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Research Article

Modifiable and Non-Modifiable Factors Related to HPV Infection and Cervical Abnormalities in Women at High Risk: A Cross-Sectional Analysis from the VALHIDATE Study

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Abstract

Migrant women, and women infected with HIV, are at enhanced risk of cervical HPV infection and HPV-related cancers. We investigated factors that can reduce these risks through public health preventive and screening interventions. We studied the prevalence and risk factors for cervical HPV infection/lesions in women with HIV-infection (HIW), in migrant women (RMW) and in a control group of resident women (SPW) who were enrolled in the study for the eVALuation and monitoring of HPV Infections and relATEd cervical diseases in high-risk women (VALHIDATE). Among 3093 evaluable women, age-standardized HPV prevalence was 36.3% (95%CI: 28.1–44.4) in HIW, 21.6% (95%CI: 15.7–27.5) in RMW, and 14.3% (95%CI: 12.5–16.1) in SPW. Adjusted prevalence of HPV infection was 2.07 times higher among HIW (95%CI: 1.75–2.45), and 1.45 times higher among RMW (95%CI: 1.17–1.80) than in SPW. Prevalence-ratios of SIL and HG-SIL were 2.67 (95%CI: 2.06–3.45) and 2.82 (95%CI: 1.28–6.20), respectively, in HIW compared to controls. A multivariate log-binomial regression model showed modifiable risk factors associated with HPV infection/lesion to have different patterns among groups. Specific public-health intervention, including health and sexual-health education, safe-sex procedures, and improvements to screening programmes, could favorably affect these highly vulnerable women.

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ABBREVIATIONS

HIV: Human Immunodeficiency Virus; HPV: Human Papillomavirus; HIW: Women with HIV infection; RMW: Recent Migrant Women; SPW: Women who attended Spontaneous Pap-screening Programs; VALHIDATE: eVALuation and Monitoring of HPV Infections and relATEd Cervical Diseases in High-Risk Women; PCR: Polymerase Chain Reaction; STI: Sexually Transmitted Infection; HR-HPVs: High-Risk HPV; HG-SIL: High Grade Intraepithelial Lesions; eCRF: Electronic Case Report Form; ASC-US: Atypical Squamous Cells of Undetermined Significance; ASC-H: Atypical Squamous Cells that cannot exclude High-Grade SIL; LG/LSIL: Low Grade SIL; HSIL: High-Grade SIL; CA: Carcinoma; UNS: Unsatisfactory Specimens; CIN 1: Cervical Intraepithelial Neoplasia Grade 1; CIN 2: Cervical Intraepithelial Neoplasia Grade 2; PRs: Prevalence Ratios; $PR_{adj,}$: Prevalence Ratios Adjusted; PR_{crude}: Crude Prevalence Ratios; Cis: Confidence Intervals; cART: Combined Antiretroviral Treatment

INTRODUCTION

Infection with human papillomavirus (HPV) is a very common sexually transmitted infection (STI); the life-time risk of cervical HPV infection in women is estimated to be 80% [1]. Several co-factors beyond sexual exposure, such as age at first sexual intercourse, host susceptibility, other STIs, smoking, use of oral contraceptives and parity have also been associated to increased risk of infection and/or disease progression [2,3]. Although up to 90% of these infections clear within 2 years, persistent infection from a high-risk HPV genotype (HR-HPVs) can evolve to cancer. Although cervical cancer screening programs have led to a substantial decrease in its incidence, cervical cancer remains the third most common female cancer worldwide with the highest burden in developing countries, where more than 80% of all the cervical cancer cases are detected [3,4]. The higher burden in resource limited settings primarily reflects lack of access to screening programs, which also contributes to the high prevalence of HPV infections and cancers in women migrating to industrialized world, who face language and social-economic barriers for healthcare access [5-13]. Host genetic factors [14] and impaired cell-mediated immunity, as with HIV-infected patients, are also associated with more persistent HPV infection and, thus, to increased risk of progression to cancer [15-19]. If the main cause of increased risk of progression to high grade intraepithelial lesions (HG-SIL) in HIV-infected patients is their inability to control replication and expression of HPV because of compromised immunity, the more widespread infection incidence seen in this population is probably also related to exposure to sexually transmitted infections and not entirely to impaired immunity.

Epidemiological studies on cervical HPV prevalence in migrant women and in HIV-infected women showed wide variation in setting, age, cytology, and tests used, with prevalence ranging from 38–80%, but generally higher than those found in the control immune-competent population [5,7,12,20,21]. Disparities in distribution of HPV infection and HPV-related cervical diseases in highly vulnerable groups reflect the health system's ability to reach all the target population, and underscore the need of specifically addressed public health interventions. Nowadays, prevention of HPV related diseases relies on HPV vaccine, regular screening and follow up, and sexual health education. This study aimed to provide an overview on factors associated with HPV infection and disease in two high-risk groups of women. We compared HIV^+ women and migrant women in their first year of migration who had no health insurance, with a control group of resident women enrolled, between Nov 2010 and Dec 2013, in the Lombardy Region epidemiological study for the eVALuation and monitoring of HPV infections and relATEd cervical diseases in high-risk women (VALHIDATE). This is an ongoing longitudinal prospective cohort study that focuses on clinical, virological and epidemiological characteristics of HPV infection and related cervical diseases in women at high risk for cervical cancer [22].

MATERIALS AND METHODS

Study Population

The present study is the cross sectional report of the baseline evaluation of female population recruited in the VALHIDATE study [22] according to the protocol approved by the Ethical Committees of the participating centers. Enrollment was conducted inviting all women consecutively visiting seven clinical centers in four general hospitals (4 gynecology units and 3 infectious diseases units) and one faith-based outpatient department for migrants lacking health insurance. Each clinical centre provides a good experience in the implementation of population-based screening programs for cervical cancer which include a three-year recall of all women aged 25-64 years, in accordance with national Italian guidelines [23]. Migrant women who had arrived in Italy within 1 year (recent migrant women, RMW) and HIV-infected women (HIW) were considered as two distinct study groups of women at high risk for HPV infection and were compared with a control group of resident women aged 18–65 years who attended spontaneous Pap-screening programs (SPW). Exclusion criteria were history of cervical cancer or surgically treated high-grade precancerous lesions, and refusal to sign the informed consent. Moreover, women in the SPW and RMW groups had not declared HIV status.

The enrollment was lower than expected by the protocol for all groups, reaching 77% of expected for HIW, 70% for SPW and 42% for RMW. The enrollment of young women less than 26 years of age was 38% of expected (508 women). Therefore, this group was analyzed together with SPW group. No protocol violation was recorded for RMW and HIW groups.

Baseline evaluation

Baseline evaluations of the women were based on medical assessment by a gynecologist, and by an infectious disease specialist for the HIW patients; demographic, socioeconomic, behavioral data and medical history were collected and recorded on a specially designed electronic case report form (eCRF) from each participating centre. In the first screening round, all consenting women received both HPV testing and cytology. Cervical specimens were collected using a brush (Cytobrush Plus® Medscand Medical AB, Sweden) to perform a conventional Pap smear evaluated according to the 2001 Bethesda System terminology by expert cytopathologists of the participating

centers. Samples were classified as negative for cellular abnormalities (NEG), atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells that cannot exclude high-grade SIL (ASC-H), low grade SIL (LSIL), high-grade SIL (HSIL), or carcinoma (CA). Unsatisfactory (UNS) specimens were excluded from the analysis. Colposcopy was performed in women with findings of ASC-US or worse and colposcopic driven biopsies were performed when indicated. Women with cervical intraepithelial neoplasia (CIN) grade 2 or more severe histological findings were referred for treatment. In cases of discordant cytology and histology, the more severe result was retained for analysis. Cyto/histological findings were then classified as low-grade SIL (LG-SIL) encompassing ASC-US, LSIL, CIN1, and high-grade SIL (HG-SIL) encompassing ASC-H, HSIL, CIN2 or worse.

The same cervical brush used for cytology was immersed and rinsed in 20 ml of PreservCyt® solution (ThinPrep Pap Test, Hologic Italia Srl, Italy), and stored at room temperature until HPV testing performed by the reference virology laboratory. Ten milliliters of each PreservCyt® solution containing cervical cells were centrifuged at 3800 ×g for 15 min at room temperature, then re-suspended in 1 mL of phosphate buffered saline (PBS), transferred into a new 1.5 mL collection test tube and stored at −20°C until nucleic acids extraction by NucliSENS® EasyMAG™ (bioMérieux, Lyon, France) commercial kit. The concentration and purity of the extracted DNA were evaluated using a spectrophotometer (Thermo Scientific NanoDrop 2000c; Thermo Fisher Scientific, Inc., Wilmington, DE). HPV DNA was detected by PCR amplification of a 450-bp segment of ORF L1 using the degenerate primer pair ELSI-f (5′-gCNCARggHCATAAYAATgg-3′) and ELSI-r (5′-CgNCCHAADggAAAYTgATC-3′) [24]. HPV DNA+ samples were genotyped by the INNO-LiPA™HPV Genotyping Extra (Fujirebio Italia, Roma, Italy) in microbiology laboratories of participating centres. Oncogenic risk of HPV types was assessed by the 2011 IARC classification [25]; genotypes classified as "carcinogenic", "probably carcinogenic" or "possibly carcinogenic" to humans, all included in the High-Risk clade, were considered High-Risk HPV (HR-HPV) in these analyses.

Statistical analysis

Demographic and behavioral characteristics (age, geographical origin, marital status, level of education, smoking habits), reproductive and sexual health data (age at first sexual intercourse, parity, number of pregnancies and deliveries, spontaneous abortion, use of contraceptives and condoms, use of estroprogestinic drugs, menopause, number of lifetime and recent sexual partners, adherence to Pap screening programs, result of the Pap Test, history of sexually transmitted infections) and clinical data (history of diseases grouped by the major diagnostic categories scheme) were included in the analysis for the association with the prevalence of HPV infection. Differences in distribution of these factors between the control group and the RMW and HIW groups were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Crude and age-standardized prevalence of HPV infection (applying direct method and using world population), were calculated with the corresponding 95% confidence intervals (95% CIs) for each study group. Prevalence of HPV was also calculated in strata of each factor considered in the analysis. To determine which factors were associated with HPV prevalence, prevalence ratios (PRs) for HPV infection, and corresponding 95% CIs, were calculated for each factor, using log-binomial regression in the three study groups. Multivariable models (PR_{adj}) were used to control for potential confounding by factors that were significantly associated with HPV prevalence in the crude analysis, and for group-specific factors. When appropriate, X^2 test for trend was also assessed. Adjustments are specified in table footnotes. Statistical analyses used SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

A similar analysis was performed for prevalence of cyto/histological abnormalities, which were defined as the more severe finding of the Pap test or the cervical biopsy results. Crude prevalence was estimated for each study group, in strata of each factor considered in the analysis, and for HG-SIL only. Prevalence ratios for cyto/histological abnormality of any grade (and corresponding 95% CIs), were calculated for each study group using multivariable-models including study centre, age and number of lifetime sexual partners as covariates, when appropriate.

RESULTS

Among 3185 women aged 18–65 years who gave their written informed consent, 3093 women were included in the analysis after the exclusion of 92 women (3%) for whom HPV or Pap test results were missing or inadequate (75 from the SPW group, 14 from the HIW group, 3 from the RMW group). Subjects included 1910 controls (SPW), 766 HIV infected women (HIW), and 417 recently immigrated women (RMW) (Table 1). The average refusal rate was 15%, with 3 out of the 8 centers showing a refusal rate lower than 10% and only 1 centre with a higher value of about 30%. Of the women in the HIW group, 708 (92.8%) were on combined antiretroviral treatment (cART), with mean $CD4^+$ cells counts of 599.9 cells/μL (95% CI: 578.8-621.1) and 636 (83.9%) had suppressed HIV viral loads (<50 copies/μL). The most represented geographical origins of women in the RMW group were Latin America (237/417, 56.8%), followed by Eastern Europe (116/417, 27.8%).

