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Parallel Screening with Papanicolaou Smear and Visual Inspection Tests Significantly Reduced False Negative Screening Results in Southern Brazil

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors designed the study, performed the statistical analysis and wrote the final version of the paper. Author ER wrote the protocol and the first draft of the manuscript. Both authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: To verify the screening performance of Pap smear and four modalities of visual inspection tests (VIT) in screening for cervical intraepithelial neoplasia CIN of grade 2, 3 or carcinoma in situ, in a low risk population.
Study Design: A transversal study validated above tests, both in separate and in combination, against colposcopic and histologic examination as gold standard.
Place and Duration of Study: RFCC (Portuguese abbreviation for "Female network against cancer") in Florianópolis, southern Brazil, between June 2010 and July 2012.
Methodology: Among 919 women eligible for the study, 882 completed all clinical and laboratory exams. All screen-positive and a random sample of 18.5% screen-negative specimen were submitted to colposcopy and, if necessary, histologic examination.
Results: The prevalence of CIN2 + in this study was 1.7%. Pap smear as the only screening test produced about 1/3 of false negative results. Among those considered normal by Pap smear, 32.1% were diagnosed as CIN1 and 17.1% as CIN2 + by

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histological examination. The false negative rate reduction from 6/15 for Pap smear test alone to 1/15 for its combination with VIT as a parallel test represents a 5/15 or 33.3% reduction (95% CI = 12-62%). The combination of all four VIT modalities into a parallel test also reduced the false negative fraction significantly.

Conclusions: This study has shown that Pap smear alone has its sensitivity too limited to be used as the only test in screening for cervical cancer. Adding VIT as a parallel test significantly improves the screening sensitivity by reducing the false negative results to less than 7% while maintaining the false negative rate at 8%.

Keywords: Screening; pap test; visual inspection tests; cervical intraepithelial neoplasia; cervical cancer.

1. INTRODUCTION

Although firmly established as priority in cancer screening, timely diagnosis of cervical cancer still eludes many women, particularly in the developing countries [1]. As such diagnosis is essential for effective treatment [2,3] the second ranking of this cancer among gynecological tumors worldwide [4] is a testimony to a slow pace in improving women cancer prevention. Brazil is no exception to this, with cervical cancer incidence reaching 17 per 100.000 women in 2 012 [5].

Cervical cancer grows slowly, starting as a HPV-dependent lesion and evolving to a cervical intraepithelial neoplasia of grade 2, 3 or carcinoma in situ (CIN2 +), with 25-50% of cases developing carcinoma in situ within 10-15 years if not treated [6]. Like many other countries, Brazil relies solely on cytological screening by Papanicolaou smear test (Pap test) and colposcopic examination (when necessary) of the cervix among women aged 25-64 years to prevent this cancer [7]. After two negative screening results, it is recommended to repeat the screening every three years.

To be effective, cervical cancer screening programs should achieve at least 70% coverage of the target population and use sufficiently sensitive and specific tests to detect CIN2 + which precede the cancer, as well as an effective treatment [8]. This was not the case in Florianopolis, the capital of the state of Santa Catarina, where household surveys between 2002 and 2009 indicated the Pap test coverage between 34.7% [9] and 39.5% [10]. In addition, a meta-analysis [11] and a systematic review [12] of this test's screening performance concluded that it cannot achieve both good sensitivity and specificity. There is a considerable amount of subjective judgment in interpreting the test results, as well as a significant variation in specimen collection, fixation and storage [13,14].

Despite a widely recognized need for improving the screening sensitivity and therefore reducing the time between diagnosis and treatment, many developing countries use only Pap test, often with low coverage. As a result, the cervical cancer incidence in these countries has diminished only slightly or not at all over the last two decades, with Brazil included in this scenario [15].

