Prevalence and Age Distribution of Human Papillomavirus Infection in a Population of Inuit Women in Nunavik, Quebec

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Abstract

Objectives: **Our aim was to study the prevalence and age distribution of human papillomavirus (HPV) infection among Inuit women in Nunavik, northern Quebec, a population at high risk of cervical cancer.**
Methods: **We recruited a cohort of Inuit women seeking routine care and living primarily in four communities of the Nunavik region. Pap smears were done and cervical specimens were tested for HPV-DNA using the PGMY-Line blot assay.**
Results: **From January 2002 until December 2007, 629 women were recruited into the study and had their cervical specimens tested. Of 554 women with complete results, the overall and high-risk HPV prevalence were 28.9% and 20.4%, respectively. Multiple-type infections were observed in 40% of HPV-positive subjects. The most common HPV type was HPV-16 (n = 31), and other common high-risk types included HPV-31, HPV-58, and HPV-52. The most prevalent papillomavirus species were α-9 (60% of infections), α-3 (44%), and α-7 (31%). Age-specific prevalence of low-risk HPV, high-risk HPV, and overall HPV showed a U-shaped curve. Of women with baseline cytology, 6.5% had an abnormal result, either atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion (LSIL), or high-grade intraepithelial lesion (HSIL). HPV-16, HPV-31, and HPV-58 were some of the most common high-risk types detected in both LSIL and HSIL specimens.**
Conclusions: **Overall and high-risk HPV prevalence was elevated in this population of Quebec Inuit women when compared with other populations that have been studied in Canada. Different HPV types seem to be important as contributors to the overall burden of infection and to the presence of cervical abnormalities, which may have implications for developing cervical screening and vaccination programs.** (Cancer Epidemiol Biomarkers Prev 2008;17(11):3141–9)

Introduction

Human papillomavirus (HPV) infection has been recognized as the central causal agent of cervical cancer (1-4), which represents the second most common neoplastic malignancy of women worldwide (4). Despite widespread efforts to ascertain the current burden of HPV infection in populations across diverse regions (5), little systematic data are available on the prevalence of HPV infection in Aboriginal populations, who are often considered a high-risk group for cervical cancer. In particular, Inuit women in Canada and Quebec show elevated incidence rates of cervical cancer (6-8) and higher mortality rates (7) when compared with the general Canadian and Quebec populations. This report provides a baseline assessment of the prevalence and age distribution of HPV infection in a population of Inuit women living in Nunavik, Quebec. We also describe the spectrum of cervical lesions detected in the population and the patterns of pairwise associations between HPV types in women with multiple infections.

Patients and Methods

Study Population and Design. The subjects included in this study are part of a prospective cohort of Inuit women who live in communities located along the coast of Ungava Bay in the geographic region of Nunavik, northern Quebec (58°N, 68°W; Fig. 1). The sampling frame for the study consisted of all women ages 15 to 69 y presenting for a regularly scheduled Papanicolaou (Pap) smear from January 2002 to December 2007 at a clinic in one of the four participating communities. Nurse practitioners systematically asked nonenrolled women if they wished to participate in the study. Written consent was obtained from interested and eligible women. A small number of additional women were recruited through a mobile mammography screening program from August to October 2004. Women were eligible for the study if they: (*a*) self-identified as Inuit; (*b*) were ages 15 to 69 y; (*c*) were born in Nunavik, Quebec; (*d*) had

Received 7/9/08; revised 8/18/08; accepted 8/25/08.

Grant support: Canadian Institutes of Health Research (CIHR) and a Team Grant on HPV Infection and Associated Diseases from the same agency. L. Hamlin-Douglas was supported by CIHR, McGill University Health Centre, and McGill University Department of Medicine. E.L. Franco was supported by a Distinguished Scientist salary award from the CIHR. M. Roger is recipient of a Research Scholar award from the Fonds de la recherche en Santé du Québec. P. Brassard was supported by a CIHR new investigator career award.

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doi:10.1158/1055-9965.EPI-08-0625

Figure 1. Location of Nunavik, Quebec in North America. Adapted from the map of the Nunavik Tourism Board.

an intact uterus and no current referral for hysterectomy; (*e*) did not report the use of vaginal medication in the previous 2 d; (*f*) did not report treatment for cervical disease in the previous 6 mo; and (*g*) were no more than 12 wk pregnant. Ethics approval was obtained from the McGill University Institutional Review Board, the Centre Hospitalier de l'Université de Montréal, and the Tulattavik Health Centre, which offers services to the study population.

