

Cervical Cancer Screening with Visual Inspection with Acetic Acid and Lugol as Primary Screening Test, a Comparable Result to Conventional PAP Smear in Northern Cameroon

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Abstract

Background: Cervical cancer is a major cause of women death worldwide. The reduction of the mortality and morbidity of this pathology depends on the early detection based on powerful suitable screening methods that will lead to optimal treatment strategies. However in some rural region of developing countries, it is very difficult to get access to standard screening methods, alternative screening methods, cheaper and easy to handle are then useful.

Objective: The aim of this work was to test the sensitivity and specificity of VIA (Visual inspection with acetic acid) and VILI (Visual inspection with lugol iodine) as screening test of cervical cancer compared to the Pap Smear, evaluating the feasibility in health formation in the North Cameroon region, of implementing epidemiological surveillance of cervical cancer based on early diagnosis using the VIA-VILI association.

Method: 309 women age 20 to 62 years were recruited in this study, 307 were included in the statistical analyzes. Each woman was screened for cervical cancer by a conventional Smear and visual inspection with acetic acid 5% and the lugol solution.

Results: We found in our study a prevalence of precancerous lesions of cervix at 12.70%. The risks factors of cervical cancer identified are age, matrimonial status, age of first sexual intercourse and parity. The association of VIA and VILI showed a sensitivity, specificity, positive and negative predictive value respectively about 93.58%; 97.01%; 82.01%, 99.04%.

Conclusion: Compared to PAP Smear, VIA or VILI could be used as an alternative screening methods for cervical cancer in developing countries. However, histology test was recommended to use a « Gold Standard » to evaluate the test accuracy of VIA/VILI because it can be used to diagnose cancer, while PAP smear cannot.

Keywords: Sensitivity; Specificity; Diagnosis; VIA-VILI; Cervical cancer

Introduction

In developed countries, the incidence and mortality due to cervical cancer is decreasing. For example in United States, between 1955 and 1992, mortality due to cervical cancer has decreased by 70%, today a reduction of 3% is observed each year. Similarly in the United Kingdom, mortality rate has decreased by 70% in 2008 compared to 30 years earlier [1]. In Cameroon, cervical cancer incidences as well as the mortality associated are progressively increasing. This growth may be due to the insufficiency of national anti-cancer program against cervical cancer, leading to a limited access to screening, high cost and rarity of vaccine against the HPV (Human Papilloma Virus) in the country, the unavailability of early screening services [2]. Consequently, cancer is diagnosed at advanced stage in Cameroon. 80% of cancer cases diagnosed at a late stage and the major part of patients will die within 12 months from the diagnosis. Cervical cancer is an avoidable and curable disease if the disease is diagnosed and treated early [3]. The slow progression of precancerous lesions to invasive cervical cancer stage could long till 10 years, representing a gap of time in which detection and treatment of lesions should be done to prevent the invasive cancer stage [4]. In developed countries, regular screening of the target population would reduce the incidence of cervical cancer to

less than 10% [5]. However, in developing countries, screening is non-existent or covers only a small part of the target [5].

The effectiveness of cervical Smear in the detection of cervical lesions has been demonstrated and this technique has significantly reduced the relative incidence of cervical cancer in developed countries since 1950 [6]. But the limits of this technique for developing countries are important, including cost, logistics and trained human resources to mobilize [7]. The possibility of detecting human papilloma virus (HPV) by molecular biology methods offers another additional approach in

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screening, but as the Smear its cost is still high and this technique requires sophisticated equipment that is expensive in our context [8].

Confronted to these challenges, the use of visual inspection tests such as VIA (Visual Inspection with Acetic Acid) and Visual Inspection with Lugol iodine (VILI), which require minimum equipment and a lower cost than other techniques appears to be a viable alternative for low-income countries like ours [9]. The aim of this work was to test in comparison to cervical Smear, the sensitivity and specificity of VIA-VILI as a diagnostic test for cervical cancer and to evaluate the feasibility and efficiency of epidemiological surveillance of cervical cancer based on early diagnosis in health facilities in the Northern region of Cameroon.

Materials and Methods

Research and obtaining of research permits and at each hospital where the survey was carried out, women are informed at the hospital reception service of free cervical cancer screening regardless of the type of consultation for which she came, even if she was came just to visit patient in the hospital. Women's community associations have also served as the information base and radio releases in the city.

In our study we first excluded all women with gynecological symptoms of cervical cancer or who were positively diagnosed before. This allowed us to avoid bills in the prevalence of the disease.