Visual inspection tests (VIT) have emerged as a viable alternative to Pap test screening in the countries with limited resources, mainly in Africa and Asia. For example, a study conducted in Dindigul, India, evaluated the effectiveness of VIT in a cluster-randomized trial [16]. Both cervical cancer incidence and mortality were reduced by 25% and 35%,

respectively, in comparison with the control group. Furthermore, the Latin America Screening Study (LAMS) evaluated diagnostic performance of visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI), Pap test and Hybrid Capture type II (HC II) tests using colposcopical and histological biopsy examinations as gold standard. It concluded that VIA e VILI could be significantly improved depending on the combination with Pap smear or HCII [17]. Other advantages of VIT include low cost, no need for laboratory procedures, swift availability of the results and hence suitability for the "see and treat" protocols [18].

The aim of this study was to evaluate the screening performance of Pap test and VIT, both as separated and combined screening tests, using colposcopical and histological examination as gold standard.

2. MATERIALS AND METHODS

This was a cross-sectional validation study of the screening performance of Pap test and four modalities of VIT: VIA and VILI with their respective magnifications by using handheld magnifiers 2x: visual inspection with acetic acid magnified (VIAM) and visual inspection with Lugol's iodine magnified (VILIM). Each of these tests were evaluated both as isolated and as parallel screening instruments where an altered test result was indicated either by Pap test according to the 2001 Bethesda System for cytological diagnoses using SIL (squamous intraepithelial lesion) terminology [19] or by any of the VIT modalities according to the IARC (International Agency for Research on Cancer) manual [20]. The histological diagnosis was reported in terms of CIN categories: (a) normal, including cervicitis and squamous metaplasia, (b) CIN1, including mild cervical intraepithelial neoplasia (CIN1) and HPV compatible cytopathic effect, (c) CIN2 +, including moderate cervical intraepithelial neoplasia (CIN2) and severe cervical intraepithelial neoplasia (CIN3) and carcinoma in situ, microinvasive squamous carcinoma, invasive squamous carcinoma and adenocarcinoma. Altered test results were further investigated by colposcopy and histological examination of colposcopy-guided biopsy, so that the histology result was gold standard for screen-positive cases. If neither Pap test nor VIT showed above defined alterations, the women were considered screen-negative and were not submitted to further exams, except for the 18.5% of them who were randomly selected for colposcopical examination, and submitted to biopsy and histological examination if indicated by the same criteria used for the screen-positive cases Fig. 1 Differently from the IARC manual, the cases considered difficult to classify as either positive or negative on Pap screening were treated as positive and investigated further.

2.1 Sample Size Calculation and Recruitment

The sample size calculation was based on expected sensitivity of 73% found in a large Brazilian study [21] and a clinically relevant improvement of at least 15% [22], plus adding 20% for anticipated unknown confounding and 10% for anticipated no-response rate (declined to participate or missed a scheduled exam), resulting in the final sample size estimate of 600 women.

Recruitment of the participants was by personal invitation made by the gynecologist to the women attending the largest clinic for female cancer prevention in Florianópolis. The clinic is administered by a nongovernmental organization and offers the screening for cervical cancer free of charge for more than two decades. The gynecologist showed a written summary of

the study protocol and explained its aims and procedures, inviting the women to take part in the study and sign the consent form. The Federal University of Santa Catarina ethics committee approved the study protocol under number 681/10.

2.2 Inclusion and Exclusion Criteria

All women who were scheduled for regular screening and signed the consent form were eligible for the study if they had an intact uterus. The women who had been submitted to hysterectomy or diagnosed with HPV, anal or genital condyloma lesions, were excluded from the study, as well as those who did not complete all tests in the study protocol (n=37).

2.3 Data Collection and Quality Control

Two specimens for Pap test were collected using Ayre spatula for ectocervix and conic brush for endocervix. At the same time, visual inspection of the cervix with the naked eye and then the four modalities of VIT were performed to all women by a trained nurse with over 20 years of experience with in the specimen collection. All VIT were re-examined by a second examiner who was a gynecologist. Both underwent a 130 hours training before the start of the study.

The criterion for punch biopsy was presence of any colposcopic abnormality such as acetowhite epithelium, punctuation, mosaic, atypical vessels and iodine negativity. Tissue samples were fixed in 10% formalin.

