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Assessment of the performance of algorithms for cervical cancer screening: Evidence from the Ludwig-McGill Cohort Study

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Abstract

Objective—There are currently multiple tests available for cervical cancer screening and the existing screening policies vary from country to country. No single approach will satisfy the specific needs and variations in risk aversion of all populations, and screening algorithms should be tailored to specific groups. We performed long term risk stratification based on screening test results and compared the accuracy of different tests and their combinations.

Methods—A longitudinal cohort study of the natural history of HPV infection and cervical neoplasia enrolled 2462 women from a low-income population in Brazil. Interviews and cervical screening with cytology and HPV DNA testing were repeated according to a pre-established protocol and the subjects were referred for colposcopy and biopsy whenever high grade lesions were suspected. We compared the specificity, sensitivity and predictive values of each screening modality. Long term risk stratification was performed through time-to-event analyses using Kaplan-Meier analysis and Cox regression.

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Results—The best optimization of sensitivity and specificity was achieved when using dual testing with cytology and HPV DNA testing, whereby the screening test is considered positive if either component yields an abnormal result. However, when allowing 12 months for the detection of lesions, cytology alone performed nearly as well. Risk stratification revealed that HPV DNA testing was not beneficial for HSIL cases, whereas it was for ASCUS and, in some combinations, for negative and LSIL cytology.

Conclusion—Our results suggest that some high risk populations may benefit equally from cytology or HPV DNA testing, and may require shorter intervals between repeat testing.

Keywords

Screening; Cervical cancer; Human papillomavirus; Epidemiology; Cervical cytology; HPV DNA testing

INTRODUCTION

Since the mid 20th century, cervical cancer screening with cytology has succeeded in lowering the incidence and mortality rates of this disease by up to 70% [1]. However, numerous studies have demonstrated that cervical cytology suffers from low sensitivity and requires well-structured quality control programs and frequent repeat testing in order to provide acceptable diagnostic accuracy [2-4]. In contrast, the more recently developed HPV DNA testing methods have been shown to have significantly higher sensitivity, though at the cost of reduced specificity [2, 5-7]. More specifically, the sensitivity of HPV DNA testing for the detection of high grade lesions is of 96% [2], which is between 30% and 50% higher than conventional cytology [5-7]. Specificity, on the other hand, is 5% to 10% lower than cytology [5, 6], ranging between 76% and 95% [2].

In addition to adequate accuracy, long term cancer risk predictions based on women's screening test result provides essential information to plan the deployment of cytology and HPV DNA testing (and their combinations) within a screening program, as well as the development of management guidelines. Five major studies [8-12] found that the long term risk of high grade lesions is lowest for individuals who test negative on both tests, is higher for those with a negative HPV DNA test but positive cytology (atypical squamous cells of undermined significance (ASCUS) or above), becomes even higher for those with a positive HPV DNA test but negative cytology and reaches its highest in individuals positive on both tests. The 10-year negative predictive value (NPV) when both tests are negative is 99.21% [12]. One study also indicated that amongst the women with negative results on both cytology and HPV DNA testing, the risk of high grade lesion development within 5 years was even lower for the subset who never had positive results on either test in the past [9]. Moreover, all five [8-12] studies have shown that the long term risk of high grade lesions amongst women with a negative HPV DNA test, regardless of their cytology result, is nearly identical to that of those for whom both tests are negative. Conversely, the risk of high grade lesions is higher in those with a positive HPV DNA test than in those with positive cytology, irrespective of the other screening test result. All studies have shown substantially lower long term risk in women with a negative HPV DNA test result than in women with negative cytology, which indicates the higher long term negative predictive value of HPV DNA

testing. Over a follow-up period of 5 years, the NPV of HPV DNA testing was shown to be of 99% [11].

The Ludwig-McGill cohort is a longitudinal study of the natural history of HPV infection and cervical neoplasia with follow up spanning up to ten years. It enrolled women from a low-income area in São Paulo in Brazil [13, 14]. The study's extended period of repeated measurements with both cytology and HPV testing provides an opportunity for long term risk stratification for the development of histologically confirmed cervical lesions according to various screening strategies and for comparing the accuracy of these tests under different scenarios. Few cohorts have repeated measurements extending beyond 10 years and which ascertain outcome with the gold standard of histological assessment. In this study, therefore, we aimed to evaluate and compare the accuracy of different screening tests and combinations, while taking into consideration possible determinants of accuracy, and assess the utility of long term risk stratification.

