Safety of screening with Human papillomavirus testing for cervical cancer at three-year intervals in a high-risk population: experience from the LAMS study*


INTRODUCTION

Based on firm documentation of efficacy and feasibility, the combined use of cervical cytology and high-risk human papillomavirus (hrHPV) testing has been proposed as an optional approach in screening for cervical cancer in the USA.1–5 One of the advantages of this approach includes the possibility of lengthening the screening intervals to three years or more, because women with a negative HPV test and normal cytology are at an extremely low risk of developing cervical cancer in the next three to five years.3

A series of large cohort studies to provide evidence on the safety of screening HPV-negative women at three-year intervals are ongoing, using various study designs.5 Until to date, the bulk of the current evidence favouring the extended screening intervals is derived from developed countries with effective screening programmes.7 In low-resource settings, the main efforts have been focused on finding the ways how to overcome the difficulties in cervical cytology, by running cross-sectional studies to compare optional screening tools, e.g. visual inspection with acetic acid (VIA)/l Lugol iodine (VILI) and cervicography.8,9 Longitudinal cohort studies capable of confirming the safety of extended screening intervals, based on hrHPV testing or any other screening techniques, are currently not available in the low-resource settings.

In a recent meta-analysis of the prospective studies on HPV testing as a predictor of cervical disease, it has been shown that the predictive value of HPV tests is largely dependent on the disease prevalence in each setting, which precludes extrapolation of the results to populations with different disease burden e.g. in different regions of Latin America.7 In Brazil and Argentina (the two largest Latin American countries), screening for cervical cancer is based on cervical cytology but flawed due to several reasons. Most notably, these failures are a consequence of the lack of structured network of public health services,

Objectives

To assess whether human papillomavirus (HPV) testing is a safe enough approach to warrant extension of the screening intervals of baseline Papicolou (Pap)+/−HPV− women in low-income settings.

Methods

Of the >1000 women prospectively followed up as part of the Latin American Screening (LAMS) Study in São Paulo, Campinas, Porto Alegre and Buenos Aires, 470 women with both baseline cytology and Hybrid Capture 2 (HC2) results available were included in this analysis. These baseline Pap-negative and HC2− or HC2+ women were controlled at six-month intervals with colposcopy, HC2 and Pap to assess the cumulative risk of incident Pap smear abnormalities and their predictive factors.

Results

Of the 470 women, 324 (68.9%) were high-risk HPV (hrHPV) positive and 146 (31.1%) were negative. Having two or more lifetime sex partners (odds ratio [OR] = 2.63; 95% CI 1.70−3.51) and women using hormonal contraception (OR = 2.21; 95% CI 1.40−3.51) were at increased risk for baseline hrHPV infection. Baseline hrHPV+ women had a significantly increased risk of incident abnormal Pap smears during the follow-up. Survival curves deviate from each other starting at month 24 onwards, when hrHPV+ women start rapidly accumulating incident Pap smear abnormalities, including atypical squamous cells (ASC) or worse (log-rank; P < 0.001), low-grade squamous intraepithelial lesions (LSIL) or worse (P < 0.001) and high-grade squamous intraepithelial lesions (HSIL) (P = 0.03). Among the baseline hrHPV− women, the acquisition of incident hrHPV during the follow-up period significantly increased the risk of incident cytological abnormalities (hazard ratio = 3.5; 95% CI 1.1−11.7).

Conclusion

These data implicate that HPV testing for hrHPV types might be a safe enough approach to warrant extension of the screening interval of hrHPV−/−Pap− women even in low-resource settings. Although some women will inevitably contract hrHPV, the process to develop HSIL will be long enough to enable their detection at the next screening round (e.g. after three years).

* LAMS [Latin American Screening] Study, funded by European Commission, INCO-DEV Contract # ICA4-CT-2001-10013.
the extent of these countries’ territories and the geographic
dispersion of their populations.\textsuperscript{10,11} For these reasons, Brazil
and Argentina are fertile grounds for studies testing optional
measures for cervical cancer screening.

