

Original Research Article

Agreement between observers for Pap smear and visual inspection tests

in Florianópolis, southern Brazil

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 atypical squamous cells of undetermined significance (ASC-US) or higher grade lesions between different examiners with Pap smear and visual inspection tests (VIT) in screening for cervical cancer.

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

24 prevention center in southern Brazil. VIT started with naked eye examination after
25 visual inspection by applying acetic acid (VIA) and Lugol's iodine (VILI) to cervix,
26 followed by additional examination with 2x magnifying glass for both modalities.

27 **Results:** Concordance between the first and the second observer regarding Pap test was
28 reasonably good ($\kappa=0.67$) but was even better regarding all VIT modalities (κ
29 range 0.76-0.83). Magnifying glass did not significantly improve the agreement.

30 **Conclusions:** VIT showed very good agreement between observers. Adding VIT to Pap
31 smear test may improve diagnostic accuracy in cervical cancer screening.

32

33 **Key words:** interobserver agreement, Pap test, visual inspection tests, cervical cancer.

34

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 Florianópolis, 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 a non-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

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

86 The Pap test results were classified according to the Bethesda System of 2001
87 [10]: negative for intraepithelial lesion or malignancy; atypical squamous cells of
88 undetermined significance (ASC-US) or cannot exclude HSIL (ASC-H); Low grade
89 squamous intraepithelial lesion (LSIL); High grade squamous intraepithelial lesion
90 (HSIL) or with features suspicious for invasion (if invasion is suspected); Squamous
91 cell carcinoma; Atypical endocervical cells (not otherwise specified (NOS) or specify in
92 comments), endometrial cells (NOS or specify in comments) and glandular cells (NOS
93 or specify in comments); atypical glandular cells (AGC), AGC-favor neoplastic;
94 endocervical adenocarcinoma in situ; Adenocarcinoma (endocervical, endometrial,
95 extrauterine, not otherwise specified (NOS); other malignant neoplasms.

96 The first observer to make the diagnosis was a laboratory technician specialized
97 in cytological tests with thirty years of work experience. The second observer was a
98 pathologist specialized in cytopathology and employed by the University Hospital of the
99 Federal University of Santa Catarina for forty years. Both observers had to classify
100 specimen as altered (thus requiring further investigation) or otherwise, where the
101 alteration of interest was defined as atypical squamous cells of undetermined
102 significance (ASC-US) or higher grade. In the case the two observers disagreed, a third
103 observer was called to decide. The latter was a pathologist specialized in cytopathology
104 with over thirty years of work experience and employed by the same laboratory as the
105 second observer. The first observer has access to the medical records standardized by
106 the Brazilian Ministry of Health but did not know whether the specimen under

107 evaluation was part of the study or not. Both the second and the third pathologist had
108 over thirty years of experience in cervical screening and worked in the same laboratory
109 but did not have access to the medical records nor the knowledge of the first observer's
110 diagnosis.

111 2.4 Diagnostic criteria and procedures for VIT

112 VIT were performed by the same nurse who collected the Pap test specimen. She
113 took a 130 hours course on VIT, based on IARC (International Agency for Research on
114 Cancer) manual [11] and administered by an experienced gynecologist specialized in
115 colposcopy and cervical cancer screening. The VIT started immediately after collection
116 of Pap and in the presence of a 100 W cold light with the application of a 5% acetic acid
117 to the cervix for one minute and a naked eye examination to make the VIA diagnosis.
118 Next, a 2% Lugol's iodine solution was applied in order to make the VILI diagnosis.
119 Both VIA and VILI naked eye examinations were followed by additional examination
120 with 2x magnifying glass in order to make VIAM and VILIM diagnoses. The second
121 VIT observer was a gynecologist who re-examined all study participants but was blind
122 to the findings of the first one. In addition, colposcopy was performed for all of them.
123 All VIT results were classified as positive or negative according to the IARC manual
124 [11].

125 Both VIA and VIAM diagnoses were classified as negative under following
126 conditions after the application of acetic acid: in the absence of acetowhite areas or if
127 these were pale or ill-defined, whitish with undiscernible margins blending with the
128 epithelium, areas with salient white line underlying the squamo-columnar junction
129 (SCJ), angular acetowhite areas, dispersed white areas far away from the SCJ or in the
130 external orifice of the cervix (EOC) if the SCJ was not visualized, acetowhitening of the

131 mucus or Nabothian cysts and normal acetowhitening in the columnar epithelium.
132 Positive diagnosis was defined when the visible presence of well-defined, opaque
133 acetowhite areas abutting a fully visible SCJ or the transformation zone or around EOC
134 if SCJ was not visible, as well as acetowhiteness of the entire cervix or its growth [11].