METHODS

Participants in the Ludwig-McGill cohort study were recruited between 1993 and 1997 from a comprehensive maternal and child health program offering services to low-income families in the city of São Paulo, Brazil, a high risk area for cervical cancer at the time the study began. Eligibility criteria included being between 18 and 60 years of age, being a permanent resident of the city of São Paulo, not being pregnant or intending to become pregnant within 12 months following enrolment, having an intact uterus with no current referrals for hysterectomy, not having used vaginal medication in the 3 days prior to enrolment and not having been treated for cervical disease in the 6 months preceding enrolment.

The participants were seen every 4 months in the first year following enrolment, and then twice yearly for up to 10 years. Over time, although most subjects complied with their pre-scheduled visits, some delayed to attend subsequent appointments, which were always set for six months later. This led to some staggering of the cumulative follow-up times. Conventional cervical cytology and HPV DNA testing were performed at each visit, whereas interviews were conducted at the first 4 visits and then yearly. Cervical smears were evaluated in the cytopathology laboratory of the Jewish General Hospital of Montreal, Canada, according to the 1991 version of the Bethesda classification system. HPV DNA testing was done at the Ludwig Institute for Cancer Research in São Paulo, Brazil, with the L1 PGMY PCR protocol followed by hybridization of the amplified products with probes for 40 HPV genotypes. If one or more of the following 13 high-risk (HR) genotypes were present: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68, the specimen was classified as HR-HPV positive; HPV positivity with types other than the above was classified as low risk (LR-HPV). In addition, cervicography was performed 3 times during the study; after one year, 2 years and 4 years. Women were referred for colposcopy and biopsy whenever high grade lesions were suspected either on cytology or on cervicography. The biopsies were interpreted following the cervical intra-epithelial neoplasia (CIN) classification by a gynecologic pathologist at the Jewish General Hospital of Montreal, Canada.

Long term risk stratification based on screening test result profiles was performed through time-to-event analyses using Kaplan-Meier plots [15] and Cox regression [16]. This was performed based both on baseline results and on the combination of screening tests over time, the latter accounting for the transient nature of HPV infections. The specificity, sensitivity and predictive values of each hypothetical screening modality were calculated, along with their corresponding 95% confidence intervals. First a cross-sectional context was considered whereby screening tests were used to detect the presence of concurrent high grade lesions, providing predictive values and accuracies for each test. Second, the ability of each test to detect lesions within 12 months rather than concurrently was examined, reflecting the common practice of 1 year follow-up visits in clinical care.

RESULTS

Of the 4990 women contacted during the course of recruitment, 2462 women accepted to participate and were deemed eligible. The rates of attrition were low and stable around 5% per visit for the first 5 years. A total of 1608 women (65.3%) achieved at least 10-12 visits to complete a minimum of 5 years of follow-up. Follow-up completion rates for years 6, 7, and 8 were 59.1%, 40.7%, and 21.6%, respectively. Expectedly, follow-up completion rates were somewhat higher among the 348 participants who underwent colposcopy and cervical biopsy at least once: 92.8%, 84.3%, 53.2%, and 27.6% for years 5, 6, 7, and 8, respectively. A total of 367 biopsies were performed, 36 of which yielded a diagnosis of cervical intra-epithelial neoplasia grade 2 or worse (CIN2+). The following results were obtained with the above 348 patients. Those obtained from the entire cohort (data not shown) with the assumption that the women who were never biopsied did not harbour cervical lesions, yielded similar interpretation.

Absolute risk/rate stratification

The concurrent risks, 12-month incidence rates and 10-year incidence rates of high grade cervical lesions on biopsy were stratified according to screening test result, as shown in table 1. In the concurrent setting (lesions ascertained at the time of screening, i.e., cross-sectionally) the risk of CIN2+ lesions increased from 1.6 % (95% CI: 0-3.3%) to 15% (95% CI: 5.3-25%) and from null to 42% (95% CI: 12-71%) when HR-HPV DNA was identified among women with negative cytology or ASCUS, respectively. In the 12-month setting, again there was a significant increase in lesion rates when HR- HPV DNA was detected in women with negative and ASCUS cytology, relative to no HPV positivity. For negative cytology, the rate of CIN2+ was 0.76 per 1000 women-months (95% CI: 0.19-3.02) among HPV-negative women to 13.48 per 1000 women-months (95% CI: 6.43-28.28) for HR-HPV positive women. For those with ASCUS, there were no incident cases among HPV negative women and 55.39 per 1000 women-months (95% CI: 23.06-133.06) incidence of CIN2+ among HR-HPV positive cases. HPV testing did not seem to contribute any risk stratification information for women with low-grade squamous intra-epithelial lesions (LSIL) or for those with high-grade squamous intra-epithelial lesions (HSIL). Interestingly, much of the risk stratification ability of HPV testing for women with normal cytology or with ASCUS disappeared in the 10-year incidence rate context.

