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Agreement between Observers for Pap smear and Visual Inspection Tests in Florianópolis, Southern Brazil

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Authors' contributions

This work was carried out in collaboration among all authors. Authors ER and EK designed the study and wrote the protocol. Author ER collected all data, performed the statistical analysis, and wrote the first draft of the manuscript. All Authors did the literature search and also wrote part of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Despite well established validity and reliability of Pap test, a significant proportion of false negative test results still remains and is partially due to the lack of agreement between observers. Visual inspection tests (VIT) share this difficulty but their results are immediately available, thus making it easier to reduce disagreement between observers if these are well trained. The objective of this paper was to verify the agreement on a typical squamous cells of undetermined significance

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(ASC-US) or higher grade lesions between different examiners with Pap smear and visual inspection tests (VIT) in screening for cervical cancer. It is part of a wider study to evaluate the screening performance of Pap test and VIT in Brazil.
Study Design: A cross-sectional study was conducted among consenting clients attending cervical cancer screening services at a non-governmental medical facility in southern Brazil.
Place and Duration of Study: "Rede Feminina de Combate ao Câncer", a female cancer prevention center in Florianópolis, southern Brazil, between June 2010 and July 2012.
Methodology: Two observers evaluated 353 Pap smear test specimen and 284 visual inspection tests (VIT) of the women screened for cervical cancer in female cancer prevention center in southern Brazil. VIT started with naked eye examination after visual inspection by applying acetic acid (VIA) and Lugol's iodine (VILI) to cervix, followed by additional examination with 2x magnifying glass for both modalities.
Results: Concordance between the first and the second observer regarding Pap test was reasonably good (kappa=0.67) but was even better regarding all VIT modalities (kappa range 0.76-0.83). Magnifying glass did not significantly improve the agreement.
Conclusion: VIT showed very good agreement between observers. Adding VIT to Pap smear test may improve diagnostic accuracy in cervical cancer screening.

Keywords: Interobserver agreement; pap test; visual inspection tests; cervical cancer.

1. INTRODUCTION

Many countries rely solely on the Pap smear test for cervical cancer screening. In Brazil, the National Institute for Cancer (abbrev. INCA in Portuguese) recommends its use for screening women between 25 and 64 years old every three years after two consecutive negative test results [1,2]. However, various errors can occur, such as those during the specimen collection and those due to different interpretations of the specimen between the examiners, as well as false negative test results [3]. This paper examines the second component and describes an attempt to reduce it by adding Visual Inspection Tests (VIT).

Visual Inspection Techniques (VIT) have been amply piloted in Asian and African countries with limited resources where the access to Pap test screening is too restricted and women health prevention programs are precarious [4-7]. Visual inspection with acetic acid (VIA) and visual Inspection with Lugol´s Iodine (VILI) have been particularly popular among VIT. Their advantages include a sensitivity similar to Pap test in detecting high-grade cervical lesions, low cost, simple execution, availability of test result immediately after the test application and thus the viability of the "see and treat" protocol [5-7]. Also, a short training course of 3-14 days can be administered to medical professionals of varying background in order to capacitate them for cervical screening. VIT are alternative screening methods which are both effective and appropriate in countries with lacking adequate laboratory facilities and well trained screening professionals [6] e.g. Brazil. However, intensive initial training and periodic refreshment and/or upgrade courses are necessary to ensure effectiveness of this strategy in reducing false negative and false positive test results [8,9].

Although interobserver agreement is an important component of diagnostic accuracy, there are very few studies on agreement between health professionals involved in cervical cancer screening with VIT, thus limiting the wider application of this method, particularly in the countries with limited resources.

The aim of this study was to verify the Interobserver Agreement (IOA) in screening for cervical cancer by Pap test and VIT in Florianópolis, southern Brazil.

2. MATERIALS AND METHODS

A cross-sectional study evaluated IOA for 353 Pap smear test specimen and 284 VIT specimen of the women who already had sexual relationships and attended cervical cancer screening in Florianopolis, the capital of the Santa Catarina state in southern Brazil, between June 2010 and June 2012. The site was a clinic specialized in this type of screening and maintained by anon-governmental organization set to prevent cancer in women (abbrev. RFCCF in Portuguese).

