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Identifying populations most susceptible to get benefit from broadening the scope for prevention of cervical cancer: Example from Uruguay

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ABSTRACT

Objectives: To identify factors associated with high-risk human papillomavirus (HPV) infection and high grade squamous intraepithelial lesion (HSIL) among a high-risk group of HPV-unvaccinated women in Montevideo.
Methods: Participants completed a questionnaire on socio-demographics, sexual behavior and gynecological history and received a gynecological examination. HPV DNA was detected by PCR using MY09/11 primers. Logistic regression analyses were performed to identify factors associated with high-risk HPV infection and HSIL.
Results: A total of 469 women with HPV DNA and cytological results completed the questionnaire. Among women older than 30 years, those with high number of sexual partners and regular housing conditions were more likely to be positive for high-risk HPV infection (adjusted OR: 2.94, 95%CI: 1.01–8.51 and 2.68, 95%CI: 1.01–7.21, respectively). A marginally non-statistically significant association between getting a HSIL and having a high number of sexual partners was also observed (adjusted OR: 3.22, 95%CI: 0.97–10.75).
Conclusions: In an era of development of new strategies for accelerating the reduction of cervical cancer incidence and mortality, our results may contribute to identify populations most susceptible to get benefit from broadening the scope for prevention of cervical cancer and could be used with other triage strategies.

1. Introduction

Cervical cancer is the third most common malignancy among women worldwide. Defined as disease of disparity, wide variations are observed between high- and low-burden countries, with incidence rates ranging from < 3 to > 50 per 100,000 [1]. The marked regional differences in incidence of cervical cancer are not only due to differences on screening programs but also to different exposure to risk factors. Thus, getting information about factors associated to getting a high grade cervical lesion or an infection with high-risk human papillomaviruses (HPV) – the necessary cause to develop cervical cancer [2] – is relevant when formulating appropriate cervical cancer control strategies.

Central and South America (CSA) region has some of the highest cervical cancer incidence and mortality rates [1]. In Uruguay, cervical cancer is the third most common cancer among women with 402 new cervical cancer cases and 175 cervical cancer deaths estimated annually and age-standardized incidence and mortality rates of 19.0 and 7.1 per 100.000 women respectively [1]. Despite the figures are among the lowest in the region, yet they are considerably higher than those found in relatively low burden countries such as United States with 6.6 new cases and 2.7 new deaths per 100,000 women [1]. Moreover, the disease acquires a particular significance in the country given the socio-economic characteristics of the affected population [3].

Abbreviations and acronyms: HPV, Human Papillomaviruses; CI, Confidence Interval; OR, Odds Ratio; SD, Standard Deviation; CSA, Central and South America; STI, Sexually Transmitted Infection; ASCUS, Atypical Squamous Cell of Undetermined Significance; LSIL, Low Grade Squamous Intraepithelial Lesion; HSIL, High Grade Squamous Intraepithelial Lesion; NILM, Negative for Intraepithelial Lesion or Malignancy

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HPV infection is one of the most common sexually transmitted infections (STI) worldwide. The estimated HPV prevalence among women with normal cytology is 11.7% worldwide and 16.1% in CSA [4]. HPV testing has been proven as an effective complementary tool for cervical cancer screening [5]. Moreover, it is starting to be recommended as primary testing, in line with available evidence showing that HPV testing is more efficacious than screening based on cytology [6,7]. Since 2007, two prophylactic vaccines are available to protect against infection with the two most common high-risk genotypes in cervical cancer, HPV16/18 [8], which are responsible for 70% of all cervical cancer cases [9]. Moreover, a second generation nona-valent vaccine protecting against infection with HPV6/11/16/18/31/33/45/52/58 has also been approved [10].

The development of new and effective cervical cancer prevention tools raise opportunities for new approaches for accelerating the reduction of cervical cancer incidence and mortality, such as combining both HPV screening and vaccination [11]. In this context is of particular interest to identify populations most susceptible to get benefit from broadening the scope for prevention of cervical cancer.

