisor

Appendix 3—Letter of Instruction to BRHSSB Staff from the CEO

BAFFIN REGIONAL HEALTH
& SOCIAL SERVICES BOARD
BAFFIN REGIONAL HOSPITAL

Jarvis L. Hoult, B.A., M.H.A., CHE
Chief Executive Officer

INTER-OFFICE MEMORANDUM

REFERENCE:

DATE: 22 February 1999

TO: Distribution List

SUBJECT: **Collaborative Study on Human Papilloma Virus and Cervical Dysplasia**

The Baffin Regional Health and Social Services Board and Baffin Regional Hospital is participating in the above study with Queen's University and Sylvia Healy. This study has been designed to determine the prevalence of HPV types associated with high or intermediate risk for cervical cancer in women in Nunavut; and, to determine what proportion of females with "high/intermediate risk HPV strains" have cervical dysplasia.

The research has been endorsed and approved by the Nunavut Research Institute with the concurrence of the Baffin Regional Health and Social Services Board.

Ms Healy has prepared the attached protocol sheet which provides the necessary directions to all staff who will be involved in this study. Should you have any questions, please direct them to Sylvia at the number indicated.

Thank you for your support and assistance in this important study.

DISTRIBUTION LIST:

All Medical Staff	**All Community Health Centers/NIC**
Laboratory	**Central Stores**

CC: Dr. Tim Cran, Chief of Staff
Dr. C. MacNeil, Director, Medical Affairs
Mr. Doug Sage, Director, Community Services
Ms. Marsha Duggan, Manager, Patient Services Hospital
Mr. Ainiak Korgak, Director, Health Protection Programs
Mr. Owen Partridge, Director, Operations and Support Services

Appendix 4a – Information for Participants - English

Baffin Regional Health Services

Dear Participant,

The Baffin Regional Health and Social Services Board and Queens University are conducting a study to research the presence of certain strains of Human Papilloma Virus in women in Nunavut, and whether this virus is present when there are abnormal pap test results. The aim of this study is to determine if HPV screening will aid with better diagnosis of Cervical Cancer.

We would like to ask if you would participate in this study.
To do so, you would need to:

1. consent to the use of part of the sample taken for your "pap test" so that we can test for the presence of this virus.
2. Consent to the use of your pap test result .
3. Complete the short questionnaire.

Participation in this study is voluntary. Please be assured that whether or not you choose to participate in the study, you usual medical care will not be affected in any way

If you are willing to participate, please sign the attached consent form. You may contact the investigators at any time for more information. Please ask your physician or Community Health Nurse to help put you in touch with Sylvia Healey or phone her at 613-533-8116. Call collect.

The duration of the study is expected to be less than two years and we may need to contact you during this time to clarify any details on the questionnaire.

Any information you provide is confidential and will be combined with data from other participants so that no individual can be identified when the data is analysed. Access to the data will be limited to the investigators in this study. Your participation will contribute to increasing the knowledge needed to prevent cancers in the future.

You can keep this letter and a copy of the consent form for your information.
Thank you for your help.