2.1 Inclusion Criteria

All women who were scheduled for regular screening and signed the consent form were

eligible for the study providing they had an intact cervix.

2.2 Exclusion Criteria

The women who had been submitted to total hysterectomy or diagnosed with HPV, anal or genital condyloma lesions, as well as those diagnosed with HIV, were excluded from the study. Among 353 women screened with Pap test, 96 were not evaluated with VIT because they missed colposcopy scheduled shortly after the Pap test.

2.3 Diagnostic Criteria and Specimen Collection for Pap test

The Pap test specimen was collected by a nurse with over 20 years of work experience. Two specimens were collected for each woman: One by scraping with Ayre spatula from ectocervix and another by endocervical brush from endocervix. Both specimens were fixed by 70% alcohol and stained by Papanicolaou technique.

The Pap test results were classified according to the Bethesda System of 2001 [10]: Negative for intraepithelial lesion or malignancy; atypical squamous cells of undetermined significance (ASC-US) or cannot exclude HSIL (ASC-H); Low-grade squamous intraepithelial lesion (LSIL); High-grade Squamous Intraepithelial Lesion (HSIL) or with features suspicious for invasion (if invasion is suspected); Squamous cell carcinoma; Atypical endocervical cells (Not Otherwise Specified (NOS) or specify in comments), endometrial cells (NOS or specify in comments) and glandular cells (NOS or specify in comments); Atypical Glandular Cells (AGC), AGC-favor neoplastic; endocervical adenocarcinoma in situ; Adenocarcinoma (endocervical, endometrial, extrauterine, Not Otherwise Specified (NOS); other malignant neoplasms.

The first observer to make the diagnosis was alaboratory technician specialized in cytological tests with thirty years of work experience. The second observer was a pathologist specialized in cytopathology and employed by the University Hospital of the Federal University of Santa Catarina for forty years. Both observers had to classify specimen as altered (thus requiring further investigation) or otherwise, where the alteration of interest was defined as atypical squamous cells of undetermined significance (ASC-US) or higher grade. In the case the two observers disagreed, a third observer was called to decide. The latter was a pathologist specialized in cytopathology with over thirty years of work experience and employed by the same laboratory as the second observer. The first observer has access to the medical records standardized by the Brazilian Ministry of Health but did not know whether the specimen under evaluation was part of the study or not. Both the second and the third pathologist had over thirty years of experience in cervical screening and worked in the same laboratory but did not have access to the medical records nor the knowledge of the first observer's diagnosis.

2.4 Diagnostic Criteria and Procedures for VIT

VIT were performed by the same nurse who collected the Pap test specimen. She took a 130 hours course on VIT, based on IARC (International Agency for Research on Cancer) manual [11] and administered by an experienced gynecologist specialized in colposcopy and cervical cancer screening. The VIT started immediately after collection of Pap and in the presence of a 100 W cold light with the application of a 5% acetic acid to the cervix for one minute and a naked eye examination to make the VIA diagnosis. Next, a 2% Lugol's iodine solution was applied in order to make the VILI diagnosis. Both VIA and VILI naked eye examinations were followed by additional examination with 2x magnifying glass in order to make VIAM and VILIM diagnoses. The second VIT observer was a gynecologist whore-examined all study participants but was blind to the findings of the first one. In addition, colposcopy was performed for all of them. All VIT results were classified as positive or negative according to the IARC manual [11].

Both VIA and VIAM diagnoses were classified as negative under following conditions after the application of acetic acid: In the absence of acetowhite areas or if these were pale or ill-defined, whitish with undiscernible margins blending with the epithelium, areas with salient white line underlying the Squamo-Columnar Junction (SCJ), angular acetowhite areas, dispersed white areas far away from the SCJ or in the External Orifice of the Cervix (EOC) if the SCJ was not visualized, acetowhitening of the mucus or Nabothian cysts and normal acetowhitening in the columnar epithelium. Positive diagnosis was defined when the visible

presence of well-defined, opaque acetowhite areas abutting a fully visible SCJ or the transformation zoneor around EOC if SCJ was not visible, as well as acetowhiteness of the entire cervix or its growth [11].

