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Original Article

Evaluation of Conventional Pap Test for Cervical Intraepithelial lesions and Cancer in a Tertiary Hospital of Bangladesh

Mehnaz Nasreen[1*]
M. Shahab Uddin Ahamad[2]
Pradip Bhattacharjee[1]
Md Quamrul Hassan[2]
Md. Zillur Rahman[1]

[1]Department of Pathology, Chittagong Medical College, Chittagong, Bangladesh

[2]Department of Pathology, Cox's Bazar Medical College, Cox's Bazar, Bangladesh

Abstract

Objective: This study was aimed to evaluate the conventional Papanicolaou (Pap) test for detection of cervical intraepithelial lesions and cancer, with histopathologic association, in a tertiary hospital of a developing country. **Methods:** A cross-sectional hospital-based study was carried out in a total of 550 women, who underwent Pap smear examination, followed by colposcopy. Specimen adequacy and reporting was assessed according to the revised Bethesda system. 195 of these women, either Pap test positive, colposcopically positive or both, subsequently had their cervical tissue examination done with routine histopathology, as histopathology is the gold standard and Pap smear test was compared with it. **Results:** Among the total of 195 positive cases, histologic diagnosis of 104 (53.33%) cases were negative for cervical intraepithelial lesions or cancer, 64 (32.82%) were cervical neoplasia grade I (CIN I), 19 (9.74%) showed features of cervical intraepithelial neoplasia grade 2 and 3 (CIN II and III) and 08 (04.11%) as squamous cell carcinoma. The sensitivity and specificity of Pap test were 89.01% and 91.31%, respectively. Positive predictive value was 91.01%, while the negative predictive value was 90.56%. **Conclusion:** The findings of this study will be utile in supporting some useful information of Pap test, which plays a potential role in detection of cervical cancer and its precursors in a developing country like Bangladesh, where HPV-DNA test or liquid-based cytology is too expensive.

Key words: Papanicolaou test; Cervical intraepithelial lesions; Cervical cancer; Histopathology.

INTRODUCTION

Cancer of the uterine cervix is the second most common cancer in women worldwide, with about 5,00,000 new cases and 2,50,000 deaths annually.[1] Almost 80% of cases occur in the developing countries, where it is the leading cause of cancer mortality in women.[2] No exact population- based data is available on screening practiced in Bangladesh and in other developing countries. However, a study in Bangladesh, revealed that cervical cancer was the leading one (24.32%) among 10 female malignancies between 15 and 45 years of age.[1,3]

Currently, cervical cancer screening by exfoliative cytology like Papanicolaou (Pap) smear examination, is the only well-established strategy for cervical cancer control, which has succeeded in decreasing the incidence of cervical cancer in developed countries.[4]

In United States, presently cancer of the uterine cervix ranks as the eighth leading cause of cancer mortality. Much credit for this dramatic gain

*Correspondence to:
Dr. Mehnaz Nasreen,
Lecturer, Department of Pathology, Chittagong Medical College, Chittagong, Bangladesh
E-mail: MehnazNasreen@gmail.com

belongs to the effectiveness of the Pap test in detecting cervical precancers that are discovered yearly by cytologic examinations.[5]

The most relieving and encouraging fact about cancer of uterine cervix is that it has a natural history more amenable to screening, and is easier to prevent and cure than any other cancer.[6] The reason that cytologic screening is so effective in preventing cervical cancer is that the majority of cancers are preceded by a long standing precancerous lesion that may exist in non-invasive, pre-clinical phase for many years, and shed abnormal cells that can be detected by Pap smear examinations.[5]

The idea of screening for the early detection of cervical cancer has gained widespread acceptance, particularly with the development of the techniques of exfoliative cytology initiated by the pioneer work of Dr. George Papanicolaou in 1943.[7] Relatively easy and highly acceptable conventional screening Pap test technique can reduce the burden of cervical cancer by detecting the disease in a pre invasive or early stage.[8]

A number of new technologies for early detection of cervical cancer are emerging, with the hope that alternative approaches will allow for a higher degree of coverage at a lower cost. Alternative screening methods can be classified as, high technology or low technology. The high-technology approaches include screening for human papilloma virus (HPV-DNA detection and typing) and screening with use of automated instruments for interpreting Pap smears. The low-technology methods are potentially applicable to developing countries, without the need to introduce more sophisticated methods. They include Visual Inspection with Acetic acid (VIA), Aided Visual Inspection, Cervical Photography, Speculoscopy etc.[9]