Kaplan-Meier survival analyses

Figure 1 shows the cumulative incidence of CIN2+ according to cytology results at baseline. The cumulative incidence was significantly higher for women with HSIL than for those with any other cytology result (Log rank $\chi^2(df3)$: 241.35; p-value=0.0000). No significant differences were seen between negative, ASCUS or low-grade squamous intra-epithelial lesion (LSIL). As for HPV DNA testing (figure 2), women testing positive for HR-HPV had significantly higher risk of CIN2+ than those who were HPV negative or had LR-HPVs (Log rank $\chi^2(df2)$: 9.69; p-value= 0.0078). The latter two groups did not seem to differ with respect to CIN2+ risk. When combining both testing methods (figure 3), higher risks were seen for the women positive on both tests using a cytology positivity threshold of ASCUS (Log rank $\chi^2(df3)$: 62.50; p-value= 0.0000), followed by the HPV DNA test negative and cytology positive women, whose cumulative risk reached that of the double positive women after 6 years. Similar risks were seen between the women with both tests negative and those with negative cytology and positive HR-HPV DNA.

Test sensitivity, specificity and predictive values

The sensitivities, specificities and predictive values were calculated for cytology, HPV DNA testing and cervicography, as shown in table 2, and the screening accuracy was summarized in a Receiver Operating Characteristic (ROC) – like plot, with sensitivity on the Y axis and the inverse of specificity on the X axis, as shown in figure 4. This was done in the cross-sectional context and, based on the assumption that disease present at the time of testing may only be detected at a later date, in the contexts of a 12 month and a cohort analysis.

In all three contexts, the highest sensitivity was observed when either cytology or HPV DNA test positivity was considered, but it was not significantly different from the high sensitivity seen with HPV DNA testing alone. As for specificity, the highest results are seen when both cytology and HPV DNA tests must be negative, or with negative cytology alone. Overall, sensitivity and specificity were better when the detection window is extended to 12 months than when it is restricted to the immediate setting or evaluated in the context of a cohort analysis.

With regards to predictive values, the highest positive predictive value, 53.5% (95% CI: 40.44-66.45), is that seen when considering both cytology and HPV DNA testing positivity in the cross-sectional context, and the highest negative predictive value, 99.1% (95% CI: 98.1-100.0), is seen when either test is negative in the 12 month setting. In this context, the consideration of either cytology or HPV DNA test results provides both the highest positive and negative predictive values, of 34.6% (95% CI: 23.9-45.3) and 99.1% (95% CI: 98.1-100.0), respectively.

DISCUSSION

Our results support the idea that dual testing with both HPV DNA testing and cytology, either simultaneously or not, is not justified for all patients. Indeed, in the cross-sectional context, there was no benefit to HPV DNA testing in cases of HSIL, as this additional result provided no tangible impact on the odds of detection of high grade lesions. On the contrary,

among women with negative, ASCUS and LSIL smears, those harbouring HR-HPV DNA were more likely to be diagnosed with high grade lesions. Previous work focusing on the use of HPV DNA testing to triage cytology tests has so far recommended this approach for ASCUS only, although its use for LSIL has been discussed [5]. When extending the detection window to 12 months, the benefit of HPV DNA testing was lost in the LSIL cases, whereas the HPV DNA triage remained useful for negative and ASCUS cases. The benefit of HPV DNA testing seen in negative smears for both the concurrent and 12 month context suggests that HPV testing could be used to counter the problem of false negative smears. However, in the 10 year cohort context, the benefit of HPV DNA testing was seen only in cases of ASCUS. The fact that it was no longer useful for negative cytology cases suggests a high HPV infection acquisition rate within the 10 year follow-up period among the women who were negative at the time of enrolment.

The Kaplan-Meier analysis for cytology not only demonstrated that HSIL significantly predicted the risk of high grade lesions, but also that this rise started immediately with positive cytology and continued to climb with time. Thus, the finding of HSIL on cytology should warrant prompt referral to colposcopy, along with close follow-up of the women in whom no high grade lesions could be detected initially. The lack of significant differences in risk amongst women with negative smears, ASCUS or LSIL is surprising as most previous studies have found moderately increased risks with LSIL [17, 18], and may be, at least in part, a reflection of the small number of women with LSIL at baseline. For HPV DNA testing, the Kaplan-Meier analysis confirms the observation that HR-HPV DNA detection is associated with increased proportions of CIN grade 2 or above as compared to no HPV or LR HPV DNA only.