In the last years there has been in Uruguay an increasing public health concern about cervical cancer control. Opportunistic screening was initiated in 1994 with a recommendation of an annual cytology regardless of age [3]. This recommendation was later revised [12]. In 2013, the Ministry of Health launched a cervical cancer awareness campaign and free vaccination was made available for 12 years-old girls [13]. Yet, epidemiological knowledge about HPV in the country was not available since a recent study presented results on HPV prevalence and genotype distribution in 568 women attending the cervical screening clinics of the National Cervical Cancer Prevention Sub-Program [14]. Shortly after, two additional studies reported on HPV prevalence and type distribution in invasive cervical cancer [15] and in women with and without cervical intraepithelial lesions [16] obtaining similar results than the first study [14].

We present here the results on the factors associated with having a high-risk HPV infection or a high grade squamous intraepithelial lesion (HSIL) among women participating in the previous study [14] in order to provide relevant information for the design of appropriate strategies towards cervical cancer control in Uruguay.

2. Methods

This was a cross-sectional study, previously explained in Ramas et al. [14]. Briefly, the program was led by the Montevideo city hall. Women attending the cervical screening public clinics of the National Cervical Cancer Prevention Sub-Program were invited to participate in the study if they were not pregnant, not having a previous history of neoplastic disease and not been vaccinated against HPV. Since the study population was considered a high-risk population, it was decided to include all women requesting a PAP test without age restrictions despite the program recommendation of starting screening at age 21. A general gynecological examination was conducted for all participants, who were previously invited to complete a self-administered standardized questionnaire. Smears were cytologically diagnosed according to the Bethesda classification system, and confirmed by histology in case of squamous intraepithelial lesion any grade results. The cytology was made without knowledge of HPV results.

Sample processing and HPV DNA detection and genotyping was performed as previously described [14]. Briefly, HPV DNA was detected by PCR using MY09/11 primer set and genotyping was performed by restriction enzyme digestion of PCR products (RFLP assay).

The questionnaire was completed by the participants prior to the gynecological examination. It had 17 questions divided into three sections. The first section had six sociodemographic items: age, educational level, designated primary care center, building material of the house, type of bathroom, access to safe water and sanitation services. The second section had six questions about gynecological history: number of pregnancies, age at first sexual intercourse, age at first pregnancy, number of sexual partners in the last year, number of living children and date of last gynecological examination. The third section had five items about associated risk factors: previous history of STI, contraceptive use, type of contraceptive, time of use, and smoking history.

A new variable – housing conditions – was constructed from the following variables: 1) access to safe water and sanitation services, 2) type of bathroom and, 3) house building material. Each category was scored from 0 to 2 points. The variable "housing conditions" was the sum of all of them. A score of six was considered "good" and a score lower than six was classified as "regular". The city of Montevideo has eight districts (A, B, C, CH, D, E, F, G). To define the variable district zone by percentage of poverty (stratified by: $< 5\%$ low, 5–15% medium and $> 15\%$ high) official data census and classifications of the Household Survey of Municipality of Montevideo 2012 were used. The concept of poverty had been previously built using the per capita household income value compared with the price of a standard basket of food [17]. The women were classified as living in one district according to their designated primary care center.

Quantitative variables were described using the mean (with standard deviation, SD); qualitative variables were described using percentages. Univariate and multivariate logistic regression models were performed to identify possible factors associated with the presence of HSIL among all women, and of high-risk HPV infection among women aged 30 or more. Women younger than 30 years were excluded from the latter analysis given the high HPV prevalence and the fact that most infections regress spontaneously in this group. Moreover, new approaches for accelerating the reduction of cervical cancer incidence and mortality by combining both HPV screening and vaccination propose to offer HPV vaccination to women aged 25–45 years, with concomitant HPV-DNA screening in women aged 30 years and above [11]. The measure of association used was the Odds ratio (ORs) with 95% confidence interval (95%CI). Only the variables that were statistically significant in the univariate analysis were included in the final multivariate logistic regression model.