Sociodemographic and Behavioral Data. A baseline questionnaire collected information on sociodemographic characteristics, sexual behavior, reproductive and contraceptive history, and some lifestyle factors. With the help of the local community, the study instrument was adapted from a previously validated questionnaire developed by one of us (EF) for use in HPV community-based surveys and was provided in English, French, and Inuktitut. The Inuktitut version was back-translated into English to ensure accuracy of translation. Additional information on pertinent risk factors was retrieved from medical charts by members of the research team.

Specimen Collection. Cervical specimens were systematically collected at accrual and at each follow-up visit requiring a Pap test. Only data from the baseline visits are included in this prevalence analysis. Ectocervical and endocervical cells were collected with a Dacron swab and used to do a Pap smear. Afterwards, the swab was immersed in a tube containing 1.5 mL of a methanol-based liquid, PreservCyt (Cytyc Corporation), which preserves the integrity of epithelial cells. Cell suspensions were kept at 4°C until they were transported on wet ice to Montreal for HPV typing. The cervical smear slides were transported to Quebec City and read blindly by an experienced cytopathologist. Cytopathology reports were based on the Bethesda system for cytologic diagnoses (9).

HPV DNA Detection. After cervical cell suspensions were centrifuged at 13,000 × *g* for 15 min at 22°C, the supernatant was discarded, the cell pellet was left to dry, and it was resuspended in 300 μL of 20 mmol/L Tris buffer (pH 8.3). DNA was purified with Master pure (ref. 10; Epicentre). The quality of DNA samples was assessed by amplification of a 268-bp region of the

human β-globin gene using GH20 and PC04 primers. HPV-DNA was detected on β-globin by PCR amplification using PGMY09-PGMY11 primers and quality-controlled Line blot assay (Roche Diagnostics), as described previously (11). HPV genotyping was accomplished with oligonucleotide probes to identify 26 genital HPV types: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 66, 68, 73, 82 (IS39 and MM4 subtypes), 83, and 84. After April 2004, an extended line blot strip was used that probed for an additional 10 genotypes: 61, 62, 64, 67, 69, 70, 71, 72, 81, and 89 (CP6108). Standard precautions were taken to prevent contamination.

The following HPV types were considered to be of high oncogenic risk (3): 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82. Low-risk and unclassified types were grouped together and included 6, 11, 40, 42, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 81, 83, 84, and 89 (CP6108; refs. 3, 12).

Statistical Analysis. Coverage of the target population was evaluated for the four principal study communities using 2001 census data. We calculated the prevalence of HPV infection by type, oncogenic risk grouping, and phylogenetic α-papillomavirus species. Age-specific prevalence was calculated for women ages 15 to 19 y and by 10-y age categories thereafter. We used Wilson's method with a continuity correction (13) to calculate 95% confidence intervals (95% CI) for type-specific HPV prevalence. CIs are reported only for HPV types whose prevalence had a relative SE <50%. For prevalence by type and phylogenetic group, coinfections contributed to multiple categories.

We investigated whether any joint infections occurred with a greater frequency than would be expected under the assumption of no association between types (14). Expected frequencies were compared with observed frequencies to detect types that co-occur. We used the Fisher's exact test to identify possible patterns in type associations rather than to formally test the significance of these associations.

All analyses were done using SAS Statistical Software version 9.1.

Results

Characteristics of the Study Population. At the time of the analysis, 629 women had been recruited into the cohort. A total of 554 women met the eligibility criteria, had a baseline questionnaire and an adequate HPV-DNA test result, and were included in the analysis of prevalence at baseline. The mean age of participating women was 35.5 years (SD, 14.4) and women ranged in age from 15 to 69 years (median, 32.2). The average age at first sexual intercourse was 15.5 years (SD, 2.5), and the mean number of live births was 3. Approximately 71% of women for whom information on Pap history was available (n = 460) had a Pap test in the previous 3 years.

Coverage of Target Population. The coverage of the target population for the four individual communities was between 42% and 71%. The combined coverage for these communities was 57%. The study captured 58% of the 15 to 19 year olds, 68% of the 20 to 24 year olds, 59% of the 25 to 44 year olds, 38% of the 45 to 54 year olds, and 66% of the 55 to 64 year olds in these communities. The age distribution in the recruited subjects mirrored that in the target population overall and for each individual community.