Women with HIV infection (HIW)

The women included in the HIW group were significantly different from the SPW group for most of the factors considered (Table 1). They were older, with a median age of 43 years compared with 34 years for the SPW group, they were more frequently foreign born (19% *vs* 7%), less frequently unmarried (27% *vs* 52%), less educated (51% were educated to the high school or university level, compared with 86% of the SPW group) and they were less frequently never-smokers (34% *vs* 61%). Women in the HIW group were younger at the time of their first sexual intercourse, 39% had more than five lifetime sexual partners compared with 22% in the control group, but tended to have had fewer partners in the last 6 months (26% declared no partners in the last 6 months compared with 7% in the SPW group). Condoms were the preferred contraceptive method in the HIW group (52.5%), whereas estroprogestinic drugs were preferred in the SPW group (70%). Parity was higher among HIW patients (76.8% *vs* 45.8%), and a higher percentage were in menopause than the SPW group (19% *vs* 7%).

Table 1: Distribution of selected socio-demographics characteristics, smoking and sexual habits, reproductive and gynecological history, in the three study groups: controls (SPW), HIV infected women (HIW), and recent migrant women (RMW).

	SPW N=1910		HIW N=766		RMW N=417		Statistic[a] (*p*-value) HIW *vs* SPW	Statistic[a] (*p*-value) RMW*vs* SPW
	N	%	N	%	N	%		
Age (years)	508	26.6%	33	4.3%	153	36.7%		
18-25							<0.01	<0.01
26-35	525	27.5%	120	15.7%	143	34.3%		
36-45	620	32.5%	333	43.5%	117	28.0%		
>45	257	13.4%	280	36.5%	4	1.0%		
Median / Mean (95% CI)	34.0 / 34.3 (33.8-34.8)		43.0 / 42.0 (41.4-42.6)		29.0 / 30.1 (29.4-30.9)		<0.01	<0.01
Geographical origin								
Italy	1768	92.6%	620	80.9%	0	0.0%	<0.01	<0.01
Africa	15	0.8%	83	10.8%	44	10.6%		
Asia	6	0.3%	9	1.2%	20	4.8%		
Europe	66	3.4%	25	3.3%	116[b]	27.8%		
Latin America	55	2.9%	29	3.8%	237	56.8%		
Marital status	988	51.7%	209	27.3%	180	43.2%		
Unmarried							<0.01	<0.01
Married	681	35.7%	266	34.7%	159	38.1%		
Cohabitant	103	5.4%	113	14.8%	35	8.4%		
Other (divorced or widow)	138	7.2%	178	23.2%	43	10.3%		
Education[c]								
Primary school	269	14.1%	375	49.0%	148	35.5%	<0.01	<0.01
Secondary school	1047	54.8%	332	43.3%	205	49.2%		
University degree	594	31.1%	58	7.6%	64	15.3%		
Smoking habit	1173	61.4%	261	34.1%	345	82.7%		
Never smoker							<0.01	<0.01
Ex smoker	206	10.8%	153	20.0%	14	3.4%		
Current smoker	531	27.8%	352	45.9%	58	13.9%		
1-10 cig./day	377	71.0%	140	39.8%	40	69.0%	<0.01	NS
> 10 cig./day	154	29.0%	212	60.2%	18	31.0%		
Age at first sexual intercourse[c]								
≤16	476	24.9%	298	38.9%	111	26.6%	<0.01	NS
17-18	713	37.3%	276	36.0%	141	33.8%		
≥19	710	37.2%	181	23.6%	164	39.3%		
Median / Mean (95% CI)	18.0 / 18.5 (18.4-18.7)		17.0 / 17.4 (17.2-17.6)		18.0 / 18.4 (18.1-18.8)		<0.01	NS

	SPW N=1910		HIW N=766		RMW N=417		Statistic[a] (*p*-value) HIW *vs* SPW	Statistic[a] (*p*-value) RMW*vs* SPW
	N	%	N	%	N	%		
Number of lifetime sexual partners[c]								
1	465	24.3%	69	9.0%	140	33.6%	<0.01	<0.01
2-5	1029	53.9%	389	50.8%	248	59.5%		
>5	414	21.7%	302	39.4%	28	6.7%		
Number of sexual partners in the last 6 months[c]								

	SPW N=1910		HIW N=766		RMW N=417		Statistic[a] (*p*-value) HIW *vs* SPW	Statistic[a] (*p*-value) RMW*vs* SPW
	N	%	N	%	N	%		
0	138	7.2%	198	25.8%	150	36.0%	<0.01	<0.01
1	1647	86.2%	543	70.9%	247	59.2%		
≥2	119	6.2%	16	2.1%	16	3.8%		
Use of any type of contraceptive methods[c]								
Never	197	10.3%	67	8.7%	91	21.8%	NS	<0.01
Only past use	747	39.1%	276	36.0%	176	42.2%		
Current use	962	50.4%	418	54.6%	150	36.0%		
Use of condom[c]								
Never	764	40.0%	146	19.1%	242	58.0%	<0.01	<0.01
Only past use	663	34.7%	208	27.2%	83	19.9%		
Current use	468	24.5%	402	52.5%	68	16.3%		
Use of IUD[c]								
Never	1761	92.2%	688	89.8%	356	85.4%	<0.01	0.03
Only past use	93	4.9%	64	8.4%	20	4.8%		
Current use	39	2.0%	3	0.4%	17	4.1%		
Use of other contraceptive methods[c,d]								
Never	1870	97.9%	738	96.3%	320	76.7%	NS	<0.01
Only past use	22	1.2%	13	1.7%	71	17.0%		
Current use	0	0.0%	1	0.1%	2	0.5%		
Use of Estro-progestinic drugs (EP)[c]								
Never	573	30.0%	392	51.2%	255	61.2%	<0.01	<0.01
Only past use	851	44.6%	341	44.5%	99	23.7%		
Only current use	197	10.3%	2	0.3%	20	4.8%		
Past and current use	272	14.2%	18	2.4%	19	4.6%		
Years of use[c] ≤5	135	49.6%	10	55.6%	14	73.7%	NS	0.03
>5	124	45.6%	8	44.4%	4	21.1%		

	SPW N=1910		HIW N=766		RMW N=417		Statistic[a] (*p*-value) HIW *vs* SPW	Statistic[a] (*p*-value) RMW *vs* SPW
	N	%	N	%	N	%		
Number of children[c]								
0	1144	59.9%	343	44.8%	165	39.6%	<0.01	<0.01
1	314	16.4%	248	32.4%	126	30.2%		
≥2	450	23.6%	174	22.7%	126	30.2%		
Number of pregnancies[c]								
0	1035	54.2%	178	23.2%	127	30.5%	<0.01	<0.01
1	298	15.6%	226	29.5%	108	25.9%		
2	348	18.2%	190	24.8%	86	20.6%		
≥3	226	11.8%	170	22.2%	96	23.0%		
Spontaneous abortion[c]								
No	1696	88.8%	643	83.9%	365	87.5%	<0.01	NS
Yes	212	11.1%	122	15.9%	52	12.5%		

	SPW N=1910		HIW N=766		RMW N=417		Statistic[a] (*p*-value) HIW *vs* SPW	Statistic[a] (*p*-value) RMW *vs* SPW
	N	%	N	%	N	%		
Menopause[c]								
No	1753	91.8%	604	78.9%	401	96.2%	<0.01	0.01
Yes	140	7.3%	144	18.8%	16	3.8%		
History of STIs and/or genital infections[c]								
No	1281	67.1%	370	48.3%	328	78.7%	<0.01	<0.01
Yes	622	32.6%	388	50.7%	85	20.4%		
History of STIs and/or genital infections by types[c]								
Genital warts	86	4.5%	139	18.2%	5	1.2%	<0.01	<0.01
Mycosis	485	25.4%	187	24.4%	47	11.3%	NS	<0.01
Bacterial vaginosis	63	3.3%	96	12.5%	24	5.8%	<0.01	0.02
HSV	39	2.0%	53	6.9%	1	0.2%	<0.01	0.01
Trichomoniasis	23	1.2%	28	3.7%	0	0.0%	<0.01	-
Chlamydia	26	1.4%	17	2.2%	1	0.2%	NS	NS
Syphilis	1	0.1%	23	3.0%	1	0.2%	<0.01	NS
Gonorrhea	0	0.0%	6	0.8%	1	0.2%	-	-
LGV	1	0.1%	2	0.3%	1	0.2%	NS	NS
At least one STI, other than warts	536	28.1%	249	32.5%	80	19.2%	<0.01	<0.01

	SPW N=1910		HIW N=766		RMW N=417		Statistic[a] (*p*-value) HIW *vs* SPW	Statistic[a] (*p*-value) RMW *vs* SPW
	N	%	N	%	N	%		
Previous PAP screening timing[c]								
Regular timing (every 2-3 years)	1296	67.9%	569	74.3%	114	27.3%	<0.01	<0.01
Irregular timing	299	15.7%	158	20.6%	87	20.9%		
Never done	309	16.2%	33	4.3%	216	51.8%		
Previous PAP screening result[c]								
Never done	309	16.2%	33	4.3%	216	51.8%	<0.01	<0.01
Negative	1518	79.5%	614	80.2%	195	46.8%		
Positive	57	3.0%	85	11.1%	4	0.9%		
Unknown	24	1.3%	30	3.9%	2	0.5%		
History of chronic or relevant diseases[c,e]								
No	1240	64.9%	389	50.8%	278	66.7%	<0.01	NS
Yes	668	35.0%	377	49.2%	139	33.3%		

NS: Not significant.
[a]Chi-square test, Fisher exact Test or T test.
[b]All women came from Eastern Europe.
[c]The sum does not up to the total because of missing values.
[d]Other contraceptive methods include: injections of hormones, ovules, tube tied, vaginal ring.
[e]Diseases classified according to Major Diagnostic Categories (MDC – version 24).

History of STIs was significantly higher for HIW, 51% of whom reported having had at least one condition compared with 33% in the SPW group, and genital warts were exceedingly higher in the HIW group (18%) than in the SPW (4.5%). Only 4% of the HIW group had never had a Pap smear previously compared with 16% of the SPW group, and they had more frequent positive Pap screening results (11% *vs* 3%).

Recent migrant women (RMW)

The RMW group also differed from controls for most of the factors considered. Women in this group were younger than controls, with a median age of 29 years. They were less educated, 65% were educated to the high school or university level compared with 86% in the control group and most of them were never-smokers (83% *vs* 61%). About 34% claimed only one partner in their lives and 36% claimed no partners in the last six months, compared with 24% and 7%, respectively, in the control group. A higher percentage of the RMW group claimed to use no contraceptive method than did the SPW group (22% *vs* 10%). Parity was higher in RMW (69.5% *vs* 45.8%). History of STIs was significantly lower for RMW only 20% of whom reported having had at least one condition. Finally, about 52% of them declared that they had never had a Pap smear previously, compared with 16% of the control group.

Prevalence of HPV infection and SIL

A total of 572 women (18.5%; 95% CI: 17.13–19.86) had a positive HPV DNA test among the 3093 women analyzed: SPW: 273; HIW: 215; RMW: 84. Age-standardized HPV prevalence was SPW: 14.3% (95% CI: 12.5–16.1); HIW: 36.3% (95% CI: 28.1–44.4); RMW: 21.6% (95% CI: 15.7–27.5) (Figure 1a). Most infections were sustained by HR-HPV types in all groups. Among HPV-infected women, crude prevalence of infection from at least one HR-HPV type was SPW: 85.72%; HIW: 76.74%; RMW: 85.60%. The adjusted prevalence ratio (PR_{adj}) of HPV infection compared with controls was HIW: 2.07 (95% CI: 1.75–2.45); RMW: 1.45 (95% CI: 1.17–1.80) (Table 2).

Squamous intraepithelial lesions (SIL) were found in cytological and/or histological samples in 288 women (9.3%; 95% CI: 8.29–10.34)—specifically, SPW: 128 (6.7%, 95% CI: 5.6–7.8); HIW: 125 (16.3%, 95% CI: 13.7–18.9); RMW: 35 (8.4%, 95% CI: 5.9–11.5) (Figure 1b). When type of cyto/histological abnormality was considered, HG-SIL was seen in 13 women in the SPW group (0.7%; 95% CI: 0.4–1.2), 17 in the HIW group (2.2%; 95% CI: 1.3–3.5), and 6 in the RMW group (1.4%; 95% CI: 0.5–3.1) (Figure 1b).