All volunteer participants gave their written informed consent to participate in the study. The study was approved by the Faculty of Medicine's Ethics Committee.

2.1. Role of the funding source

The authors declare that the sponsors did not have any role in the study design, collection, analysis and interpretation of the data.

3. Results

A total of 469 women with valid HPV DNA and cytological results completed the questionnaire between October 2008 and December 2010. The age range was 14–70 and the overall mean age (SD) was 33.3 (10.9). More than a third of women (n = 183, 39.0%) were younger than 30 years old. Most of participants had their first sexual intercourse before the age of 15 (63.8%) whereas 17.1% reported not having had a sexual partner or only one in the last twelve months. The most common number of full-term pregnancies was two, and 22.6% of the women had their first children before the age of 18. Almost a third of women had a university degree, and 41.8% never smoked. Most of participants came from peripheral districts (A, G, D, E, and F) whereas the representation of participants from the richest districts (C, B and CH) was low. Almost half of the women (45.8%) came from districts with percentages of poverty $>$ 15% (A, D and F).

A total of 224 women (47.8%; 95%CI: 43.2–52.4) were negative for intraepithelial lesion or malignancy (NILM). Prevalence of ASCUS, LSIL and HSIL were 5.1% (n = 24; 95%CI: 3.3–7.5), 35.0% (n: 164; 95%CI: 30.7–39.5) and 12.2% (n: 57; 95%CI: 9.3–15.5), respectively. Overall high-risk HPV prevalence among all participants was 24.5% (95%CI:

Table 1
Association between HSIL cytological result and sociodemographic, sexual and reproductive factors (LSIL and ASCUS excluded).