HPV-DNA Prevalence. HPV-DNA was detected in 28.9% of subjects (n = 160), and 32 different HPV types were identified. The most common HPV types detected (Fig. 2) were HPV-16 (5.6%), HPV-31 (3.6%), HPV-61 (3.6%), and HPV-84 (3.1%). Of the HPV-positive women, 70.6% (n = 113) were infected with at least one high-risk type and 46.3% (n = 74) had exclusively high-risk types, for an overall high-risk prevalence of 20.4%. Infections with HPV-16 or HPV-18 (n = 40) made up 25% of all HPV infections and 35.3% of all high-risk infections. The most common high-risk types (Fig. 2) after HPV-16 and HPV-31 were HPV-58 (n = 15; 2.7%) and HPV-52 (n = 13; 2.3%). HPV-18 was detected in 1.6% of subjects (n = 9). Among low-risk types, HPV-6 was detected in only 0.4% of subjects (n = 2) and HPV-11 was not detected in this population. The most common low-risk types after HPV-61 and HPV-84 (Fig. 2) were HPV-62 (n = 16; 2.9%) and HPV-67 (n = 12; 2.2%). The most prevalent papillomavirus species overall (Table 1) were α-9 (n = 96; 60% of infections), α-3 (n = 71; 44.4%), and α-7 (n = 49; 30.6%).

The age-specific prevalence of HPV infection (Fig. 3) was highest among women <20 years old (58%) and decreased with age until there was a second peak of 28.1% in women ages 60 to 69 years. High-risk types were more commonly detected than low-risk types in all age groups except for women >40 years old, among whom low-risk types were twice as prevalent as high-risk types (Fig. 4). Similarly to overall HPV infection, the age-specific high-risk HPV prevalence showed a U-shaped curve, with the highest prevalence in women <20 years (46.9%), decreasing prevalence with age, and a second peak in women ages 60 to 69 years (12.5%). The age-specific low-risk HPV prevalence pattern had a more pronounced U-shape than for overall or high-risk prevalence.

The prevalence of single-type infections was 17.3% (n = 96) in the overall study population and 60% among HPV-positive women. Among these women, the most common high-risk HPV types were HPV-16 (n = 13), HPV-52 (n = 7), and HPV-31 (n = 6; Table 1). The most common low-risk types were HPV-61, HPV-70, HPV-84, and HPV-89 (n = 6 for each). The prevalence curve for single infections was U-shaped, with about 20% prevalence in the youngest and oldest age groups, but a decrease in prevalence among 40- to 49-year-olds (10.4%) and 50- to 59-year-olds (13.5%). High-risk types were common in single infections of women <40 years of age (Fig. 4), but made a smaller contribution to single infections in older women.

Multiple-type infections were observed in 64 women (11.6% of the study population, 40% of HPV-positive women). Most multiple infections involved both high-risk and low-risk types (60.9%) and less frequently only high-risk types (26.6%) or only low-risk types (12.5%; Fig. 4). The prevalence of multiple infections was markedly higher among women age ≤20 years (39.5%) than in women of other age groups, and most of these infections involved at least one high-risk type. Overall, the most common HPV types involved in multiple infections (Table 1) were HPV-16 (n = 18), HPV-31 (n = 14),