The HIW had significantly higher prevalence of any grade SIL (PR_{adj}: 2.67; 95% CI: 2.06–3.45) and HG-SIL (PR_{adj}: 2.82; 95% CI: 1.28–6.20) than did the controls. The RMW group had higher prevalence of any grade SIL than did the controls, (PR_{adj}: 1.26; 95% CI: 0.88–1.81) and HG-SIL (PR_{adj}: 2.22; 95% CI: 0.83–5.92) but the adjusted prevalence rate did not reach a statistical significance (Table 2).

Effect of age on prevalence of HPV infection and SIL

A significant decreasing trend in HPV prevalence by age was observed in the three study groups (Figure 2a, Table 3), and was most pronounced in the HIW group, with HPV prevalence of 51.5% (95% CI: 33.5–69.2) in the 18–25 years old (y.o.) subgroup (considered as reference category), followed by 41.7% in 26–35 y.o. women and 24% in both those 36–45 y.o. and >45 y.o.,

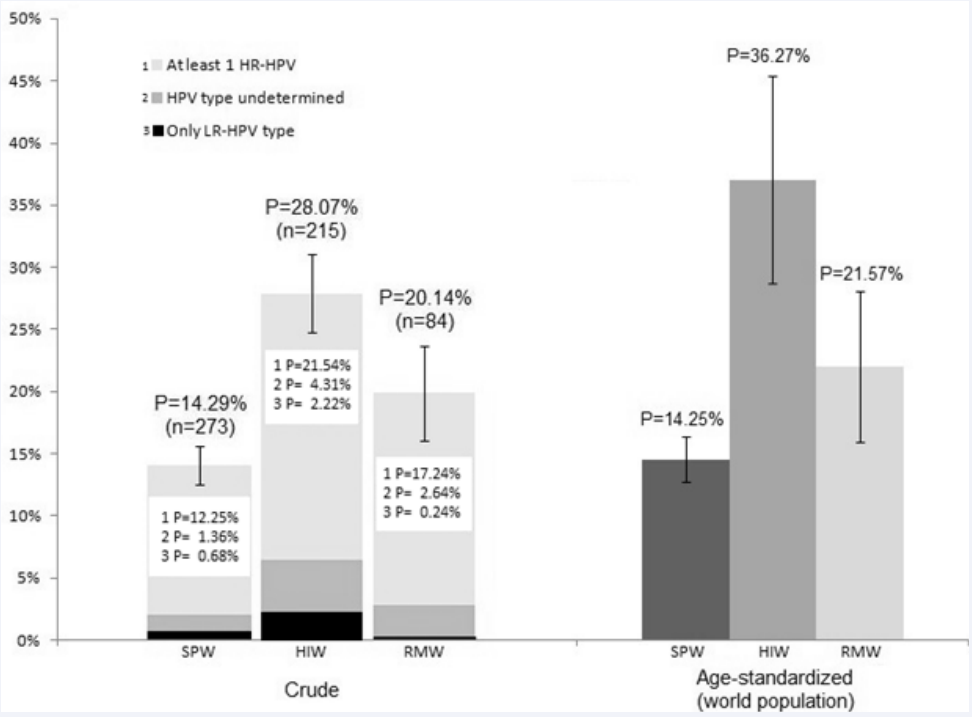

Figure 1a Prevalence of HPV Infection. Crude and Age-standardized(world population)prevalence (P) of HPV infection and corresponding 95% confidence intervals (CI), in the control group (SPW), the HIV infected women group (HIVW), and recent migrant women group (RMW).

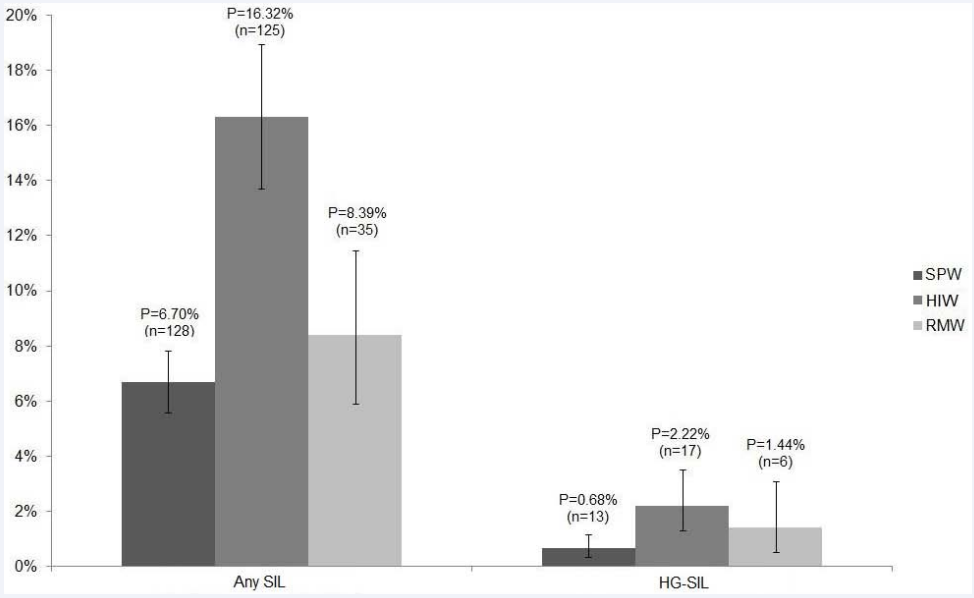

Figure 1b Prevalence of SIL and HG-SIL. Crude prevalence (P)and corresponding 95% confidence intervals (CI) of any cyto/histological abnormality and high grade intraepithelial lesions in the control group (SPW), the HIV infected women group (HIVW), and the recent migrant women group (RMW).

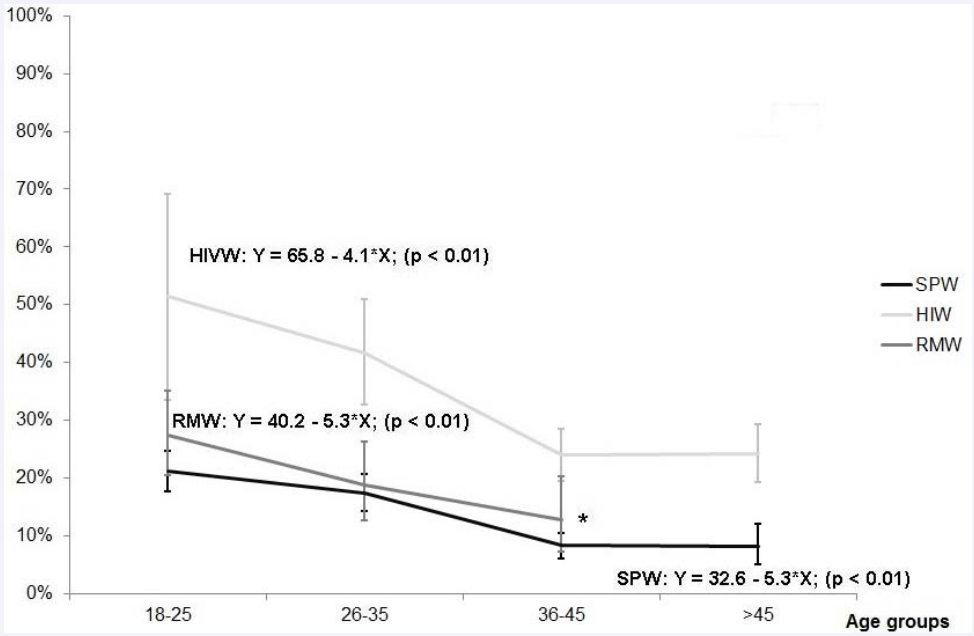

Figure 2a Prevalence of HPV Infection. Prevalence and corresponding 95% confidence intervals (CI) of HPV infection by age groups, in the control group (SPW), the HIV infected women group (HIVW), and the recent migrant women group (RMW).

reflecting risk reductions of about 19% (PR_{crude}: 0.81) and 53% (PR_{crude}: 0.47) respectively (Table 3).

The control group showed a similar trend, although HPV prevalence was always lower than in the HIW group (Figure 2a). Age-specific HPV prevalence decreased from 21.3% to 8.4 in 18–25 y.o., 36-45 y.o. women (PR_{crude}: 0.39, 95% CI: 0.29–0.54). The RMW group showed a less marked downward trend; age-specific prevalence was always higher than controls, and ranged from 27.5% in 18–25 y.o. women to 12.8% in 36–45 y.o. women (PR_{crude}: 0.47; 95% CI: 0.27–0.80). We had too few subjects older than 45 years in this study group to allow any comparison for this age group. The prevalence ratio of SIL (any grade) was reduced in SPW older than 25 years and stable for HIW and RMW. Correlation between age and HG-SIL were not investigated because of the low number of events observed in all study groups (Table 4). In the HIW group, the prevalence of SIL was significantly higher through all age groups compared with controls, with a prevalence of 24% (95% CI: 11.1–42.3) for women aged 18–25 years and 17%

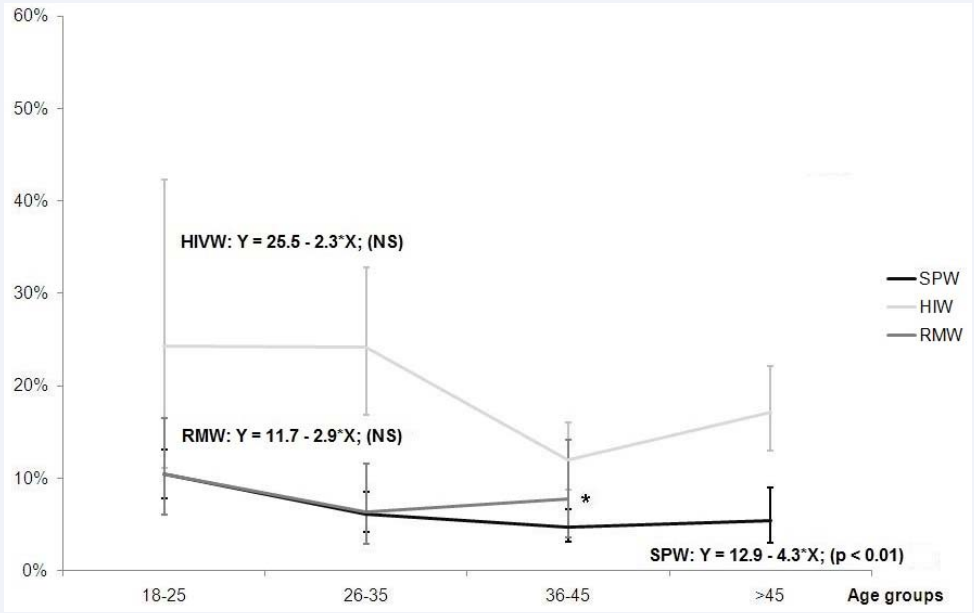

Figure 2b Prevalence of HPV Infection. Prevalence and corresponding 95% confidence intervals (CI) of HPV infection by age groups, in the control group (SPW), the HIV infected women group (HIVW), and the recent migrant women group (RMW).

(95% CI: 12.9–22.1) for women aged 45 years or older (Table 4). Because of the low number of SIL observed in the RMW group (35 out of 417 women), the result interpretation was not possible for this study group.

Other factors associated to HPV prevalence

We investigated the association between a wide range of factors and the prevalence of HPV infection for each study group (Table 3) and summarized the factors significantly associated to HPV prevalence also when major confounders were considered (Figure 3a). In the multivariate log-binomial regression model, the main factors significantly associated to HPV prevalence in at least one of the three study groups were age, marital status, smoking habits, number of lifetime sexual partners, use of any contraceptive method, use of condoms, number of pregnancies and deliveries, having had STI (mainly genital warts), and previous positive Pap screening results; however, the strength (and significance) of the associations differed among groups (Table 3). Figure 3a shows all the factors modifiable by specifically addressed health information campaigns and significantly associated with change in HPV prevalence for at least one of the groups studied in this analysis.