This is a cross-sectional study conducted in the Northern region Cameroon from May to August 2016 in the following hospitals: Regional Hospital of Garoua, District Hospital of Guider and Esperance Hospital of Djamboutou (Garoua). 309 women were recruited, 307 were included in the statistical analyzes. Inclusion Criteria were all women between the ages of 20 and 65 attending hospitals and consenting to participate to the study. Exclusion criteria were women with hysterectomy or cervical conisation, pregnancy, active vaginal bleeding and those with a history of precancerous and cancerous lesions. After written consent was obtained, interview on the socio-demographic characteristics and the gynecological and obstetric history was administered to each woman. Then they were screened for cervical cancer by a conventional Smear, visual inspection after applying 5% acetic acid and lugol iodine.

Conventional Smear

After obtaining informed consent, the reassured woman is placed in a gynecological position, then a sterile single use speculum was introduced into her vagina until the cervix was perfectly observed. It was first taken for conventional smear before the visual examination. The pathologist did not have access to the result of VIA and VILI until he had examined the sample. The codes were used for identification. We note the macroscopic characteristics of the cervix, the anatomic condition of the cervix, the state of vaginal discharge if present, cervicitis, or any other visible anomaly of the cervix.

A spatula and cytobrush were used to remove the cells by simple scraping. The sample was spread on a slide and immediately fixed with alcohol and dried. All the slides were sent to the anatomo-cytopathology laboratory of the University Hospital Center of Yaounde, colored and interpreted by an anatomo-pathologist. The results are given according to the classification Bethesda system 2001.

Acetic acid 5% was prepared in the morning when we arrived from the hospital. This preparation was applied on cervix using cotton swap and interpreted after 1 minute under bright light. The test considered positive if a white areas, well delimited and near to the squamous junction appears on cervix and negative in the absence of this whitening.

The lugol solution used was ready preparation buying in a biomedical materials and reagents distribution center in Garoua city. Lugol's iodine solution was applied on cervix using cotton swap and interpreted after 1 minute. Normal cells absorb lugol and take black or brown coloration. In case of a positive test, iodo-negative area appears and take a mustard or saffron yellow color. The iodo-negative area is clearly delineated and clearly visible. It is important to know that the VILI is realized after the VIA [9-11].

The software R commander version 13.2.0 was used for the analysis of the data. The bilateral Chi² test was used. A variable was statistically significant at p<0.05. The evaluation of the performance of the tests was carried out by calculating the sensitivity, specificity and the positive and negative predictive values.

Results

Performance of Visual inspection after application of acetic acid (VIA) and Visual inspection after application of lugol's iodine (VILI)

Pap Smears revealed 39 positive cases corresponding to a prevalence of 12.70%. (Table 1) shows the distribution of lesions according to grade.

According to the visual inspection after application of acetic acid, 14.65% (45/307) of cases were positives, 2 cases of false negatives and 8 cases of false positives were identified. (Table 2) [12,13].

The visual inspection after application of lugol's iodine revealed 14.33% [44/307] of positive cases. 3 cases of false negatives and 8 cases of false positives were identified (Table 3). The sensitivity (Se), specificity (Sp), positive predictive values (PPV) and negative values (NPV) of the several tests are presented in Table 4.

Combined performance of VIA and VILI

The association of the VIA with the VILI yields sensitivity, specificity, positive predictive value and a negative predictive value of 94.87%; 97.01%; 82.22% and 98.5% respectively. Higher negative predictive values obtained in this study means that if a subject is declared negative to the test, we can effectively accept that result at 100%.

Diagnosis	effectif	Percentage (%)
ASC-H	1	0.32
ASC-US	6	1.95
HSIL	9	2.93
LSIL	23	7.49
NIL/M	268	87.29
TOTAL	307	100

Table 1: Distribution of dysplastic lesions according to grade.

Note: ASC-H: Atypical Squamous cell cannot Exclude High grade, ASC-US: Atypical Squamous cell of Undefined Signification, HSIL: High Squamous Intra-epithelial Lesion, LSIL: Low Squamous Intra-epithelial Lesion, NIL/M: No Intra-epithelial Lesions or Malignancy.

Results of smear	Results of VIA	
	Negative	Positive
ASC-H	0	1
ASC-US	0	6
HSIL	0	9
LSIL	2	21
NIL/M	260	8

Table 2: Contingency Table of Smear Results with VIA Results.

Result of smear	Result of VILI	
	Negative	Positive
ASC-H	0	1
ASC-US	0	6
HSIL	0	9
LSIL	3	20
NIL/M	260	8

Table 3: Contingency table of smear results with VILI results.

