



## 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.

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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:

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