Sincerely

Sylvia Healey
Research Coordinator

Appendix 4b — Information for Participants - Inuktitut

ᕿᑭᖅᑖᓗᒻᒥ ᐋᓐᓂᐊᖅᑐᓕᕆᓂᒃᑯᑦ ᖃᒪᒃᑯᑦ
Baffin Regional Health Services

ᐃᓚᒋᔭᐅᔪᑦ,

ᕿᑭᖅᑖᓗᒻᒥ ᐋᓐᓂᐊᕐᓂᓕᕆᓂᕐᒧᑦ ᐊᒻᒪ ᐃᓅᓯᓕᕆᓂᕐᒧᑦ ᑲᑎᒪᔨᖏᑦ ᐊᒻᒪ ᑯᐃᓐ ᓯᓚᑦᑐᓴᕐᕕᐊᕐᔪᐊᓗ ᖃᐅᔨᓴᕈᑕᐅᔭᕐᓇᓂᐊᕐᑐᒥᒃ ᐊᖅᑭᒃᓯᐃᕙᓪᓕᐊᔪᒃ ᐊᓐᓂᐊᖅᑖᕈᑕᐅᓯᓇᔭᐅᕙᑦᑐᖅ ᐱᔾᔪᑎᒋᓪᓗᒍ ᐃᓪᓕᐊᕐᑯᑦ ᐊᕐᓇᓂ ᓄᓇᕗᒥ, ᐊᒻᒪ ᑖᓐᓇ ᐊᓐᓂᐊᖅ ᑕᑯᕙᐅᓯᒪᓪᓚᕆᒻᒪᑦ ᓇᓪᓕᖕᒧᑦᑕᖅᑎᓪᓗᒍ ᐃᓪᓕᐊᒥᑦ ᖃᐅᔨᓴᕈᑎᒥᓂᕐᓂ. ᑖᓐᓇ ᖃᐅᔨᓴᕈᑕᐅᓂᐊᖅᑐᖅ ᖃᐅᔨᔾᔭᑕᐅᒐᓯᐊᕐᒪᑦ ᐱᓪᓕᐊᒃᑯᑦ ᖃᐅᔨᓴᕐᓂᕆᔭᕗᑦ ᑲᒪᒋᔭᐅᒍᓐᓇᓂᖅᓴᐅᒐᔭᕐᑕᕆᐊᖓ ᐊᓐᓂᐊᖃᖅᑐᖃᓕᕐᓂᖅᐸᑦ ᐃᓪᓕᐊᒃᑯᑦ.

ᐊᐱᕆᔪᒪᕙᒋᑦ ᐃᓚᒋᔭᐅᔪᒪᒐᔭᕐᒪᖔᖅᐱᑦ ᑕᐃᕙᓂ ᖃᐅᔨᓴᕈᑕᐅᔪᓂᒃ ᐃᓚᒋᔭᐅᓂᐊᕈᕕᑦ, ᐃᒪᐃᒋᐊᖃᕋᔭᖅᐳᑎᑦ:

1) ᐊᑎᓕᐅᕈᕕᑦ ᑕᐃᒪ ᐱᖅᓯᕕᐅᓐᓂᕈᕕᑦ "ᐃᓪᓕᐊᓐᓂᑦ ᖃᐅᔨᓴᕈᑕᐅᓂᐊᖅᑐᒥᑦ" ᖃᐅᔨᓴᕈᑎᒋᓂᐊᖅᓯᑎᒍ ᐊᓐᓂᐊᖅᑕᕈᑕᐅᕙᑦᑐᒧᑦ.
2) ᐊᑎᓕᐅᕈᕕᑦ ᐊᑐᖅᑕᐅᒐᔭᖅᑐᖅ ᐃᓪᓕᐊᓐᓂᑦ ᐱᖅᓯᕕᐅᓂᒥᓂᑦ ᐊᑐᖅᑕᐅᒍᓐᓇᕋᔭᖅᑐᖅ ᖃᐅᔨᖅᑕᐅᔪᑦ ᖃᓄᐃᑦᑐᓂᖓᓂᒃ.
3) ᐊᐱᖅᑯᑎᓕᐊᕆᓯᒪᔪᖅ ᑭᐅᖃᑦᑕᖅᓗᒍ

ᐃᓚᒋᔭᐅᔪᒪᒍᕕᑦ ᖃᐅᔨᓴᕈᑕᐅᔪᓂ ᐊᖏᖅᓯᒪᓂᑦ ᒪᓕᒡᓗᒍ ᐃᓚᒋᔭᐅᒐᔭᖅᑐᑎᑦ. ᖃᐅᔨᒪᓂᐊᖅᐳᑎᑦ ᐃᓚᒋᔭᐅᔪᒍᕕᑦ ᐃᓚᒋᔭᐅᔪᖏᒃᑯᕕᑦ, ᖃᐅᔨᓴᕈᑎᒥ ᐊᑭᓕᒋᐊᖅᓴᔭᕐᖏᑦᓯᐊᖅᑐᑎᑦ