This prompted us to design the Latin American Screening
Study (LAMS Study), a multicentre collaborative trial evaluating
eight different screening techniques for cervical cancer in
different regions of Brazil and Argentina.\textsuperscript{12} A cohort of
over 12,000 women was enrolled from five different
regions, the study design, baseline data and tentative
results of hrHPV testing and VIA/VILI being reported.\textsuperscript{13,14}

Based on the completion of the prospective follow-up of
over 1000 of these women,\textsuperscript{13} the present study reports the
acquisition of cytological abnormalities among baseline
hrHPV-positive and hrHPV-negative women, derived from
this low income, relatively unassisted and previously incom-
pletely studied Latin American population. The main aim
was to assess, whether hrHPV testing is a safe enough
approach to warrant extension of the screening intervals
of those women who test Papanicolaou (Pap)-
and hrHPV-negative at baseline. If applicable, such an extension
would be of great interest to health authorities planning new
measures for cervical cancer prevention in a setting with
limited health-care resources.

\textbf{SUBJECTS AND METHODS}

\textbf{Study design}

LAMS study is a multicentric study, sponsored by the
European Commission through its INCO-DEV programme
(ICA4-CT2001-10013). In this study, consecutive women
from the cities of Campinas, São Paulo and Porto Alegre
(Brazil) as well as Buenos Aires (Argentina) were recruited
to undergo gynaecological examination and testing with
conventional Pap smear, VIA or VILI, cervicography and
screening colposcopy. Women were sampled for hrHPV
testing by Hybrid Capture 2 (HC2). All centres performed
screening colposcopy. Women with these conditions were treated according to
the study protocol as described elsewhere.\textsuperscript{13,14} Therefore, the
follow-up workup for women considered ‘normal’
was to assess, whether hrHPV testing is a safe enough
approach to warrant extension of the screening intervals
of those women who test Papanicolaou (Pap)-
and hrHPV-negative at baseline. If applicable, such an extension
would be of great interest to health authorities planning new
measures for cervical cancer prevention in a setting with
limited health-care resources.

\textbf{Enrolment and eligibility of the women}

Slightly different protocols were used to recruit the women
in different clinics. In São Paulo, Porto Alegre and Buenos
Aires, eligible women were informed of the study protocol
by their local health units, inviting them to participate. In
Campinas, in addition to this same approach, students and
employees of the University Hospital were invited through
an open announcement, widely distributed in the university
facilities.

Women were considered eligible, if they met all of the follow-
ing criteria: (1) age between 15 and 60 years; (2) no previ-
sous surgical procedure of the cervix or corpus; (3) had no
history of abnormal Pap test in the past year; (4) free of
known current genital condyloma (external or in the
cervix), cervical intraepithelial neoplasia (CIN) or cervical
carcinoma; (5) had no sexual intercourse during the three
days prior to the examination; (6) did not have any con-
formed or clinically suspect immunosuppression (HIV,
or other conditions that might compromise the immune
system).

\textbf{Diagnostic setting}

After signing the informed consent, women undertook a
questionnaire addressing clinical and epidemiological risk
factors of HPV, CIN and cervical cancer. All women under-
went thorough pelvic examination in this sequence: (1) col-
lection of the Pap smear, (2) collection of HC2 sample and
(3) VIA. In Porto Alegre, most women underwent VILI
shortly after VIA. All women, who had at least one of
these examinations abnormal, were referred for colposcopic
examination. In Buenos Aires and Campinas, women
underwent screening colposcopy even when their exams
were negative. Abnormal colposcopy prompted punch biop-
sies of the cervix, and women with high-grade squamous
intraepithelial lesions (HSIL) were treated by conization.

Women had their second visit scheduled for one and a
half months (average 45 days), to become informed about their exam/biopsy results and to be allotted to either (1) the
treatment- or (2) the follow-up group. Treatment was
offered to all women who had high-grade lesion (CIN2–3)
confirmed in the cervical biopsy. Altogether, 32 cases of
invasive cervical cancer were diagnosed during the recruit-
ment phase and all were treated according to each insti-
tution’s regular protocols.

\textbf{Follow-up}

A total cohort of 1011 women completed at least one
follow-up visit. In the present study, however, we analysed
the follow-up data derived from a cohort of 689 women,
who attended at least one follow-up visit and who had
both baseline cytology and HC2 results available. This
group was further reduced to 470, because 219 women
had ASC (atypical squamous cells) or worse in their baseline
cytology or CIN1 or worse in their baseline cervical biopsy.
Women with these conditions were treated according to
the study protocol as described elsewhere.\textsuperscript{13,14} Therefore, the
study sample in the present study consists of 470 women
with negative baseline cytology and normal colposcopy
and/or normal biopsies, who attended at least one follow-up
visit.

