

Human Papillomavirus Infection in Ulaanbaatar, Mongolia: A Population-Based Study

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Abstract

Data on human papillomavirus (HPV) and cervical cancer burden in Central Asia are scarce. To investigate HPV infection in Ulaanbaatar, the capital of Mongolia, we obtained cervical cell specimens from a population of 969 women ages 15 to 59 years. DNA of 44 HPV types was detected using a GP5+/6+ PCR-based assay. Seropositivity for L1 proteins of HPV 16, 18, 31, 33, 45, 52, and 58 was assessed using multiplex HPV serology. Cytologic abnormalities were detected in 127 women (13.1%), among whom 6 cervical intraepithelial neoplasia grade 3 and 2 invasive cervical cancers were diagnosed. Overall HPV DNA prevalence was 35.0%, being highest (48.5%) in women ages <25 years. High-risk types were detected in 24.5% of women. HPV DNA prevalence declined with age but remained >25% in all age groups. HPV seroprevalence was also very high

(38.0%) and increased steadily from 33.2% to 48.9% in women ages <25 and 50 to 59 years, respectively. However, the proportion of women positive for both HPV markers of any individual HPV type was low. HPV16 was the most frequently detected type by PCR (6.1%), serology (23.0%), or both (2.1%). Lifetime number of sexual partners and induced abortions were shown to be directly associated with HPV DNA and/or seroprevalence. HPV prevalence in Ulaanbaatar was higher than that detected by similar HPV testing protocols in other populations in Asia or elsewhere and would suggest an important, yet unquantified, cervical cancer burden. Improving cervical cancer prevention, through screening and HPV vaccination, is an important public health issue for Mongolia. (Cancer Epidemiol Biomarkers Prev 2008;17(7):1731–8)

Introduction

The establishment of the viral etiology of cervical cancer has prompted a shift in the primary and secondary prevention of cervical cancer toward human papillomavirus (HPV) vaccination (1) and HPV DNA test-based screening (2), respectively, the planning of which requires population-based epidemiologic data on HPV type-specific prevalence. To this end, the IARC has carried out surveys in representative samples of women worldwide, disclosing wide geographic variations in HPV prevalence and some differences in the relative frequency of individual HPV types (3). There remains, however, a considerable lack of data on HPV infection and cervical cancer in many parts of the world, notably Central Asia.

Mongolia covers 1.6 million km² and is sparsely populated, meaning that accurate cancer statistics are difficult to obtain. Estimates of cervical cancer incidence (18.2/100,000) and mortality (10.2/100,000) classify Mongolia as an area of intermediate cervical cancer risk (4), but no population-based cancer registries exist in

Mongolia. A hospital-based cancer survey had suggested that in 1982 cervical cancer was the most common cancer among women corresponding to an age-standardized incidence of 37.8/100,000 or 23.2% of all cancer in women (5). In the past two decades, Mongolia has undergone significant socioeconomic changes accompanied by a loss in primary health-care infrastructure and rapid migration to the capital. More than one-third of the 2.6 million inhabitants of Mongolia now live in the capital city of Ulaanbaatar, where 62% of the population is below 30 years old (6).

To help inform public health choices for cervical cancer prevention in Central Asia, we report on genital infection and serologic markers of HPV in a large cross-sectional sample of the general female population in Ulaanbaatar, Mongolia.

Materials and Methods

Study Subjects. No reliable resident lists were available in Ulaanbaatar. However, as the majority of women ages 20 to 50 years in Ulaanbaatar were employed outside the home (7), it was decided that a representative sample of the female population of Ulaanbaatar could be obtained through employee lists. Some additional sampling of the youngest and oldest age groups underrepresented in the workplace was, however, made.

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Contact was thus made with two large multibranch corporations, chosen to represent a broad spectrum of commercial activities (including financial, manufacturing, retail, transport, and educational sectors). Centralized employee lists held by the respective occupational health departments were used to invite women to participate in the study. At each study site, the study team (which included one gynecologist, two nurses, and two interviewers), in collaboration with the occupational health services, arranged informational meetings with employees. At each meeting, a brief presentation on various issues concerning cervical cancer prevention was given followed by the main research goals and sample collection procedures of the study. Following these meetings, all female employees ages 15 to 59 years received personal invitations to the respective occupational health clinic, where all clinical examinations took place. Among a total of 1,106 invited employees, 865 (78%) chose to participate.