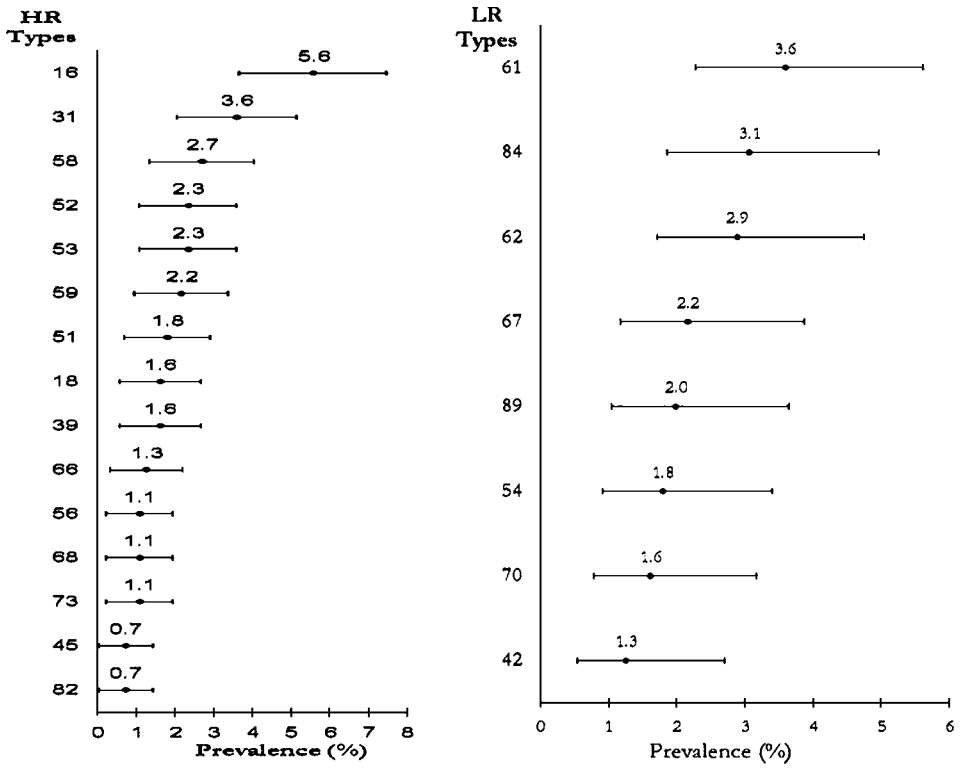

Figure 2. Detection of HPV types among all subjects (n = 554). Point estimates with 95% CI are displayed for the most common high-risk and low-risk HPV types. HPV types with a relative SE of more than 50% are not presented. Listed here are the other HPV types that were tested for, with the number of infections in parentheses: HPV-26 (n = 1), HPV-33 (n = 3), HPV-35 (n = 2), HPV-6 (n = 2), HPV-11 (n = 0), HPV-40 (n = 1), HPV-55(n = 4), HPV-64 (n = 0), HPV-69 (n = 0), HPV-71 (n = 0), HPV-72 (n = 2), HPV-81 (n = 3), and HPV-83 (n = 2). HR, high-risk; LR, low-risk.

HPV-61 (n = 14), and HPV-62 (n = 12). The most common species involved in multiple infections were α-9 (n = 61; 95% of multiple type infections), α-3 (n = 45, 70%), and α-7 (n = 30, 47%).

Clustering of HPV Types. To explore the tendency of particular HPV types to appear together in multiple infections, the joint positivity of the 13 most common HPV types (≥1.8% baseline prevalence) was investigated. All pairwise frequency combinations at baseline are shown in Table 2. Each observed frequency was compared with the expected frequency under the assumption of no association between individual HPV types. With a total of 78 possible pairwise combinations, one would expect a few observed frequencies to depart significantly from expected frequencies by chance alone. If one assumes that the 13 types analyzed are distributed in a completely random manner, then we would expect about 5% (or 4) of the associations to exceed the 5% significance level and about 1% (or 1) to exceed the 1% significance level. We found a total of 25 pairs that exceeded the 5% level of significance, more than half of which exceeded the 1% level. In all cases, the observed frequencies were significantly greater than the corresponding expected value. The most common joint excesses involved HPV-58 (n = 7), HPV-31 (n = 6), HPV-54 (n = 5), HPV-62 (n = 5), HPV-16 (n = 4), and HPV-67 (n = 4), four of which are in the α-9 species.

Distribution of High-risk and Low-risk Genotypes by Cytologic Diagnosis. Of subjects with a baseline cytology result (n = 523), 34 women (6.5%) had an abnormal cytology result at enrollment (Table 3) that was classified as either atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), or high-grade intraepithelial lesion (HSIL). Seventeen women (3.3%) had LSIL or HSIL abnormalities detected. Only 2.6% of specimens were inadequate, indicating good practices for specimen collection and preparation; 3.1% of the study population (n = 17) had no baseline cytology result. The mean age of women with normal cytology results was 35.9 years (SD, 14.4); it was 33.7 years (SD, 16.0) with ASCUS, 21.6 years (SD, 6.6) with LSIL, and 30.5 years (SD, 8.5) with HSIL.

The overall HPV prevalence in women with normal cytology was 25.4%; it was 64.7% with ASCUS and 94.1% with LSIL/HSIL (Table 3). Similarly, there was increasing prevalence of high-risk-HPV types, from 17% in normal cytology to 52.9% in ASCUS and 94.1% in LSIL/HSIL. More modest increases were observed across categories for low-risk HPV infection. The steepest increase in prevalence across the cytologic outcome categories was in HPV-16/HPV-18, which was detected in 4.9% of normal Pap smears, 35.3% of ASCUS specimens, and 52.9% of LSIL/HSIL specimens. Multiple high-risk infections also showed a high prevalence in women with ASCUS (5.9%) and LSIL/HSIL (23.5%) compared with those with normal cytology (2.2%).