Inspite of all these promising technologies, conventional Pap test remains the most dependable one, as there are still doubts as to whether liquid-based cytology performs better than the conventional one in early cervical cancer detection or whether to depend on VIA, the specificity of which is somewhat lower than Pap smear.[8,10] HPV-DNA testing (HCT II test) is still more expensive, as is the case of HPV vaccine, and only available in a few laboratories of developing countries like Bangladesh. Moreover, compared to Pap smear test, HPV DNA test is more time consuming and requires sophisticated laboratory infrastructure and facilities, whereas its clinical implication is still unknown.[11]

Hence, the present study was undertaken with the intention of assessing the validity of conventional Pap smear, using histologic results as the gold standard for both cervical intraepithelial lesion and cancer in a tertiary hospital of a developing country, Bangladesh. The results of this study might be utile in supporting some useful information for the development of a suitable screening program in this country.

MATERIALS AND METHODS

A hospital-based cross-sectional study was carried out in the Department of Pathology, Chittagong Medical College, Chittagong, Bangladesh, during the period from July 2010 to June 2011. Patients with complaints related to cervical pathology, attending in the out-patient Department of Obstetrics and Gynaecology of Chittagong Medical College Hospital are the study population. By convenience sampling, a total of 550 women of different age groups were selected for this study. The patients in the range of 18–70 years of age, having the history of post-coital bleeding or pervaginal spotting or irregular vaginal bleeding or post menopausal bleeding and clinically unhealthy-looking cervix after pervaginal examination were included in this study. Unmarried patient below 18 years of age, patient already treated for cervical intraepithelial neoplasia or cancer and patients who already had hysterectomy operation, were excluded from the study.

Detailed history and informed written consent was taken from all patients. Subsequently cervical smear was collected for conventional Pap test of all 550 patients. On the following day, colposcopic examination findings were recorded in these patients. Biopsy was taken from all Pap positive and colposcopically positive cases. The tests were done on the tenth to twentieth day of menstrual cycle and in absence of pervaginal spotting or bleeding. Pap test and biopsy were done in two settings.

Pap smear and colposcopic examination were performed in all 550 cases. Biopsy was performed the following day in 195 cases who were either Pap positive or colposcopically positive or both. Data analysis was done using computer based software SPSS version-15.0.

RESULTS AND OBSERVATIONS

Among the total of 550 patients, 89 (16.19%) were Pap test positive and 461 (83.81%) were negative cases (Table 1). The age of the patients with cervical intraepithelial lesions and malignancy was between 21 and above 50 years, with the mean age being 41.6 years. A progressive rise was seen in the frequency of cytopathological abnormalities with increasing

age, and maximum frequency was observed in older women (Table 2). Colposcopic examination of the total 550 patients revealed 186 (33.81%) cases to be positive, while 364 (66.19%) cases were negative (Table 3). Among 89 Pap test positive women, 80 cases were found to be colposcopically positive and 9 women were negative (Table 4). Again, out of 186 colposcopically positive patients, 106 were Pap test negative (Table 5). Thus, cervical biopsy was taken from 195 cases, which were either colposcopically positive or Pap test positive or both. Histopathological examination of these 195 cases revealed that 104 (53.33%) cases were negative for

Table 1: Distribution of Pap smear findings

Pap smear findings	No. of patients	Percentage (%)
NILM	461	83.8
ASC-US	03	0.5
AGC	02	0.4
LSIL	66	12.0
HSIL	10	1.8
SCC	08	1.5
Total	550	100.0

NILM – Negative for intra-epithelial lesions and malignancy
ASC-US – Atypical squamous cells of undetermined significance
AGC - Atypical glandular cells
LSIL – Low-grade squamous intraepithelial lesion
HSIL – High-grade squamous intraepithelial lesion
SCC – Squamous cell carcinoma

Table 3: Distribution of colposcopic findings among the study subjects

Colposcopic findings	No. of patients	Percentage (%)
*Positive	186	33.8
*Negative	364	66.2
Total	550	100.0

*Colposcopically positive finding means abnormality in topography, vascular pattern, color and surface contour of the cervix, while the others with healthy cervix were the negative cases.