The first examiner of Pap smear was an experienced laboratory technician who had access to the clinical records of the women examined. All screen-positive and 18.5% of randomly selected screen-negative specimen were re-examined by a second examiner who was an experienced pathologist specialized in cervical cytology and blinded for the previous screening results Fig. 1. The agreement between the first and the second observer was deemed good with kappa statistic of 0.67 and its 95% confidence interval between 0.54 and 0.80. If the examiners disagreed in their diagnoses, a third one was called to decide. The latter was also an experienced pathologist employed by another laboratory for cervical cytology.

2.4 Statistical Analysis

Individual clinical and laboratory data were digitalized and analyzed by Stata software version 9.0 by means of a specialized program (an ado file) in the public domain named “diagti”. It provides maximum likelihood estimates equivalent to those used in bivariate logistic regression. Sensitivity, specificity, positive and negative predictive values, as well as the rates of false negative and positive results, were all verified for the VIT and Pap tests, including their 95% confidence intervals (CI) based on binomial distribution. For the purpose of this analysis, all tests were dichotomized to either presence or absence of CIN2 +. Statistical significance for the type I error was fixed at 5% ($p<0.05$).

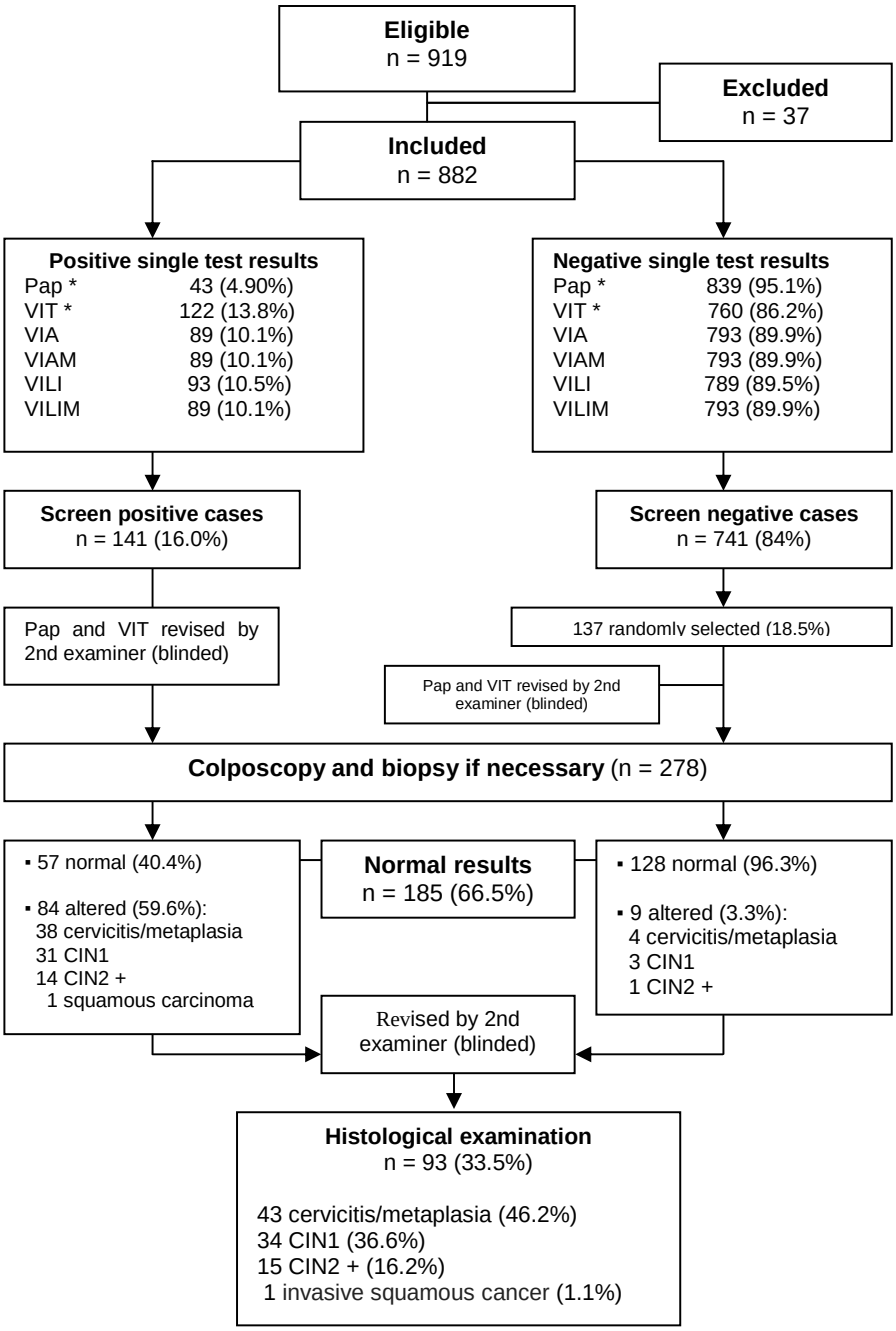

Fig. 1. Fluxogram of testing procedures

** PAP positive if ASC-US or higher grade, negative otherwise*
** VIT positive if VIA or VIAM or VILI or VILIM positive for CIN2 +; negative otherwise*
*** at least one of the test results altered.*

3. RESULTS AND DISCUSSION

Among 919 women eligible for the study between July 2010 and June 2012, 882 (96%) completed all examinations Fig. 1. All specimens were considered satisfactory for the Pap test by the first examiner. Pap test as only screening device produced a large fraction of false negative results Table 1.

Table 1. Concordance between Pap test and visual inspection test results with histologic examination results

Histological examination									