Two efforts were made to enrich the number of participants in the youngest and oldest age groups underrepresented in the workplace. Firstly, all participating employees were asked if they had close female relatives (a mother, sister, or daughter) living in Ulaanbaatar. A total of 284 eligible relatives were enumerated and contacted, of which 105 (37%) participated in the study, including 14 women ages <20 years and 58 women ages >45 years. Secondly, as the majority of 15- to 20-year-olds in Ulaanbaatar were still pursuing their education, a sample of students was invited from the resident list of a university dormitory. Fifty-two of the 98 invited students participated in the study, all of whom reported that they were sexually active.

On arrival at the study clinic, all participants read and signed an informed consent form explaining the main research goals, sample collection procedures, potential benefits and harms, and confidentiality of data collected for the study. The informed consent form respected the recommendations of the ethical review committees of the IARC and the Mongolian Health Ministry, which both approved the study.

A standard questionnaire, similar to that used in other IARC-coordinated HPV surveys, was administered to all study participants by trained interviewers, including questions on sociodemographic characteristics, sexual behavior of the women and of their partners, reproductive factors, use of contraceptive methods, and smoking habits.

A total of 1,022 women thus agreed to participate in the population study. Major reasons given for nonparticipation were women considering themselves not to be ill and therefore not in need of screening (365 women), virginity (74 women, including 46 students), and menstruation and/or pregnancy at time of recruitment (19 and 8 women, respectively).

Sample Collection Procedures. Samples were collected between September and November 2005. A total of 1,002 of 1,022 participants accepted to undergo both collection of cervical cells for HPV DNA testing and liquid-based cytology and to give 5 mL blood for serologic testing (10 self-reported virgins, 2 hysterectomized women, and 8 menstruating women provided a blood sample only and are not included in reported analyses).

Samples of exfoliated cervical cells from the endocervix and ectocervix were collected by the study gynecologist. After application of a speculum, a cytobrush (Cervex brush, Rovers Medical Devices) was inserted to its full length into the endocervical canal and turned five times in an anticlockwise direction. The brush containing cellular material was agitated in a vial containing 20 mL PreservCyt solution (Cytec) and then discarded. Exfoliated cervical cell samples in PreservCyt solution were stored at room temperature for up to 2 months and then at 4°C.

Venous blood samples (5 mL) were drawn into vacuum containers. After clotting and centrifugation at 2,000 rpm for 5 min, 1 mL serum was transferred into a pre-labeled 2.0 mL Safe-lock Eppendorf tube. Serum samples were stored at room temperature for up to 8 h and then at -20°C.

Pathology. Slides for liquid-based cytology were prepared using a Thin Prep 2000 processor (Cytec) and stained according to manufacturer's instructions at the Institute of Pathology, Heidelberg University. Reading of the slides was done in the Referral Center for Gynecopathology and was reported according to the Bethesda 2001 terminology system (8).

All women with abnormal cervical findings [with the exception of atypical squamous cells of undetermined significance (ASCUS) negative for high-risk HPV DNA] were referred for further diagnostic procedures including repeat cytology and colposcopy-directed biopsy under the supervision of one of us (D.A.). Depending on the local histopathologic assessment of biopsy material, women were treated according to standard local protocols. The majority of biopsy specimens were confirmed in Germany.

HPV DNA Testing. HPV DNA testing was done in the Department of Pathology at the VU University Medical Center on exfoliated cervical cells in PreservCyt, aliquoted before liquid-based cytology using protocols to minimize any possible contamination. DNA was extracted from the PreservCyt sample using a High Pure PCR Product Purification Kit according to the manufacturer's recommendations (Roche Applied Science). β -Globin PCR analysis was done firstly to confirm the presence of human DNA in all specimens. The overall presence of HPV DNA was determined by performing a general GP5+/6+ primer-mediated PCR (9). HPV positivity was assessed by hybridization of PCR products in an enzyme immunoassay using two HPV oligoprobe cocktails that, together, detect the following 44 HPV types: HPV 6, 11, 16, 18, 26, 30 to 35, 39, 40, 42 to 44, 45, 51 to 59, 61, 64, 66 to 73, 81 to 86, 89, and JC9710. Subsequent HPV typing was done by reverse-line blot hybridization of PCR products as described previously (10).

HPV types considered high risk for this analysis included HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 (11).

HPV Serology Testing. Antibodies to the L1 protein of HPV types 16, 18, 31, 33, 45, 52, and 58 were tested for at the German Cancer Research Center using a multiplex method based on a glutathione S-transferase capture immunosorbent assay combined with fluorescent-bead technology (12, 13). Antibodies bound to antigens on

beads were quantified in the Luminex analyzer (Luminex), which also identifies the antigen by the internal bead color. Antibody quantity was determined as the median R-phycoerythrin fluorescence intensity from at least 100 beads of the same antigen.