Among women with either negative cytology or negative HPV DNA testing at baseline, the cumulative incidence of high grade lesions increased dramatically after 6 to 7 years. This observation, which was not seen in other 10-year long studies [8, 12], is consistent with a higher HPV acquisition rate in this population. This is in keeping with the high frequency of male unfaithfulness reported by the participants, and suggests that extended screening intervals may not be appropriate in certain high risk populations. In addition, there were no significant differences in risk between women who were negative on cytology (either HPV positive or negative), women who were negative for HPV (either cytology positive or negative) and women who were negative for both. Thus, a woman with a negative result on either test can be considered to have equally low long term risks of lesion, which does not warrant testing with a second modality. This is contrary to what we observed with a shorter follow-up period, as discussed above, as well as to that seen in similar studies [8-10] whereby women with negative cytology but positive HR HPV DNA testing were at higher risk of developing lesions after 5 years as compared with those with negative HPV DNA tests. Again, this may be a reflection of the higher rate of HPV acquisition in this population, which may have a more pronounced negative impact on the baseline predictive ability of HPV DNA testing than cytology.

Focusing on the cross-sectional context, the screening modality which provided the best optimization of sensitivity and specificity was dual testing, whereby a woman was considered to have a positive screening result if she has either ASCUS or worse on cytology

or HR-HPV DNA. This is consistent with the findings of other groups, which also demonstrated that dual testing had the highest sensitivity and an acceptable specificity, when compared with other screening options [18]. Comparing each test alone, HPV DNA testing appears superior with a more significantly increased sensitivity in relation to the loss incurred for specificity. Our results are in keeping with the evidence that HPV DNA testing is more sensitive and less specific than cytology for the detection of concurrent high grade cervical lesions [5-7].

If we consider that lesions can be detected within 12 months of testing, the combination of either cytology or HPV DNA testing still remained optimal, as it was in the immediate detection context, although cytology alone performed nearly as well. Indeed, in this context HPV DNA testing provided only a minimal gain in sensitivity. This suggests that in situations where immediate follow-up is not possible, cervical cytology may be the most appropriate screening method to optimize sensitivity and specificity. In the long term detection context, which ranges up to 10 years, results were generally poor and no modality clearly stood out as superior. These results are in keeping with the long term negative and predictive values depicted in the Kaplan-Meier plots, which failed to show significant differences between screening tests. To our knowledge, no other researchers have looked at test accuracy with extended detection periods such as this.

Study limitations must be kept in mind when considering our findings. Although this was not found to be the case after the first year [19], differential losses to follow-up cannot be completely excluded in the long term for this 10-year cohort study. In addition, a certain amount of non-differential misclassification of cytology results is unavoidable [20], and some misclassification of biopsy results is expected, especially in the case of CIN 2, which is known to be poorly reproducible [21]. Nevertheless, this longitudinal study with repeated measurements provides an adequate context for exploring the long term predictive values of screening tests, contributing to our knowledge on screening modalities and their most appropriate use in high-risk populations.

CONCLUSION

In summary, the addition of HPV DNA testing is beneficial for patients with ASCUS cytology, and may be beneficial for those with negative smears and even LSIL smears, as well. There is no benefit of HPV DNA testing for patients in whom HSIL was detected on cytology. The long term negative predictive values are equivalent for negative cytology smears and negative HPV DNA tests and the protective effect of these negative results begin to drop significantly after 6 years. These results, which do not corroborate the superior negative predictive values of HPV DNA testing as found by other groups, suggests that some high risk populations with high infection acquisition rates may benefit equally from cytology or HPV DNA testing, and may require shorter intervals to ensure a safe screening program.

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HIGHLIGHTS

- HPV DNA testing is not useful for HSIL smears.
- High risk groups benefit from adapted screening policies.

Figure 1.

Kaplan-Meier curves depicting cumulative risk of CIN grade 2 or worse according to baseline cytology result.

Figure 2.
Kaplan-Meier curves depicting cumulative risk of CIN grade 2 or worse according to baseline HPV testing results.

Figure 3.

Kaplan-Meier curves depicting cumulative risk of CIN grade 2 or worse according to dual testing with cytology and HPV DNA testing at baseline.

ROC-like plot comparing screening tests

Figure 4.