Pap test alterations	**Total**	**Cervicitis and/or Metaplasia**		**CIN1**		**CIN2 +**		**Invasive Carcer**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Normal	28	14	50.0	9	32.1	5	17.9	0	0.0
Inflammatory	37	24	64.9	12	32.4	1	2.7	0	0.0
ASC-US	8	2	25.0	6	75.0	0	0	0	0.0
ASC-H	6	1	16.7	3	50.0	1	16.7	1	16.7
LSIL	7	1	14.3	3	42.9	3	42.9	0	0.0
HSIL	7	1	14.3	1	14.3	5	71.4	0	0.0
VIT results									
Negative	15	7	46.7	5	33.3	3	20.0	0	0.0
Positive	78	36	46.2	29	37.2	12	15.4	1	1.3
Total	93	43	46.2	34	36.6	15	16.1	1	1.1

Pap = Papanicolaou test; VIT = Visual inspection tests; VIT (+) = VIA or VIAM or VILI or VILIM positive; VIT (-) = VIA, VIAM, VILI and VILIM all negative; CIN = Cervical intraepithelial neoplasia; CIN2+ = CIN 2, 3 and carcinoma in situ

Among those considered normal, 32.1% were diagnosed as CIN1 and 17.9% as CIN2 + by histological examination. The latter also found 32.4% CIN1 and 2.7% CIN2 + among the specimen considered inflammatory alterations by Pap test. In other words, cytological and histological examinations agreed poorly due to a large fraction of false negative results by the former which misclassified about 1/3 of CIN1 and 1/5 CIN2 + as normal or merely inflammatory alterations.

Histological results also showed that most ASC-US and ASC-H diagnoses by Pap test were in fact CIN1 Table 1. Almost 43% of Pap smear test LSIL diagnoses were judged as CIN1 and further 43% as CIN 2+ by histological examination. On the other hand, the latter confirmed vast majority (71.4%) of the HSIL diagnoses by Pap test.

As the cut-off category for screen-positive result of Pap test became more restrictive (higher rank), its sensitivity was reduced from 60% to 33.3% Table 2. PPVs also increased from 33.3% under least restrictive criteria to 71.4% under most restrictive case definition, whereas NPV was around 99% for all criteria.

VIT produced low fractions of false positive (7.5%) and false negative (20.0%) results Table 3. All of the four modalities applied showed close agreement regarding their screening performance, with sensitivity range of 73.3-80%, specificity range of 92.5-94.7%, NPV over 99% and PPVs between 15.5% and 19.3%.

