Original article

Cervical Pap smear examination - A cost-effective screening test to reduce the mortality of cervical cancer.

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Abstract:

An organized cervical cancer screening programme on a national level in Bangladesh can reduce mortality from cervical cancer. The Papannicolaou (PAP) smear is a highly effective screening test for the detection of cervical neoplastic changes. The success of the test has resulted in unrealistic expectations of the accuracy of the test by both referring medical practitioners and the public. This study is a comparison between interpretation based on cytopathological and histopathological tests and was undertaken to estimate the accuracy rate of the papanicolaou (PAP) test done among 2300 patients in two tertiary private medical college and hospital in the cytopathology and histopathology department during the period from June 2010 to July 2011 and women who have undergone for pap smear cytology test along with biopsy were selected. Detail history with clinical examination was performed and the findings were correlated. The reporting of PAP smears is done according to Bethesda 2001 classification and the CIN (cervical intraepithelial neoplasia) *grading* is used for histopathology reporting. The overall accuracy rate of the test was 90% (4 false negatives out of 40 positively selected patients). Considering the histopathology reports as the gold standard, PAP smear test is also found to be equally sensitive. But it is advised to perform biopsy (diagnostic test) if any abnormalities are detected in PAP smear cytology(screening test).

Introduction :

Worldwide, approximately 500,000 new cases of cervical cancer and 274,000 deaths are attributable to cervical cancer yearly, making cervical cancer the second most common cause of death from cancer in women.[1] Fortunately, the incidence of cervical cancer has decreased by more than 50% in the past 30 years, largely due to the increasing use of cervical cancer screening with cervical cytology.[2] Although worldwide cervical cancer rates have decreased dramatically with the increase in screening efforts, incidence and prevalence in developing countries remains high due to lack of screening programs, with approximately 80% of all cervical cancer deaths occurring in the developing world.[1] The Papanicolaou test, also known as the *Pap test* or the *Pap smear*, was developed in the 1940s by Georgios Papanikolaou.

It involves exfoliating cells from the transformation zone of the cervix to enable examination of these cells microscopically for detection of cancerous or precancerous lesions.[2]

Evidence shows that approximately 99-100% of cervical cancers are attributable to infection by high-risk types of the human papillomavirus(HPV) and may be transmitted easily via sexual intercourse or direct contact.[3,4] More than 100 types of HPV exist, 12 of which can involve the anogenital region and are considered "high risk" or oncogenic in nature. These include HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. Of these, HPV 16 is responsible for the largest number of CIN 3 and cervical cancer cases [3] Although HPV is a necessary factor in the development of cervical dysplasia that can eventually lead to cervical cancer, most women infected

with HPV will not develop cervical dysplasia.[5] Whether an HPV infection will progress relates to the persistence of the infection and also possibly to the immune response and smoking status of the woman.[6]

Abnormal cervical cytology is very common in young women, and most abnormal cytology resolves without treatment in adolescents. In addition, women under the age of 21 account for only 0.1% of all cervical cancers.[2]

Both the U.S. Preventive Services Task Force (**USPSTF**) and the American Cancer Society (**ACS**) issued age-appropriate screening strategies for cytology (Pap smears) for cervical cancer screening in 2012 (see Table).[7,8]

Table. Summary of 2012 Screening Guidelines from the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology

Parameters	ACS Recommendations
Age to start screening	Begin screening with cytology at 21 years old, regardless of sexual history
Screening interval age 21–29	Screen with cytology every 3 years.
Screening interval age 30-65	Screen with cytology and every 5 years.
Age to stop screening	Age 65, if the woman has adequate negative prior screening and is not otherwise at high risk for cervical cancer
Screening after hysterectomy	Not indicated for women without a cervix and without a history of a high-grade precancerous lesion (eg, CIN II or CIN III) in the past 20 years or cervical cancer ever.
HPV-vaccinated women	Screen according to the same recommendations as for unvaccinated women

These guidelines do not address special populations (eg, women with a history of cervical cancer, women who were exposed in utero to diethylstilbestrol, women who are immunocompromised) who may require more intensive or alternative screening.

Results from cervical cytology specimens are reported according to the *2001 Bethesda System Classification*, as listed below.[9]

Negative for intraepithelial lesion or malignancy (NIL or M)

Reactive cellular changes associated with inflammation, radiation and intrauterine contraceptive device

Epithelial cell abnormality

Squamous cell
- Atypical squamous cells (ASC) of undetermined significance (**ASC-US**) or atypical squamous cells that cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesions (**LSIL**), includes human papillomavirus (HPV), mild dysplasia, and CIN 1
- High-grade squamous intraepithelial lesions (**HSIL**), includes moderate to severe dysplasia, carcinoma in situ, CIN 2, and CIN 3(**Fig-iii**).
- Squamous cell carcinoma(**Fig-iv**)

Glandular cell
- Atypical glandular cells (AGC), specify endocervical, endometrial, or not otherwise specified (NOS)
- Atypical endocervical cells, favor neoplastic, specify endocervical or NOS
- Endocervical adenocarcinoma in situ (AIS)
- Adenocarcinoma

Other malignant neoplasm
- Endometrial cells in a woman 40 years of age or older.