Median fluorescence intensity values were dichotomized as antibody positive or antibody negative. Seropositivity cutoffs were HPV type specific and defined previously in a study of 371 female Korean students reporting never to have had penetrative sexual intercourse and who had no evidence of genital HPV DNA for 25 HPV types in self-collected vaginal cell samples (13). The cutoff was defined as 5 SD above the mean of the final distribution of median fluorescence intensity values for these 371 subjects after an iterative process to exclude outliers (13). A set of 188 informative "bridging" sera tested with the cutoff defining sera were also retested with samples from the present study to allow the cutoff to be standardized to the exact assay conditions of the present sample batch.

For the following analyses, seropositivity for "any HPV" refers to that for types 16, 18, 31, 33, 45, 52, or 58.

Statistical Analysis. HPV prevalence was standardized by age by use of the world standard population reported by Doll et al. (14) as a reference population.

Observed and expected numbers of women seropositive for any combination of two HPV types were computed and the corresponding 95% confidence interval (95% CI) were obtained using the Poisson distribution.

Odds ratios (OR) for HPV DNA positivity and HPV seropositivity with corresponding 95% CI were calculated using unconditional logistic regression, adjusted for age (<25, 25-29, 30-34, 35-39, 40-44, 45-49, and ≥50 years) and lifetime number of sexual partners (1, 2, 3, ≥4). Tests for linear trend of OR were done giving an increasing score for each level of the categorized variable and fitting them into the model as continuous variables.

Table 1. Prevalence of HPV DNA by cytologic findings among 969 women, Ulaanbaatar, Mongolia, 2005

HPV type	Cytology								
	Normal			Abnormal			Total		
	Single	Multiple	Total (%)	Single	Multiple	Total (%)	Single	Multiple	Total (%)
Negative	—	—	585 (69.5)	—	—	45 (35.4)	—	—	630 (65.0)
Positive	154	103	257 (30.5)	42	40	82* (64.6)	196	143	339 (35.0)
High risk	78	93	171 (20.3)	29	37	66 (52.0)	107	130	237 (24.5)
Low risk	68	72	140 (16.6)	11	27	38 (29.9)	79	99	178 (18.4)
Uncharacterized	8	—	8 (1.0)	2	—	2 (1.6)	10	—	10 (1.0)
High risk									
16	13	27	40 (4.8)	9	10	19 (15.0)	22	37	59 (6.1)
18	8	12	20 (2.4)	0	4	4 (3.2)	8	16	24 (2.5)
31	11	17	28 (3.3)	11	7	8 (6.3)	12	24	36 (3.7)
33	6	8	14 (1.7)	3	7	10 (7.9)	9	15	24 (2.5)
35	4	11	15 (1.8)	1	9	10 (7.9)	5	20	25 (2.6)
39	6	3	9 (1.1)	1	2	3 (2.4)	7	5	12 (1.2)
45	5	15	20 (2.4)	0	1	1 (0.8)	5	16	21 (2.2)
51	5	10	15 (1.8)	2	6	8 (6.3)	7	16	23 (2.4)
52	1	12	13 (1.5)	4	5	9 (7.1)	5	17	22 (2.3)
56	4	13	17 (2.0)	0	3	3 (2.4)	4	16	20 (2.1)
58	4	12	16 (1.9)	4	5	9 (7.1)	8	17	25 (2.6)
59	2	5	7 (0.8)	3	2	5 (3.9)	5	7	12 (1.2)
68	0	2	2 (0.2)	0	0	0 (0.0)	0	2	2 (0.2)
73	7	13	20 (2.4)	1	2	3 (2.4)	8	15	23 (2.4)
82	2	7	9 (1.1)	0	2	2 (1.6)	2	9	11 (1.1)
Low risk									
6	1	3	4 (0.5)	1	1	2 (1.6)	2	4	6 (0.6)
11	5	5	10 (1.2)	2	2	4 (3.2)	7	7	14 (1.4)
26	2	3	5 (0.6)	0	2	2 (1.6)	2	5	7 (0.7)
30	2	0	2 (0.2)	0	2	2 (1.6)	2	2	4 (0.4)
32	1	0	1 (0.1)	0	0	0 (0.0)	1	0	1 (0.1)
40	1	4	5 (0.6)	0	2	2 (1.6)	1	6	7 (0.7)
42	6	10	16 (1.9)	1	6	7 (5.5)	7	16	23 (2.4)
43	2	5	7 (0.8)	1	1	2 (1.6)	3	6	9 (0.9)
53	1	2	3 (0.4)	1	2	3 (2.4)	2	4	6 (0.6)
54	2	4	6 (0.7)	0	0	0 (0.0)	2	4	6 (0.6)
55	4	1	5 (0.6)	0	2	2 (1.6)	4	3	7 (0.7)
66	12	13	25 (3.0)	1	5	6 (4.7)	13	18	31 (3.2)
67	2	6	8 (1.0)	0	3	3 (2.4)	2	9	11 (1.1)
70	6	14	20 (2.4)	1	4	5 (3.9)	7	18	25 (2.6)
81	7	13	20 (2.4)	2	3	5 (3.9)	9	16	25 (2.6)
83	2	4	6 (0.7)	0	4	4 (3.2)	2	8	10 (1.0)
Jc9710	11	9	20 (2.4)	0	5	5 (3.9)	11	14	25 (2.6)
Cp6108	1	5	6 (0.7)	1	0	1 (0.8)	2	5	7 (0.7)