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

142 Biopsy was performed for all VIT-positive cases, including white acetic
143 epithelium, mosaic or point-like forms, atypical vascular presentations, enlarged
144 glandular orifices and iodine-negative areas. Differently from the IARC manual, the
145 cases considered difficult to classify as either positive or negative on VIT screening
146 were treated as positive and investigated further, thus increasing the possibility of false
147 positive test results.

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

151 2.5 Ethical approval

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

154

155 **3 Results**

156 Mean age of the women who participated in the study was 31.6 years (range
 157 18.0-54.0) for Pap and 29.8 years (range 18.0-53.0) for VIT. The age of the menarche
 158 for Pap was reported at 13.0 years (range 10.0-16.0) and that of the first sexual
 159 intercourse was at 16.6 years (range 13.0-23.0). For VIT the age of the menarche was
 160 reported at 12.7 years (range 10.0-16.0) and that of the first sexual intercourse was at
 161 16.9 years (range 13.0-23.0). Thus the mean age and the age of the menarche was very
 162 similar between the women screened by Pap test and by VIT.

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

166 Table 1– Interobserver agreement for Pap test: kappa statistic and its 95% confidence
 167 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	171
Observer 2						0,23
(+)	-	-		18	9	(0.0-0.54)
(-)	-	-		4	6	
Total				22	15	173

175 Pap test positive (+) if lesion grade $\geq$ ASC-US, otherwise negative (-)

176

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).

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

Test	Observer 2		Kappa	Test	Observer 2		Kappa
	(+)	(-)	CI 95%		(+)	(-)	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.

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 (CIN 1) 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.

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

200

Histopathology Results									
CO Results	Cervicitis and/or Metaplasia		CIN 1		CIN 2/3		Carcinoma		
	Total	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

201

202 ASC-US = atypical squamous cells of undetermined significance;

203 ASC-H = atypical squamous cells of undetermined significance cannot exclude HSIL ;

204 LSIL = Low grade squamous intraepithelial lesion ;

205 HSIL = High grade squamous intraepithelial lesion;

206 CIN 1 = cervical intraepithelial neoplasia grade 1 ;

207 CIN 2/3 = cervical intraepithelial neoplasia grade 2 or 3;

208 VIT (+) = any positive results on VIA, VIAM, VILI or VILIM;

209 VIT (-) = VIA, VIAM, VILI and VILIM all negatives.

210

211

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

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

220

221 **4 Discussion**

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

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

235 Despite above obstacles, the concordance between the first two observers in the
236 present study ($\kappa=0.67$) was better than the one reported in another study based on
237 hundred specimen which were initially evaluated by an experienced laboratory
238 technician and revised by three pathologists, achieving mean κ value of 0.56 [13].
239 Yet another Brazilian study also found good agreement between the first two observers
240 ($\kappa=0.67$) but their poor agreement with the third one ($\kappa=0.02$) [14]. The
241 concordance between the first observer and an expert panel was pretty good
242 ($\kappa=0.75$), thus indicating a good diagnostic accuracy of the first observer. A lack of
243 precise guidelines for diagnostic interpretation of Pap test contributed to only modest
244 agreement ($\kappa=0.46$) in an important multicentric study which concluded that better
245 training and more rigorous quality control may improve the agreement level [15]. The
246 present study range of κ values (0.76-0.83) confirm this conclusion regarding VIT.
247 Extensive training of the observers with particular attention to the difficulties in
248 diagnostic classification has been emphasized in the literature [5,7-9,16,17] but its
249 routine implementation among screening professionals remains a challenge.

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

253 VILI and VILIM had the highest IOA rates, probably due to the fact that the
254 diagnoses were made immediately after the Lugol's iodine application as opposed to a
255 one minute wait for VIA. In addition, the whitening of acetic acid in VIA may be
256 difficult to localize when the area of lesion is small, within transformation zone, next to
257 a large area of immature metaplasia or glandular tissue. Also, acetic acid may
258 occasionally cause bleeding of the cervix which interferes with accurate VIT diagnosis
259 [19].

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

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

281 The importance of adequate specimen collection of the transformation zone has
 282 been well established in the literature [3,23-25] and confirmed in Table 3 of the present
 283 study. This finding goes along with the report that 80% of pre-malignant and malignant
 284 cervical lesions originated from SCJ and thus difficult to reach, so that the lesions are

285 not well represented in the specimen [27]. Some studies have shown that even after
286 very careful specimen collection, less than 20% of the cells collected actually reach the
287 lamina (so - called transference error) and that the specimen collection instruments may
288 be source of error as well [24,25].

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

296

297 5 Conclusions

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

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

303 The results of this study give support to the notion that better standardization of
304 the VIT diagnostic criteria, extensive training of screening professionals followed by
305 periodic update and quality control monitoring of screening sites hold promise of
306 significantly improving cervical cancer screening. Nevertheless, more studies are
307 needed to better evaluate the VIT validity and reliability before recommending these

308 methods for parallel screening with or as substitution for the Pap test in the countries
309 with limited resources.

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