ᐃᓚᒋᔭᐅᔪᒪᒍᕕᑦ, ᐊᑎᓕᐅᖅᓗᒍ ᐸᐃᑉ ᐊᖏᕈᑎᐅᔪᖅ. ᑐᑭᓯᒋᐊᒃᑲᓐᓂᕈᒪᒍᕕᑦ, ᐊᐱᖅᓱᐊᒃᑲᓐᓂᕈᓐᓇᖅᑕᐃᑦ ᓗᑦᑖᓇᔭᐃᑦ ᐅᕝᕙᓗᓐᓃᑦ ᓄᓇᓕᐅᑦ ᐃᓗᐊᓂ ᐊᓐᓂᐊᓯᐅᖅᑎ ᑐᑭᓯᒋᐊᖅᑎᒋᔨᓐᓇᖅᓴᖅᑎᑦ ᓯᐅᕝᕕᐊ ᕼᐄᓕᒧᑦ, ᖃᐅᔨᓴᖅᓂᒧᑦ ᑐᑭᒧᐊᕆᔨᐅᔪᖅ. ᖃᐅᔨᒋᐊᕐᕕᐅᑐᐃᓐᓇᕆᐊᖃᖅᓴᔾᔪᑎᑦ ᑐᑭᓯᒋᐊᒃᑲᓐᓂᕆᐊᖃᕐᓂᕈᑦᑕ ᐊᐱᖅᑯᑎᐅᑉ ᐃᓗᐊᓂ ᑭᐅᔭᒥᓂᕆᔭᖅᓂᒃ. 613-533-8116. ᑕᕝᕗᖓ ᐊᑭᓕᖅᑕᐅᑎᓪᓗᒍ.

ᐊᖅᖁᒃ ᒪᕐᕈᒃ ᑐᓪᓚᓂ ᖃᐅᔨᓴᖅᓂᖅᑲᕐᓂᐊᖅᒪᑕ, ᐃᓚᓐᓂᒃ ᐊᐱᕆᒍᒪᓐᓂᕈᑦᑕ ᑐᑭᓯᒋᐊᖅᓗᑕ ᑭᐅᓯᒪᔭᕐᓂᒃ ᐊᐱᖅᑯᑎᐅᑉ ᐃᓗᐊᓂᑦ ᖃᐅᔨᒪᖁᔨᕗᒍᑦ.

ᑭᐅᔾᔪᑏᓕᒫᖅᓯᐊᑎᑦ ᑭᒃᑯᑐᐃᓐᓇᕐᓄᑦ ᑕᑯᔭᖅᓯᒪᓐᖑᒐᖏᓪᓚᑕ ᖃᐅᔨᒪᖁᔨᔪᒍᑦ. ᐃᓚᒋᓕᐅᑎᓂᐊᖅᑐᐃᑦ ᓄᐊᑉᐸᓪᓕᐊᔪᑦ ᑭᒃᑯᑐᐃᓐᓇᖅᓃᓐᖏᒪᖅᑐᑦ ᓇᓗᓇᐃᖅᓯᒪᔾᔭᐅᑎᓪᓗ ᑭᓇᐅᓐᓂᕆᐊᖓ ᖃᐅᔨᖅᑕᒥᓂᖅ. ᐃᓚᒋᔭᐅᔪᓐᓇᖅᓂᕆᔭᐃᑦ ᐊᑐᕐᓂᖅᑲᒻᒪᕆᓐᓂᐊᖅᑐᖅ ᖃᐅᔨᔾᔪᑕᐅᒃᑲᓐᓂᕐᓂᐊᕐᒪᓪᓗ ᐊᑐᕐᓂᖅᑲᒻᒪᕆᓐᓂᐊᕆᓪᓗᓂᓗ ᐊᓐᓂᐊᖅᑕᖃᑦᑕᓂᐊᖅᑐᓄᑦ ᓯᕗᓂᒃᓴᓐᓂ.

ᑖᓐᓇ ᑎᑎᖅᑲᖅ ᐱᑦᔪᓐᓇᖅᑕᐃᑦ ᐊᒻᒪ ᐊᖏᕈᑎ ᐊᑎᓕᐅᖅᓯᒪᔭᐃᑦ ᐱᑦᔪᓐᓇᕐᒥᔭᐃᑦ ᖃᐅᔨᔾᔪᑎᒋᓂᐊᖅᕕᒋᑦ ᖁᔭᓐᓇᒦᒃ ᐃᑲᔪᖅᓯᐃᑦ.