*Including six cervical intraepithelial lesions grade 3/carcinoma *in situ* (3x HPV16, HPV33, HPV35, and HPV35/53/66) and two invasive cervical cancers (HPV16 and HPV16/33).

Table 2. Seropositivity overall and by strata of HPV DNA positivity for the corresponding types among 969 women, Ulaanbaatar, Mongolia 2005

HPV type	By HPV DNA positivity of the same type				Overall (n = 969) % Seropositivity
	Positive		Negative		
	n	% Seropositivity	n	% Seropositivity	
HPV16	59	33.9	910	22.3*	23.0
HPV18	24	16.7	945	19.7	19.6
HPV31	36	11.1	933	12.9	12.8
HPV33	24	8.3	945	9.1	9.1
HPV45	21	23.8	948	16.7	16.8
HPV52	22	4.6	947	10.7	10.5
HPV58	25	12.0	944	4.8	5.0
Any of the above	172	48.3	797	35.8 [†]	38.0

* χ^2 for seropositivity by DNA status (adjusted for age and lifetime number of sexual partners) = 3.71.

[†]P = 0.046. χ^2 for seropositivity by DNA status (adjusted for age and lifetime number of sexual partners) = 10.99; P < 0.001.

Results

Of 1,002 women who provided cervical cell samples, 5 had inadequate HPV DNA results (β -globin negative), 5 had inadequate serology, and 23 had inadequate cytology, leaving 969 women with all three results available. Among them, 127 (13.1%) had abnormal cytologic findings, including 73 (7.5%) ASCUS, 9 (0.9%) atypical glandular cells of undetermined significance (AGUS), 3 (0.3%) atypical squamous cells cannot exclude high-grade squamous intraepithelial lesions (ASC-H), 29 (3.0%) low-grade squamous intraepithelial lesions (LSIL), and 13 (1.3%) high-grade squamous intraepithelial lesions (HSIL). All women with cytologic abnormalities were called back, except those who had HPV DNA-negative ASCUS. A histologic diagnosis was obtained for 68 of 88 women for whom further diagnostic workup was indicated, among whom six cervical intraepithelial neoplasia grade 3 and two invasive cervical cancers were diagnosed and treated.

Overall HPV DNA prevalence was 35.0% (Table 1). The corresponding overall prevalence age-standardized

to the world population was 36.7% (95% CI, 33.6-39.9). Of HPV-positive women, 196 (57.8%) had single-type infections and 143 (42.2%) had multiple-type infections. High-risk HPV types were detected more frequently (24.5% of all women) than low-risk types (18.4%). The prevalence of high-risk HPV types in ASCUS/ASC-H/AGUS, LSIL, and HSIL was 37.7%, 75.9%, and 92.3%, respectively. The most common high-risk types among women without cervical abnormalities were HPV16 (4.8%), HPV31 (3.3%), HPV18 (2.4%), HPV45 (2.4%), and HPV73 (2.4%). HPV16 was also the most common type among women with cervical abnormalities (15.0%).

Thirty-eight percent of women were seropositive for at least one of the seven high-risk types (Table 2). The most common type was HPV16 (23.0%) followed by HPV18 (19.6%) and HPV45 (16.8%). Seroprevalence of HPV16 and any of the seven available types was significantly more frequent in women who were HPV-positive than woman who were HPV-negative for HPV DNA of the same type(s), whereas the difference was not significant for the other individual HPV types.