Variable	NILM N = 224	(%)	HSIL N = 57	(%)	Crude OR (95%CI)	Adjusted[a] OR (95%CI)	p-value for trend
Age (years)							
< 30	82	(36.6)	25	(43.9)	Ref.	–	
30 – 39	70	(31.3)	14	(24.6)	0.66 (0.32–1.36)	–	
40 – 49	54	(24.1)	11	(19.3)	0.67 (0.30–1.47)	–	
≥ 50	15	(6.7)	6	(10.5)	1.31 (0.46–3.74)	–	
Missing	3	(1.3)	1	(1.8)	1.09 (0.11–10.98)	–	
Age of first sexual relationship							.639
≥ 15	146	(65.2)	34	(59.6)	1	1	
< 15	73	(32.6)	16	(28.1)	0.94 (0.49–1.82)	1.28 (0.60–2.75)	
Missing	5	(2.2)	7	(12.3)	**6.01 (1.80–20.10)**	2.02 (0.42–9.71)	
Education							
≥ High school	65	(29.0)	12	(21.1)	Ref.	–	
< High school	149	(66.5)	39	(68.4)	1.42 (0.70–2.88)	–	
Missing	9	(4.5)	10	(10.5)	3.25 (0.99–10.63)	–	
Sexual partners over last year							**0.029**
0 – 1	50	(22.3)	6	(10.5)	Ref.	Ref.	
2 – 4	99	(44.2)	14	(24.6)	1.17 (0.43–3.25)	1.30 (0.46–3.66)	
≥ 5	23	(10.3)	8	(14.0)	2.89 (0.90–9.32)	3.22 (0.97–10.75)	
Missing	52	(23.2)	29	(50.9)	**4.65 (1.78–12.15)**	**3.54 (1.20–10.40)**	
Pap test in the last 3 years							
Yes	177	(79.0)	51	(89.5)	Ref.	–	
No	6	(2.7)	1	(1.8)	0.59 (0.07–4.15)	–	
Missing	41	(18.3)	5	(8.8)	0.43 (0.16–1.13)	–	
Ever had an STI							0.827
No	151	(67.4)	29	(50.9)	Ref.	Ref.	
Yes	36	(16.1)	8	(14.0)	1.16 (0.49–2.74)	1.01 (0.41–2.52)	
Missing	37	(16.5)	20	(35.1)	**2.82 (1.44–5.52)**	1.31 (0.55–3.12)	
Smoke							
Never	94	(42.0)	27	(47.4)	Ref.	–	
Former	18	(8.0)	1	(1.8)	0.19 (0.03–1.52)	–	
Current	96	(42.9)	20	(35.1)	0.73 (0.38–1.38)	–	
Missing	16	(7.1)	9	(15.8)	1.96 (0.78–4.92)	–	
Steady partner							0.503
Yes	171	(76.3)	38	(66.7)	Ref.	Ref.	
No	45	(20.1)	11	(19.3)	1.10 (0.52–2.32)	1.03 (0.46–2.28)	
Missing	8	(3.6)	8	(14.0)	**4.50 (1.59–12.75)**	2.08 (0.61–7.10)	
Full-term pregnancies							
0 − 1	64	(28.6)	19	(33.3)	Ref.	–	
2 − 3	95	(42.4)	23	(40.4)	0.82 (0.41–1.62)	–	
≥ 4	50	(22.3)	9	(15.8)	0.61 (0.25–1.46)	–	
Missing	15	(6.7)	6	(10.5)	1.34 (0.46–3.95)	–	
Age at first pregnancy[b]							0.391
≥ 18	125	(58.4)	23	(46.9)	Ref.	Ref.	
< 18	53	(24.8)	13	(26.5)	1.33 (0.63–2.28)	1.62 (0.68–3.87)	
Missing	21	(9.8)	8	(16.3)	**2.83 (1.26–6.32)**	2.06 (0.80–5.33)	
Contraceptive use							
No	93	(41.5)	21	(36.8)	Ref.	–	
OC	76	(33.9)	21	(36.8)	1.22 (0.62–2.41)	–	
Any	1	(0.4)	1	(1.8)	4.43 (0.27–73.70)	–	
Missing	54	(24.1)	14	(24.6)	1.14 (0.54–2.44)	–	
Years of OC use[c]							
< 1	15	(14.0)	2	(9.5)	Ref.	–	
1 − 4	38	(35.5)	5	(23.8)	0.99 (0.17–5.65)	–	
≥ 5	35	(32.7)	5	(23.8)	1.07 (0.19–6.15)	–	
Missing	19	(17.8)	9	(42.9)	3.55 (0.67–18.97)	–	
Housing conditions							
Good	39	(17.4)	8	(14.0)	Ref.	–	
Regular	165	(73.7)	44	(77.2)	1.30 (0.58–2.98)	–	
Missing	20	(8.9)	5	(8.8)	1.22 (0.35–4.21)	–	
District by poverty rate[d]							
Low poverty	40	(17.9)	14	(24.6)	Ref.	–	
Median poverty	57	(25.4)	18	(31.6)	0.90 (0.40–2.02)	–	
High poverty	105	(46.9)	16	(28.1)	0.44 (0.20–1.00)	–	
Missing	22	(9.8)	9	(15.8)	1.16 (0.43–3.13)	–	

Low Grade Squamous Intraepithelial Lesion (LSIL) and Atypical Squamous Cell of Undetermined Significance (ASCUS) excluded from the analysis. HSIL = High Grade Squamous Intraepithelial Lesion; NILM = Negative for Intraepithelial Lesion or Malignancy;OR = Odd Ratio; STI = sexually transmitted infections; OC = oral contraceptives.

[a] Adjusted for significant variables of crude analysis.

[b] Includes only women with children.

[c] Includes only OC users.

[d] < 5% Low. 5–15% Medium and > 15% High.

Table 2
Association between high-risk HPV infection and sociodemographic. sexual and reproductive factors (women younger than 30 years excluded).