ᖁᔭᓐᓇᒦᒃ ᐃᑲᔪᕈᓐᓇᖅᓯᐃᑦ.

ᑕᕝᕙᐃᓐᓇᖅᑐᖅ,

Sylvia Healey
ᓯᐅᕝᕕᐊ ᕼᐄᓕ
ᖃᐅᔨᓴᖅᓂᒧᑦ ᑐᑭᒧᐊᕆᔨ

ᕿᑭᖅᑕᓗᒻᒥ ᐋᓐᓂᐊᖅᑐᓕᕆᔨᒃᑯᑦ ᖃᒪᔪᑦ
Baffin Regional Health Services

Study of Human Papilloma Virus and Cervical Dysplasia

CONSENT FORM

The research procedures described in the attached letter have been explained to me and any questions that I have asked have been answered to my satisfaction. I know that I may now or in the future ask any questions I have about the research procedures. I have been assured that records relating to my care will be kept confidential and that no information will be released that will disclose my personal identity without my permission.

I understand that I am free to withdraw from the study at any time. I also understand that if I withdraw from the study the care I get from the Health Board will not be affected.

I ______________________________ consent to participate in the Human Papilloma Virus and Cervical Dysplasia study.
Investigators: Sylvia Healey, Dr Kristan Aronson, Dr Yang Mao.

I consent to the use of part of the sample taken with my pap test for testing for Human Papilloma Virus.

I consent to the use of my pap test result and any follow-up-up test results related to my pap tests.

I consent to completing the questionnaire. I understand that my personal data will be kept confidential.

______________________________ Signature

______________ Date

______________________________ Witness

______________ Date

Name: ______________________ MCP# ______________
Address ______________________
____
____

Appendix 5a—Consent Form - Inuktitut

ᕿᑭᖅᑖᓗᒻᒥ ᐋᓐᓂᐊᖅᑐᓕᓂᕐᒧᑦ ᑲᒪᔩᑦ
Baffin Regional Health Services

<u>ᖃᐅᔨᓴᕐᓂᖅ ᐃᓪᓕᐊᒃᑯᑦ ᐋᓐᓂᐊᖑᔪᒥᒃ</u>

ᐊᖏᕈᑎ ᐸᐃᑉᒥ

ᖃᐅᔨᓴᕈᑎᑦ ᐃᓗᓕᖏᑦ ᓇᓗᓇᐃᔭᖅᑕᐅᓯᒪᔪᑦ ᐃᓚᒋᓕᐅᑎᓯᒪᔪᒥ ᐸᐃᑉᒥ ᑐᑭᓯᓇᓕᖅᑎᑕᐅᕙᑕᖅᑐᑦ ᐅᕙᓄᑦ ᐊᐱᖅᑯᑎᒃᑲᓗ ᑭᐅᔭᐅᕙᒃᑕᕆᖅᑐᑦ ᓈᒻᒪᒋᓪᓗᒋᓪᓗ. ᖃᐅᔨᒪᔪᖓ ᐊᐱᖅᑯᑎᕐᑲᓕᕐᓂᕈᒪ ᒫᓇᒃᑯᑦ ᓯᕗᓂᓂᐊᖅᑕᓂᓪᓘᓐᓃᑦ ᐊᐱᓕᔪᓇᕋᒪ ᖃᐅᔨᓴᕐᓂᐅᑉ ᒥᑦᓵᓄᑦ. ᖃᐅᔨᑎᑕᐅᕙᑕᖅᑐᖓ ᓄᐊᑕᐅᔪᑦ ᐅᕙᓂᑦ ᑭᒃᑯᐃᓇᕐᓄᑦ ᑕᑯᔭᐅᔪᒪᕐᓂᐊᖅᓯᒪᖏᑦᑐᐊᖏᑦ ᐊᒻᒪ ᓄᐊᑕᐅᓯᒪᔪᑦ ᐅᕙᓂᑦ ᑭᒃᑯᑮᔭᕐᓄᑦ ᑐᓂᔭᐅᔭᖏᑦᑐᐊᖏᑦ ᐊᖏᓚᐅᖏᓐᓂᓕᒪᓂ.

