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Cytohistological correlation and accuracy of the pap smear test in diagnosis of cervical lesions: a hospital based cross-sectional study from Odisha, India

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Information about the article

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Abstract

Background

Cervical carcinoma is one of the most common causes of mortality among women. Early detection can be done by Papanicolaou (Pap) smear test - a simplest, safe, cost effective and non invasive procedure. The main objective of this study was to categorize Pap smears for cytohistological examination as well as clinically correlate to analyze sensitivity, specificity and positive predictive value of Pap smear.

Methods

In this prospective study 417 Pap smears performed, cytohistological correlation was done in 104 cases because patients had undergone both Pap smear and cervical biopsy. Detailed history was taken and clinical examination was done. Pap smear sample was collected from cervix and reporting was made according to Bethesda 2001 classification. Cytological findings were correlated with histopathology.

Results

Overall concordance rate was 60.7%. Concordance rate for malignancy was 100%, for inflammatory lesions 70.8% and for cervical intraepithelial neoplasia (CIN) 33.3%. Common age group presented for screening was40-50 years. Commonest clinical presentation was bleeding per vaginum.

Conclusion

The study provides good cyto-histopathology correlation in detecting high grade lesions and malignancy. Although Pap smear sensitivity was low but can be increased by adequate sampling and avoiding technical errors. Bethesda system is strongly recommended for adequacy of sampling to minimize inconsistency. Regular screening should be advised to the patients for the early detection of cervical carcinoma.

Keywords

Biopsy, cervical cancer, cervical intraepithelial neoplasia, cytohistology, Pap smear

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Background

Cervical cancer in women is the second most common cancer worldwide next to breast cancer. This is considered as a vital reproductive health problem in women and a prime cause of mortality among young women [1]. Global report published by WHO in 2014, shows almost 266,000 women died from cancer of the cervix in the year 2012 [2].Worldwide the Impact of cervical cancer on women's life is indubitable [1].

Especially developing countries are the worst hit by this preventable disease which is considered as a significant public health concern. According to a report, more than 83% of 493,000 new cases of cervical cancer and higher mortality rate are seen in developing countries [3]. The main reason is lack of effective screening programs which can detect and treat preliminary stage of this life threatening disease [4].

According to the China Cancer Registration Annual Report 2004, cervical cancer was in the 8th position for the cause of malignancy among women, with a crude incidence rate of 8.55 per 100,000 women [5].A report by Ferlay *et al*. showed that cervical cancer is a major health challenge in Bangladesh and it constitutes 17,686 new cases each year, an estimated 10,364 deaths annually [6].Among Pakistani women, cervical cancer is the fourth most common type of cancer; with an age standardized risk (ASR) of 7.5 per 100,000 women and the incidence of disease burden is likely to be on the rise [7].A study in Malaysia showed that cervical cancer is the third most common cancer among women, as an estimated 8.4% of all women cancers [8].According to a survey in Korea, cervical cancer was accounted for 9.8% of all new cancer cases in 2002, with a total number of 4,500 invasive cervical cancer (ICC) cases and 3,000 carcinoma in situ (CIS) cases [9, 10]. A report on human papilloma virus (HPV) and cancer shows that every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 die from the disease. A large number of females (432.2 million) aged 15 years and older are the most vulnerable. Among all the South Asian countries, India has the highest age standardized incidence of cervical cancer at 22, compared to 19.2 in Bangladesh, 13 in Sri Lanka, and 2.8 in Iran. So, this is a crucial time to understand the epidemiological pattern and diagnoseproperly cervical cancer cases in India [11].

Pap test is named after George Papanicolaou, who introduced it as a cervical screening test in 1943. This is a very simple, quick noninvasive, painless procedure. Clinician collects cellular sample from in and around the cervix by a wooden scraper. Afterwards the sample is placed on a glass slide and rinsed in liquid fixative and finally stained for cytological examination [12, 13].