The follow-up workup for women considered ‘normal’
after baseline assessment was similar in all study centres,
with follow-up visits being scheduled at six-month intervals.
The study protocol determined that women should be
re-examined four times (optimal moments should have been 6, 12, 18 and 24 months; see below). At each follow-up visit, women responded to a brief questionnaire addressing any relevant gynaecological events and epidemiological features changed since the previous control (e.g. sexual partners, smoking). The total follow-up time encompassed in this report approaches 50 months, but the bulk of the data covers approximately 36 months (median follow-up time = 24.4 months; 90% central range = 6.8–32.2 months) (Figure 1).

**Difficulties with follow-up**

Longitudinal studies in low-income settings are known to be affected by severe loss-to-follow-up phenomena. The researchers tried to keep consultations as close as possible to these target points, but several factors made it impossible to maintain follow-up on schedule. First and foremost, difficulties to contact women that had missed one of the follow-up consultations led to a delay on several scheduled consultations. Most women in the present study belong to low-income populations, and therefore home addresses and telephone contact numbers fluctuate over time. Table 1 shows the distribution of women at each ‘target’ follow-up point according to the actual time point at which they attended consultations. The researchers tried to circumvent the patients’ difficulties to attend consultations by offering transportation to the clinics and by re-scheduling consultations at the patients’ conveniences. Follow-up therefore ranged from 6 to 49 months, although the bulk of data covers 36 months.

![Figure 1 Schematic overview of the study design](image)

**Cervical cytology (pap smear)**

Conventional Pap smears were taken using the Ayre spatula and endocervical brush, fixed in 95% ethanol and stained by the modified Pap method. Final cytological diagnoses were issued by using the Bethesda System and were classified as normal/inflammatory, ASC, atypical glandular cells, LSIL, HSIL or cancer.

**Hybrid capture 2**

The specimens for HC2 were tested with probe B for hrHPV types: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) and the tests were classified positive at the relative light unit/positive control (RLU/CO) ratio of 1 pg/mL or greater. These RLU/CO ratios provide a semi-quantitative estimate of the amount of HPV DNA in the specimens, i.e. the viral load in the sample. Storage of specimens and reagents, as well as exams processing, were carried out in manufacturer-certified laboratories, under the responsibility of the investigators, following the manufacturer’s instructions (Digene Diagnostics Inc., USA). São Paulo and Buenos Aires processed their own HC2 samples in-house, whereas Campinas and Porto Alegre had their HC2 specimens processed at Campinas University hospital laboratory.

**Statistical analysis**

All statistical calculations were performed with the R-environment for statistical computing, and 95% CI were calculated where appropriate. Intra-class correlation coefficients were calculated to assess the agreement (i.e. re-incidence or repetition of Pap abnormalities) in pairs of cytological assessment rounds. A logistic regression model was used to analyse the power of epidemiological (and clinical) variables as predictors of the baseline hrHPV status, calculating odds ratio (OR) and 95% CI. Multivariate survival (Cox proportional hazards) analysis was used to calculate hazard ratios (HR) for incident Pap smear abnormalities in three distinct cohorts: (1) the complete sample; (2) women with positive baseline hrHPV; (3) women with negative baseline hrHPV, adjusted for clinical and epidemiological features as well as their hrHPV status at baseline and during follow-up. Univariate survival (Kaplan-Meier) analysis was used to calculate the survival curves (in the whole cohort) for accumulation of incident HSIL during the follow-up, separately for baseline hrHPV-positive women.
and -negative women. For cases of ASC or worse and LSIL or worse, the patients' status at their last follow-up visit was considered. This strategy was implemented to avoid censoring cases with transient conditions, such as ASC or LSIL, which would afterwards develop more severe cytological abnormalities or simply subside. The curves were compared using log-rank (Mantel-Cox) statistics.

RESULTS

Table 2 summarizes the predictors of baseline hrHPV status in multivariate regression analysis. Of the 470 women, 324 (68.9%) were hrHPV positive and 146 (31.1%) were negative. Having two or more lifetime sex partners (OR = 2.63; 95%CI 1.70–3.51) and women using hormonal contraception (OR = 2.21; 95%CI 1.40–3.51) were at increased risk for baseline hrHPV infection. Other implicated risk factors of hrHPV, e.g. age at first intercourse and smoking habits, were not significant predictors of baseline hrHPV status in this cohort.