The histological classification of cervical precancerous lesion has evolved from time and the terms from the different classification systems are currently used interchangeably.The precancerous lesion,cervical intraepithelial neoplasia or CIN is defined as a spectrum of intraepithelial cellular atypia of mild degree at the base of the cervical squamous epithelium or squamous like metaplastic columnar epithelium of cervix to severe degree involving the full thickness of the epithelial lining.[10] The original terminology of dysplasia and carcinoma in situ(WHO) classification was replaced by the cervical intraepithelial neoplasia (CIN terminology) proposed by Richart,[11] in order to emphasise a continuum of disease. Recently the Bethesda system of terminology has been introduced to sub-classify the lesions into grades: high grade and low grade Squamous Intraepithelial Lesion(SIL).[12] The terminologies are compared in the table below:

WHO system (Dysplasia terminology)	CIN terminology	Bethesda terminology
Mild dysplasia	CIN I	Low grade SIL
Moderate dysplasia	CIN II	High grade SIL
Severe dysplasia	CIN III	High grade SIL
Carcinoma in situ	CIN III	High grade SIL

Cytological (Left hand side) and Histological (Right hand side) correlation of spectrum of cervical intraepithelial neoplasia and carcinoma are given in the picture below (Fig 1-IV) :
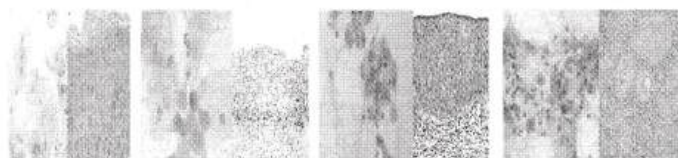

Fig-1   Fig-II: Fig-III: Fig-iv

FIG-1: Normal squamous epithelium for comparison. FIG-II:Low grade dysplasia (CIN1)and Mild squamous dysplasia (CIN1, LGSIL). FIG-III:High grade dysplasia(CIN3) and Severe squamous dysplasia(CIN3,HSIL).FIG IV:Squamous cell carcinoma.

Squamous cell carcinoma is the most common histological classification of cervical cancer, accounting for approximately 80% of cases. On histological examination, squamous cell carcinoma are composed of nests of malignant squamous epithelium, either keratinizing or non-keratinizing, invading the underlying cervical stroma[13]

Materials And Methods :

This cross-sectional study was carried out on 2300 women with clinically symptomatic cervix attending the cytopathology department at two private tertiary medical college hospital of Dhaka, during the period from June 2010 to July 2011.They have all undergone for pap smear cytology test. Cervical biopsy was done on the basis of positive PAP smear and or clinically suspicious for cervical malignancy. Patients who have epithelial abnormality are considered as positive PAP smear. 40 patients who have positive PAP smear cytology test and or clinically suspicious for malignancy along with biopsy, were selected. Among 40 patients, 36 have positive PAP smear findings, other 4 patients have clinically suspicious cervix for malignancy but negative PAP smear findings. Clinical examination and detail history like age, parity, socio-economic status and chief complaints was noted. The age range of the subjects varied from 20 to 69 years with Parity Between 0 To >5.

Inclusion Ctriteria :

1.Patients having positive PAP smear cytology findings along with cervical biopsy.

2.Clinically suspicious for malignancy but NIL or M (negative for intraepithelial lesion or malignancy) along with cervical biopsy.

Exclusion Ctriteria

Patients having normal PAP smear findings or negative for intraepithelial lesion and malignancy(NIL or M).

The PAP smear cytological examination was carried out by the conventional papanicolaou method. The samples for cervical smears were collected from squamocolumnar junction of cervix with the help of Ayer's spatula and stained by PAP stain.Correlation of cytological findings with histological counterpart was done, considering histology as the gold standard. The reporting of PAP smears was done according to *Bethesda 2001 classification* and the CIN (cervical intraepithelial neoplasia) *grading* is used for histopathological changes.The technique of biopsy included cervical punch biopsy.

Results :

Out of 2300 patients having PAP smear test,40 patients who have PAP smear test along with cervical biopsy were studied. Among those 40 patients having PAP smear examination 4 (10%) patients were NIL or M, 23(57.5%) were LSIL, 10(25%) were HSIL and 3(7.5%) were carcinoma. Biopsy was done in 4 parients of NIL or M due to clinically suspicious for positive epithelial lesion.There was no patient of ASCUS in this study.

In the 40 biopsied patients,26(65%) were CIN I , 5(12.5%) patients were CIN II, 7(17.5%) were CIN III and 2(5%) were carcinoma on histology.