The major advantage of Pap test is the detection of cervical cancer at an early stage and its cost-effectiveness. Developed countries widely use it which minimized the incidence and mortality of this disease at least 70%. Well organized screening programmes, accessibility to treatment, reduction in parity, and other risk factors also contributed to achieve this goal [13].As cervical cancer has a pre malignant phase, which could extend for several years, so repeated Pap tests are strongly recommended to reduce the impact of individual false negative rate.

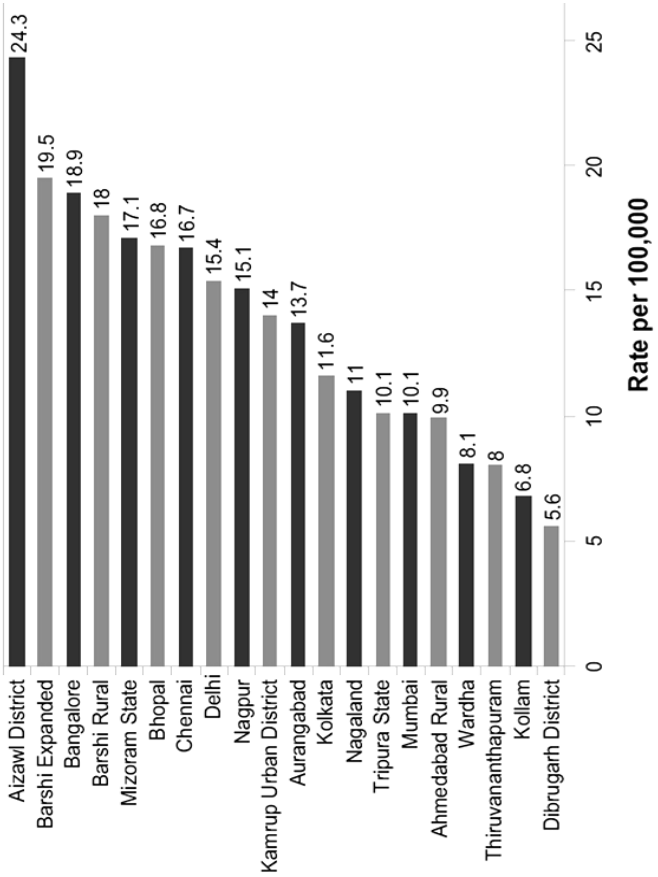

Figure - 1 Age adjusted incidence rates of cervix uteri-females (rate per 100,000) in the various populations of India based cancer registries [14].

Although there are different research works carried out on cervical cancer from different parts of India, but no peer reviewed literatures are available from Rourkela, Odisha state. The 2010 age-adjusted rate for cervical cancer in the various registries are indicated in Figure 1 [14].

This study was undertaken to facilitate early diagnosis of cervical cancer and to determine the accuracy of Pap test by correlating with histopathology, as well as clinically compare to evaluate sensitivity, specificity and positive predictive value of Pap smear.

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Material and Methods

Study Period

This study was conducted in two years period, September 2010 to September 2012.

Study design and the participants

Out of 417 Pap smears performed104 cases underwent both Pap test as well as biopsy and were included in this study. Experimentation was done in Ispat General Hospital, Rourkela, Odisha, India.