Table 2. Screening performance of the Pap test with progressively more restrictive definition of a screen-positive case with histologic examination as gold standard

Screening tests	Histological examination		Sens.	Spec.	PPV	NPV	FNR	FPR
	CIN2 + Present n	CIN2 + Absent n	CI 95%	CI 95%	CI 95%	CI 95%	CI 95%	CI 95%
Pap [1]								
Positive	9	18						
Negative	6	849	60.0%	97.9%	33.3%	99.3%	40.0%	2.1%
Total	**15**	**867**	**35.6-80.2**	**96.7-98.7**	**18.6-52.2**	**98.5-99.7**	**18.1-65.5**	**1.3-3.2**
Pap [2]								
Positive	9	10						
Negative	6	857	60.0%	98.85%	47.4%	99.3%	40.0%	1.2%
Total	**15**	**867**	**35.8-80.2**	**97.9-99.4**	**27.3-68.3**	**98.5-99.7**	**18.1-65.5**	**0.6-2.1**
Pap [3]								
Positive	8	6						
Negative	7	861	53.3%	99.3%	57.1%	99.2%	46.7%	0.7%
Total	**15**	**867**	**30.1-75.2**	**98.5-99.7**	**32.6-78.6**	**98.3-99.6**	**23.2-71.3**	**0.3-1.4**
Pap [4]								
Positive	5	2						
Negative	10	865	33.3%	99.8%	71.4%	98.8%	66.7%	0.2%
Total	**15**	**867**	**15.2-58.3**	**99.2-99.9**	**35.9-91.8**	**97.9-99.4**	**40.8-86.6**	**0.1-0.8**

Sens. = sensibility; Spec. = specificity; PPV = positive predictive value; NPV = negative predictive value; FNR = false negative rates; FPR = false positives rates, Pap = Papanicolaou smear test; CIN = Cervical intraepithelial neoplasia; CIN2 + = CIN 2, CIN 3 or carcinoma in situ; Pap [1] = positive if ACS-US, ASC-H, AGC-US, AGC-H, LSIL, HSIL or cancer, negative otherwise Pap [2] = positive if ASC-H, AGC-H, LSIL, HSIL or cancer; negative otherwise Pap [3] = positive if AGC-US, AGC-H, HSIL or cancer; negative otherwise Pap [4] = positive if HSIL or cancer; negative otherwise

Using the VIT modalities as parallel screening tests produced a false negative rate of 20%, i.e. only half of that for the Pap test alone Table 4 under the least restrictive case definition. The rate was further reduced to only 6.7% with a more restrictive case definition for Pap test which considered alterations above ASC-US as screen-positive cases. Further restrictions of the case definition did not show relevant improvements in the false negative rate. The false positive rate did not exceed 8% for any combination of the tests Table 4. In other words, combining Pap test with VIT as a parallel screening test increased sensitivity to 93.3%, while maintaining high (92.1%) specificity.

The false negative rate reduction from 6/15 for Pap test alone to 1/15 for above parallel tests screening by adding VIT means a 5/15 or 33.3% reduction, with exact binomial 95% confidence interval (CI) between 12% and 62%. The combination of all four VIT modalities into a single test, where any positive result defines case as screen-positive, reduced the false negative fraction to 3/15, i.e. by 20% (95% IC 4.3-48.1%). Both reductions were calculated as percentages of maximum possible reduction and were statistically significant ($P < .05$).

The prevalence of CIN2 + in this study was 1.7%. This is within expected range for a low risk population but still higher than in similar studies in India [16] and Africa [23,24]. A variety of

risk factors may have contributed to this difference, such as proportion of rural population which typically has more difficulties to access medical services, cultural differences regarding sexual behavior, as well as social and educational influences [25].