Table 3. Concomitant seropositivity for seven HPV types among 969 women, Ulaanbaatar, Mongolia, 2005

HPV type	Seropositivity						
	16	18	31	33	45	52	58
16							
Observed	223	131	83	52	98	67	23
Observed/expected (95% CI)		3.0 (2.5-3.6)	2.9 (2.3-3.6)	2.6 (1.9-3.4)	2.6 (2.1-3.2)	2.9 (2.2-3.6)	2.1 (1.3-3.1)
18							
Observed		190	79	48	113	64	25
Observed/expected (95% CI)			3.3 (2.6-4.1)	2.8 (2.0-3.7)	3.5 (2.9-4.2)	3.2 (2.5-4.1)	2.7 (1.7-3.9)
31							
Observed			124	57	84	75	30
Observed/expected (95% CI)				5.0 (3.8-6.5)	4.0 (3.2-5.0)	5.7 (4.5-7.2)	4.9 (3.3-7.0)
33							
Observed				88	67	68	32
Observed/expected (95% CI)					4.8 (3.7-6.0)	7.3 (5.7-9.3)	7.3 (5.0-10.3)
45							
Observed					163	80	30
Observed/expected (95% CI)						4.7 (3.7-5.8)	3.7 (2.5-5.3)
52							
Observed						102	29
Observed/expected (95% CI)							5.7 (3.8-8.2)
58							
Observed							48

Of seropositive women, 210 (57.1%) were positive for antibodies to more than one high-risk HPV type (data not shown). Seropositivity for all the seven available HPV types was observed significantly more often than expected if a woman was seropositive for a different type (Table 3). Observed/expected ratios > 5.0 were found for the combinations of HPV 31 and 52, HPV 33 and 52 or 58, and HPV 52 and 58.

Figure 1 shows the prevalence of HPV DNA (HPV 16 and/or 18, other high-risk types and low-risk types only) and of HPV antibodies (against seven high-risk types and HPV 16 and/or 18) by age group. HPV DNA prevalence was 48.5% among women ages <25 years and steadily decreased with age down to 26.0% at ages 45 to 49 years. Age-specific patterns were similar for the prevalence of HPV 16 and/or 18 DNA (Fig. 1). In contrast to the age-specific pattern of HPV DNA prevalence, HPV seroprevalence was lowest among younger women and increased with age (to 48.9% for all seven types and 34.3% for HPV 16 and/or 18, respectively, at ages ≥ 50 years).

Figure 2 describes HPV DNA and serology results among women positive for either marker, stratified by broad age group. The proportion of women positive for HPV16 DNA or antibodies was similar among women ages <35 years (27.6%) and ages ≥ 35 years (26.6%). However, older women were less likely to be HPV16 DNA positive (with or without corresponding antibodies) and more likely to be HPV16 seropositive only. This pattern was similar for HPV18 and for overall seropositivity for the seven high-risk types tested. The proportion of women positive for both DNA and antibodies of any individual HPV type was relatively low at any age (Figure 2).

Table 4 shows associations between the prevalence of HPV DNA and antibodies with selected characteristics of study participants. Age-specific decreases in HPV DNA prevalence (OR for ≥ 50 versus <25 years, 0.5; 95% CI, 0.3-0.8), and corresponding increases in HPV antibody prevalence (OR for ≥ 50 versus <25 years, 2.0; 95% CI, 1.2-3.1), were confirmed to be significant after adjustment for lifetime number of sexual partners. Neither occupational group nor education level were significant risk

factors for HPV DNA or antibody positivity. Single women were shown to have a significantly higher prevalence of HPV DNA (OR, 1.8; 95% CI, 1.2-2.8), but not of HPV antibodies, compared with married women. Prevalence of both HPV DNA and antibodies were significantly associated with increasing lifetime number of sexual partners and OR for four or more versus one lifetime sexual partner were similar for the two markers (1.6 and 1.5, respectively). Associations of lifetime number of sexual partners with positivity for HPV DNA or HPV antibodies were stronger among women ages <35 years [OR (95% CI) ≥ 4 versus 1, 2.1 (1.2-3.8) and 2.1 (1.1-3.8), respectively] than among older women (data not shown). Women reporting that their current partner had had extramarital sexual relationships showed no significant excess of HPV-DNA positivity but an increased risk at borderline statistical significance for antibody positivity. Women reporting induced abortions (63% of all study participants) showed a higher prevalence of both HPV DNA (OR, 1.6; 95% CI, 1.2-2.2) and antibodies (OR, 1.4; 95% CI, 1.0-1.9). Although history of induced abortion was strongly related to multiple sexual partners, the association between history of induced abortion and HPV positivity was not modified by adjustment for lifetime sexual partners (OR adjusted for age only, 1.6 for HPV DNA and 1.5 for HPV antibody positivity; data not shown). The few participants who reported a previous Pap smear also showed a significantly higher prevalence of HPV DNA (OR, 1.9; 95% CI, 1.2-3.1) but not of HPV antibodies. Associations with increasing severity of cytologic abnormality were confirmed for both HPV DNA and antibody prevalence but were much stronger for HPV DNA (OR HSIL versus normal, 30.7; 95% CI, 3.9-240) than for HPV antibodies (OR, 5.5; 95% CI, 1.5-20).