Negative VILI and VILIM diagnoses included the following findings: Normal cervix where squamous epithelium turned black or brown and the columnar epithelium remained pale, colorless or partially brown in the transformation zone, or thin yellow, ill-defined non-iodine uptake areas on the cervix located far away from the SCJ, with or without extension to the vagina. Positive diagnosis was defined as well defined, thick, mustard or saffron yellow area touching the SCJ or occupying a large portion of the cervix [11].

Biopsy was performed for all VIT-positive cases, including white acetic epithelium, mosaic or point-like forms, atypical vascular presentations, enlarged glandular orifices and iodine-negative areas. Differently from the IARC manual, the cases considered difficult to classify as either positive or negative on VIT screening were treated as positive and investigated further, thus increasing the possibility of false positive test results. All VIT-positive and ASC-US or higher grade Pap test results were submitted to histological examination as gold standard.

Individual clinical and laboratory data were entered and analyzed by Stata software version 12.1. Kappa statistic was used to measure agreement between observers. The type I error was fixed at 5% ($P<0.05$).

2.5 Ethical Approval

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

3. RESULTS

Mean age of the women who participated in the study was 31.6 years (range 18.0-54.0) for Pap and 29.8 years (range 18.0-53.0) for VIT. The age of the menarche for Pap was reported at 13.0 years (range 10.0-16.0) and that of the first sexual intercourse was at 16.6 years (range 13.0-23.0). For VIT the age of the menarche was reported at 12.7 years (range 10.0-16.0) and that of the first sexual intercourse was at 16.9 years (range 13.0–23.0). Thus the mean age and the age of the menarche was very similar between the women screened by Pap test and by VIT.

Concordance of 0.67 between the first and the second observer regarding Pap test was reasonably good (Table 1). However, concordance indices between these two observers and the third one were poor (kappa values of 0.14 and 0.23).

Concordance between the first and the second observer regarding VIT was pretty good for all modalities considered separately as well as pulled together, with kappa values ranging between 0.76 and 0.83 (Table 2).

Interobserver concordance was low between Pap test and histological examination as gold standard and resulted in high proportion of false negative results of the specimen Pap-diagnosed as normal or inflammatory. Among the former, 32.1% were cervical intraepithelial neoplasia grade 1 (CIN1) and 17.9% were in fact CIN 2 or CIN 3, whereas 32.4% of the cases Pap-diagnosed as inflammatory were considered CIN 1 and 2.7% CIN 2 or CIN 3 by histological examination (Table 3). Three quarters of the ASC-US and half of the ASC-H diagnoses via Pap test turned out to be CIN 1.

Within Pap-diagnosed LSIL category, 42.9% were diagnosed as CIN 1 and the same percentage as CIN 2 or CIN 3 by histological examination. Within Pap-diagnosed HSIL category, 71.4% were in agreement with the gold standard.

Among VIT-positive cases, 53.8% were confirmed as such by the gold standard, of which 37.2% were CIN 1, 15.4% were CIN 2 or CIN 3 and 1.2% were cancer cases (Table 3). On the other hand, among 15 VIT-negative cases, 46.7% were confirmed as such by the gold standard, one third were diagnosed as CIN 1 and one fifth as CIN 2 or CIN 3.

4. DISCUSSION

Interobserver agreement is an important component of diagnostic accuracy of both Pap and VIT tests. Adequate training of health professionals for cervical cancer screening plays a key role in achieving good accuracy of these tests, particularly in reducing the false negative rate, as reported in another Brazilian study [12].