Table 3. Screening performance of the Visual inspection tests for screening CIN2 + using histologic examination as gold standard

Screening tests	Histological examination		Sens.	Spec.	PPV	NPV	FNR	FPR
	CIN2 + Present n	CIN2 + Absent n	CI 95%	CI 95%	CI 95%	CI 95%	CI 95%	CI 95%
VIT								
Positive	12	65						
Negative	3	802	80.0%	92.5%	15.4%	99.6%	20.0%	7.5%
Total	15	867	54.8-92.9	90.5-94.1	9.2-25.3	98.9-99.9	5.4-45.4	5.8-9.4
VIA								
Positive	11	46						
Negative	4	821	73.3%	94.7%	19.3%	99.5%	26.7%	5.3%
Total	15	867	48.1-89.1	93.0-96.0	11.1-31.3	98.8-99.8	9.1-52.5	4.0-7.0
VIAM								
Positive	11	53						
Negative	4	814	73.3%	93.3%	17.2%	99.5%	26.7%	6.1%
Total	15	867	48.1-89.1	92.1-95-3	9.9-28.2	98.6-99.8	9.1-52.5	4.7-7.9
VILI								
Positive	12	57						
Negative	3	810	80.0%	93.4%	17.4%	99.6%	20.0%	6.6%
Total	15	867	54.8-93.0	91.6-94.9	10.2-28.0	98.9-99.9	5.4-45.4	5.1-8.4
VILIM								
Positive	12	55						
Negative	3	812	80.0%	93.7%	17.9%	99.6%	20.0%	6.3%
Total	15	867	54.8-93.0	91.8-95.1	10.6-28.8	98.9-99.9	5.4-45.4	4.9-8.1

VIT = Visual inspection tests; CIN = Cervical intraepithelial neoplasia; CIN2 + = CIN2, CIN 3 or carcinoma in situ; VIT (+) = VIA or VIAM or VILI or VILIM positive; VIT (-) = VIA, VIAM, VILI, VILIM all negative;

High proportion of false negative Pap test results was mainly due to its misclassification of ASC-US, ASC-H and LSIL as normal or inflammatory alterations. Specimen collection and fixation errors may have contributed to this result, as well as overseeing small lesions or those located in hardly accessible sampling areas [3,17]. Other studies have found similar difficulties to correctly diagnose low grade abnormalities [13,26,27] but more severe abnormalities and particularly HSIL showed much closer agreement with histological examination for CIN2 +. The same was observed for all VIT modalities.

Pap smear test sensitivity in this study falls within the range of 11 and 99% from a meta-analysis [11] and a systematic review which reported variation between 30% and 87% [12].

The same goes for specificity whose variation ranges from 14% to 97% and from 86% to 100% according to the same sources. The Pap smear diagnostic performance in the present study was similar to that in the LAMS [17] which found low to moderate sensitivity and high specificity of this test in diagnosing HSIL and CIN2 +.

Table 4. Screening performance of the Pap test in parallel with Visual inspection tests for screening CIN2 + using histologic examination as gold standard

Screening tests	Histological examination		Sens.	Spec.	PPV	NPV	FNR	FPR
	CIN2 + Present n	CIN2 + Absent n	CI 95%	CI 95%	CI 95%	CI 95%	CI 95%	CI 95%
Pap [1]								
Positive	9	18						
Negative	6	849	60.0%	97.9%	33.3%	99.3%	40.0%	2.1%
Total	15	867	35.6-80.2	96.7-98.7	18.6-52.2	98.5-99.7	18.1-65.5	1.3-3.2
VIT								
Positive	12	65						
Negative	3	802	80.0%	92.5%	15.4%	99.6%	20.0%	7.5%
Total	15	867	54.8-92.9	90.5-94.1	9.2-25.3	98.9-99.9	5.4-45.4	5.8-9.4
Pap [1] & VIT								
Positive	14	69						
Negative	1	798	93.3%	92.1%	16.9%	99.9%	6.7%	8.0%
Total	15	867	70.2-98.8	90.1-93.7	10.3-26.3	99.3-100	0.3-28.7	6.3-9.9
Pap [1] & VIT [1]								
Positive	14	36						
Negative	1	831	93.4%	95.9%	28.0%	99.9%	6.7%	4.2%
Total	15	867	70.2-98.8	94.3-97.0	17.5-41.7	99.3-100	0.3-28.7	3.0-5.6
Pap [1] & VIT	**							
Positive	46	38						
Negative	4	794	92.0%	95.4%	54.8%	99.5%	8.0%	4.6%
Total	50	832	81.2-96.9	93.8-96.7	44.2-65.0	98.7-99.8	2.6-18.2	3.3-6.2