No significant associations with HPV DNA or antibodies were found for place of birth (55% of study participants were born outside Ulaanbaatar), smoking status (13% were ever-smokers), age at first intercourse (mean age, 20.4 years), age at menarche (mean age, 14.8 years), number of pregnancies (mean, 2.5 among 763 parous women), spontaneous abortion (reported by 19% of women), menopause mean age, 47.9 years or use of

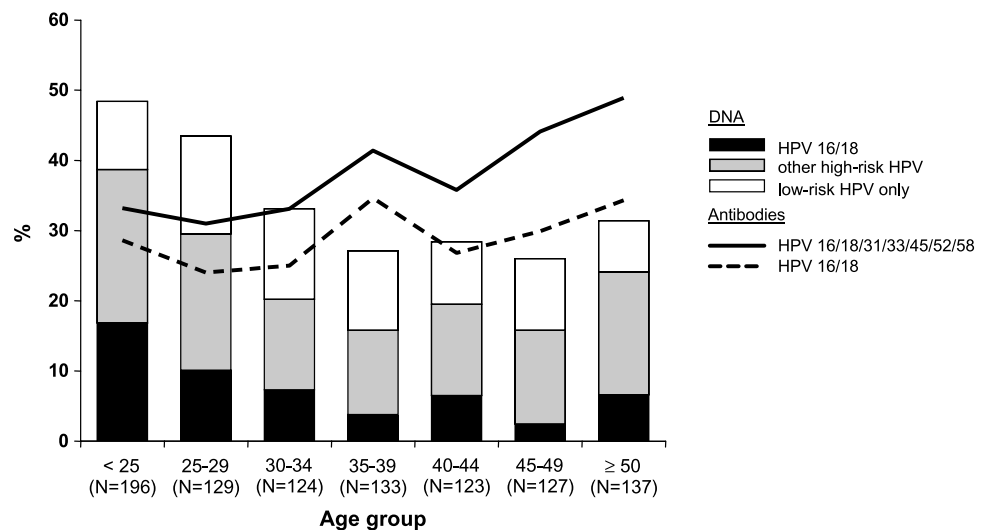


Figure 1. Age-specific prevalence of HPV DNA and antibodies, Ulaanbaatar, Mongolia, 2005.

oral contraceptives (21%), intrauterine device (31%), or condoms (24%; data not shown).

Discussion

The major finding of the present study, the first carried out in Mongolia or Central Asia, was the disclosure of a high burden of HPV prevalence in the general female population. The age-standardized prevalence of HPV DNA found in Ulaanbaatar (35%) was higher than that observed in previous studies done using the same HPV testing protocol, including those in South America (13-18%), India (17%), or sub-Saharan Africa (26%; ref. 3), where cervical cancer risk is documented to be very high (15). HPV prevalence was especially high among women ages ≤ 25 years, among whom the prevalence of HPV 16 or 18 DNA was 16%. Correspondingly, HPV seroprevalence was higher than that reported in previous seroepidemiologic surveys, albeit determined with different techniques and cutoff definitions. For example, the 23% HPV16 seroprevalence found in Ulaanbaatar compares to 5% to 15% reported for populations as diverse as the United States (16), Costa Rica (17), Finland (18), Spain (19), Korea (13, 20), and Taiwan (21). These findings of high HPV prevalence, and low activity of cervical cancer screening (only 9% of

study participants reported a previous Pap smear), would imply a large underlying burden of cervical cancer in Ulaanbaatar, perhaps underestimated by the scarce cancer statistics available for Mongolia (5).

Although HPV DNA prevalence was highest in women ages < 25 years (48.5%) and declined with age, it remained $> 25\%$ across all age groups, where the majority of infections continued to be constituted by high-risk HPV types. Thus, Mongolian women seem to show, at the same time, a peak of HPV prevalence in young women as found in high-resource countries in Europe, Asia (22), and the United States (23), where a strong decrease of HPV positivity is clear after age 25 years, but also high HPV prevalence into middle age as seen in low-resource countries at high cervical cancer risk, such as India and Nigeria (22). In contrast, the prevalence of HPV antibodies increased between young and middle age as shown previously (16, 17, 20, 21, 24). A subsequent decrease in HPV antibody prevalence has been reported among women ages ≥ 50 years (16, 17, 20, 24), suggesting a waning immunity with age. In Ulaanbaatar, however, HPV seroprevalence continued to increase in older women (21).