The vast majority of incident cytological abnormalities diagnosed during the follow-up were found among women who tested hrHPV positive at baseline. However, the prevalence of incident ASC, LSIL and HSIL at three follow-up time points (6-, 12-, 24-months) did not differ among hrHPV+ and hrHPV− women. At six months, 41 women had newly diagnosed abnormal Pap tests, only one of those being hrHPV− at baseline. However, most of the women (191/224) who attended the six-month follow-up visit had a positive baseline hrHPV test. At 12- and 24-month visits, women with positive baseline hrHPV still represented the majority among those with incident Pap smear abnormalities (data not shown).

The actual time points at which women attended the follow-up consultations are depicted, in quartiles, in Table 1. The number of cases at each visit ranged from a minimum of 235 (third visit, planned to target women 18 months after baseline assessment) to a maximum of 301 (second visit, planned to target women 18 years after baseline assessment). Women that were enrolled in the study were included in all follow-up visits. Survival curves deviate from each other starting at month 24 onwards, when hrHPV+ women start rapidly accumulating incident Pap smear abnormalities, including ASC or worse (log-rank; P < 0.001) and LSIL or worse (P < 0.001) and HSIL (P = 0.03).

The risk estimates for incident Pap smear abnormalities during a 24-month follow-up period in Cox analysis are depicted in Table 4. Positive baseline hrHPV status (HR = 3.4; 95%CI 1.8–6.4) and age at first intercourse below 18 years (HR = 1.9; 95%CI 1.2–3.0) were the two significant predictors of incident cytological abnormalities in the present (whole) cohort. Among the sub-cohort of baseline hrHPV− women, none of the recorded epidemiological variables were shown to be significant predictors. Among the baseline hrHPV− women, the acquisition of incident hrHPV during the follow-up period proved to increase the risk of incident cytological abnormalities (HR = 3.5; 95%CI 1.1–11.7).

Table 2 Predictors of the baseline hrHPV status in multivariate analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Positive (n = 324)</th>
<th>Negative (n = 146)</th>
<th>OR*</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>141 (45.3)</td>
<td>57 (39.6)</td>
<td>0.80</td>
<td>[0.23–1.28]</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>183 (56.5)</td>
<td>87 (60.4)</td>
<td>Ref.</td>
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<tr>
<td>First intercourse</td>
<td></td>
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<tr>
<td>&lt; 18 years</td>
<td>181 (55.8)</td>
<td>66 (45.2)</td>
<td>1.37</td>
<td>[0.88–2.13]</td>
</tr>
<tr>
<td>≥ 18 years</td>
<td>143 (44.2)</td>
<td>80 (54.8)</td>
<td>Ref.</td>
<td></td>
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<tr>
<td>Life time partners</td>
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</tr>
<tr>
<td>≥ 2</td>
<td>234 (72.2)</td>
<td>74 (50.7)</td>
<td>2.63</td>
<td>[1.70–3.51]</td>
</tr>
<tr>
<td>1</td>
<td>90 (27.8)</td>
<td>72 (49.3)</td>
<td>Ref.</td>
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<tr>
<td>Contraceptive methods</td>
<td></td>
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<tr>
<td>Hormonal</td>
<td>144 (44.6)</td>
<td>42 (28.8)</td>
<td>2.21</td>
<td>[1.40–3.51]</td>
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<tr>
<td>Non-hormonal</td>
<td>137 (42.4)</td>
<td>87 (59.6)</td>
<td>Ref.</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Yes</td>
<td>76 (23.4)</td>
<td>37 (25.3)</td>
<td>0.69</td>
<td>[0.42–1.16]</td>
</tr>
<tr>
<td>Past</td>
<td>49 (15.2)</td>
<td>22 (15.1)</td>
<td>0.90</td>
<td>[0.49–1.64]</td>
</tr>
<tr>
<td>Never</td>
<td>199 (61.4)</td>
<td>87 (59.6)</td>
<td>Ref.</td>
<td></td>
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</tbody>
</table>