Experimentation and data collection

At the beginning of the experimentation, it was confirmed that patient was not menstruating, passed 10-20 days of her menstrual cycle, and had not douched or used tampons or vaginal medication in past 24 hours. Patients were placed in the lithotomy position and the procedure was done by the study investigator Dr. Reena Naik, in assistance of a well trained and experienced nurse/midwife. An unlubricated sterile Cusco's bivalve speculum was introduced to observe the cervix, in ample light condition. Then with the help of Endocervical brush/Ayre's spatula, transformation zone was scraped by rotating the spatula in clock wise direction in squamo columnar junction, and endocervical smear were made on a clean slide and fixed with 95% ethyl alcohol for at least 15 minutes. Afterwards the smear was send to laboratory for conventional Papanicolaou staining, in which tinctorial dyes and acids are selectively retained by cells. Unstained cells are invisible under light microscope [15, 16].The Pap smears were interpreted in the Department of Pathology, by two pathologists according to Bethesda 2001 classification [17]and for histology WHO classification was used[18].Once the cytology specimen was collected, the cervix was painted with a cotton wool soaked in 3–5% VIA and examined after 1 min for aceto-white reaction. Any suspicious or visible lesions were then biopsied. Some patients with abnormal positive Pap smear results were also called back for tissue biopsy. These patients were referred for proper follow up and management in the gynaecological clinic.

Inclusion criteria

Patients with chief complaints of backache, hypogastric pain, pain during sexual intercourse, postcoital bleeding, discharge from vagina, were included in the study for Pap screening.

Exclusion criteria

Patients who refused to participate; patients having vaginal bleeding other than postcoital and postmenopausal were excluded. Patients with abnormal result from previous screening, those with any visible mass/lesions before application of VIA on the cervix were not considered. Patients with metastatic disease, double primary cancers, and other comorbid conditions such as diabetes, hypertension, ischemia, tuberculosis, autoimmune disorder were excluded for biasness.

Ethical committee approval

Individual consent was obtained from the participants before the smear was taken. Approval for the study was obtained from the review board of ethical committee of the Institution (Reference number - 40/dated 28-02-11). The present research was conducted according to the declaration of Helsinki (Latest version).

Sample size calculation

Jain *et al*., 2012 done a study and it showed sensitivity of the pap smear test was 78%, with Precision 10%, Desired confidence level (%)= 95, the no. of diseased subjects needed for the current study was 66[19].

Outcome variable

Presence of abdominal pain, bleeding P/V, P/V discharge, weight loss, pelvic organ prolapse, vaginal burning and itching, inflammation, atypical squamous cell of undetermined significance (ASCUS), low grade squamous intraepithelial neoplasia (LSIL), high grade squamous intraepithelial neoplasia (HSIL), carcinoma were set up as outcome variable.

Explanatory variables

The demographic factors age, caste, religion, *etc*. were considered as explanatory variables.

Data management and statistical analysis

Data analysis and interpretation was done by descriptive statistics. T test was performed to obtain the statistical significance between the variables. Statistical Package for Social Science (SPSS) software was used (Licensed version 16).

Results

Table - 1 Cytological diagnostic categories (n=104)n(%)	
Normal	28(26.9)
Inflammation	56(53.8)
ASCUS	3(2.8)
LSIL	9(8.6)
HSIL	2(1.9)
cancer	6(5.8)

Table - 1 shows the cytological diagnostic categories. Inflammatory lesion was the mostly diagnosed condition which covered more than half of the cases (53.8%). In ASCUS category only 3cases were found. LSIL 8.6%, HSIL 1.9% and malignancy in 5.8% cases were observed.

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Table - 2 Correlation of Pap smear finding with clinical finding (n=104)

Sign/ Symptoms	Normal (29)	Inflammation (55)	ASCUS (3)	LSIL (9)	HSIL (2)	Carcinoma (6)
Bleeding P/V	20(68)	34(61)	2(66)	5(55)	2(100)	5(83)
P/V discharge	5(17)	12(21)	1(33)	1(11)	-	3(50)
Abdominal pain	7(24)	3(5)	-	1(11)	2(100)	3(50)
Weight loss	1(3)	17(30)	1(33)	4(44)	1(50)	4(66)
Pelvic organ prolapse	2(6)	6(10)	2(66)	-	1(50)	-
Vaginal burning and itching	-	3(5)	-	2(22)	-	-

P/V – per vaginal

Clinico-cytological correlation is depicted in table 2.Patients came to OPD with most common complaint of bleeding per vaginum. All the patients of high grade lesion had bleeding per vaginum and pain in lower abdomen as major symptoms.