In this population with high prevalence of both HPV DNA and antibodies, there was a shift from markers of active HPV infection (DNA) to markers of a past infection (antibodies) with increasing age, so that the concordance between the two markers was lower than that observed in previous population-based studies using similar glutathione S-transferase-L1 fusion-based (13) or virus-like particle-based (17, 20) assays. The proportion of HPV DNA-positive women that were seropositive for the same type was relatively low, thus suggesting recent HPV exposure and/or lack of seroconversion.

In agreement with findings from the majority of previously studied countries, HPV16 was the most frequently detected type in the general Ulaanbaatar population for both DNA (3) and antibodies (17, 20, 24). However, the predominance of HPV16 seen among HPV DNA-positive women was not observed to the same extent for seropositivity, and the majority of seropositive women were positive for antibodies to multiple types as observed in previous studies using virus-like particle-based assays (17, 24). This is expected given that HPV types share a common sexual route of transmission and antibodies are a cumulative marker of all past infections. Some cross-reactivity of the assay, however, cannot be ruled out, particularly for the phylogenetically related types (e.g., HPV 33, 52, and 58).

Consistent with previous studies of HPV DNA (25, 26) and antibodies (16, 17, 20, 24), lifetime number of sexual partners was the most important risk factors for HPV positivity, but the risk increase for multiple sexual partners was modest. The associations of positivity for HPV DNA or antibodies were stronger among women ages < 35 years. A novel finding was the association of HPV positivity also with induced abortion, which was reported by a majority of women. The association of induced abortions with HPV markers was not confounded by lifetime number of sexual partners and may be a proxy of higher-risk sexual behavior and/or some iatrogenic transmission through insufficiently sterilized medical instruments. The association with history of a previous Pap smear might suggest some confounding by reflex Pap testing among women with other symptomatic

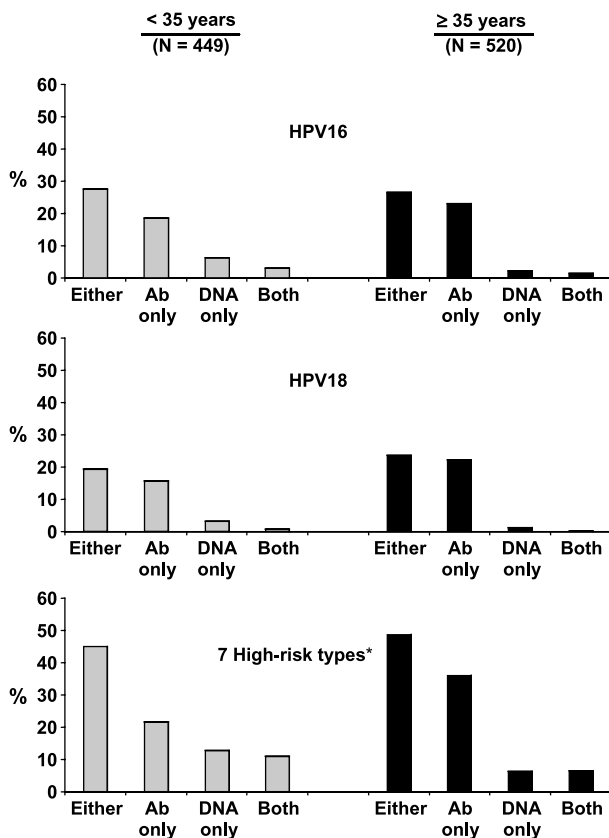


Figure 2. Comparison of HPV DNA and antibody positivity among women positive for either marker, by age group, Ulaanbaatar, Mongolia, 2005. *Including HPV 16, 18, 31, 33, 45, 52, and 58.

Table 4. OR (95% CI)* for HPV DNA and antibody positivity according to selected participant characteristics, Ulaanbaatar, Mongolia, 2005