Variable	HR-HPV-N = 220	(%)	HR-HPV + N = 66	(%)	Crude OR (95%CI)	Adjusted[a] OR (95%CI)	p-value for trend
Age (years)							
30 – 39	109	(49.5)	37	(56.1)	Ref.	–	
40 – 49	81	(36.8)	16	(24.2)	0.58 (0.30–1.12)	–	
≥ 50	27	(12.3)	12	(18.2)	1.31 (0.60–2.84)	–	
Missing	3	(1.4)	1	(1.5)	0.98 (0.10–9.73)	–	
Age of first sexual relationship							
≥ 15	160	(72.7)	49	(74.2)	Ref.	–	
< 15	46	(20.9)	12	(18.2)	0.85 (0.42–1.73)	–	
Missing	14	(6.4)	5	(7.6)	1.17 (0.40–3.40)	–	
Education							
≥ High school	61	(27.7)	13	(19.7)	Ref.	–	
< High school	150	(68.2)	47	(71.2)	1.47 (0.74–2.91)	–	
Missing	9	(4.1)	6	(9.1)	3.13 (0.95–10.32)	–	
Sexual partners over last year							0.084
0 – 1	42	(19.1)	7	(10.6)	Ref.	Ref.	
2 – 4	95	(43.2)	22	(33.3)	1.39 (0.55–3.50)	1.44 (0.57–3.65)	
≥ 5	25	(11.4)	12	(18.2)	**2.88 (1.01–8.28)**	**2.94 (1.01–8.51)**	
Missing	58	(26.4)	25	(37.9)	**2.59 (1.02–6.54)**	2.53 (0.99–6.56)	
Pap test in the last 3 years							
Yes	183	(83.2)	52	(78.8)	Ref.	–	
No	3	(1.4)	0	(0.0)	–	–	
Missing	34	(15.5)	14	(21.2)	1.45 (0.72–2.90)	–	
Ever had an STI							
No	156	(70.9)	41	(62.1)	Ref.	–	
Yes	29	(13.2)	9	(13.6)	1.18 (0.52–2.69)	–	
Missing	35	(15.9)	16	(24.2)	1.74 (0.88–3.45)	–	
Smoke							
Never	91	(41.4)	36	(54.5)	Ref.	–	
Former	20	(9.1)	2	(3.0)	0.25 (0.06–1.14)	–	
Current	89	(40.5)	23	(34.8)	0.65 (0.36–1.19)	–	
Missing	20	(9.1)	5	(7.6)	0.63 (0.22–1.81)	–	
Steady partner							
Yes	165	(75.0)	47	(71.2)	Ref.	–	
No	48	(21.8)	13	(19.7)	0.95 (0.48–1.90)	–	
Missing	7	(3.2)	6	(9.1)	3.01 (0.97–9.39)	–	
Full-term pregnancies							
0 – 1	41	(18.6)	11	(16.7)	Ref.	–	
2 – 3	100	(45.5)	39	(59.1)	1.45 (0.68–3.11)	–	
≥ 4	74	(33.6)	16	(24.2)	0.81 (0.34–1.90)	–	
Missing	5	(2.3)	0	(0.0)	–	–	
Age at first pregnancy[b]							
≥ 18	154	(71.3)	44	(71.0)	Ref.	–	
< 18	43	(19.9)	9	(14.5)	0.73 (0.33–1.62)	–	
Missing	19	(8.8)	9	(14.5)	1.66 (0.70–3.92)	–	
Contraceptive use							
No	99	(45.0)	27	(40.9)	Ref.	–	
OC	57	(25.9)	19	(28.8)	1.22 (0.63–2.39)	–	
Any	1	(0.5)	1	(1.5)	3.67 (0.22–60.56)	–	
Missing	63	(28.6)	19	(28.8)	1.11 (0.57–2.15)	–	
Years of OC use[c]							
< 1	5	(8.8)	4	(21.1)	Ref.	–	
1 – 4	14	(24.6)	3	(15.8)	0.27 (0.04–1.64)	–	
≥ 5	25	(43.9)	6	(31.6)	0.30 (0.06–1.47)	–	
Missing	13	(22.8)	6	(31.6)	0.58 (0.11–2.95)	–	
Housing conditions							0140
Good	41	(18.6)	5	(7.6)	Ref.	Ref.	
Regular	160	(72.7)	55	(83.3)	**2.82 (1.06–7.49)**	**2.68 (1.01–7.21)**	
Missing	19	(8.6)	6	(9.1)	2.58 (0.70–9.55)	2.56 (0.56–8.12)	
District by poverty rate[d]							
Low poverty	33	(15.0)	12	(18.2)	Ref.	–	
Median poverty	62	(28.2)	28	(42.4)	1.24 (0.56–2.76)	–	
High poverty	101	(45.9)	24	(36.4)	0.65 (0.30–1.45)	–	
Missing	24	(10.9)	2	(3.0)	0.23 (0.05–1.12)	–	