Table-3 Cytological finding in different age groups (n=104)

Age (Years)	Normal	Inflammation	ASCUS	LSIL	HSIL	Carcinoma	Total
21-30	01	01	-	-	-	-	02
31-40	08	14	01	01	-	-	24
41-50	16	33	01	06	01	01	58
51-60	02	04	01	01	01	03	12
61-70	01	03	-	01	-	02	07
>71	-	01	-	-	-	-	01
Total	28	56	03	09	02	06	104

Cytological finding according to age groups is shown in table 3. Mostly women in 41-50 years age group underwent Pap smear testing. The vast majority for malignancy was 51-60years and intraepithelial lesion was observed mostly in 41-50years of age group.

Table - 4 Cyto-Histological Correlation (n=102)

Histological / Cytological	Normal	Chronic cervicitis	CIN-I	CIN-II & III	Carcinoma	Total
Normal	18	10	-	-	-	28
Inflammation	15	34	06	-	-	55
ASCUS	-	02	01	-	-	03
LSIL	04	01	03	-	-	08
HSIL	-	01	-	01	-	02
Carcinoma	-	-	-	-	06	06
Total	37	48	10	01	06	102

CIN –cervical intraepithelial neoplasia

Cyto-histological correlation shown in table -4. According to Bethesda 2001 classification, LSIL cytology diagnostic category histologically equivalent to HPV/mild dysplasia/CIN 1. Similarly, HSIL category histologically equivalent to moderate and severe dysplasia, CIN 2 and CIN 3, CIS and with features suspicious for invasion.

Concordance rate for different lesions was calculated and given below:

Histological diagnosis	Concordance rate
Normal	(48.6%),
Chronic cervicitis (figure 2)	(70.8%),
CIN-I (figure 3)	(33.3%),
CIN-II and III (figure 4)	(100%),
Malignancy (figure 5)	(100%).

Table - 5 Statistical values of Pap smear for different grades of disease (%)

Particulars	Normal	Inflammatory	LSIL	HSIL	Carcinoma
Sensitivity	48.6	70.8	30	100	100
Specificity	84.6	71.1	94.5	99	100
PPV	64.2	61.8	37.5	50	100
NPV	74.3	70.2	92.5	100	100
Diagnostic Accuracy	71.5	65.6	88.2	99	100
P value	0.0133*				

*P<0.05 statistically significant
PPV – positive predictive value, NPV - negative predictive value

Different statistical values of Pap-smear for different grades of diseases represented in table - 5.Diagnostic accuracy was almost 100% for HSIL and malignancy except for PPV in HSIL which was 50%. Sensitivity and specificity was also moderately good for inflammatory lesions. Pap smear was least sensitive in diagnosing LSIL (30%), but specificity (94.5%) and diagnostic accuracy was good (88.2%). Overall statistical value of Pap smear in diagnosing cervical dysplasia, sensitivity, specificity, PPV, NPV and diagnostic accuracy were 79.4%,58.3%,86.1%,46.6% and74.5% respectively. Sensitivity and Diagnostic accuracy was moderately good, PPV was good, but NPV and specificity was quite low.

Discussion

Pap test has dramatically declined in the incidence of cervical cancer, a major health burden especially in underdeveloped nations such as Latin America and Southern Asia. As 35-55 years age group is the most vulnerable, so screening frequency should be increased based on resourcesto 'once every 10 years' and then 'once every 5 years'.