Risk factor	No. women	HPV DNA		HPV antibodies [†]	
		n positive (%)	OR (95% CI)	n positive (%)	OR (95% CI)
Age group					
<25	196	95 (48.5)	1 (-)	65 (33.2)	1
25-29	129	56 (43.4)	0.7 (0.5-1.2)	40 (31.0)	0.9 (0.5-1.4)
30-34	124	41 (33.1)	0.5 (0.3-0.8)	41 (33.1)	1.0 (0.6-1.6)
35-39	133	36 (27.1)	0.4 (0.2-0.6)	55 (41.4)	1.4 (0.9-2.2)
40-44	123	35 (28.5)	0.4 (0.3-0.7)	44 (35.8)	1.2 (0.7-1.9)
45-49	127	33 (26.0)	0.4 (0.2-0.6)	56 (44.1)	1.7 (1.0-2.6)
≥50	137	43 (31.4)	0.5 (0.3-0.8)	67 (48.9)	2.0 (1.2-3.1)
χ^2_1 for trend			<i>P</i> < 0.001		<i>P</i> < 0.001
Occupation					
Manual worker	434	147 (33.9)	1 (-)	162 (37.3)	1 (-)
Clerk	434	146 (33.6)	1.0 (0.8-1.4)	174 (40.1)	1.1 (0.8-1.4)
Unemployed/students	93	44 (47.3)	1.4 (0.9-2.2)	30 (32.3)	0.8 (0.5-1.3)
Education					
≥Senior high school	555	194 (35.0)	1 (-)	212 (38.2)	1 (-)
≤Junior high school	411	143 (34.8)	1.1 (0.8-1.4)	154 (37.5)	1.0 (0.7-1.3)
Marital status					
Married	701	208 (29.7)	1 (-)	275 (39.2)	1 (-)
Single	201	107 (53.2)	1.8 (1.2-2.8)	61 (30.4)	0.7 (0.5-1.2)
Widow/separated	65	23 (35.4)	1.3 (0.7-2.3)	32 (49.2)	1.3 (0.8-2.2)
Lifetime no. sexual partners					
1	407	121 (29.7)	1 (-)	145 (35.6)	1 (-)
2	249	88 (35.3)	1.3 (0.9-1.8)	91 (36.6)	1.1 (0.8-1.5)
3	147	62 (42.2)	1.8 (1.2-2.7)	59 (40.1)	1.3 (0.9-1.9)
≥4	157	62 (39.5)	1.6 (1.1-2.3)	69 (44.0)	1.5 (1.0-2.1)
χ^2_1 for trend			<i>P</i> = 0.005		<i>P</i> = 0.042
Husbands' extramarital sexual relationships					
Never	234	72 (30.8)	1 (-)	77 (32.9)	1 (-)
Ever	471	169 (35.9)	1.0 (0.7-1.5)	189 (40.1)	1.4 (1.0-2.0)
Induced abortion					
Never	325	103 (31.7)	1 (-)	102 (31.4)	1 (-)
Ever	606	217 (35.8)	1.6 (1.2-2.2)	250 (41.3)	1.4 (1.0-1.9)
History of Pap test					
Never	856	291 (34.0)	1 (-)	327 (38.2)	1 (-)
Ever	83	38 (45.8)	1.9 (1.2-3.1)	28 (33.7)	0.7 (0.4-1.1)
Cytology					
Normal	842	257 (30.5)	1 (-)	312 (37.1)	1 (-)
AGUS/ASCUS/ASC-H	85	42 (49.4)	2.2 (1.4-3.5)	34 (40.0)	1.1 (0.7-1.8)
LSIL	29	28 (96.6)	61.1 (8.2-455)	12 (41.4)	1.4 (0.7-3.0)
HSIL	13	12 (92.3)	30.7 (3.9-240)	10 (76.9)	5.5 (1.5-20)
χ^2_1 for trend			<i>P</i> < 0.001		<i>P</i> = 0.020

*Adjusted for age and lifetime number of sexual partners.

[†]L1 antibodies for HPV 16, 18, 31, 33, 45, 52, and 58.

sexually transmitted diseases. The fact that the mean number of sexual partners in Ulaanbaatar was higher (2.1) compared with previous similar surveys in other geographic areas (range, 1.1-1.7; ref. 25), coupled with the fact that 70% of study participants reported their husbands had had extramarital sexual relationships, may explain, in part, the high circulating level of HPV, which is known to be highly sexually transmissible (27). Indeed, the burden of other sexually transmitted disease is also high in Ulaanbaatar (28, 29). HPV prevalence was 36% in a study of 110 women attending a sexually transmitted disease clinic in Ulaanbaatar (29).

Strengths of the present study include a relatively large sample size (especially among young unmarried women), the use of a standardized and well-validated HPV DNA test allowing valid comparisons with similar studies around the world, and the use of high-throughput serologic technology that allows the simultaneous analysis of antibodies against seven HPV types (12). The main limitation was the need to resort to an occupational rather than a residential population list for

invitation of study participants, which may have affected the socioeconomic balance of the sample. However, it is worth bearing in mind that the majority of women in Ulaanbaatar are part of the workforce (61%; ages 19-54 years; ref. 7) and that participation rates were higher than those usually obtained through population lists (3). Although our present findings do not inform us directly about HPV prevalence of the Mongolian women living outside the country's capital, we observed no difference in HPV prevalence between women who were born in Ulaanbaatar from the majority who had migrated to the city from other provinces. Given that more than one-third of the population of Mongolia currently lives in the capital and that this process of urbanization can be expected to continue, sexual health and cervical cancer prevention are clearly important public health issues in Mongolia.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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