OR, odds ratio; hrHPV, high-risk HPV
*Adjusted with logistic regression

Discussion

During the past few years, HPV detection technology has become standardized and cost-effective, and HPV tests have recently gained increasing importance as potential tools in cervical cancer screening.1,2 HPV testing has an almost 100% negative-predictive value for the absence of significant cervical lesions when the test is negative. This has prompted several professional societies, e.g. the American Cancer Society (ACS) and the American College of Obstetrics and Gynecology (ACOG) to issue guidelines recommending a combined use of HPV tests with cytology. Useful as these guidelines might be in high-resource settings, it is imperative to realize that these are based on the epidemiological profile of the populations where HPV testing has been shown to predict future cervical abnormalities, which is not necessarily the case in many low-resource settings.13,18,19
While testing optional screening tools in low-resource settings, our LAMS study provides data that enables tackling the validity of these ACS and ACOGs guidelines in another type of environment, where the prevalence of HPV infection and cervical cancer are dramatically different. Importantly, several co-factors are needed to make hrHPV infections capable of producing clinically significant cervical disease (CIN2–3), and these potential co-factors (e.g. reproductive factors, sexual behaviour, smoking, nutrition, concomitant gynaecological infections) are known to differ substantially among women living in high- and low-resource settings.20,21 Thus, if HPV testing is to be proposed as a suitable screening tool for these unprivileged conditions, the performance of this technology needs to be established in prospective cohort studies conducted under field conditions in these particular settings.6,7 This is exactly what the LAMS study has done, and the data provided in the present study should constitute an important tool for health policy-makers, while confirming the significant predictive value of hrHPV test as determinant of incident Pap smear abnormalities also among these low-income women (Table 1; Figure 1).

The sample of the present study (n = 470) represents a selected sub-cohort derived from over 12,000 women examined at baseline in the LAMS study, of whom over 1000 completed at least one follow-up visit.13 Despite this selection, this series of patients is consistent with the large cross-sectional studies, as to the epidemiological risk factors of cervical disease.6,7

Table 3  Cytological abnormalities at each follow-up visit according to the results of a previous follow-up cytology

<table>
<thead>
<tr>
<th>Visit</th>
<th>Second</th>
<th>Third</th>
<th>Last</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neg. ASC/AGC LSIL HSIL Miss.</td>
<td>Neg. ASC/AGC LSIL HSIL Miss.</td>
<td>Neg. ASC/AGC LSIL HSIL Miss.</td>
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<tr>
<td>First visit</td>
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<tr>
<td>Negative</td>
<td>145 13</td>
<td>2 0 65</td>
<td>126 8 3 0 89</td>
</tr>
<tr>
<td>ASC/AGC</td>
<td>12 2</td>
<td>1 0 6</td>
<td>10 4 0 0 6</td>
</tr>
<tr>
<td>LSIL</td>
<td>10 4</td>
<td>1 0 4</td>
<td>15 0 1 0 2</td>
</tr>
<tr>
<td>HSIL</td>
<td>0 0</td>
<td>0 0 1</td>
<td>0 0 0 1 7</td>
</tr>
<tr>
<td>Missing</td>
<td>102 6</td>
<td>2 0 93</td>
<td>62 2 2 0 137</td>
</tr>
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**ICC = 0.193**

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<tr>
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<td>Negative</td>
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<tr>
<td>ASC/AGC</td>
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<td>LSIL</td>
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<tr>
<td>HSIL</td>
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<td>– – – –</td>
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<tr>
<td>Missing</td>
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**ICC = 0.166**

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<tr>
<td>ASC/AGC</td>
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<td>LSIL</td>
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<td>HSIL</td>
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<td>Missing</td>
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**ICC = 0.135**

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<td>Neg. ASC/AGC LSIL HSIL Miss.</td>
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<td>Second visit</td>
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<td>ASC/AGC</td>
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<td>HSIL</td>
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**ICC = 0.179**

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<tr>
<td>ASC/AGC</td>
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<td>HSIL</td>
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<tr>
<td>Missing</td>
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</table>

**ICC = 0.279**

Neg., negative (normal); Miss., missing (not attending) that specific follow-up visit; ICC, intra-class correlation coefficient (agreement); ASC, atypical squamous cells; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions

*One patient treated with hysterectomy and excluded from follow-up.

Figure 2  Cumulative incidence of cytological abnormalities during 36 months of follow-up in Kaplan-Meier and log-rank analysis. Baseline hrHPV-positive women are depicted with a dotted line. Note: different scales for the Y (probability) axis were used in each plot.
epidemiological factors linked to HPV infection. This was not the main focus of this study, however, but instead we wanted to assess the accumulation of cytological abnormalities during the follow-up of baseline hrHPV+ and hrHPV− women. As shown by the significant results, the sample size was clearly large enough for this specific purpose.