Table 1. Interobserver agreement for Pap test: kappa statistic and its 95% confidence intervals (CI)

Pap Test	Observer 2		Kappa CI 95%	Observer 3		Kappa CI 95%
	(+)	(-)		(+)	(-)	
Observer 1			0,67			0.14
(+)	33	17	(0.56-0.78)	12	6	(0.0-0.45)
(-)	10	293		10	9	
Total	43	310		22	15	
Observer 2						
(+)	-	-		18	9	0.23
(-)	-	-		4	6	(0.0-0.54)
Total				22	15	

Pap test positive (+) if lesion grade ≥ ASC-US, otherwise negative (-)

Table 2. Interobserver agreement for visual inspection tests: kappa statistic and its 95% confidence intervals (CI)

Test	Observer 2		Kappa CI 95%	Test	Observer 2		Kappa CI 95%
	(+)	(-)			(+)	(-)	
VIA				**VIAM**			
Observer 1			0.77	Observer 1			0.77
(+)	66	23	(0.65-0.88)	(+)	67	22	(0.65-0.88)
(-)	4	191		(-)	5	190	
Total	70	214		Total	72	212	
VILI				**VILIM**			
Observer 1			0.81	Observer 1			0.83
(+)	71	22	(0.70-0.93)	(+)	69	20	(0.71-0.94)
(-)	0	191		(-)	0	195	
Total	71	213		Total	69	215	
VIT							
Observer 1			0.76				
(+)	155	4	(0.64-0.87)				
(-)	30	95					
Total	185	99					

VIA = visual inspection with acetic acid; VIAM = visual inspection with acetic acid magnified; VILI = visual inspection with lugol's iodine; VILIM = visual inspection with lugol's iodine magnified; VIT = visual inspection tests; VIT (+) = any positive results on VIA, VIAM, VILI or VILIM; VIT (-) = VIA, VIAM, VILI and VILIM all negative

A reasonable agreement between the first and the second observer regarding Pap test result, and their poor agreement with the third observer, may be explained by inadequate staining and/or fixation of the specimen as reported occasionally by the former. Low quality of the staining material, high workload for the screening professionals and different classification standards for morphological alteration used by the observers may have contributed to disagreement on Pap test diagnoses in some cases. However, it should be kept in mind that the third observer re-examined only the specimen with discrepant diagnosis between the first and the second observer, which were likely more difficult to classify and therefore to agree upon.

Despite above obstacles, the concordance between the first two observers in the present study (kappa=0.67) was better than the one reported in another study based on hundred specimen which were initially evaluated by an experienced laboratory technician and revised by three pathologists, achieving mean kappa value of 0.56 [13]. Yet another Brazilian study also found good agreement between the first two observers (kappa=0.67) but their poor agreement with the third one (kappa=0.02) [14]. The concordance between the first observer and an expert panel was pretty good (kappa=0.75), thus indicating a good diagnostic accuracy of the first observer. A lack of precise guidelines for diagnostic interpretation of Pap test contributed to only modest agreement (kappa=0.46) in an important multicentric study which concluded that

better training and more rigorous quality control may improve the agreement level [15]. The present study range of kappa values (0.76-0.83) confirm this conclusion regarding VIT. Extensive training of the observers with particular attention to the difficulties in diagnostic classification has been emphasized in the literature [5,7-9,16,17] but its routine implementation among screening professionals remains a challenge.

Small magnification (2x) did not improve the IOA of either VIA or VILI in the present study. However, the studies with larger magnification (4x) showed its beneficial effect on diagnostic accuracy, especially in improving test specificity [18].

VILI and VILIM had the highest IOA rates, probably due to the fact that the diagnoses were made immediately after the Lugol's iodine application as opposed to a one minute wait for VIA. In addition, the whitening of acetic acid in VIA may be difficult to localize when the area of lesion is small, within transformation zone, next to a large area of immature metaplasia or glandular tissue. Also, acetic acid may occasionally cause bleeding of the cervix which interferes with accurate VIT diagnosis [19].