ᑐᑭᓯᒪᔪᖓᓗ ᖃᖓᒃᑯᑐᐃᓐᓇᖅ ᐃᓚᒋᔭᐅᔪᒪᙱᓐᓇᓂᐊᕐᓂᒪ ᖃᐅᔨᓴᕈᑎᐅᔪᒥ. ᑐᑭᓯᒪᔪᖓᑕᐅᖅ ᐃᓚᒋᔭᐅᔪᓐᓃᕐᓂᕈᒪ ᖃᐅᔨᓴᕈᑎᒥᑦ ᑲᒪᒋᔭᐅᓂᓕᕆᑦᑕᕋᐃᓐᓂᐊᕐᐱᖏᓐᒥ ᐊᑦᑐᖅᑕᐅᓂᖃᕐᔭᕆᐊᖏᑦ.

ᐅᕙᖓ____ ᐊᖏᖅᐳᖓ ᐃᓚᒋᔭᐅᔪᒪᓚᒪ ᐃᓪᓕᐊᒃᑯᑦ ᐋᓐᓂᐊᖅᑖᕆᔭᐅᓯᑦ ᖃᐅᔨᓴᕐᓂᕆᔭᖏᓐᓂ.

ᖃᐅᔨᓴᖅᑎᑦ: ᓯᐅᓪᕕᐊ ᕼᐃᓕ, ᔫᑦᑕᖅ ᑯᓇᑦᑕᖅ ᐊᐃᑯᓴᖅ ᐊᒻᒪ ᔫᑦᑕᖅ ᔭᓐ ᒪᐅ.

ᐊᖏᖅᐳᖓ ᐃᓚᒋᐊᕐᓂᑦ ᐱᖅᓯᕚᐅᓯᒪᓂᖕᓚ ᐃᓚᖓᓂᒃ ᖃᐅᔨᓴᖅᑕᐅᕙᓕᓪᓗᖓ ᐊᓂᐊᒥ ᖃᐅᔨᓴᖅᑎᓄᑦ

ᐊᖏᖅᐳᖓ ᖃᐅᔨᓴᕈᑕᐅᕙᓕᓂᖅᓱᖓ ᐃᓚᒋᐊᓂᑦ ᐱᖅᓯᕚᐅᔪᑎᒥᓂᖅ ᖃᐅᔨᓴᕈᑕᐅᕙᓗ ᐊᒻᒪ ᐊᓯᖏᑦ ᖃᐅᔨᒋᐊᒃᑲᓂᕈᑕᓕᖅᑭᖃᑦᑕᕙᓪᓗᒋᑦ ᖃᐅᔨᓴᕈᑎᒥᓃᑦ ᐃᓚᒋᐊᓂᑦ.

ᐊᖏᖅᐳᖓ ᐊᐱᖅᑯᑎ ᐱᔭᕇᕐᓂᐊᖅᑯ. ᑐᑭᓯᒪᒐᓗᐊᖓᓗ ᐅᕙᓂᑦᓕᖅᑐᖅ ᓄᐊᑕᐅᔪᑦ ᑭᒃᑯᑐᐃᓐᓇᕐᓄᑦ ᑕᑯᔭᐅᔪᓐᓇᖏᓐᓇᖏᑦᑐᐊᖏᑦ.

____
ᐊᑎᓕᐅᕐᕕᒃ

____
ᐅᓪᓗᖓ

____
ᖃᐅᔨᖅᑲᑕᐅᔪᖅ

____
ᐅᓪᓗᖓ

ᐊᑎᑦ: ______________________

ᑐᖅᑭᑎᑦ: _____________________

Appendix 6 – Questionnaire

ᖃᑭᖅᑕᓗᒍᒥ ᐊᓐᓂᐊᖅᑐᓕᕆᓂᖅᓯᒪᓂ ᑲᒪᒋᐊᓂ
Baffin Regional Health Services

Confidential when completed!