HR-HPV- = Negative for high-risk human papillomavirus; HR-HPV- = Positive for high-risk human papillomavirus; OR = Odd Ratio; STI = sexually transmitted infections; OC = oral contraceptives.

[a] Adjusted for significant variables of crude analysis.

[b] Includes only women with children.

[c] Includes only OC users.

[d] < 5% Low. 5–15% Medium and > 15% High.

20.7–28.7), and among participants aged 30 years or more, 23.1% (95%CI: 18.3–28.4).

Table 1 shows the results of the univariate and multivariate analyses on the likelihood of getting a HSIL. After adjusting for age at first sexual relationship, number of sexual partners over last year, previous history of STI, having a steady partner and age at first pregnancy, we found that a high number of sexual partners (i.e. more than five) increased the risk of HSIL (adjusted OR = 3.22, 95%CI: 0.97–10.75). However, this association was marginally non-statistically significant. Missing values categories of variables related to sexual behavior (age at first sexual relationship, sexual partners over last year, STIs history, having steady partner and age at first pregnancy) showed a statistical significant association with getting a HSIL. Nevertheless, all but a high number of sexual partners lost the statistical significance in the multivariable model. Other variables such as education, having had a PAP test in the last three years, smoking or contraceptive use did not show association with HSIL.

The association of the different variables with high-risk HPV infection among women older than 30 years (n = 286) was also explored (Table 2). In the univariate analysis, only a high number of sexual partners and regular housing conditions were found to be associated with an increased risk of high-risk HPV infection. The association was still observed in the multivariate analysis for both variables (adjusted OR: 2.94, 95%CI: 1.01–8.51 and 2.68, 95%CI: 1.01–7.21, respectively).

4. Discussion

This is, to our knowledge, the first study analyzing factors associated with high-risk HPV infection and high grade cervical lesions in Uruguay. Previous studies examined overall HPV prevalence and type distribution in Uruguayan women with or without cervical lesions [14–16]. The results of those studies evidenced the relatively high HPV prevalence in the country as compared with other regions, but the factors associated with HPV infection had not been yet ascertained.

Overall, one half of our sample presented abnormal cytological results. This prevalence is considerably higher than those found in other equivalent studies [15,18,19] and shows a potential high overcalling of cytology in our sample. However, most of the abnormal cytological results (35%) were LSIL which most often resolve spontaneously without needing any kind of intervention and may thus be classified as normal cytological results. Moreover, our sample was composed mainly by young women (mean age = 33.3) coming from districts with percentages of poverty > 15% (46%). In addition, they might attend the cervical screening clinics for additional reasons such as seeking contraceptive advice or pregnancy confirmation, services which were also offered for free in the clinics. Thus, they could be considered as a high risk group where percentages of abnormal cytology are expected to be higher. The overall prevalence of high-risk HPV infection was 24.5%, slightly higher than the 20.8% found in a previous study from Uruguay [15]. Among women 30 years or older, the prevalence of high-risk HPV infection dropped to 23.1%.