A large multicentric study in India and Africa achieved moderate IOA for VIA, with mean kappa value of 0.38 (range 0.15-0.65) across 11 sites [20]. Considerably higher kappa of 0.77 for VIA in the present study may be due to longer training of the observers and lesser specimen variation in a single center study. The same type of study in Karnataka, India, found low-to-moderate agreement (kappa=0.36) between a nurse and a physician after a 2-week training to diagnose CIN2 or higher grade lesion by VIA, using IARC diagnostic criteria [21]. In the view of these results, it seems worth providing a more extensive training for screening professionals in order to improve IOA with VIT.

Average kappa of 0.57 was obtained for IOA among three VIA experts who evaluated 144 photographs of the cervix after application of acetic acid, without any aid from the clinical data [22]. The women who participated in the study were from India, South Africa and Peru. The results indicate potential of VIA for controlling the quality of screening programs at an affordable cost, even in the countries with limited resources. Where there is a substantial lack of trained screening professionals, nurses can be trained to perform the screening. However, the effectiveness of the training critically depends on its periodic reinforcement, mainly in order to reduce false positive test results and consequently the screening costs [21]. Internet may provide a low-cost alternative to sending digitalized photographs of the cervix to a quality control center. Monitoring whether local screening site has achieved reasonable IOA (kappa 0.40 or higher) can be used among criteria of a good quality cervical cancer prevention [7].

Table 3. Concordance between Pap test and VIT results with histological examination as gold standard

		Histopathology results							
CO results	**Total**	**Cervicitis and/or metaplasia**		**CIN 1**		**CIN 2/3**		**Carcinoma**	
		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									
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	1,2
Total	93	43	46,2	34	36,6	15	16,1	1	1,1

ASC-US = atypical squamous cells of undetermined significance; ASC-H = atypical squamous cells of undetermined significance cannot exclude HSIL; LSIL = low grade squamous intraepithelial lesion; HSIL = high grade squamous intraepithelial lesion; CIN 1 = cervical intraepithelial neoplasia grade 1; CIN 2/3 =cervical intraepithelial neoplasia grade 2 or 3; VIT (+) = any positive results on VIA, VIAM, VILI or VILIM; VIT (-) = VIA, VIAM, VILI and VILIM all negatives

The importance of adequate specimen collection of the transformation zone has been well established in the literature [3,23-25] and confirmed in Table 3 of the present study. This finding goes along with the report that 80% of pre-malignant and malignant cervical lesions originated from SCJ and thus difficult to reach, so that the lesions are not well represented in the specimen [26]. Some studies have shown that even after very careful specimen collection, less than 20% of the cells collected actually reach the lamina (so-called transference error) and that the specimen collection instruments may be source of error as well [24,25].

A case-control study found that blood and inflammation of the cervix significantly contribute to diagnostic errors in Pap screening [26]. Also, false negative results were highly influenced by the presence of atypical cells, either isolated or in small number, and chromatin. In addition, reinforcing the motivation of screening professionals and periodic refreshment courses may reduce diagnostic errors [6,9,27]. Other factors that reduce diagnostic accuracy are the difficulties in visualizing endocervix and the lack of experience in recognizing adenocarcinoma [11,28].

Based on the experience with VIT in Brazil [12,17] and other developing countries [16,18,23,24] health policy implications for cervical cancer screening are to include VIT as a part of regular women health exams and provide adequate training for the health professionals who perform it. Even in the countries with reasonable coverage of Pap test screening, adding VIT may significantly reduce the false negative test results while keeping the false positive rate at <10% [12], thus providing a low cost alternative to more sophisticated screening methods.

5. CONCLUSION

IOA for VIT was very good in the present study as indicated by the kappa range between 0.77 and 0.83 for VIA, VIAM, VILI and VILIM. Magnifying (2x) did not improve the IOA.

IOA was better for VIT than for Pap test, although the difference did not reach statistical significance.

The results of this study give support to the notion that better standardization of the VIT diagnostic criteria, extensive training of screening professionals followed by periodic update and quality control monitoring of screening sites hold promise of significantly improving cervical cancer screening. Nevertheless, more studies are needed to better evaluate the VIT validity and reliability before recommending these methods for parallel screening with or as substitution for the Pap test in the countries with limited resources, in particular the type and duration of training for the health professionals.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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