Women with normal cytology and ASCUS results had mostly single-type infections whereas women with LSIL and HSIL results had predominantly multiple-type infections. When analyzed separately, all women with a LSIL cervical cytology were positive for HPV, whereas one woman with a HSIL cervical cytology was HPV-DNA–negative. It should be noted that a year later this woman tested positive for HPV-16, and it is possible that the initial test failed to detect an existing and persistent infection. The most common HPV type was HPV-16 for

all cytologic outcome groups. The most common HPV types were both high-risk and low-risk types for women with normal cervical cytology but mostly high-risk types for ASCUS, LSIL, and HSIL results. Overall, 52.9% (n = 9) of women with ASCUS results had infection with a high-risk type. Considering women <30 years of age with ASCUS, 88.9% (n = 9) had a high-risk infection, whereas only 12.5% (n = 1) of women >30 years were positive for high-risk-HPV, a statistically significant difference by a two-tailed Z test. The most common HPV types in women with ASCUS results were HPV-16, HPV-18, and HPV-33. Women with LSIL and HSIL cervical cytology shared three of their most common high-risk types: HPV-16, HPV-31, and HPV-58.

Discussion

The analysis presented here is a cross-sectional study of the type- and age-specific HPV-DNA prevalence in a population of Quebec Inuit women enrolled in a cohort study. To our knowledge, this work is the first published report of its kind in this population. These data represent a starting point for understanding the burden of HPV

Table 1. Frequency of HPV species and types in single and multiple infections (n = 160)

HPV species/type	All infections*	Single infections	Multiple infections†
	n (%)	n (%)	n (%)
Species A1	7 (4.4)	0 (0.0)	7 (10.9)
42	7 (4.4)	0	7
Species A3	71 (44.4)	26 (27.1)	45 (70.3)
61	20 (12.5)	6	14
62	16 (10.0)	4	12
72	2 (1.3)	2	0
81	3 (1.9)	1	2
83	2 (1.3)	1	1
84	17 (10.6)	6	11
89	11 (6.9)	6	5
Species A5	15 (9.4)	6 (6.3)	9 (14.1)
26	1 (0.6)	1	0
51	10 (6.3)	4	6
69	0 (0.0)	0	0
82	4 (2.5)	1	3
Species A6	26 (16.3)	7 (7.3)	19 (29.7)
53	13 (8.1)	4	9
56	6 (3.8)	0	6
66	7 (4.4)	3	4
Species A7	49 (30.6)	19 (19.8)	30 (46.9)
18	9 (5.6)	2	7
39	9 (5.6)	4	5
45	4 (2.5)	2	2
59	12 (7.5)	3	9
68	6 (3.8)	2	4
70	9 (5.6)	6	3
Species A8	1 (0.6)	0 (0.0)	1 (1.6)
40	1 (0.6)	0	1
Species A9	96 (60)	35 (36.5)	61 (95.3)
16	31 (19.4)	13	18
31	20 (12.5)	6	14
33	3 (1.9)	0	3
35	2 (1.3)	1	1
52	13 (8.1)	7	6
58	15 (9.4)	4	11
67	12 (7.5)	4	8
Species A10	6 (3.8)	0 (0.0)	6 (9.4)
6	2 (1.3)	0	2
11	0 (0.0)	0	0
55	4 (2.5)	0	4
Species A11	6 (3.8)	0 (0.0)	6 (9.4)
64‡	0 (0.0)	0	0
73	6 (3.8)	0	6
Species A13	10 (6.3)	3 (3.1)	7 (10.9)
54	10 (6.3)	3	7
Species A15	0 (0.0)	0 (0.0)	0 (0.0)
71	0 (0.0)	0	0
Total	160 (100)	96 (100)	64 (100)

*Relative contribution to total number of infections (n = 160). Because HPV types from different species may contribute to multiple infections, the sum of percentages exceeds 100%.
†Contribution to total number of multiple infections (n = 64). Because HPV types from different species may be involved in multiple infections, the sum of percentages exceeds 100%.
‡Subtype of HPV–34.