ᑭᐅᔭᐃᐃᓐᓇᓂᑦ ᑕᑯᔨᑦᓴᖅᓱᐊᖅᑐᑦ ᐊᖏᖅᓯᓚᖅᑐᑦ
ᐱᔨᖅᖃᕐᕕᒃ!

Study on Human Papilloma Virus and Cervical Dysplasia	ᖃᐅᔨᓴᓂᖅ ᐃᓕᓴᐊᐅᑎᑦ ᐊᓐᓂᐊᖅᑐᓕᕆᓂᖅ
This Questionnaire asks a variety of questions which may be related to your health. Please complete each question as best you can. If you any questions about the survey or would like help filling it out, please ask your doctor or nurse or call: _____ at _____ **Please return this questionnaire to your doctor or nurse.**	ᐅᓇ ᐊᐱᖅᑎᑎ ᖃᐅᔨᓴᓂᐊᓕᓐᓂᐊᖅᑐᑦ ᐊᐱᖅᑎᖃᖅᑐᑐᒃ ᑎᒥᐃᑦ ᖃᐅᔨᓴᓂᓕᕆᔨᒃᑯᓂᖅ ᓴᓇᓂᓕᕆᔨᒃᑯᓂᖅ ᐱᔨᖅᖃᕐᕕᒃ. ᐱᔨᖅᖃᖅᑲᓇᖅᑐᑦ ᐊᐱᖅᑎᑎᑦ ᑭᐅᔭᓕᖅᑕᕐᓂᒃ ᒪᓕᒐᓂᖅ. ᖃᐅᔨᓴᓂᐊᓕᓐᓂᐊᖅᑐᑦ ᐊᐱᖅᑎᑎᖃᐅᔨᒃᑯᑦ ᖃᐅᔨᓴᕐᓂᑎᑦ ᑲᑎᒪᔨᖅ, ᐃᓚᖓᑕᐅᓂᖅ ᑲᑎᒪᔨᓴᓂᐊᓕᕆᔨᒃᑯᑦ ᐊᐱᖅᑎᖃᖅᑐᑐᒃ ᓄᓇᕗᒻᒥᐅᑦ, ᐊᐱᖅᑎᑎᖃᐅᔨᒃᑯᑦ ᓄᓇᕗᑦ ᐊᐱᖅᑎᖃᖅᑐᑐᒃ ᐃᓕᓴᐅᔪᓂᖅ ᐊᐱᖅᑎᑎᖃᐅᔨᒃᑯᑦ ᐃᓕᓴᐅᔪᓂᖅ ᐊᐱᖅᑎᑎᖃᐅᔨᒃᑯᑦ ᐃᓕᓴᐅᔪᓂᖅ ᐅᖃᓕᒫ:_____ ᐅᕙᓂᑐᑦ: _____ ᐅᓇ ᐅᑎᖅᑎᑭᓕᒃ ᓄᓇᕗᓂᖅ ᐊᐱᖅᑎᖃᐅᔨᒃᑯᑦ ᐃᓕᓴᐅᔪᓂᖅ.
Guide to filling out this questionnaire: Please choose answers by marking an 'X' in the circle 'O' or writing in the space provided.	ᒪᓕᒐᓂᐊᓕᓐᓂᐊᖅᑐᑦ ᐊᐱᖅᑎᑎᑦ ᐱᔨᑦᑕᕙᓂᐊᓕᖅᑐᓂᖅ: ᓂᕈᐊᖅᓯᖏᓐᓂᕆᓂᑦ ᐱᔨᑦᓴᒃ ᐃᒪᐃᑐᓕᓴᐅᔪ "X" ᐊᓕᒪᓗᑭᑦ ᐃᓗᐊᓂ ᐊᐱᖅᑎᑎᑦ ᓴᓂᐊᓂ ᐅᓰᓄᓴᒃᑎᑦ ᑎᑎᕋᖏᓐᓂᑦᓯᓗᑦ ᐱᔨᑦᑎᑦ.