Other factors associated to SIL

The prevalence of any grade SIL and its corresponding estimated prevalence ratio, and the prevalence of HG-SIL, for all factors considered in the HPV analysis are shown in Table (4). Figure 3b summarizes factors associated significantly to prevalence of any grade SIL in the adjusted models (which considered only major potential confounders—study centre, age and number of partners, when appropriate—because of a low number of positive tests). The main factors significantly associated to SIL in at least one of the three study groups were age, marital status, smoking habits, number of lifetime sexual partners, condom use, history of genital warts, adherence to Pap screening programs and results of previous Pap screening (Table 4). Figure (3b) shows modifiable factors significantly found to change prevalence in cervical abnormalities for at least one of the groups analyzed.

DISCUSSION

We report the results of the cross-sectional part of the VALHIDATE study based on a co-testing evaluation (cytology and HPV testing plus genotyping), designed to be representative of women at high risk of HPV infection and related cervical diseases across a wide age range. Although this study is from a limited geographic area, it is the first population-based study on prevalence, age distribution, and risk factors for HPV infection and related cervical lesions in HIV-infected women (HIW) and recently migrant women (RMW) compared with a control group (SPW) of women resident in Lombardy (Italy). The crude, age-standardized prevalence and adjusted prevalence ratio of HPV infection are significantly higher in the testing groups than in the control group of resident women; and the crude and adjusted prevalence ratios of cervical intraepithelial abnormalities (any grade and high-grade SIL) were higher in HIW than in the control group. Cervical cancer prevention strategies are evolving because of the introduction of preventive vaccines and the availability of HPV testing for primary screening in addition to the well-established effectiveness of cytology screening introduced in the mid-50s.

Randomized trials [26-28] have shown that HPV testing provides greater sensitivity than cytology for detection of CIN, and that the detection of high-risk HPV types could be a better predictor of increased risk [29,30]. However, as reflex cytology is needed to detect underlying cellular abnormalities in HPV$^+$ women, HPV testing is recommended for those older than 30 years when the prevalence of transient infections falls. In the ARTISTIC trial [31] infection prevalence from high risk HPV

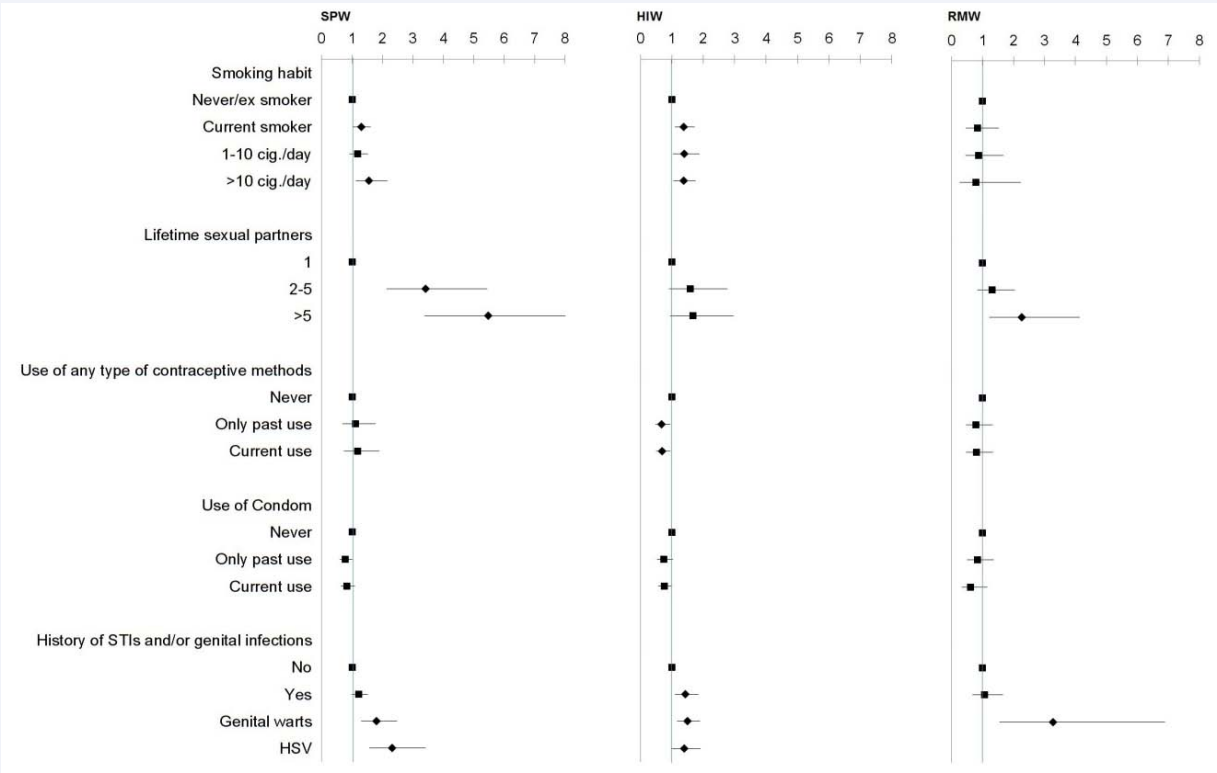

Figure 3a Adjusted PR (95%CI) for modifiable factors significantly associated to HPV infection in at least one study group (i.e. controls: SPW, the HIV-positive women: HIVW and the recent migrant women: RMW). Diamonds correspond to significant PR.

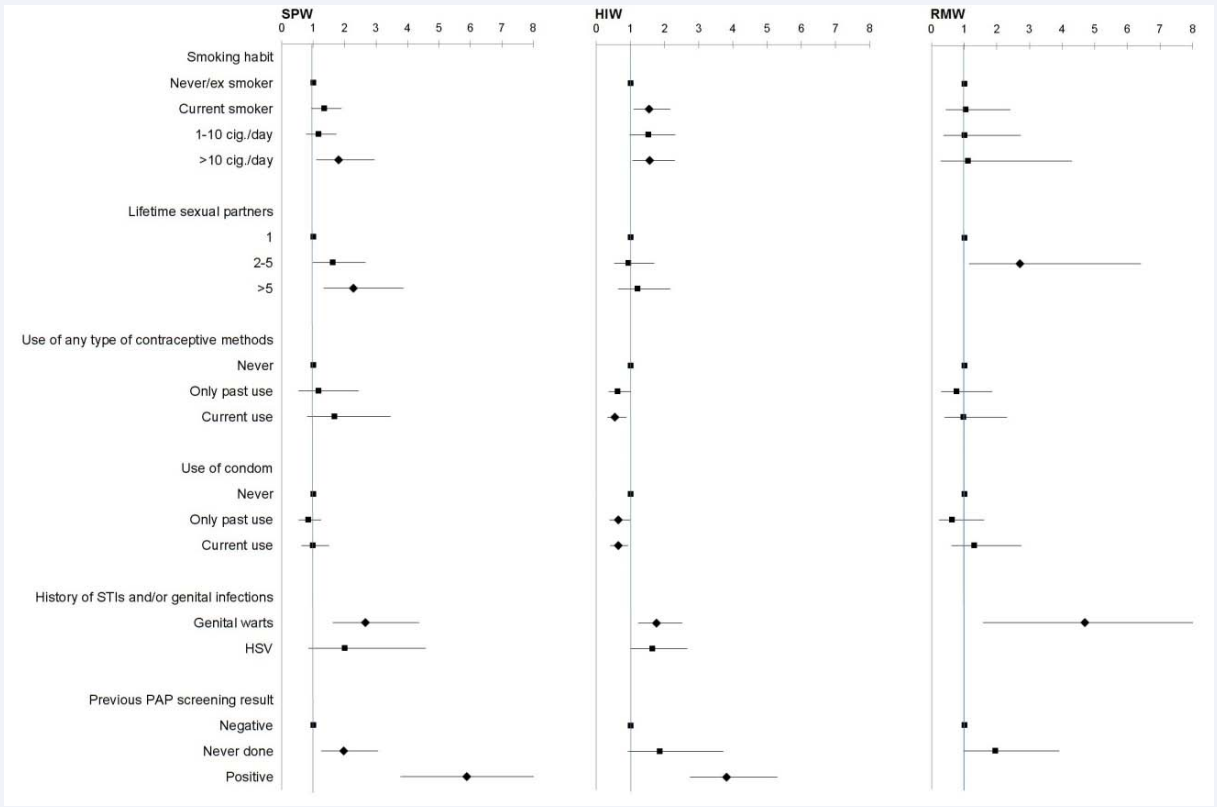

Figure 3b Adjusted PR (95%CI) for modifiable factors significantly associated to cyto/histological abnormalities in at least one study group (i.e. controls: SPW, the HIV-positive women: HIVW and the recent migrant women: RMW). Diamonds correspond to significant PR.

Table 2: Prevalence and prevalence ratios (PR) comparing the HIW and the RMW groups versus the SPW group, and corresponding 95% confidence intervals (CI), for HPV infection, and cyto/histological abnormalities (any grade and HG-SIL).

	SPW N=1910		HIW N=766		RMW N=417	
	N	%	N	%	N	%
HPV positive test result	273	14.3%	215	28.1%	84	20.1%
Crude PR[a] (95% CI)	1[c]		**1.96 (1.68-2.30)**		**1.41 (1.13-1.76)**	
Adjusted PR[b] (95% CI)	1[c]		**2.07 (1.75-2.45)**		**1.45 (1.17-1.80)**	
Any grade SIL	128	6.7%	125	16.3%	35	8.4%
Crude PR[a] (95% CI)	1[c]		**2.44 (1.93-3.07)**		1.25 (0.88-1.79)	
Adjusted PR[d] (95% CI)	1[c]		**2.67 (2.06-3.45)**		1.26 (0.88-1.81)	
HG-SIL	13	0.7%	17	2.2%	6	1.4%
Crude PR[a] (95% CI)	1[c]		**3.26 (1.59-6.68)**		2.11 (0.81-5.53)	
Adjusted PR[d] (95% CI)	1[c]		**2.82 (1.28-6.20)**		2.22 (0.83-5.92)	

[a]Prevalence ratio estimates from univariate log-binomial regression model.
[b]Prevalence ratio estimates from multivariate log-binomial regression model adjusted for age groups, smoking habit, and number of lifetime sexual partners.
[c]Reference category.
[d]Prevalence ratio estimates from multivariate log-binomial regression model adjusted for age groups and number of lifetime sexual partners.

Table 3: Number (N), prevalence (P), and prevalence ratios (PR) of HPV infection and corresponding 95% confidence intervals (CIs), according to selected socio-demographics characteristics, smoking and sexual habits, reproductive and gynecological history, in the control group (SPW), the HIV group (HIW), and the recent migrant group (RMW).