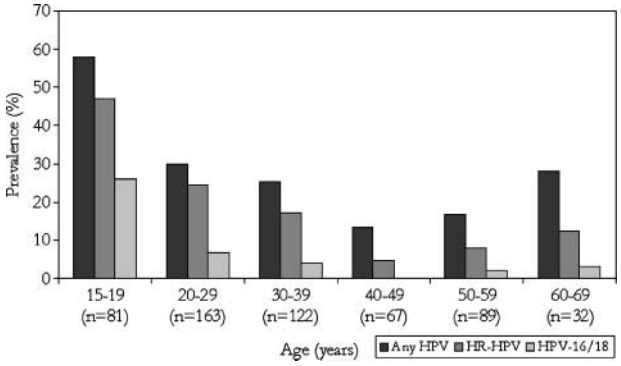

Figure 3. Age-specific prevalence of any HPV-DNA, high-risk HPV, and HPV-16/HPV-18 (n = 554). HPV-DNA of any type was detected in 58% of women ages 15-19 y, 30.1% in ages 20-29 y, 25.4% in ages 30-39 y, 13.4% in ages 40-49 y, 16.9% in ages 50-59 y, and 28.1% in ages 60-69 y. High-risk types were detected in 46.9% of women ages 15-19 y, 24.5% in ages 20-29 y, 17.2% in ages 30-39 y, 4.5% in ages 40-45 y, 7.9% in ages 50-59 y, and 12.5% in ages 60-69 y. Low-risk types were detected in 37% of women ages 15-19, 11.7% in ages 20-29 y, 9.8% ages 30-39 y, 9% in ages 40-49 y, 12.4% in ages 50-59 y, and 25% in ages 60-69 y. HPV types 16 or 18 were detected in 25.9% of women ages 15-19 y, 6.7% in ages 20-29 y, 4.1% in ages 30-39 y, 0% in ages 40-49 y, 2.2% in ages 50-59 y, and 3.1% in ages 60-69 y.

infection, which may help to assess the public health impact of HPV-DNA genotyping in cervical cancer screening and HPV vaccination among Quebec Inuit women. Should widespread vaccination take place, continued surveillance may help to evaluate if phenomena such as type-replacement occur in the postvaccination population. In addition, the longitudinal study that involves these participants will allow us to analyze the persistence of HPV infection in future work.

It is important to examine the limitations of this study before discussing its results. The study population is small and was selected nonrandomly, which means that participants may differ from nonparticipants in their HPV status and characteristics related to HPV infection. We were unable to assess whether women who declined to participate differed significantly from those who accepted and whether the women approached were representative of the target population. We have, however, obtained reasonably good coverage overall for the four main communities (58%) and a similar age distribution in our study population when compared with the target population. In the follow-up to a Nunavik-wide health survey conducted in 2004, it was found that a large proportion of women across most age groups had a Pap test in the previous two years: 72.3% of women ages 18 to 24 years, 84.7% of 25- to 34-year-olds, 80.3% of 35- to 44-year-olds, 80% of 45- to 54-year-olds, 71% of 55- to 65-year-olds, and 46% of women 65 years and older (15). Because women in Nunavik seem to be relatively compliant with Pap screening, we expect that our sampling procedure produced a study population that is roughly representative of the general population. Interestingly, when the history of Pap screening in the previous three years was examined among study participants for whom this information was available, compliance was lower than for the 2-year Pap history in the ''general population'' across several age groups. We found that 76.5% of women ages 18 to 24 years, 84.3% of 24- to 34-year-olds, 62.4% of 35- to 44-year-olds, 70% of 45- to 54-year-olds, 66.7% of 55- to 64-year-olds, and no women 65 years and older had attended Pap screening in the previous 3 years. Therefore, women in the study population may slightly overrepresent some characteristics associated with noncompliance with Pap screening. The cross-sectional nature of the data presented here implies that any observed patterns in the age distribution of HPV-DNA should be interpreted with caution. These patterns may represent a true biological phenomenon or a cohort effect (16).

The prevalence of HPV-DNA in this Quebec Inuit population was 28.9% overall and 25.4% in cytologically normal women. This estimate of overall prevalence is similar to reports in other ''high-risk'' screening populations in Canada such as Montreal university students (17) and attendees of an inner city clinic in Winnipeg (18), and elevated when compared with a more representative screening population sampled from across health regions in Ontario (19). The age composition of these first two populations is considerably younger than in our study, which suggests that the Quebec Inuit may be at higher risk of HPV infection than other ''high-risk'' populations in Canada. A comparison with the Ontario data suggests that our population may have as much as a 2-fold higher burden of HPV infection than the general population overall, and close to a 3-fold higher prevalence in women ages <20 years.

The most prevalent HPV types in our population were the high-risk types HPV-16 (5.6%) and HPV-31 (3.6%) and the low-risk types HPV-61 (3.6%) and HPV-84 (3.1%). HPV-18 was detected in only 1.6% of the population, HPV-6 was detected in 0.4%, and no HPV-11 was detected. The HPV-16 prevalence was lower than in all other Canadian studies (17-19), whereas HPV-18 was elevated only when compared with what Sellors et al. (19) found in their Ontario population. A higher prevalence of HPV-6 (9.1%) and HPV-11 (7%) was detected in Winnipeg Aboriginals (18) whereas a more modest, but still elevated, prevalence was detected in