	Se en%	Sp en%	PPV en%	NPV en%
VIA	94.87	97.01	82.22	99.23
VILI	92.30	97.01	81.81	98.85
Association VIA/VILI	94.87	97.01	82.22	99.23

Table 4: Sensitivity (Se), Specificity (Sp), Positive Predictive Value (PPV), Negative Predictive Value (NPV).

Relationship between socio-demographic characteristics and results of Smear

Table 5 presents the relationship between socio-demographic characteristics and the onset of cervical dysplasia. We found that a higher proportion of dysplastic lesions occurred in women over 30 year's olds. The average age of beginning of precancerous lesions is relatively young at 36.89 years. This study reports a significant difference between age and appearance of dysplasia ($p < 0.04$) [14,15].

Marital status was associated with the presence of cervical dysplasia lesions. Unmarried women had significantly ($p < 0.02$) more dysplasia than those who keep on in marriage. Our study benefited from information on the number of sexual partners for each participant in the study. Although women with multiple sexual partners had a higher proportion of dysplastic lesions, we did not find a significant difference ($p < 0.35$) between the number of sexual partners and precancerous lesions [4].

The average age of first sexual intercourse was 17.52 years. According to our analysis, 75% of women had sexual intercourse before 19 years old. We noticed a significant association ($p < 0.008$) between age at the first intercourse and dysplasia lesions. Those who had sexual intercourse between 13 and 18 years had significantly more dysplasia. Parity has been described elsewhere as risk factor for cervical cancer it. A parity greater or equal to 5 is considered as a risk factor for cervical cancer [16]. In our study, we observed an increased proportion of dysplasia in relation to the number of pregnancies in the study population, but association between the number of pregnancies and the presence of precancerous lesions was not significant ($p < 0.35$). On the other hand, we found a significant association ($p < 0.01$) between parity and dysplasia. Women with a number of births greater or equal to 5 have more dysplasia than those with a lower number of births.

Discussion

Conscious on the critical role of early diagnostic in cancer management, cancer research has led to the development of many fast and non-invasive screening methods that allow not only to diagnose the disease, but also help in providing an idea concerning treatment outcomes. In developing countries, colposcopy or cytology based screening methods for cervical cancer are difficult of access due to low capacity of health services in rural area. The use of alternative low-cost technique screening based on visual inspection such as VIA and VILI has been proposed for cervix cancer detection in developing countries [9,17]. In this study we evaluated how PAP Smear test, VIA and VILI

could be used as screening methods in Nord west of Cameroon. The gold standard test for cervical cancer screening is indeed colposcopy, it has been used to demonstrated limit of the PAP Smear in terms of accuracy, sensitivity, specificity, and negative predictive values in detecting high-grade, cervical, pre-malignant lesions [18]. But in the context of our study, we were unable to get access to this test. However considering the robust meta- analysis made by Peirson et al. on 24 studies, it emerges that the use of PAP Smear screening is associated with a reduction in the incidence of invasive cervical cancer and cervical cancer mortality [19]. Giving this fact the value of PAP Smear as controls is based on substantial protective effect that it has demonstrated [20,21]. In this study made on 307 women from the Nord West region of Cameroon, taking PAP Smear as the standard test, we found that VIA and VILI screening methods displayed sensitivity and specificity above 92% and 97% respectively, corresponding as described in other studies, to a large overlapping between visual inspection methods and PAP Smears [22,23]. The VIA identified 100% of precancerous lesions of high grade and failed to identified 2 precancerous lesions of low grade on the 29 confirmed by the Pap Smear, corresponding to an error of 6.89%. Similarly, in regard to PAP Smears result from VILI gave 3 false negatives and 8 false positive. The sensitivity of our VIA is higher than that obtained in a study in Gabon but with a lower specificity [15]. In more robust studies, VIA has demonstrated higher sensitivity in detection of precancerous lesions of the cervix, but its implementation is associated to high numbers of false-positive results [17]. Akinoa et al. have observed that the negative predictive Value of VIA is 100%, while the positive predictive value is too low [12]. Here we associated VIA and VILI screening, for the purpose to define a more accurate system based on the use of the two methods. In accord with the study of previous published studies, we found that there was no advantage to associate the two visual inspection methods for Cervix cancer screening [23,24]. Our result in accord with Huchko et al. [24] didn't show any significant difference between the VIA and VILI methods in terms of sensitivity, specificity, positive predictive value and negative predictive value. So, each of these two visual methods could be used alone. Rather, Consul et al. [23] has suggested that the association of screening methods should improve sensitivity, but at a cost of low specificity and more false-positive results [23].

Overall our data showed that VIA alone or VILI alone could be implemented as valuable test to screen cervix cancer in rural regions where it is difficult to implement more expensive screening test.

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