	SPW (N=1910)			HIW (N=766)			RMW (N=417)		
	HPV infection N=273 N (P)	Crude PR[a] (95% CI)	Adjusted PR[b] (95% CI)	HPV infection N=215 N (P)	Crude PR[a] (95% CI)	Adjusted PR[c] (95% CI)	HPV infection N=84 N (P)	Crude PR[a] (95% CI)	Adjusted PR[d] (95% CI)
Age (years)									
18-25	108 (21.3)	1[e]	1[e]	17 (51.5)	1[e]	1[e]	42 (27.5)	1[e]	1[e]
26-35	92 (17.5)	0.82 (0.64-1.06)	**0.72 (0.56-0.93)**	50 (41.7)	0.81 (0.55-1.20)	0.84 (0.60-1.17)	27 (18.9)	0.69 (0.45-1.05)	0.66 (0.43-1.02)
36-45	52 (8.4)	**0.39 (0.29-0.54)**	**0.40 (0.29-0.55)**	80 (24.0)	**0.47 (0.32-0.68)**	**0.48 (0.34-0.67)**	15 (12.8)	**0.47 (0.27-0.80)**	**0.46 (0.27-0.78)**
>45	21 (8.2)	**0.38 (0.25-0.60)**	**0.45 (0.29-0.69)**	68 (24.3)	**0.47 (0.32-0.70)**	**0.49 (0.35-0.70)**	0 (0.0)	-	-
χ^2trend (*p*-value)		***43.42 (<0.001)***	***36.67 (<0.001)***		***20.23 (<0.001)***	***22.60 (<0.001)***		***8.63 (0.003)***	***10.36 (0.001)***
Geographical origin									
Italy	250 (14.1)	0.87 (0.59-1.29)	0.84 (0.59-1.21)	168 (27.1)	0.84 (0.64-1.10)	0.90 (0.67-1.19)	-	-	-
Africa	3 (20.0)	1.40 (0.51-3.89)	2.03 (0.77-5.40)	27 (32.5)	1.18 (0.85-1.65)	1.15 (0.81-1.61)	8 (18.2)	0.89 (0.46-1.72)	0.96 (0.50-1.83)
Asia	0 (0.0)	-	-	1 (11.1)	0.39 (0.06-2.50)	NA	1 (5.0)	0.24 (0.04-1.63)	NA
Europe	12 (18.2)	1.28 (0.76-2.17)	1.10 (0.68-1.79)	8 (32.0)	1.15 (0.64-2.05)	1.04 (0.59-1.82)	23 (19.8)	0.98 (0.64-1.50)	0.92 (0.60-1.41)
Latin America	8 (14.5)	1.02 (0.53-1.95)	1.28 (0.70-2.34)	11 (37.9)	1.37 (0.85-2.21)	1.27 (0.77-2.09)	52 (21.9)	1.23 (0.83-1.83)	1.20 (0.81-1.78)
Marital status									
Unmarried	196 (19.8)	1[e]	1[e]	77 (36.8)	1[e]	1[e]	47 (26.1)	1[e]	1[e]
Married	35 (5.1)	**0.26 (0.18-0.37)**	**0.44 (0.30-0.65)**	54 (20.3)	**0.55 (0.41-0.74)**	**0.65 (0.47-0.89)**	21 (13.2)	**0.51 (0.32-0.81)**	**0.61 (0.37-1.00)**
Cohabitant	17 (16.5)	0.83 (0.53-1.31)	0.89 (0.57-1.40)	36 (31.9)	0.86 (0.63-1.19)	0.90 (0.66-1.24)	8 (22.9)	0.88 (0.45-1.69)	0.90 (0.47-1.72)

Table 3: Number (N), prevalence (P), and prevalence ratios (PR) of HPV infection and corresponding 95% confidence intervals (CIs), according to selected socio-demographics characteristics, smoking and sexual habits, reproductive and gynecological history, in the control group (SPW), the HIV group (HIW), and the recent migrant group (RMW).

	SPW (N=1910)			**HIW (N=766)**			**RMW (N=417)**		
	HPV infection N=273 N (P)	Crude PR[a] (95% CI)	Adjusted PR[b] (95% CI)	HPV infection N=215 N (P)	Crude PR[a] (95% CI)	Adjusted PR[c] (95% CI)	HPV infection N=84 N (P)	Crude PR[a] (95% CI)	Adjusted PR[d] (95% CI)
Other (divorced or widow)	25 (18.1)	0.91 (0.63-1.33)	1.31 (0.86-1.98)	48 (27.0)	**0.73 (0.54-0.99)**	0.88 (0.63-1.21)	8 (18.6)	0.71 (0.36-1.39)	0.83 (0.41-1.67)
Education									
Primary school	28 (10.4)	1[e]	1[e]	107 (28.5)	1[e]	1[e]	32 (21.6)	1[e]	1[e]
Secondary school	148 (14.1)	1.36 (0.93-1.99)	1.07 (0.74-1.55)	89 (26.8)	0.94 (0.74-1.19)	0.92 (0.73-1.16)	42 (20.5)	0.95 (0.63-1.43)	0.86 (0.57-1.29)
University degree	97 (16.3)	**1.57 (1.06-2.33)**	1.20 (0.81-1.76)	18 (31.0)	1.09 (0.72-1.65)	1.13 (0.76-1.67)	10 (15.6)	0.72 (0.38-1.38)	0.68 (0.36-1.28)
χ^2trend (*p*-value)		**5.09 (0.024)**	1.23 (0.268)		0.00 (0.967)	0.00 (0.960)		0.81 (0.369)	1.56 (0.211)
	SPW (N=1910)			**HIW (N=766)**			**RMW (N=417)**		
	HPV infection N=273 N (P)	Crude PR[a] (95% CI)	Adjusted PR[b] (95% CI)	HPV infection N=215 N (P)	Crude PR[a] (95% CI)	Adjusted PR[c] (95% CI)	HPV infection N=84 N (P)	Crude PR[a] (95% CI)	Adjusted PR[d] (95% CI)
Smoking habit									
Never/ Ex smoker	170 (12.3)	1[e]	1[e]	99 (24.0)	1[e]	1[e]	73 (20.3)	1[e]	1[e]
Current smoker	103 (19.4)	**1.57 (1.26-1.97)**	**1.30 (1.04-1.62)**	116 (33.0)	**1.38 (1.10-1.73)**	**1.38 (1.10-1.73)**	11 (19.0)	0.93 (0.53-1.65)	0.84 (0.47-1.51)
1-10 cig/day	71 (18.8)	**1.53 (1.19-1.97)**	1.18 (0.92-1.52)	44 (31.4)	1.31 (0.97-1.77)	**1.39 (1.04-1.88)**	8 (20.0)	1.98 (0.51-1.89)	0.87 (0.45-1.68)
>10 cig/day	32 (20.8)	**1.69 (1.20-2.37)**	**1.56 (1.13-2.16)**	72 (34.0)	**1.42 (1.10-1.83)**	**1.37 (1.06-1.76)**	3 (16.7)	0.82 (0.29-2.35)	0.78 (0.27-2.24)
χ^2trend (*p*-value)		***15.53 (<0.001)***	***7.36 (0.007)***		***7.73 (0.005)***	***6.18 (0.013)***		*0.11 (0.745)*	*0.35 (0.556)*
Age at first sexual intercourse									
≤16	83 (17.4)	1[e]	1[e]	93 (31.2)	1[e]	1[e]	28 (25.2)	1[e]	1[e]
17-18	105 (14.7)	0.84 (0.65-1.10)	1.07 (0.83-1.39)	69 (25.0)	0.80 (0.61-1.04)	0.92 (0.71-1.20)	28 (19.9)	0.79 (0.50-1.25)	0.84 (0.53-1.33)
≥19	84 (11.8)	**0.68 (0.51-0.90)**	1.18 (0.88-1.59)	47 (26.0)	0.83 (0.62-1.12)	1.01 (0.72-1.41)	28 (17.1)	0.68 (0.43-1.08)	0.78 (0.49-1.26)
χ^2trend (*p*-value)		***7.44 (0.006)***	*0.35 (0.554)*		*2.02 (0.155)*	*0.02 (0.885)*		*2.67 (0.102)*	*1.00 (0.317)*
Number or lifetime sexual partners									
1	19 (4.1)	1[e]	1[e]	11 (15.9)	1[e]	1[e]	23 (16.4)	1[e]	1[e]
2-5	154 (15.0)	**3.66 (2.30-5.82)**	**3.42 (2.15-5.44)**	106 (27.2)	1.71 (0.97-3.01)	1.59 (0.91-2.78)	51 (20.6)	1.25 (0.80-1.96)	1.31 (0.84-2.05)
>5	100 (24.2)	**5.91 (3.69-9.48)**	**5.47 (3.39-8.81)**	95 (31.5)	**1.97 (1.12-3.48)**	1.68 (0.96-2.97)	10 (35.7)	**2.17 (1.17-4.05)**	**2.25 (1.23-4.14)**
χ^2trend (*p*-value)		***70.16 (<0.001)***	***60.87 (<0.001)***		***5.75 (0.017)***	*2.32 (0.128)*		***4.39 (0.036)***	***5.37 (0.021)***
Number of sexual partners in the last 6 months									
0	21 (15.2)	1[e]	1[e]	62 (31.3)	1[e]	1[e]	31 (20.7)	1[e]	1[e]
1	210 (12.8)	0.84 (0.55-1.27)	0.76 (0.51-1.13)	146 (26.9)	0.86 (0.67-1.10)	0.82 (0.65-1.05)	50 (20.2)	0.98 (0.66-1.46)	0.89 (0.59-1.33)
≥2	42 (35.3)	**2.32 (1.46-3.68)**	1.11 (0.70-1.76)	5 (31.3)	1.00 (0.47-2.12)	0.82 (0.35-1.92)	3 (18.8)	0.91 (0.31-2.64)	0.74 (0.25-2.13)

	SPW (N=1910)			HIW (N=766)			RMW (N=417)		
	HPV infection N=273 N (P)	Crude PR[a] (95% CI)	Adjusted PR[b] (95% CI)	HPV infection N=215 N (P)	Crude PR[a] (95% CI)	Adjusted PR[c] (95% CI)	HPV infection N=84 N (P)	Crude PR[a] (95% CI)	Adjusted PR[d] (95% CI)
χ^2trend (*p*-value)		***22.73 (<0.001)***	*1.67 (0.196)*		*1.01 (0.316)*	*2.56 (0.110)*		*0.03 (0.867)*	*0.52 (0.470)*
Use of any type of contraceptive methods									
Never	18 (9.1)	1[e]	1[e]	26 (38.8)	1[e]	1[e]	19 (20.9)	1[e]	1[e]
Only past use	90 (12.1)	1.32 (0.82-2.13)	1.11 (0.69-1.77)	69 (25.0)	**0.64 (0.45-0.93)**	**0.68 (0.48-0.96)**	34 (19.3)	0.93 (0.56-1.53)	0.79 (0.47-1.32)
Current use	165 (17.2)	**1.88 (1.18-2.98)**	1.19 (0.75-1.89)	116 (27.8)	**0.72 (0.51-1.00)**	**0.69 (0.51-0.95)**	31 (20.7)	0.99 (0.60-1.65)	0.80 (0.48-1.34)
	SPW (N=1910)			**HIW (N=766)**			**RMW (N=417)**		
	HPV infection N=273 N (P)	Crude PR[a] (95% CI)	Adjusted PR[b] (95% CI)	HPV infection N=215 N (P)	Crude PR[a] (95% CI)	Adjusted PR[c] (95% CI)	HPV infection N=84 N (P)	Crude PR[a] (95% CI)	Adjusted PR[d] (95% CI)
Use of condom									
Never	104 (13.6)	1[e]	1[e]	47 (32.2)	1[e]	1[e]	50 (20.7)	1[e]	1[e]
Only past use	90 (13.6)	1.00 (0.77-1.30)	**0.77 (0.60-1.00)**	51 (24.5)	0.76 (0.54-1.06)	0.75 (0.54-1.04)	17 (20.5)	0.99 (0.61-1.62)	0.83 (0.51-1.36)
Current use	77 (16.5)	1.21 (0.92-1.59)	0.84 (0.64-1.10)	112 (27.9)	0.87 (0.65-1.15)	**0.76 (0.58-1.00)**	10 (14.7)	0.71 (0.38-1.33)	0.61 (0.33-1.15)
Use of IUD									
Never	260 (14.8)	1[e]	1[e]	187 (27.2)	1[e]	1[e]	70 (19.7)	1[e]	1[e]
Only past use	8 (8.6)	0.58 (0.30-1.14)	1.00 (0.50-1.98)	21 (32.8)	1.21 (0.83-1.75)	1.30 (0.90-1.86)	2 (10.0)	0.51 (0.13-1.93)	0.65 (0.17-2.45)
Current use	4 (10.3)	0.69 (0.27-1.77)	1.01 (0.41-2.52)	1 (33.3)	1.23 (0.25-6.10)	NA	5 (29.4)	1.50 (0.70-3.22)	1.78 (0.83-3.79)
Use of Estro-progestinic drugs (EP)									
Never	76 (13.3)	1[e]	1[e]	109 (27.8)	1[e]	1[e]	51 (20.0)	1[e]	1[e]
Only past use	108 (12.7)	0.96 (0.73-1.26)	0.92 (0.71-1.20)	92 (27.0)	0.97 (0.77-1.23)	0.97 (0.77-1.23)	17 (17.2)	0.86 (0.52-1.41)	0.81 (0.50-1.33)
Only current use	33 (16.8)	1.26 (0.87-1.84)	0.99 (0.68-1.42)	1 (50.0)	1.80 (0.45-7.26)	NA	5 (25.0)	1.25 (0.56-2.78)	1.00 (0.45-2.21)
Past and current use	55 (20.2)	1.52 (1.11-2.09)	1.18 (0.87-1.61)	7 (38.9)	1.40 (0.77-2.55)	1.36 (0.76-2.42)	4 (21.1)	1.05 (0.43-2.60)	1.13 (0.50-2.71)
Years of use ≤5	31 (23.0)	**1.73 (1.19-2.51)**	1.20 (0.83-1.74)	4 (40.0)	1.44 (0.66-3.12)	1.58 (0.73-3.40)	1 (7.1)	0.36 (0.05-2.40)	NA
>5	20 (16.1)	1.22 (0.77-1.91)	1.06 (0.69-1.64)	3 (37.5)	1.35 (0.54-3.35)	1.05 (0.44-2.52)	2 (50.0)	2.50 (0.91-6.87)	2.63 (0.93-7.46)
χ^2trend (*p*-value)		*2.67 (0.102)*	*0.29 (0.589)*		*0.98 (0.323)*	*0.27 (0.603)*		*0.11 (0.743)*	-
Number of deliveries									
0	218 (19.1)	1[e]	1[e]	105 (30.6)	1[e]	1[e]	38 (23.0)	1[e]	1[e]
1	32 (10.2)	**0.53 (0.38-0.76)**	0.69 (0.48-1.01)	69 (27.8)	0.91 (0.70-1.17)	0.92 (0.72-1.19)	24 (19.0)	0.83 (0.52-1.30)	0.91 (0.58-1.43)
≥2	23 (5.1)	**0.27 (0.18-0.41)**	**0.45 (0.28-0.72)**	41 (23.6)	0.77 (0.56-1.05)	0.78 (0.57-1.08)	22 (17.5)	0.76 (0.47-1.21)	1.02 (0.59-1.76)
χ^2trend (*p*-value)		***47.37 (<0.001)***	***12.44 (<0.001)***		*2.75 (0.097)*	*2.23 (0.136)*		*1.43 (0.232)*	*0.00 (0.963)*
Number of pregnancies									
0	200 (19.3)	1[e]	1[e]	55 (30.9)	1[e]	1[e]	25 (19.7)	1[e]	1[e]
1	36 (12.1)	**0.63 (0.45-0.87)**	0.76 (0.54-1.06)	68 (30.1)	0.91 (0.70-1.17)	1.01 (0.76-1.34)	27 (25.0)	1.27 (0.79-2.05)	1.36 (0.85-2.19)
2	25 (7.2)	**0.37 (0.25-0.55)**	**0.58 (0.37-0.90)**	44 (23.2)	0.76 (0.53-1.09)	0.77 (0.57-1.07)	18 (20.9)	1.06 (0.62-1.83)	1.27 (0.73-2.23)