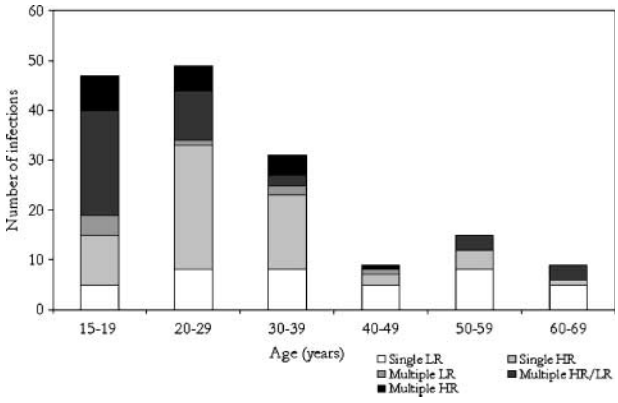

Figure 4. Distribution of single and multiple type infections by age (n = 554).

Table 2. Observed and expected frequencies of joint positivity for the most common HPV types (n = 554)

	Observed and expected pairwise frequencies of joint infection											
HPV type	31	51	52	53	54	58	59	61	62	67	84	89
16	5* (1.1)	2 (0.6)	0 (0.7)	4* (0.7)	2 (0.6)	3† (0.8)	3† (0.7)	3 (1.1)	3 (0.9)	0 (0.7)	2 (1.0)	2 (0.6)
31		1 (0.4)	1 (0.5)	4* (0.5)	3* (0.4)	2 (0.5)	1 (0.4)	5* (0.7)	3† (0.6)	3* (0.4)	1 (0.6)	1 (0.4)
51			0 (0.2)	1 (0.2)	1 (0.2)	3* (0.3)	1 (0.2)	2† (0.4)	3* (0.3)	0 (0.2)	1 (0.3)	0 (0.2)
52				1 (0.3)	1 (0.2)	2† (0.4)	1 (0.3)	1 (0.5)	0 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)
53					2† (0.2)	2† (0.4)	0 (0.3)	3* (0.5)	2 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)
54						3* (0.3)	0 (0.2)	1 (0.4)	3* (0.3)	2† (0.2)	1 (0.3)	1 (0.2)
58							1 (0.3)	2 (0.5)	2 (0.4)	2† (0.3)	2† (0.5)	0 (0.3)
59								1 (0.4)	3* (0.3)	0 (0.3)	2† (0.4)	1 (0.2)
61									2 (0.6)	1 (0.4)	1 (0.6)	1 (0.4)
62										0 (0.3)	1 (0.5)	3* (0.3)
67											2† (0.4)	0 (0.2)
84												0 (0.3)

NOTE: Expected frequencies appear in parentheses. Asterisks and daggers indicate that the significance level was exceeded.
*$P < 0.01$.
†$P < 0.05$.

other studies (17, 19). The prevalence of HPV-31 (3.6%) was higher in the study population than the 2.6% that was reported in Montreal university students (17) and 0.6% in Ontario women (19), but lower than in both Aboriginal (6.6%) and non-Aboriginal (4.1%) women in Winnipeg (18). This evidence suggests that our study population has lower prevalence of HPV-6, HPV-11, HPV-16, and HPV-18, but higher prevalence of HPV-31, than most other populations studied in Canada.

The low prevalence of HPV-6 and HPV-11 should be interpreted with the knowledge that health care providers in the region report seeing cases of condyloma and that a history of physician-reported condyloma was found in 15% of women whose medical charts were reviewed (n = 447). The lower prevalence of HPV-18, particularly in women with HSIL (among whom no HPV-18 was detected), may suggest that HPV-18 is relatively less represented in LSIL and HSIL lesions than in other populations. These results should be interpreted cautiously, however, because the number of abnormal Pap results reported is small. Nonetheless, it is interesting to note that women with LSIL and HSIL cytology shared three of their most common high-risk types: HPV-16, HPV-31, and HPV-58. Thus, this population may benefit from the cross-protection of HPV-31 by vaccines that protect against high-risk types HPV-16 and HPV-18 (20, 21).

The prevalence of high-risk types was 20.4% overall in our population, which is comparable with other populations in Canada (17), although slightly lower than the 26% high-risk prevalence that was observed in Inuit women residing in the Canadian territory of Nunavut (22). However, the high-risk prevalence reported in Ontario by Sellors et al. (19) was only 12.7% overall, and the age-specific prevalence in 15- to 19-year-olds was 15.7%, almost a third of what we saw in our study. This suggests that high-risk types may be more prevalent in Quebec Inuit women than in the general population, particularly among young women.