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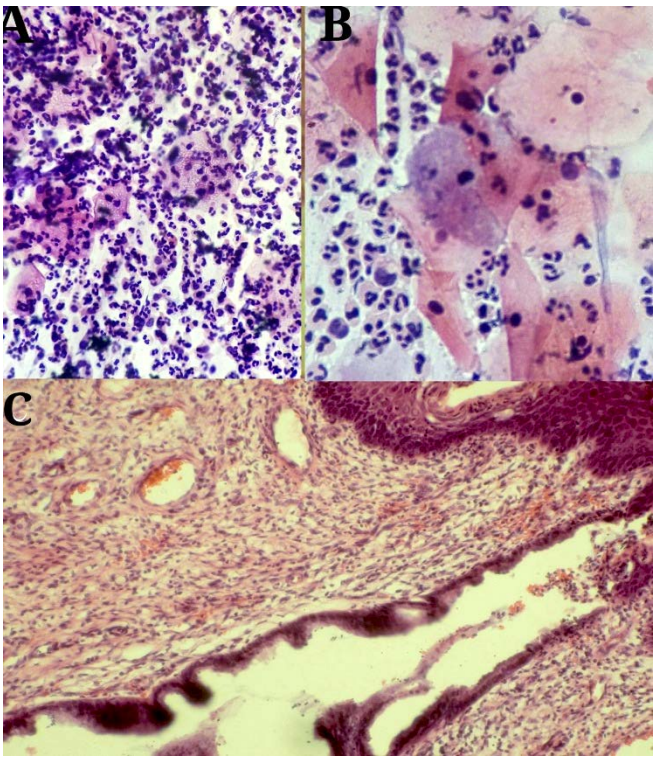

Figure 2- Pap smearA) inflammation (10X), B) clue cell(40X) Biopsy C) chronic cervicitis (H&EX20)

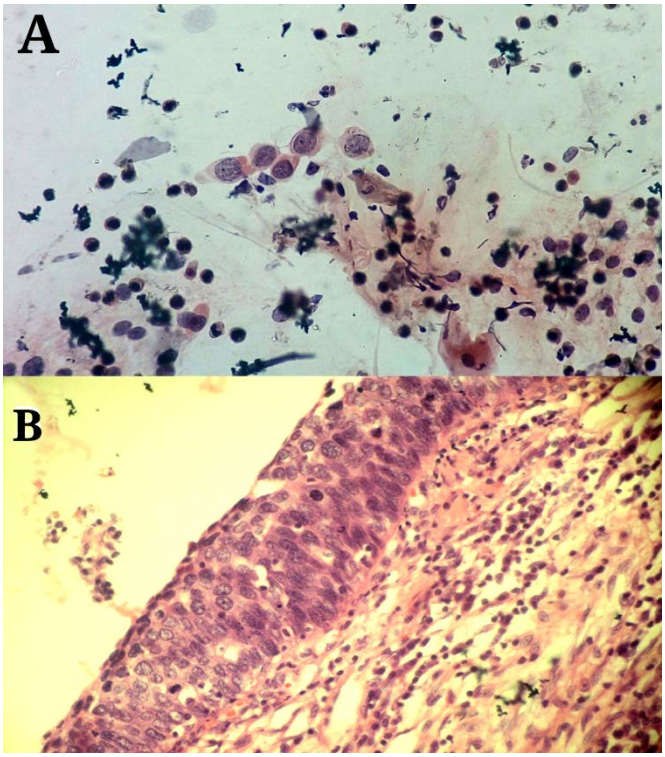

Figure 4 - Pap smear A) HSIL (40X) Biopsy B) CIN - III (H&EX20)