Sensitivities and specificities for each screening algorithm were plotted in this Receiver Operating Characteristic (ROC) like curve for each temporal context, with solid squares representing the cross-sectional context, open diamonds representing the 12 month context and crosses representing the cohort analysis. Overall, the test accuracies were better when allowing 12 month for the detection of lesions. Specifically, the algorithm yielding the best results was dual testing with both HPV DNA testing for high risk types and cytology with a diagnostic threshold of atypical squamous cells of undetermined significance (ASCUS).

Table 1

Risks and rates of CIN grade 2 or worse according to dual cytology and HPV DNA testing result in different analysis settings. (Neg: Negative; ASCUS: Atypical squamous cells of undetermined significance; LSIL: Low-grade squamous intraepithelial lesion; HSIL: High-grade squamous intraepithelial lesion; LR: Low oncogenic risk; HR: High oncogenic risk)

Screening test		Cross-sectional setting		12 month setting		Cohort analysis	
Cytology	HPV DNA testing	Proportion CIN2+	95% CI	Incidence rate (per 1000/women-months)	95% CI	Incidence rate (per 1000/women-months)	95% CI
Neg	Neg	0.016	0.00-0.033	0.76	0.19-3.02	0.55	0.29-1.02
	LR only	0.00		0.00		0.39	0.05-2.75
	HR	0.15	0.053-0.25	13.48	6.43-28.28	1.01	0.48-2.12
ASCUS	Neg	0.00		0.00		0.00	
	LR only	N/A		N/A		0.00	
	HR	0.42	0.12-0.71	55.39	23.06-133.08	3.82	0.96-15.29
LSIL	Neg	1.00		484.00	68.18-3434.95	N/A	
	LR only	0.00		0.00		0.00	
	HR	0.43	0.21-0.64	64.05	37.19-110.30	1.14	0.16-8.08
HSIL	Neg	0.50	0.00-1.00	85.33	21.34-341.19	20.16	6.50-62.51
	LR only	0.50	0.00-1.00	N/A		0.00	
	HR	0.68	0.49-0.87	179.85	113.31-285.46	34.39	17.20-68.75

Table 2

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for various screening test combinations in three different analysis settings. (PPV: Positive predictive value; NPV: Negative predictive value)

		Sensitivity		Specificity		PPV		NPV	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
Cytology	Cross-sectional	53.8%	36.8-70.9	90.7%	87.6-93.8	41.1%	28.0-54.2	96.3%	94.1-98.4
	12 month	77.3%	61.6-93.1	92.8%	89.9-95.7	12.7%	0.0-29.0	91.8%	88.2-95.4
	cohort analysis	42.9%	26.3-60.6	90.9%	87.1-93.9	34.9%	21.0-50.9	93.3%	89.9-95.9
HPV DNA testing	Cross-sectional	81.3%	70.1-92.5	75.7%	70.7-80.7	35.1%	25.3-45.0	96.9%	94.2-99.4
	12 month	78.6%	66.3-91.0	80.3%	75.4-85.3	29.7%	19.3-40.0	97.2%	95.2-99.1
	cohort analysis	52.8%	35.5-69.6	71.8%	66.4-76.7	17.9%	11.2-26.6	92.9%	88.8-95.8
Both cytology and HPV DNA testing	Cross-sectional	53.5%	37.2-69.8	90.9%	87.5-94.4	53.5%	40.4-66.4	94.5%	91.7-97.4
	12 month	68.1%	50.0-86.2	92.8%	89.7-96.0	10.4%	0.0-25.7	88.6%	83.9-93.2
	cohort analysis	33.3%	18.6-51.0	93.5%	90.1-96.0	37.5%	21.1-56.3	92.3%	88.8-95.0
Either cytology and HPV DNA testing	Cross-sectional	84.9%	75.9-94.0	78.4%	74.0-82.8	33.9%	24.8-42.9	98.6%	97.1-100.0
	12 month	88.4%	79.5-97.4	82.1%	77.7-86.5	34.6%	23.9-45.3	99.1%	98.1-100.0
	cohort analysis	61.1%	43.5-76.9	69.2%	63.7-74.3	18.8%	12.2-27.1	93.8%	89.9-96.6
Cervicography	Cross-sectional	53.0%	26.7-79.3	69.0%	58.6-79.3	18.8%	5.1-32.3	90.2%	86.6-97.7
	12 month	45.5%	8.5-82.5	74.9%	66.4-83.3	20.5%	6.1-34.8	94.0%	88.8-99.2
	cohort analysis	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A