	SPW (N=1910)			HIW (N=766)			RMW (N=417)		
	HPV infection N=273 N (P)	Crude PR[a] (95% CI)	Adjusted PR[b] (95% CI)	HPV infection N=215 N (P)	Crude PR[a] (95% CI)	Adjusted PR[c] (95% CI)	HPV infection N=84 N (P)	Crude PR[a] (95% CI)	Adjusted PR[d] (95% CI)
≥3	12 (5.3)	**0.27 (0.16-0.48)**	**0.44 (0.24-0.80)**	48 (28.2)	0.79 (0.48-1.30)	0.90 (0.66-1.25)	14 (14.6)	0.74 (0.41-1.35)	0.99 (0.52-1.88)
χ^2trend (*p*-value)		***43.93 (<0.001)***	***11.06 (0.001)***		*1.12 (0.290)*	*1.35 (0.248)*		*0.98 (0.322)*	*0.03 (0.859)*
Spontaneous abortion									
No	255 (15.0)	1[e]	1[e]	180 (28.0)	1[e]	1[e]	74 (20.3)	1[e]	1[e]
Yes	18 (8.5)	**0.56 (0.36-0.89)**	0.80 (0.50-1.28)	35 (28.7)	1.02 (0.75-1.39)	1.05 (0.78-1.41)	10 (19.2)	0.95 (0.52-1.72)	1.01 (0.56-1.81)
Menopause									
No	260 (14.8)	1[e]	1[e]	173 (28.6)	1[e]	1[e]	80 (20.0)	1[e]	1[e]
Yes	9 (6.4)	**0.43 (0.23-0.82)**	0.95 (0.48-1.88)	34 (23.6)	0.82 (0.60-1.13)	1.11 (0.79-1.56)	4 (25.0)	1.25 (0.52-2.99)	1.73 (0.69-4.31)
Self reported History of past STIs and/or genital infections									
No	166 (13.0)	1[e]	1[e]	78 (21.1)	1[e]	1[e]	65 (19.8)	1[e]	1[e]
Yes	106 (17.0)	**1.32 (1.05-1.65)**	**1.23 (0.99-1.53)**	134 (34.5)	**1.64 (1.29-2.08)**	**1.42 (1.10-1.84)**	19 (22.4)	1.13 (0.72-1.77)	1.06 (0.68-1.65)
Self reported History of past STIs and/or genital infections by types									
Genital warts	26 (30.2)	**2.23 (1.59-3.14)**	**1.80 (1.31-2.49)**	59 (42.5)	**1.72 (1.35-2.18)**	**1.49 (1.17-1.89)**	3 (60.0)	**3.02 (1.44-6.35)**	**3.26 (1.55-6.88)**
Mycosis	70 (14.4)	1.01 (0.79-1.30)	0.98 (0.77-1.25)	65 (34.8)	**1.35 (1.06-1.72)**	1.12 (0.85-1.48)	10 (21.3)	1.05 (0.59-1.89)	1.06 (0.60-1.88)
Bacterial vaginosis	14 (22.2)	1.58 (0.99-2.55)	1.35 (0.86-2.13)	23 (24.0)	0.84 (0.58-1.22)	0.68 (0.47-1.01)	3 (12.5)	0.60 (0.20-1.76)	0.53 (0.18-1.55)
HSV	14 (35.9)	**2.59 (1.68-4.00)**	**2.33 (1.58-3.43)**	22 (41.5)	**1.54 (1.09-2.17)**	**1.39 (1.01-1.91)**	0 (0.0)	-	-
Trichomoniasis	3 (13.0)	0.91 (0.32-2.63)	0.81 (0.29-2.28)	11 (39.3)	1.43 (0.89-2.29)	**1.61 (1.00-2.61)**	-	-	-
Chlamydia	4 (15.4)	1.08 (0.43-2.67)	1.01 (0.42-2.44)	5 (29.4)	1.05 (0.50-2.22)	1.09 (0.52-2.26)	0 (0.0)	-	-
Syphilis	0 (0.0)	-	-	9 (39.1)	1.42 (0.84-2.39)	1.26 (0.79-2.03)	0 (0.0)	-	-
Gonorrhea	-	-	-	1 (16.7)	0.59 (0.10-3.57)	NA	0 (0.0)	-	-
LGV	0 (0.0)	-	-	0 (0.0)	-	-	0 (0.0)	-	-
At least one STI, other than warts	80 (14.9)	1.15 (0.90-1.47)	1.09 (0.86-1.38)	75 (30.1)	**1.43 (1.09-1.88)**	1.26 (0.94-1.70)	16 (20.0)	1.01 (0.62-1.65)	0.95 (0.59-1.55)
Previous PAP screening timing									
Regular timing (every 2-3 years)	180 (13.9)	1[e]	1[e]	152 (26.7)	1[e]	1[e]	27 (23.7)	1[e]	1[e]
Irregular timing	38 (12.7)	0.92 (0.66-1.27)	1.02 (0.75-1.40)	46 (29.1)	1.09 (0.82-1.44)	1.02 (0.78-1.34)	15 (17.2)	0.73 (0.41-1.28)	0.78 (0.45-1.38)

	SPW (N=1910)			HIW (N=766)			RMW (N=417)		
	HPV infection N=273 N (P)	Crude PR[a] (95% CI)	Adjusted PR[b] (95% CI)	HPV infection N=215 N (P)	Crude PR[a] (95% CI)	Adjusted PR[c] (95% CI)	HPV infection N=84 N (P)	Crude PR[a] (95% CI)	Adjusted PR[d] (95% CI)
Never done	55 (17.8)	1.28 (0.97-1.69)	1.03 (0.77-1.37)	14 (42.4)	**1.59 (1.04-2.42)**	1.19 (0.77-1.83)	42 (19.4)	0.82 (0.54-1.26)	0.90 (0.55-1.47)
Previous PAP screening and result									
Never done	55 (17.8)	**1.42 (1.08-1.87)**	1.12 (0.83-1.50)	14 (42.4)	**1.81 (1.19-2.76)**	1.42 (0.90-2.23)	42 (19.4)	0.92 (0.63-1.36)	0.99 (0.63-1.54)
Negative	190 (12.5)	1[e]	1[e]	144 (23.5)	1[e]	1[e]	41 (21.0)	1[e]	1[e]
Positive	23 (40.4)	**3.22 (2.29-4.54)**	**2.00 (1.46-2.74)**	46 (54.1)	**2.31 (1.81-2.94)**	**1.88 (1.46-2.43)**	1 (25.0)	1.19 (0.21-6.63)	NA
Unknown	5 (20.8)	-	-	8 (26.7)	-	-	0 (0.0)	-	-
VALHIDATE cyto/histological test result									
Negative	197 (11.1)	1[e]	1[e]	136 (21.2)	1[e]	1[e]	64 (16.8)	1[e]	1[e]
Positive	76 (59.4)	**5.41 (4.46-6.57)**	**4.09 (3.38-4.95)**	79 (63.2)	**2.98 (2.44-3.64)**	**2.53 (2.01-3.18)**	20 (57.1)	**3.41 (2.37-4.91)**	**3.01 (2.07-4.38)**

NA, Not Appropriate: prevalence ratio estimate from multivariate log-binomial regression model was not reported because only one patient was positive to the HPV test in this factor's level.
[a]Prevalence ratio estimates from univariate log-binomial regression models.
[b]Prevalence ratio estimates from multivariate log-binomial regression models adjusted for study center, age, level of education, smoking habit and number of lifetime sexual partners, when appropriate.
[c]Prevalence ratio estimates from multivariate log-binomial regression models adjusted for study center, age, smoking habit, number of lifetime sexual partners and number of CD4, when appropriate.
[d]Prevalence ratio estimates from multivariate log-binomial regression models adjusted for age, geographical origin and number of lifetime sexual partners, when appropriate. [e]Reference category.

Table 4: Number (N), prevalence (P), and prevalence ratios (PR) of cyto/histological abnormality (any lesion) and corresponding 95% confidence intervals (CIs), according to selected socio-demographics characteristics, smoking and sexual habits, reproductive and gynecological history, in the control group (SPW), the HIV group (HIW), and the recent migrant group (RMW). The number (N) and prevalence (P) of high grade intraepithelial lesions (HG-SIL) were also showed.