Several studies have analyzed the association between reproductive factors and cervical carcinoma [20,21]. High parity and early age at first full-term pregnancy have been shown to increase cervical cancer risk. However, those factors have not shown a clear pattern regarding association with HPV infection [22–27]. We did not find a positive association between reproductive factors and HR-HPV infection or HSIL in our study. As expected, a high number of sexual partners was found to be consistently associated with getting a high grade cervical lesion [28] and a high-risk HPV infection [22,29–31]. Despite the association between tobacco use and HSIL and high risk-HPV infection is well established [30,32], it was not observed in our sample, where prevalence of tobacco use was high (48%). This could be partially explained by the fact that the question asking for tobacco use in our study was not exactly formulated in the same way than in population-based tobacco surveys, which could limit the quality of the data obtained from this variable. Women aged 30 years old or more living in regular housing conditions were more likely to be positive for high-risk HPV infection than those living in good housing conditions. Other socioeconomic variables such as educational level and district of the city did not show different outcomes despite those are present in other CSA studies [19,27–31]. This could be explained by the fact that almost half of our sample came from districts with percentages of poverty > 15% (46%), with a low percentage of women from richest districts of the city participated in this study. It must be noted that the distribution of public health services is not homogeneous in the all districts of the city. High rates of participation and follow-up in cancer screening programs are usually mainly achieved in highest social strata [33–35]. However, our results seem indicate that those may use alternative sectors of the health system.

This study provides novel data from unvaccinated population in Montevideo, which nucleate almost a half of the country population. We found that both strategies used in cervical cancer screening, HPV testing and cytology, identified the same risk factor for HSIL and high-risk HPV infection, a high number of sexual partners. HPV testing also identified housing conditions as risk factor for having a high-risk HPV infection. Our results may help identifying risk groups of women that could have a greater benefit from broadening the scope for prevention of cervical cancer with HPV-screening, HPV-vaccination or a combination of both, and highlight the relevance of this baseline information when formulating appropriate strategies towards cervical cancer control in the country. Moreover, our proposal of risk stratification of the women according to different sociodemographic, sexual and reproductive factors could be used as triage strategy, together with other currently recommended or evaluated triage algorithms such as the use of HPV genotype [36], methylation status [37,38] and p16 expression [39].

Despite that, it had several limitations. Our work was not population-based and thus, our results do not necessarily represent the level of high-risk HPV infection and HSIL in the general female Uruguayan population. The cross-sectional nature of the study design does not allow for establishing a causal relationship of high-risk HPV infection or HSIL with the cofactors investigated. In addition, self-administered questionnaires can be subject to biases. Actually, the pattern showed for the missing values of some sexual behavior variables (age at first intercourse and pregnancy, number of sexual partners in the last year, having a steady partner, and a history of sexual transmission disease) can be interpreted as the questionnaire was not an appropriate tool to explore sensitive matters in a conservative society with social taboos about the topic. This problem was also observed in a similar Canadian study with other cultural beliefs. [25]. However, the results from this kind of surveys may indicate which groups of women are susceptible to have a greater benefit from other existing strategies for cervical cancer control. Finally, the absence of robustness in data on some risk factors hampered their full assessment.

5. Conclusions

Our study provides a comprehensive description of factors associated with high-risk HPV infection and HSIL among unvaccinated women in Montevideo, using detailed information from an opportunistic sample. Our results are valuable from a public health perspective, since it can help to target groups which can get greater benefits from health programs. The identification of the risk factors is also required to adequately interpret associations with potential to selection bias in epidemiologic studies. These baseline data may be useful to assess the impact of the recently implemented national HPV vaccination program and the whole new reforms in the Uruguayan public health system [13]. Moreover, in an era of development of new strategies for accelerating the reduction of cervical cancer incidence and mortality, our results may contribute to identify populations most susceptible to get benefit from broadening the scope for prevention of cervical cancer and could

be used in combination with other currently recommended or evaluated triage strategies.

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MM has received occasional travel fund to conferences/symposia/meetings by Roche. All other authors declare no conflicts of interest.

Ethical adherence

The authors state that the manuscript adheres to the international ethical standards in publishing scientific articles. The study was approved by the Faculty of Medicine's Ethics Committee and all volunteer participants gave their written informed consent to participate in the study.

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