Multiple-type infections were more common in our population than in prevalence studies across geographically diverse regions (19, 23, 24). The higher rate of detection of multiple infections could be related in part to the use of an assay that allowed the identification of nearly all genital genotypes compared with other studies that did not detect all these genotypes. Infection with multiple HPV types seems to increase the risk of developing high-grade lesions and invasive cancer (25), likely through a synergistic effect of coinfecting types. Trottier et al. (12) found evidence that multiple infections involving HPV-16 and HPV-58, in particular, might be associated with an elevated risk of squamous intraepithelial lesions, compared with infections with these types alone. The authors proposed that other oncogenic HPV types of the α-9 family may also be modulated by coinfection because types within the same species tend to share some biological properties and may interact similarly to influence the development and progression of cytologic abnormalities.

The clustering analysis presented here was not designed to formally test the significance of pairwise associations of coinfecting types. It is interesting to note, however, that four of the seven most common HPV types to be involved in joint excesses were in the α-9 family,

Table 3. HPV infection status by cytology result (n = 523)

Cytology	Overall	Any HPV	HR-HPV	LR-HPV	HPV-16/18	Multiple HR/LR	Multiple HR
	n (%)	n (%)*	n (%)	n (%)	n (%)	n (%)	n (%)
Normal	489 (93.5)	124 (25.4)	83 (17.0)	70 (14.3)	24 (4.9)	29 (5.9)	11 (2.2)
ASCUS	17 (3.3)	11 (64.7)	9 (52.9)	4 (23.5)	6 (35.3)	2 (11.8)	1 (5.9)
LSIL/HSIL	17 (3.3)	16 (94.1)	16 (94.1)	6 (35.3)	9 (52.9)	6 (35.3)	4 (23.5)
Total	523 (100)	151 (28.9)	108 (20.7)	80 (15.3)	39 (7.5)	37 (7.1)	16 (3.1)

Abbreviations: HR, high risk; LR, low risk.
*Percent of the cytology class with any HPV infection.

and of the 25 joint excesses that were flagged as significant, 17 involved an α-9 species. If particular HPV types are involved in multiple infections in our population and are associated with the risk of development and progression of precancerous and cancerous lesions, this knowledge may be useful in integrating HPV-DNA testing into cervical screening programs. It was reassuring to observe that of all pairwise combinations, none resulted in observed frequencies that were significantly lower than that expected by chance alone. Such combinations would have suggested that the two putative types tend to compete for the same niche and exclude each other, a finding that could flag the possibility of type replacement if one of the types were to be eliminated by vaccination.

Several studies have reported a decrease in HPV prevalence with age that is accompanied by a ''resurgence'' in older women. A study of Colombian women (23) and one in Costa Rica (16) reported an increased prevalence of HPV infection in women age 55 years or older; in Mexico (26), this second peak in prevalence was observed in women ages 45 years and older. In our study, an increase in HPV prevalence was observed in women ages 50 years and older, among whom low-risk types and single-type infections were most common, but some multiple infections with high-risk types were still observed. Numerous hypotheses have been proposed for the U-shaped prevalence pattern observed in populations of women. If older women in the study population were comparatively more exposed to HPV earlier in their lives than young women today, a cohort effect (16) rather than a true biological effect could explain this phenomenon. Some biological hypotheses have also been proposed to explain the increased prevalence in older women, including reactivation of latent infections due to hormonal changes resulting from decline in ovarian function (26) and decreased immune response with aging (27, 28). Finally, age-related changes of the cervix may affect the sampling of cells and thus the detection of particular HPV types (29).

In conclusion, our results show a high prevalence of HPV infection and, in particular, multiple type infections in a population of Inuit women undergoing routine screening in Nunavik, Quebec. Whereas the youngest women showed a large proportion of multiple high-risk infections, an increase in HPV prevalence that was observed in the older age groups was characterized by mostly single infections with low-risk types. The data presented here may help to inform efforts to integrate HPV genotyping into cervical cancer screening and to develop vaccination strategies for this high-risk population.

Disclosure of Potential Conflicts of Interest

E. Franco: Support from Merck-Frosst Commercial Research Grant; Merck, GSK, Gen-Probe, Roche, Consultant/Advisory Board.

Acknowledgments

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We thank the Tulattavik Health Centre, the Nunavik Regional Board of Health and Social Services, the participating communities, and the many collaborating health care professionals and research staff, including Annie Pelletier, Nathalie Boulanger, Marie-Andrée Robitaille, Brigitte Richer, Solange Piché, Pierre Forest, Hélène Voyer, Simon Gagnon, Diane Gaudreau, and Sarah Vahey, who made this project possible.

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