	SPW (N=1910)			HIW (N=766)			RMW (N=417)		
	Any lesion N=128		HG-SIL N=13	Any lesion N=125		HG-SIL N=17	Any lesion N=35		HG-SIL N=6
	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[b] (95% CI)	N (P)
Age (years)									
18-25	53 (10.4)	1[c]	3 (0.6)	8 (24.2)	1[c]	0 (0.0)	16 (10.5)	1[c]	1 (0.7)
26-35	32 (6.1)	**0.53 (0.34-0.82)**	5 (1.0)	29 (24.2)	0.96 (0.48-1.89)	3 (2.5)	9 (6.3)	0.53 (0.24-1.17)	0 (0.0)
36-45	29 (4.7)	**0.44 (0.28-0.68)**	3 (0.5)	40 (12.0)	**0.47 (0.24-0.91)**	5 (1.5)	9 (7.7)	0.69 (0.32-1.50)	5 (4.3)
>45	14 (5.4)	**0.56 (0.32-0.99)**	2 (0.8)	48 (17.1)	0.67 (0.35-1.29)	9 (3.2)	1 (25.0)	NA	0 (0.0)
χ^2trend (*p*-value)		***10.42 (0.001)***			*2.70 (0.100)*			*1.18 (0.277)*	
Geographical origin									
Italy	121 (6.8)	1.36 (0.65-2.84)	13 (0.7)	97 (15.7)	0.79 (0.53-1.19)	12 (1.9)	-	-	-
Africa	0 (0.0)	-	0 (0.0)	17 (20.5)	1.30 (0.81-2.11)	3 (3.6)	3 (6.8)	0.86 (0.28-2.69)	1 (2.3)
Asia	0 (0.0)	-	0 (0.0)	2 (22.2)	1.39 (0.40-4.80)	1 (11.1)	2 (10.0)	2.01 (0.49-8.14)	0 (0.0)
Europe	4 (6.1)	0.86 (0.33-2.25)	0 (0.0)	3 (12.0)	0.72 (0.25-2.12)	0 (0.0)	11 (9.5)	1.14 (0.58-2.26)	2 (1.7)
Latin America	3 (5.5)	0.89 (0.29-2.68)	0 (0.0)	6 (20.7)	1.34 (0.64-2.81)	1 (3.4)	19 (8.0)	0.84 (0.45-1.59)	3 (1.3)

Table 4: Number (N), prevalence (P), and prevalence ratios (PR) of cyto/histological abnormality (any lesion) and corresponding 95% confidence intervals (CIs), according to selected socio-demographics characteristics, smoking and sexual habits, reproductive and gynecological history, in the control group (SPW), the HIV group (HIW), and the recent migrant group (RMW). The number (N) and prevalence (P) of high grade intraepithelial lesions (HG-SIL) were also showed.

	SPW (N=1910)			**HIW (N=766)**			**RMW (N=417)**		
	Any lesion N=128		HG-SIL N=13	Any lesion N=125		HG-SIL N=17	Any lesion N=35		HG-SIL N=6
	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[b] (95% CI)	N (P)
Marital status									
Unmarried	80 (8.1)	1[c]	7 (0.7)	46 (22.0)	1[c]	7 (3.3)	20 (11.1)	1[c]	0 (0.0)
Married	26 (3.8)	0.67 (0.40-1.11)	4 (0.6)	34 (12.8)	**0.60 (0.40-0.91)**	4 (1.5)	8 (5.0)	0.53 (0.23-1.18)	3 (1.9)
Cohabitant	7 (6.8)	0.89 (0.42-1.89)	1 (1.0)	16 (14.2)	0.65 (0.38-1.09)	1 (0.9)	3 (8.6)	0.85 (0.27-2.69)	1 (2.9)
Other (divorced or widow)	15 (10.9)	1.86 (0.98-3.53)	1 (0.7)	29 (16.3)	0.73 (0.46-1.14)	5 (2.8)	4 (9.3)	0.79 (0.28-2.28)	2 (4.7)
Education									
Primary school	12 (4.5)	1[c]	0 (0.0)	64 (17.1)	1[c]	5 (1.3)	16 (10.8)	1[c]	3 (2.0)
Secondary school	81 (7.7)	1.45 (0.80-2.62)	8 (0.8)	54 (16.3)	0.92 (0.65-1.28)	12 (3.6)	14 (6.8)	0.60 (0.30-1.18)	2 (1.0)
University degree	35 (5.9)	1.07 (0.56-2.03)	5 (0.8)	6 (10.3)	0.59 (0.27-1.31)	0 (0.0)	5 (7.8)	0.67 (0.26-1.74)	1 (1.6)
χ^2trend (*p*-value)		*0.25 (0.615)*			*1.42 (0.233)*			*1.43 (0.232)*	
	SPW (N=1910)			**HIW (N=766)**			**RMW (N=417)**		
	Any lesion N=128		HG-SIL N=13	Any lesion N=125		HG-SIL N=17	Any lesion N=35		HG-SIL N=6
	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[b] (95% CI)	N (P)
Smoking habit									
Never/ex smoker	81 (5.9)	1[c]	7 (0.5)	55 (13.3)	1[c]	6 (1.5)	29 (8.1)	1[c]	5 (1.4)
Current smoker	47 (8.9)	1.34 (0.95-1.90)	6 (1.1)	70 (19.9)	**1.54 (1.09-2.17)**	11 (3.1)	6 (10.3)	1.04 (0.45-2.41)	1 (1.7)
1-10 cig./day	30 (8.0)	1.16 (0.77-1.74)	4 (1.1)	27 (19.3)	1.51 (0.98-2.31)	6 (4.3)	4 (10.0)	1.00 (0.37-2.73)	0 (0.0)
>10 cig./day	17 (11.0)	**1.81 (1.10-2.96)**	2 (1.3)	43 (20.3)	**1.56 (1.06-2.29)**	5 (2.4)	2 (11.1)	1.11 (0.29-4.30)	1 (5.6)
χ^2trend (*p*-value)		***4.66 (0.031)***			***5.37 (0.020)***			*0.02 (0.901)*	
Age at first sexual intercourse									
≤16	38 (8.0)	1[c]	4 (0.8)	50 (16.8)	1[c]	8 (2.7)	14 (12.6)	1[c]	2 (1.8)
17-18	49 (6.9)	1.00 (0.66-1.51)	4 (0.6)	44 (15.9)	0.98 (0.67-1.42)	7 (2.5)	13(9.2)	0.75 (0.37-1.53)	3 (2.1)
≥19	40 (5.6)	0.98 (0.62-1.54)	5 (0.7)	28 (15.5)	0.96 (0.61-1.50)	1 (0.6)	8 (4.9)	0.46 (0.20-1.07)	1 (0.6)
χ^2trend (*p*-value)		*0.01 (0.927)*			*0.04 (0.841)*			*3.30 (0.069)*	
Number or lifetime sexual partners									
1	19 (4.1)	1[c]	1 (0.2)	11 (15.9)	1[c]	2 (2.9)	6 (4.3)	1[c]	2 (1.4)
2-5	70 (6.8)	1.62 (0.99-2.66)	8 (0.8)	57 (14.7)	0.93 (0.52-1.69)	7 (1.8)	28 (11.3)	**2.71 (1.15-6.41)**	4 (1.6)
>5	39 (9.4)	**2.28 (1.34-3.88)**	4 (1.0)	55 (18.2)	1.19 (0.65-2.16)	7 (2.3)	1 (3.6)	NA	0 (0.0)
χ^2trend (*p*-value)		***9.71 (0.002)***			*1.19 (0.275)*			-	
Number of sexual partners in the last 6 months									
0	7 (5.1)	1[c]	1 (0.7)	37 (18.7)	1[c]	7 (3.5)	11 (7.3)	1[c]	3 (2.0)
1	102 (6.2)	1.15 (0.55-2.43)	10 (0.6)	84 (15.5)	0.81 (0.57-1.17)	10 (1.8)	23 (9.3)	1.12 (0.56-2.24)	3 (1.2)

	SPW (N=1910)			HIW (N=766)			RMW (N=417)		
	Any lesion N=128		HG-SIL N=13	Any lesion N=125		HG-SIL N=17	Any lesion N=35		HG-SIL N=6
	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[b] (95% CI)	N (P)
≥2	18 (15.1)	1.96 (0.83-4.63)	1 (0.8)	3 (18.8)	0.89 (0.30-2.61)	0 (0.0)	0 (0.0)	-	0 (0.0)
χ^2trend (*p*-value)		*3.60 (0.058)*			*0.99 (0.320)*			-	

	SPW (N=1910)			HIW (N=766)			RMW (N=417)		
	Any lesion N=128		HG-SIL N=13	Any lesion N=125		HG-SIL N=17	Any lesion N=35		HG-SIL N=6
	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[b] (95% CI)	N (P)
Use of any type of contraceptive methods									
Never	8 (4.1)	1[c]	2 (1.0)	17 (25.4)	1[c]	4 (6.0)	7 (7.7)	1[c]	0 (0.0)
Only past use	38 (5.1)	1.16 (0.55-2.44)	4 (0.5)	44 (15.9)	0.61 (0.36-1.01)	5 (1.8)	13 (7.4)	0.76 (0.31-1.86)	4 (2.3)
Current use	82 (8.5)	1.67 (0.81-3.46)	7 (0.7)	63 (15.1)	**0.54 (0.33-0.88)**	7 (1.7)	15 (10.0)	0.96 (0.40-2.31)	2 (1.3)
Use of condom									
Never	49 (6.4)	1[c]	7 (0.9)	32 (21.9)	1[c]	6 (4.1)	20 (8.3)	1[c]	4 (1.7)
Only past use	41 (6.2)	0.83 (0.55-1.25)	4 (0.6)	30 (14.4)	**0.63 (0.40-0.99)**	4 (1.9)	5 (6.0)	0.62 (0.24-1.61)	1 (1.2)
Current use	37 (7.9)	0.98 (0.64-1.50)	2 (0.4)	61 (15.2)	**0.62 (0.41-0.93)**	6 (1.5)	9 (13.2)	1.30 (0.61-2.75)	0 (0.0)
Use of IUD									
Never	123 (7.0)	1[c]	13 (0.7)	113 (16.4)	1[c]	14 (2.0)	30 (8.4)	1[c]	4 (1.1)
Only past use	4 (4.3)	0.83 (0.31-2.24)	0 (0.0)	10 (15.6)	1.01 (0.56-1.85)	2 (3.1)	2 (10.0)	1.40 (0.36-5.38)	1 (5.0)
Current use	0 (0.0)	-	0 (0.0)	1 (33.3)	NA	0 (0.0)	2 (11.8)	1.55 (0.41-5.84)	0 (0.0)
Use of Estro-progestinic drugs (EP)									
Never	33 (5.8)	1[c]	4 (0.7)	70 (17.9)	1[b]	11 (2.8)	22 (8.6)	1[b]	4 (1.6)
Only past use	47 (5.5)	0.94 (0.61-1.44)	4 (0.5)	48 (14.1)	0.79 (0.56-1.11)	4 (1.2)	9 (9.1)	0.96 (0.46-2.01)	1 (1.0)
Only current use	20 (10.2)	1.51 (0.88-2.59)	3 (1.5)	2 (100.0)	-	0 (0.0)	1 (5.0)	NA	0 (0.0)
Past and current use	27 (9.9)	1.52 (0.93-2.48)	2 (0.7)	3 (16.7)	0.98 (0.34-2.80)	1 (5.6)	2 (10.5)	1.25 (0.32-4.84)	0 (0.0)
Years of use≤5	19 (14.1)	1.73 (0.99-3.03)	2 (1.5)	2 (20.0)	1.31 (0.38-4.51)	0 (0.0)	1 (7.1)	NA	0 (0.0)
>5	8 (6.5)	1.00 (0.48-2.11)	0 (0.0)	1 (12.5)	0.67 (0.11-4.19)	1 (12.5)	0 (0.0)	-	0 (0.0)
χ^2trend (*p*-value)		*0.39 (0.535)*			*0.05 (0.832)*				

	SPW (N=1910)			HIW (N=766)			RMW (N=417)		
	Any lesion N=128		HG-SIL N=13	Any lesion N=125		HG-SIL N=17	Any lesion N=35		HG-SIL N=6
	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[b] (95% CI)	N (P)
Number of deliveries									
0	90 (7.9)	1[c]	10 (0.9)	54 (15.7)	1[c]	6 (1.7)	17 (10.3)	1[c]	1 (0.6)
1	15 (4.8)	0.81 (0.46-1.45)	2 (0.6)	48 (19.4)	1.23 (0.86-1.75)	8 (3.2)	5 (4.0)	0.41 (0.15-1.08)	0 (0.0)
≥2	23 (5.1)	1.07 (0.61-1.88)	1 (0.2)	23 (13.2)	0.85 (0.53-1.36)	3 (1.7)	13 (10.3)	1.22 (0.54-2.73)	5 (4.0)
χ^2trend (*p*-value)		*0.01 (0.934)*			*0.09 (0.766)*			*0.03 (0.868)*	