General Information			
	Month	*Day*	*Year*
1. Today's Date	/	/	
2. Is anyone helping you complete this questionnaire? O No O Yes Name: _____			

ᖃᐅᔨᒪᓕᒃᑲᓂᖅ			
	ᑕᕆᓂᖅ	ᐅᑉᓯᖅ	ᓂᕆᔨᖅ
1. ᐅᑉᓗᒥ	/	/	
2. ᐃᓕᓴᕐᓂᑎᑦ ᐊᐱᖅᑎᑎᓂᒃ?			
O ᐊᑦᓴ O ᐃ ᐊᑎᖅᓴ:_____			

3. When were you born?
Month *Day* *Yr*
/ /

4. What is your address?

5. Have you ever smoked before?
O No O Yes
If no, go to Question ᖃ

6. How old were you when you first started smoking cigarettes?
_____ years old

7. how many years in total did you smoke?
_____years

8. Of the entire time you smoked, how many cigarettes, on average, did you smoke per day?
_____ per day

Do you smoke cigarettes now?
O No → How old were you when you stopped smoking?

O Yes → ON average, about how many cigarettes do you smoke now?
_____ per day.

9. What was the highest grade of schooling including university that any member of your household went to?
_____

3. ᖃᓄᖅ ᐃᓚᖓᓂᕐᑭᑦ?
ᑕᕐᑭᖅᓄᖅ ᑎᑦᓴᖅᓄᖅ ᐊᑦᕿᔪᖅᓄᖅ
/ /

4. ᑐᖃᑭᑎᑦ ᓇᓂᓇᐃᑭᓐ

5. ᓯᓚᓕᐊᕐᑐᓕᐅᕐᓯᒪᐃᑦ?
0 ᐊᓚᖅ 0 ᐃ
ᐊᓚᑭᕈᐃᑦ ᐊᐱᕐᔪᑎᒍᓕᑦ 9ᒧᑦ.

6. ᓯᓚᓕᐊᕐᑐᓗᐅᕿᐃᑦ ᐊᑦᕿᔪᓕᓕᐅᕐᓯᒪᓴᐃᑦ

_____ ᐊᑦᕿᔪᒥᓂᖅ

7. ᐊᑦᕿᔪᑦ ᑲᑎᑦᓗᑭᑦ ᓯᓚᓕᐊᕐᑐᓕᕐᓯᒪᓕᕐᓂᑎᑦ

_____ ᐊᑦᕿᔪᑦ

8. ᓯᓚᓕᐊᕐᑐᑭᓇᓵᓕᒪᓵ, ᖃᑦᓯᓂᖅ
ᓯᓚᓕᐊᕐᑐᖃᑦᑕᕐᓯᒪᐃᑦ ᐅᑦᓗᑦ ᐊᑕᐅᓯᑦᒥ?

_____ ᐅᑦᓗᕐᓂ ᐊᑕᐅᓯᕐᓂ.

ᓯᓚᓕᐊᕐᑐᑐᖃᑦᑕᕐᑭᑦ ᒪᓇᓇ?
0 ᐊᓚᖅ -) ᖃᑦᓯᓂᖅ ᐊᑦᕿᔪᒥᖃᕐᓂᑎᑦ
ᓯᓚᓕᐊᕐᑐᑭᓇᐃᓕᓕᓂᕐᑭᑦ?
_____ ᐊᑦᕿᔪᒥᖃᕐᑎᑦᓗᓐᓄᖅ

0 ᐃ -) ᖃᑦᓯᓂᖅ ᓯᓚᓕᐊᕐᑐᑐᖃᑦᑕᕐᑭᑦ
ᐅᑦᓗᑦᒥ ᐊᑕᐅᓯᑦᒥ?

_____ ᐅᑦᓗᕐᓂ ᐊᑕᐅᓯᕐᓂ.

9. ᖃᑦᓯᐅᑦ ᐃᓕᓂᐊᕐᑕᐅᓯᒪᔪᕐᓂ
ᖃᓄᑦᓯᓂᕐᓂ ᓇᓯᒪᔪᓄᖅ ᐱᖃᓯᐅᑎᓂᓇᕐᓂᑐᓄᖅ
ᐃᓕᓂᐊᕐᓂᓯᒪᔪᖃᕐᓂᑦ ᓯᓕᑐᑦᓴᐱᓂᔪᑦᒥ.

_____