On correlation of PAP smear cytology results with histopathology, 91.30% (21 out of 23 patients) of LSIL (CIN) category correlate with histological diagnosis. The correlation in HSIL (CIN II+CIN III) was 80% (3+5=8 out of 10 patients) and 66.66% (2 out of 3 patients) in the carcinoma category.(table-1). 4 patients of NSL or M in PAP cytology result revealed, CIN I as 3 patients and 1 patient as CIN III. These 4 patients gave false negative result (Table-I).

Table-1 shows the comparison between cytology and histology in 40 patients:

PAP smear diagnosis	Histological diagnosis				
	CIN I	CIN II	CIN III	Carcinoma	Total
NIL or M	3	1	-	-	4
LSIL	21	1	1	-	23
HSIL	2	3	5	0	10
Carcinoma	-	-	1	2	3
Total	26	5	7	2	40

The majority of patients (15+16=30) 77.5% were in the 30-49 years age group and majority (80%) are of intraepithelial lesion. Carcinoma is found in late age group (table-II). 52.5% patients were below 19 years of age at first coitus and another 47.5% from 20-29 years of age(table-II).

The majority of patients, 85 % are multiparous(table-II).

Table-II: Distribution of 40 cases of precancerous and cancerous lesion by Age, Age at first coitus and Parity:

Age (Years)	CIN I	CIN II	CIN III	Carcinoma	Total	%
20 – 29	5	-	-	1	6	12.5
30 – 39	12	2	1	-	15	37.5
40 – 49	8	3	5	-	16	40
50 – 59	-	-	1	1	2	5
60 – 69	1	-	-	-	1	5
Total	26	5	7	2	40	100
Age at 1st coitus						
15 – 19	11	3	4	1	21	52.5
20 – 24	10	1	3	-	14	35
25 – 29	5	1	-	-	4	10
>29	-	-	-	1	1	2.5
Parity						
Nulliparous					2	5
1 – 5					34	85
>5					4	10

P/V discharge is found to be the commonest complaints in different lesions of the cervix, however p/v bleeding in found to be more specific for cervical carcinoma. Unhealthy cervix with PV bleeding and discharge are found to be more common in advance lesions, however tenderness and dysuria are found to be associated with in all type of lesion (Table-III).

Table III: Correlation of PAP smear findings with clinical finding:

PAP smear diagnosis	Clinical findings				
	Lower abdominal tenderness	P/V bleeding	P/V discharge	Unhealthy cervix	Dysuria
NSILor M	4/4	4/4	4/4	4/4	4/4
LSIL	20/21	19/23	18/23	20/23	15/23
HSIL	8/10	9/10	8/10	10/10	5/10
Carcinoma	3/3	3/3	1/3	3/3	0/3

The results of the PAP smear cytology compared with histological diagnosis incurred 4 false negative results giving an accuracy rate of 90%(36 out of 40 biopsied patients).

Considering the histopathology reports as the gold standard, PAP smear test is also found to be equally sensitive. But it is advised to perform biopsy if any abnormalities are detected in PAP smear because technical errors like sampling error was found to be the most common cause of false negative reports.

Discussion :
The accuracy of pap smear cytology as method of diagnosis of cervical cancer is very good in this study. Measured against histology as a gold standard, an accuracy rate of 90 % was obtained on cytology, which is nearly similar to the study of Divya H (83% accuracy).[15] and Vaishali J.(81% accuracy).[16] It is a safe, easily carried out and relatively cheap procedure with a high pick-up rate.

The abnormal PAP smears were seen mainly among the sexually active age group and multiparous.[3,4] In a study done by Pradhan P [14],the abnormal smears were seen mainly among age group of 21-40 years and carcinoma was also found mainly among that age group. In our study, abnormal PAP smear was among 20-59 years and carcinoma was found mainly among the age group 20-59 years as well. About 85% patients are multiparous.

The most common presentation with cervical lesion in order of frequency are irregular vaginal bleeding, whitish discharge per vagina, bleeding/pain on coitus, cachexia, lower abdominal pain, dysuria, painful defecation and anorexia. In our study, P/V discharge and lower abdominal pain was found to be the commonest complaints in different lesions of the cervix, however pain and P/V bleeding were found to be more specific for cervical carcinoma. Pradhan P [15] also found the similar findings.

Conclusion :
PAP smear screening test is found to be nearly equally sensitive to histopathological examination for early detection of different cervical lesions. However, there is no cervical cancer screening programme on a national level in Bangladesh.PAP smear cytology is available and is being carried in an uncoordinated manner. Cases are found purely by chance when these women attend the Gynaecology department and referred to cytopathology department for PAP smear examination. Women at risk are therefore not routinely screened and thus has contributed to late diagnosis and poor results of treatment. It is now felt that an organized screening programme, aimed at the entire female population in a developing country like Bangladesh, should significantly reduce the mortality of cervical cancer.

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