Table 4: Association between Pap smear and colposcopic findings (n = 550)

		Pap smear results		Total (%)
		Positive (%)	Negative (%)	
Colposcopic findings	Positive (%)	80 (14.55)	106 (19.26)	186 (33.81)
	Negative (%)	09 (1.64)	355 (64.55)	364 (66.19)
Total (%)		89 (16.19)	461 (83.81)	550 (100.0)

Chi-square test statistics:
χ^2 = 149.147, P = 0.000; Highly significant ($P < 0.001$).

Table 2: Distribution pattern of Pap smear findings in different age groups

Age in groups	Pap smear test						Total no. (%)
	NILM (%)	ASCUS (%)	AGC (%)	LSIL (%)	HSIL (%)	SCC (%)	
≤20 years	32 (5.8)	00 (0.0)	00 (0.0)	00 (0.0)	00 (0.0)	00 (0.0)	32 (5.8)
21–30 years	179 (32.5)	00 (0.0)	00 (0.0)	11 (2.0)	00 (0.0)	00 (0.0)	190 (34.5)
31–40 years	155 (28.2)	00 (0.0)	00 (0.0)	30 (5.5)	00 (0.0)	00 (0.0)	185 (33.7)
41–50 years	75 (13.6)	03 (0.5)	02 (0.4)	20 (3.6)	10 (1.9)	00 (0.0)	110 (20.0)
>50 years	20 (3.6)	00 (0.0)	00 (0.0)	05 (0.9)	00 (0.0)	08 (1.5)	33 (6.0)
Total	461 (83.7)	03 (0.5)	02 (0.4)	66 (12.0)	10 (19)	08 (1.5)	550 (100.0)

cervical intraepithelial neoplasia or cancer, 64 (32.82%) cases were cervical intraepithelial neoplasia grade 1 (CIN I), 19 (9.74%) showed features of cervical intraepithelial neoplasia grade 2 and 3 (CIN II and III) and 08 (04.11%) as squamous cell carcinoma (Table 6). Validity test was done (Table 7).

Table 5: Association between Pap smear and histopathology results (n = 550)

		Histopathologic results		Total (%)
		Positive (%)	Negative (%)	
Pap smear results	Positive (%)	81 (41.54)	08 (4.10)	89 (45.64)
	Negative (%)	10 (5.13)	96 (49.23)	106 (54.36)
Total (%)		91 (46.67)	104 (53.33)	195 (100.0)

Chi-square test statistics:
χ^2 = 126.101, P = 0.000; Highly significant ($P < 0.001$).

Table 6: Histopathological findings of 195 patients

HPF	No. of patients
Chronic Cervicitis	104
CIN I	64
CIN II	14
CIN III	05
SCC	08
Grand total	195

HPF– Histopathological findings
CIN I– Cervical intraepithelial neoplasia, Grade I
CIN II – Cervical intraepithelial neoplasia, Grade II
CIN III – Cervical intraepithelial neoplasia, Grade III
SCC – Squamous cell carcinoma

Table 7: Validity test of conventional Pap smear

Validity test	Percentage
Sensitivity	89.01%
Specificity	92.31 %
Positive predictive value	91.01 %
Negative predictive value	90.56 %

DISCUSSION

In this study, samples were taken from a population attending the outpatient department of a teaching hospital where patients come directly or are referred from different health centers of the country. They did not visit the tertiary health institute for cancer screening purpose, but rather with specific gynecological complaints, such as abnormal vaginal bleeding, lower abdominal pain or discomfort, something coming down per vagina and/ or postcoital bleeding. This population was not similar to general population of the country, but we still considered it acceptable, because of the availability of the woman to be screened and an expected higher prevalence of cervical neoplasia, that will help us to evaluate Pap test.