Indeed, testing hrHPV positive at baseline significantly increased the probability of contracting incident Pap smear abnormality during the 50 months of prospective follow-up (Table 1). This was true for all cytological cut-offs used, i.e. ASC-US, LSIL and HSIL, all of which were significantly more frequent among baseline hrHPV+ women (Figure 1). As shown by the survival curves in Figure 1, all degrees of cytological abnormalities start accumulating after the first 24 months of prospective follow-up and continue to do so until the end of the 50-month observation period. A similar trend has been demonstrated in several ongoing or concluded cohort studies in Europe as well.22–24 In the HART (HPV in Addition to Routine Testing) study, the proposed strategy of reserving cytology exclusively to triage women with positive HPV tests has been severely challenged by the high frequency of low-grade abnormalities found in women with incident hrHPV infection, where HPV infection always precedes their related lesions, where HPV infection always precedes their related lesions, where HPV infection always precedes their related lesions. Because of these temporal relationships, Pap smear abnormalities. Similarly, women who tested hrHPV+ at baseline but who cleared their infection, still held their elevated risk of incident Pap smear abnormalities. Such patients were quite few, however, compromising the power of the analysis. On the other hand, most of the Pap abnormalities found in women with incident hrHPV infections were low-grade (data not shown in Tables). This is consistent with the known dynamics of HPV infections and their related lesions, where HPV infection always precedes the development of abnormal Pap by several months. Because of these temporal relationships, Pap smear abnormalities associated with these newly developed hrHPV infections are of lower grade as compared with those who had hrHPV at baseline. However, similar type of results have been reported in those cohort studies conducted in countries with high standards of living and high-resource primary health care.22–24,26–29 This is another argument in favour of the concept that extending the screening interval of HPV −/Pap− women is safe; even if they contract an incident hrHPV, the Pap smear abnormality to be detected in the next screening round (e.g. after three years) is likely to be of low-grade only.

Another debated issue in the literature is the type of HPV testing that should be optimal for screening, the response
still pending.\textsuperscript{30,31} This is due to multiple reasons, not the least due to the fact that HPV testing technology is still evolving. HC2 (Digene Corp., Gaithersburg, MD, USA) was the option found at the time of study design to be the most suitable for the detection of hrHPV infections in this series. Being cost-effective, easy to collect and fairly reproducible, the technique had the approval for clinical use by the US Food and Drug Administration and its Brazilian counterpart (Agência Nacional de Vigilância Sanitária; ANVISA). The major limitation of this technique is the failure to identify the specific HPV types, which would be highly advantageous in this type of study. Because one of the main aims of this study was to compare the validity of HPV testing in Brazilian and Argentinian women, likely to show different patterns of HPV exposure as compared with the European and North-American women studied in the published reports,\textsuperscript{8,12,13,21} the distribution of HPV genotypes in the infected women would be useful.

Prophylactic HPV vaccines are emerging as an appealing strategy for the primary prevention of cervical cancer. Two vaccines are already available; both having as their primary target the hrHPV types 16 and 18.\textsuperscript{32} These two HPV types were responsible for 50% and 20% of cervical cancer cases, respectively, in large population-based surveys.\textsuperscript{33} In the HPV vaccine era, it is likely that further attention will be focused on HPV testing, because efficacy of the vaccines seems to be conditioned by the HPV status of the women.\textsuperscript{34}

Taken together, the present study provides firm evidence first time also in low-resource settings, suggesting that hrHPV infection (both baseline and incident) is a significant risk factor for incident Pap smear abnormalities within a relatively short follow-up time. Until now, such data were available only in cohort studies performed in developed countries with completely different disease burden and resources for organized cervical cancer screening. This implies that HPV testing for hrHPV types might be a safe enough approach to be linked with extension of the screening interval of hrHPV +/Pap− women. Even if some of them will inevitably contract an incident hrHPV, the process to develop high-grade cytological abnormality will be long enough to enable detection of this incident abnormal Pap at the next screening round (e.g. after three years), most likely still at the stage of low-grade. This information should have important implications in planning alternative screening strategies particularly in the developing countries, where all resources for public health care are strictly limited.

Cervical screening with HPV testing in low-resource settings

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