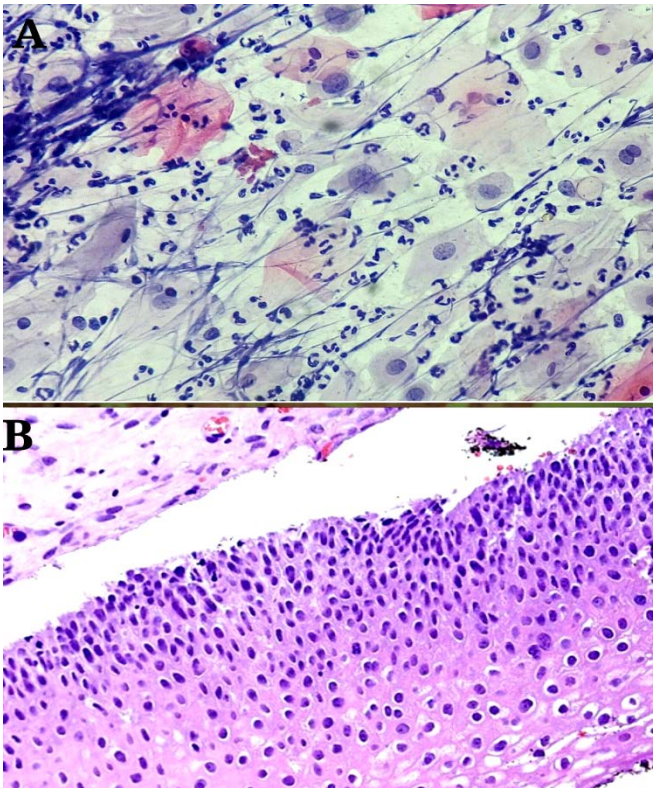

Figure 3 - Pap smear A) LSIL (40X) Biopsy B) CIN-I (20X)

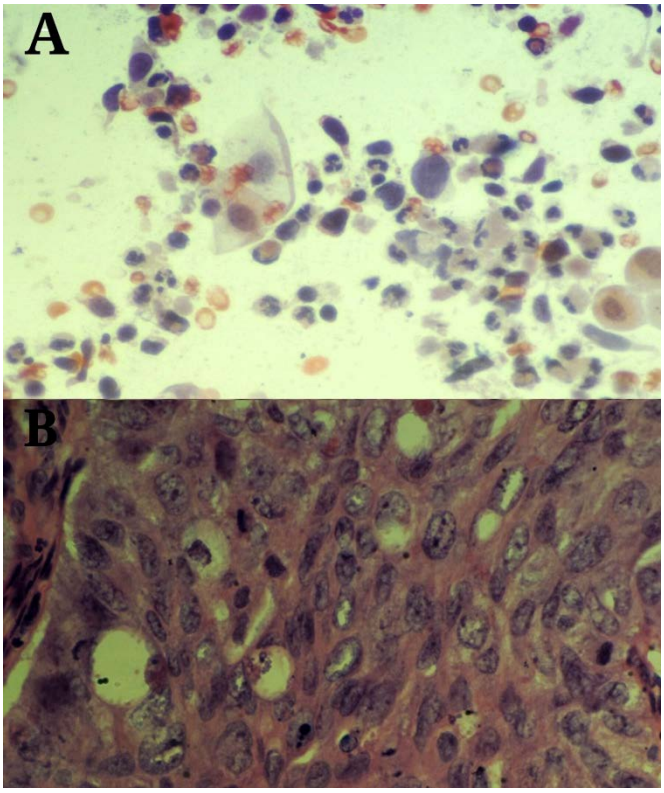

Figure 5 - Pap smear A) SCC (40X) Biopsy B) SCC (H&EX40)

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In developing countries several attempts were made and targeted a smaller group, by camp approach, hospital-based screening, high-risk screening *etc*. The reason is difficulties of launching population-based programs.

Cytological and clinical findings in different age group

Most common age for carcinoma was 50-70 years and for dysplasia was 40-60 years. As the age progresses there is an increased incidence of dysplasia converting to carcinoma. The most common clinical presentation in our study was irregular bleeding P/V. We found most of the patients with post menopausal bleeding had frank carcinoma (5 out of 6) which was similar to another study by Lavanya *et al*.[20]

Cyto-Histological Correlation

In our study infected patients were treated with antibiotics then repeat Pap smear was done and bleeding P/V patients were directly recommended for it. The rates of concordance for individual lesion were calculated. The overall concordance rate of the study was 62(60.7%). The discordance case being 40(39.2%). The overall concordance rate is comparable with earlier findings[21].Few earlier researchers Nawaz*et al*. [22], Yeoh *et al*.[23], Rasbridge *et al.*[24]and Jain *et al.* [19] had reported concordance rate of 74%, 52%, 81.2% and 70% respectively. Concordance rate for squamous cell carcinoma in this study was 100% as compared to some previous reports (100%, 97.33%, 60% and 83.6%)[21-23,19].This could be due to the fact that most patients in developing countries come to the hospital in advanced stages.