*CIN: Cervical intraepithelial neoplasia; CIN 2+ = CIN 2, 3 ou carcinoma insitu; VIT = Visual inspection tests; VIT (+) = VIA or VIAM or VILI ou VILIM positive for CIN 2 or higher grade; VIT (-) = VIA, VIAM, VILI, VILIM all negative; Pap[1] positive if ACS-US, ASC-H, AGC-US, AGC-H, LSIL, HSIL or cancer; negative otherwise VIT[1] = VIA or VIAM or VILI or VILIM positive for CIN1, 2, 3 or CIS, and VIA, VIAM, VILI and VILIM all negative; ** Histological examination: CIN1, CIN 2, CIN 3 or CIS*

Using the cut-off point of CIN 2 or higher to define screen-positive cases, the present study found that diagnostic parameters of VIA and VIAM outperformed those reported in a systematic review [28] but found lower sensitivity and higher specificity for VIA compared to a recent meta-analysis [29]. Other similar studies in India [30] and Peru [31] also found no significant improvement with magnification glass for VIA. It is worth noticing that all

diagnostic parameters for VIT in these studies obtained lower values than in the present study. The latter also found VILI more sensitive but less specific than VIA, similar to the other studies [17,23,32,33].

Better training of the VIT examiners may explain better diagnostic performance of these tests in the present study which dispensed 130 hours (a 40 day course) for their training, including discussions of less clear-cut cases and extensive use of the IARC Visual Inspection manuals [20]. On the other hand, other studies reported much shorter trainings of 3-14 days [34-36].

All four VIT modalities took on average 2 minutes to complete. Only 1.1% of the women examined related soreness as a collateral effect of VIT application.

Colposcopical examination may find a significant fraction of VIT positive results to be false positive. However, when used in parallel with Pap test to screen out CIN2 +, both false positive and false negative fractions were reduced to an acceptable level according to the histological examination as gold standard. Compared to the Pap test alone, a statistically significant reduction of false negative fraction by a third with above parallel tests is also of great clinical relevance.

A Colombian study too found that adding VIA or VILI to Pap test increased sensitivity by 15% without a significant reduction in specificity [37]. In this as well as in the present study, the same examiner performed all VIT, underlying the importance of reducing the variation between examiners. To maintain this yield in sensitivity in routine screening for cervical cancer, good quality training of health professionals and quality control of the testing process seems to be essential.

Histological examination in the present study showed that a less restrictive VIT (CIN grade 1 or higher) in combination with standard Pap test case definition can improve the sensitivity of diagnosing CIN2 +. Compared to a more restrictive VIT case definition such as CIN2 +, the former increased the positive predictive values by almost 13% while maintaining the other diagnostic parameters within an acceptable level. In other words, the gain in specificity due to lower cut-off did not incur a large loss in specificity. In a low risk population, the best cut-off category for screen positivity seems to be CIN grade 1 or higher because of the difficulty in distinguishing between CIN1 and CIN2 +, especially in the case of metaplasia.

It is important to take into account the VIT results which seemed inconclusive to the first examiner were further investigated, i.e. considered screen-positive, differently from the IARC manual which considers such results as screen-negative [20]. Given the serious consequences of false negative diagnosis in this context and fallibility of histological examination as gold standard [38], a slightly higher false positive rate may be a price worth paying.

4. CONCLUSION

In conclusion, this study has shown that Pap test alone has its sensitivity too limited to be used as the only test in screening for cervical cancer in southern Brazil. Adding VIT as a parallel test significantly improves the screening sensitivity by reducing the false negative results to less than 7% while maintaining the false negative rate at 8%.

CONSENT

All authors declare that written informed consent was obtained from the patient and the institution that offered medical diagnosis and treatment for publication of this report.

ETHICAL APPROVAL

The Ethics Committee of the Federal University of Santa Catarina approved the study protocol under number 681/10 on February 26, 2010.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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