In the present study, the mean age of the women was 35.55 (SD ± 10.74) with a range of 18–70 years. The mean age of the women in this study was lower than similar study of Pinto et al.[12] with mean age being 37.6% and also other investigator Cronje et al.,[13] which was 38.6%, as we included women from age of 18 years. This was done purposely as the marital age in our country is lower than the developed countries and their sexual activity begins at a much earlier age.[14]

Most of the patients included in this study were married when they were in their teens. These patients had increased risk of HPV infection as there is a biological predisposition of the immature cervix of the adolescent girls to persistent HPV infection, which augments the risk of development of cervical cancer. It can take as long as 20 years after HPV infection for the cancer to develop.[15]

In the present study, there was no malignant case in the age groups between 18 and 50 years. A total of 08 cases (24.2%) were found to be malignant in over 50 years. It is interesting to note that 26.4% of the patients in this study were in the range of 41–50 years and above and both high-grade lesion and malignancy were seen in these age groups than in any other age group. In another study, Engineer and Misra[16] show that the frequency of malignant disease was high in 36–45 years of age and in older age group. No case of carcinoma of cervix was seen in patients younger than 25 years.

It was found that majority of the women (64.5%) were using contraceptive pills, which is known to be a risk factor of cervical cancer. Alam et al.[17] described that the predominant etiological factors in our country are early marriage, early sexual activity, oral contraceptive pills, multiple preg-

nancies, and first child at a young age, low socio-economic status, and inadequate screening program.

Another well-established risk factor of cervical cancer is multiparity. The study of Misra et al.[18] have pointed out the number of pregnancies as a great risk factor in the development of cervical dysplasia. In this study, 8 cases of carcinoma cervix were encountered in women with more than 4 children and precancerous lesions in women of younger age group with average 2 children. It appears that it is essential to provide all women (regardless of their age) with 2 or more children with cytologic screening to yield meaningful results.[16]

It is to be noted that all the 550 patients except one, included in this study had no previous history of Pap smear screening for cervical cancer. Based on our findings, it was felt that women of high parity irrespective of the age (with three or more children) and older women beyond 40 years of age should be screened at least once in their lifetime to detect any premalignant or malignant lesion in the cervix. Misra et al.[18] have also stressed the need of a single lifetime screening as a feasible approach for control of cervical cancer in developing countries.

The sensitivity of Pap smear in present study was 89.01%. The sensitivity of this study is higher than the studies of India[19] (36–72%) and Costa Rica[20] (77.7%). The higher sensitivity in our study is because women selected for this study belonged to a hospital population, which does not represent the general population. The specificity of Pap smear in present study was 92.3%. This finding is almost similar to the findings of India (88.98%) and Costa Rica (94.2%).

The result of the present study was compared with other studies done in our country. Hussain et al.[14] studied Pap smear of 200 patients in our country, and found 54.3% sensitivity and 94.5% specificity. Present study had 92.3% specificity, which was nearer to Hussain et al. but lower than Israt et al.,[11] which was 100%. This may be explained by the fact that in the study of Israt et al., they initially found 99 negative Pap smear cases (negative for intraepithelial lesion and malignancy) from a total of 117 cases. These 117 cases, when subjected to colposcopy, 75 cases were detected as negative for intraepithelial lesions and malignancy, while the rest of 42 cases were positive. Histopathologic examination was done only on positive 42 cases. The initial 75 colposcopically negative cases were not subjected to histopathology, regardless of the result obtained via Pap smear. There is ample possibility that among those 75 colposcopically negative cases, there may have been Pap smear positive cases, which, if subjected to biopsy, could have increased the number of false positive cases.

On the contrary, sensitivity of this study was found to be 89.01%, which was higher than the study of both Hussain et al. (54.3%) and Israt et al. (64%), respectively.

In this study false negative result of Pap smear was 10.98% and was limited in the diagnosis of cervical intraepithelial lesions. No false negative result was found in case of cervical cancer. It was much lower than the study of Israt et al.,[11] where false negative result of Pap test was 36%. False negative result may be due to failure in obtaining adequate material as with advancing of age the junction tends to move up into the endocervical canal and at the time of menopause, the junction is usually located within the endocervical canal. The other causes might be air-drying artifacts, cytological under grading and missing of low grade cervical intraepithelial lesions in only few cells during cytological examination.

CONCLUSION

Although Pap smear has many drawbacks, yet it can be carried out safely in a tertiary hospital in our country, where necessary infrastructure, cytotechnologists, and cytopathologists are available. In this regard, it can be suggested that in women, between 41 and 50 years and above should be given priority, as they are prone to develop premalignant lesions and cervical cancer more than the younger age group.

In cases where Pap smear test is positive, histopathology may be combined with Pap test to increase the sensitivity test and yield better result.

The false-negative rate of conventional Pap test can be reduced by skillful sampling and interpretation.

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