Discrepancies & false negative rate

Jain *et al.* reported that discordance cases were under diagnosed or over diagnosed on cytology due to less cellularity with hemorrhagic background, air dying and fixation artifacts [19]. Another study showed that a main component of false negative rate appeared to be sampling and preparation artifacts [23].So in order to decrease false negative rate, it is strongly recommended to repeat the smear at regular intervals. It has also been observed that error rate declined dramatically with 3 consecutive annual smears. Nawaz *et al*. reported that prime factors like air drying, blood or inflammation obscuring the cellularity were main causes for discrepancies [22].Some researchers found interpretative error; sampling error and air drying were the reasons for under diagnosis [25, 26]. The concordance rate for CIN-I in present study was 33.3% corroborates with others[21-23; 19].In this researchit was observed that CIN-I sensitivity was low but can be increased by adequate sampling and avoiding technical faults like drying and fixation artifacts and inflammations.

Table - 6 Comparison of Pap smear values in different studies (%)

Study	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Jain *et al*., 2012[19]	78	26.9	91	11.3	73.2
Saha *et al*., 2005 [21]	76	83.3	86.4	71.4	79.1
Tuon *et al*., 2002[27]	77	-	74	45	-
Bruce *et al*., 1996 [28]	89.4	64.8	88.9	-	-
Present study	79.4	58.3	86.1	46.6	74.5

This study shows significant correlation between Pap smear and cervical histology. This is clear from the findings that the PPV of Pap smear test was highest for malignancy. This was similar to reports by most other workers, where highest PPV (91.8%) was for malignancy. Statistical significance was also observed between cytology and histology [29].

Conclusion

Pap smear is cost effective, non invasive screening test for early detection and management of cervicalcarcinoma. Present research confirmed its excellent sensitivity, specificity and PPV in detecting high grade lesion and carcinoma. Relatively lower CIN sensitivity can be improved by adequate sampling and avoiding technical errors. Bethesda system is strongly recommended for adequacy of sampling to minimize inconsistency. Regular screening should be advised to the patients. Govt. and NGOs can take a prime role by health education, campaigning and promotion about cervical cancer and its screening benefits at an early stage.

Limitations & future scope of the study

This study involved a limited time period of two years, and the sample size was less. Conducting broad spectrum multi-centric studies in future is recommended. Automated liquid-based Pap cytology test was not performed, but it is common practice in developed countries. So future researchers may include this procedure which increases the detection rate for preneoplastic squamous intraepithelial lesions, when compared with the conventional Pap technique.

Abbreviations

Age standardized risk (ASR), atypical squamous cell of undetermined significance (ASCUS), cervical intraepithelial neoplasia (CIN),carcinoma in situ (CIS), high grade squamous intraepithelial neoplasia (HSIL), human papillomavirus (HPV), invasive cervical cancer (ICC), low grade squamous intraepithelial neoplasia (LSIL), negative predictive value (NPV), Papanicolaou (Pap) smear, positive predictive value(PPV),P/V – per vaginal

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Competing interests

Authors declare that they do not have any competing interest.

Authors' contribution

Dr. Reena Naik and Dr. Kishori Moni Panda, designed the study, conducted, interpreted the data, drafted the manuscript, and revised it critically for important intellectual content. Dr. Minj Aruna Mukti, Dr. Rabiratna Panda, Dr. Sanghamitra Satpathi, and Dr. Prativa Kumari Behera conducted the research formulated and analyzed the data. All authors critically revised the manuscript and approved finally for the publication.

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