	SPW (N=1910)			HIW (N=766)			RMW (N=417)		
	Any lesion N=128		HG-SIL N=13	Any lesion N=125		HG-SIL N=17	Any lesion N=35		HG-SIL N=6
	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[b] (95% CI)	N (P)
Number of pregnancies									
0	80 (7.7)	1[c]	8 (0.8)	28 (15.7)	1[c]	4 (2.2)	12 (9.4)	1[c]	0 (0.0)
1	19 (6.4)	1.08 (0.65-1.80)	3 (1.0)	40 (17.7)	1.10 (0.71-1.72)	7 (3.1)	7 (6.5)	0.71 (0.29-1.73)	1 (0.9)
2	21 (6.0)	1.23 (0.71-2.15)	2 (0.6)	30 (15.8)	1.01 (0.63-1.62)	2 (1.1)	7 (8.1)	0.89 (0.35-2.26)	1 (1.2)
≥3	8 (3.5)	0.77 (0.35-1.70)	0 (0.0)	27 (15.9)	1.00 (0.61-1.63)	4 (2.4)	9 (9.4)	1.11 (0.45-2.73)	4 (4.2)
χ^2trend (*p*-value)		*0.01 (0.922)*			*0.02 (0.886)*			*0.05 (0.825)*	
Spontaneous abortion									
No	119 (7.0)	1[c]	13 (0.8)	107 (16.6)	1[c]	15 (2.3)	30 (8.2)	1[c]	5 (1.4)
Yes	9 (4.2)	0.76 (0.38-1.50)	0 (0.0)	18 (14.8)	0.89 (0.56-1.41)	2 (1.6)	5 (9.6)	1.09 (0.44-2.71)	1 (1.9)
Menopause									
No	119 (6.8)	1[c]	11 (0.6)	101 (16.7)	1[c]	12 (2.0)	34 (8.5)	1[c]	5 (1.2)
Yes	6 (4.3)	0.89 (0.39-2.06)	2 (1.4)	19 (13.2)	0.85 (0.52-1.41)	4 (2.8)	1 (6.3)	NA	1 (6.3)

	SPW (N=1910)			HIW (N=766)			RMW (N=417)		
	Any lesion N=128		HG-SIL N=13	Any lesion N=125		HG-SIL N=17	Any lesion N=35		HG-SIL N=6
	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[b] (95% CI)	N (P)
Self reported history of past STIs and/or genital infections									
No	80 (6.2)	1[c]	7 (0.6)	51 (13.8)	1[c]	3 (0.8)	24 (7.3)	1[c]	6 (1.8)
Yes	47 (7.6)	1.21 (0.86-1.72)	6 (1.0)	71 (18.3)	1.27 (0.87-1.84)	13 (3.4)	10 (11.8)	1.47 (0.73-2.96)	0 (0.0)
Self reported history of past STIs and/or genital infections by types									
Genital warts	15 (17.4)	**2.67 (1.63-4.36)**	3 (3.5)	35 (25.2)	**1.75 (1.22-2.51)**	6 (4.3)	2 (40.0)	**4.68 (1.58-13.90)**	0 (0.0)
Mycosis	27 (5.6)	0.80 (0.53-1.20)	3 (0.6)	33 (17.7)	0.99 (0.64-1.52)	5 (2.7)	5 (10.6)	1.34 (0.55-3.28)	0 (0.0)
Bacterial vaginosis	7 (11.1)	1.58 (0.77-3.24)	0 (0.0)	14 (14.6)	0.79 (0.45-1.39)	2 (2.1)	3 (12.5)	1.30 (0.43-3.98)	0 (0.0)
HSV	5 (12.8)	1.99 (0.86-4.59)	0 (0.0)	14 (26.4)	**1.63 (1.00-2.66)**	2 (3.8)	0 (0.0)	-	0 (0.0)
Trichomoniasis	2 (8.7)	1.30 (0.34-4.93)	0 (0.0)	5 (17.9)	0.86 (0.23-3.26)	2 (7.1)	0 (0.0)	-	0 (0.0)
Chlamydia	2 (7.7)	1.16 (0.30-4.40)	0 (0.0)	2 (11.8)	0.73 (0.19-2.71)	0 (0.0)	0 (0.0)	-	0 (0.0)
Syphilis	0 (0.0)	-	0 (0.0)	5 (21.7)	1.35 (0.61-3.01)	0 (0.0)	0 (0.0)	-	0 (0.0)
Gonorrhea	-	-	-	2 (33.3)	2.17 (0.69-6.78)	1 (16.7)	0 (0.0)	-	0 (0.0)
LGV	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)
At least one STI, other than warts	32 (6.0)	0.96 (0.65-1.44)	3 (0.6)	36 (14.5)	1.10 (0.70-1.75)	7 (2.8)	8 (10.0)	1.26 (0.59-2.71)	0 (0.0)
Previous PAP screening timing									
Regular timing (every 2-3 years)	85 (6.6)	1[c]	11 (0.8)	89 (15.6)	1[c]	10 (1.8)	8 (7.0)	1[c]	2 (1.8)
Irregular timing	10 (3.3)	0.54 (0.28-1.02)	1 (0.3)	26 (16.5)	1.10 (0.73-1.64)	4 (2.5)	5 (5.7)	0.86 (0.29-2.53)	0 (0.0)

	SPW (N=1910)			HIW (N=766)			RMW (N=417)		
	Any lesion N=128		HG-SIL N=13	Any lesion N=125		HG-SIL N=17	Any lesion N=35		HG-SIL N=6
	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[a] (95% CI)	N (P)	N (P)	PR[b] (95% CI)	N (P)
Never done	33 (10.7)	1.44 (0.93-2.21)	1 (0.3)	8 (24.2)	1.44 (0.72-2.86)	2 (6.1)	22 (10.2)	1.76 (0.80-3.88)	4 (1.9)
Previous PAP screening and result									
Never done	33 (10.7)	**1.96 (1.26-3.06)**	1 (0.3)	8 (24.2)	1.85 (0.92-3.72)	2 (6.1)	22 (10.2)	1.95 (0.98-3.91)	4 (1.9)
Negative	75 (4.9)	1[c]	11 (0.7)	73 (11.9)	1[c]	5 (0.8)	12 (6.2)	1[c]	2 (1.0)
Positive	19 (33.3)	**5.88 (3.79-9.14)**	1 (1.8)	38 (44.7)	**3.81 (2.74-5.31)**	8 (9.4)	1 (25.0)	NA	0 (0.0)
Unknown	1 (4.2)	-	0 (0.0)	4 (13.3)	-	1 (3.3)	0 (0.0)	-	0 (0.0)

NA, Not Appropriate: prevalence ratio estimate from multivariate log-binomial regression model was not reported because only one patient was positive to the cyto/histological test in this factor's level.
[a]Prevalence ratio estimates from multivariate log-binomial regression models adjusted for study center, age, and number of lifetime sexual partners.
[b]Prevalence ratio estimates from multivariate log-binomial regression models adjusted for age and number of lifetime sexual partners.
[c]Reference category.

types fell from 27.3% in 20–29-y.o. women to 10.3% in those aged 30–39 years. In our study we confirmed that HPV infection is strongly linked to age with the highest burden in younger ages, both in the general population and in the testing groups although at different prevalence levels: prevalence fall from 27.5% to 12.8% in RMW, from 51.5% to 24% in HIW, and from 21.3% to 8.4% in SPW in the 18–26 y.o. and 36–45 y.o. subgroups, respectively. The prospective longitudinal study to evaluate sensitivity and positive predictive value of HPV testing in these high-risk populations is ongoing.

The small sample size and young age of the RMW group could have affected the ability to identify statistical associations between risk factors and HPV infection or cervical lesions. We chose to enroll only migrant women in their first year of migration, a population with a large proportion of young and healthy women who rarely seek medical attention except for pregnancy and emergencies. The HPV prevalence estimated from the RMW group (20.1%; 95% CI: 16.2–24.0), reflects both their young age and geographical origins (i.e. Latin America and Eastern Europe) [32-34]. The VALHIDATE study, which recruited migrant women from a Catholic outpatient primary health care ward for uninsured migrating people, may thus provide interesting data on health, sexual and reproductive habits of this population with limited access to public health facilities and for whom such data are limited, even if they only partially represent the migrant population in Lombardy [35].

The greater susceptibility to infection in high-risk women enrolled in this study has been attributed to several factors ranging from immunological, behavioral or social causes [36]. Lack of access to screening programs is suggested to be the major cause of an excess burden of cervical pre-cancer and cancers in migrant women [5]. In HIV-infected people, increased risk of reactivation of latent infections and reduced viral clearance by the impaired immune system, as well as greater exposure to STIs has been proposed to explain the higher prevalence of HPV infection in all age classes, its longer persistence and the higher risk of invasive diseases [37].

Our data are not addressed to verify the role of immune mechanisms underlying the greatest susceptibility of HIV-infected women to HPV diseases but we investigated the behavioral or social causes associated with higher risk of infection that can be modified through specifically addressed public health intervention and cervical cancer screening. We found that in the HIW group, cigarette smoking and history of past STIs (namely, history of genital warts, genital HSV infection and trichomoniasis) are independently associated with increased risk of HPV infection, whereas being married and using contraceptives—particularly condoms—are associated with decreased risk of HPV infection. The smaller association in the HIW group between number of lifetime sexual partners and HPV infection than in the other groups could be explained by their high use of condoms. Condoms were used by most of the HIV-infected patients who were cared for and followed up in outpatient wards for HIV^+ persons as part of safe-sex procedures recommended to prevent transmission of HIV and other STIs [38]. The effectiveness of condom use in preventing HPV transmission is not proven but several studies show a trend of protective effect [39,40] along with protection against other STIs. In the other two groups, SPW and RMW, who prefer estroprogestinic drugs as contraceptive method, the number of lifetime and recent sexual partners play an important role in risk for HPV infection, as already reported in literature [41]. The risk of HPV-related cervical abnormalities is affected differently by some factors that could be addressed through public health intervention. Cigarette smoking and STIs are associated with increased risk, and condom use with reduced risk, of SIL in HIV-infected women. High number of sexual partners and STIs are related to increased risk of SIL in SPW and RMW.

Adherence to Pap screening programs has been reported to influence the prevalence of SIL [42]. More than 50% of migrant women declared that they never had a Pap smear previously, in compared with 16% of the controls and 4% of the HIV-infected women. Risk of SIL was found to be greater in women who had never had Pap screening than for those with a previous positive Pap test, even when adjusted by age. A low adherence to Pap

screening programs was strongly associated with increased HPV risk in both RMW and SPW. This parameter was not confirmed for risk of SIL in HIW, although a higher prevalence of SIL was found in HIW who had never had a previous Pap test, compared with those with regular or even irregular Pap screening (24.2% *vs* 15.6 and 16.5% respectively). Some questions on best practices for HPV screening in the general population and in high risk women (age to begin HPV screening, interval between the two HPV screening rounds, time and screening method after HPV vaccination) [26-28,43-45] remain unanswered.

CONCLUSIONS

Several conclusions can be inferred from our data. HPV-based screening provides greater prevention than Pap screening when performed in women over 30 years of age, allowing an earlier detection of invasive diseases at the first screening round; this gain could be larger in settings where the quality of cytology is lower; moreover HPV-based screening allows a safe extension of screening intervals to 5 years [28,42]. In this work we found some important differences in risk factors that influence HPV infection in selected populations, and provide some data to guide specific public health interventions for cancer prevention. Development of the optimal screening strategy depends on several considerations besides the most appropriate screening test. Knowledge of modifiable epidemiological factors that affect HPV infections in women could help identify a global strategy of intervention that includes health education and sexual health education, promotion of safe sex procedures, and allocation of resources for measures to promote adhesion to screening and preventing programs in more vulnerable people.

In conclusion, our results showed that a very wide range of social and behavioral determinants can affect women's sexual health and their risk of cervical HPV infections and diseases. Several factors included in our analyses could be modified through public health intervention and programs; interventions specifically aimed at decreasing social and behavioral risk factors could be added to HPV screening and vaccine, both for the general population and for those who are more vulnerable to HPV infection and related cancers.

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Conflict of Interest

The authors declare that have neither conflicts of interest to be declared in relation to the article nor funding or personal relationships with people or organizations that could inappropriately influence this article.

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