

# A Study on Effectiveness of Pap Smear in Mass Screening of Premalignant Lesions of Cervix

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## ABSTRACT

**Background and objectives:** A study on the accuracy of Pap smear was conducted in Pantai Hospital, Sungai Petani, Malaysia involving 125 patients from the Department of Obstetrics and Gynaecology. Cervical cancer is a significant health issue for women; being the second most common cancer among women in Malaysia hence early detection of precancerous lesions can prevent progression to cervical carcinoma. The objective of this study was to measure the sensitivity, specificity, positive predictive value, negative predictive value, percentage of false-negative, percentage of false-positive and yield of Pap smear by comparing Pap smear results with colposcopy guided cervical biopsy.

**Materials and methods:** The study was conducted among 125 patients who have undergone both Pap smear and colposcopy-guided cervical biopsy using a cross-sectional study with a purposive sampling method. The data obtained were analyzed statistically.

**Results:** 125 patients participated in this study, giving Pap smear a sensitivity of 38%, specificity of 64%, positive predictive value of 80.85%, negative predictive value of 20.51%, false-positive for intraepithelial lesion or malignancy of 38%, false-negative for intraepithelial lesion or malignancy 62%. Of the total 125 patients studied, 62.4% were indicated to have a cervical biopsy due to clinical suspicion and among them biopsy report was positive for intraepithelial lesion or malignancy in 79.5%.

**Conclusion:** The sensitivity and specificity of Pap smear as a screening tool for precancerous cervical lesions is low. It is therefore inadequate to be used alone as a screening tool. The study also shows that having a high index of clinical suspicion even when the Pap smear results were normal was important in order not to miss a precancerous cervical lesion as early detection can prevent progression to cervical cancer. Hence, a more experienced doctor with a high index of clinical suspicion is vital.

**Keywords:** Biopsy, Cervical cancer, Colposcopy, Pap smear screening, Sensitivity, Specificity.

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## INTRODUCTION

Globally, cervical cancer is the fourth most common cancer among women with an estimated number of new cases to be 528,000 in 2012. It accounts for about 7.5% of deaths among female cancer patients.<sup>1</sup> It is the second most common after breast cancer in Malaysia and has an age-standardized rate of 10.3 per 100,000 among Indians followed by 9.5 per 100,000 among Chinese and 5.3 per 100,000 among Malay.<sup>2</sup>

In developed countries, there had been a large decrease in the incidence and mortality of cervical cancer, attributed to the presence of screening programs for cervical precancerous lesions, and human papillomavirus (HPV) vaccination. In England, incidence of cervical cancer fell from 14 to 16/100,000 in 1970 to mid-1980s, to 9/100,000 in 1995, while cervical cancer mortality had fallen from 11.2/100,000 in 1950, to 3.7/10,000 in 1997.<sup>3</sup> In Finland, Iceland and Sweden, screening was done for over 80% of the population in the 1960s, and cervical cancer incidence dropped by approximately 50% over the next two decades. In the United States, where routine screening (cytology, with or without HPV testing) is done, incidence and mortality of cervical cancer had decreased over the past decades, whereas in countries where cytological screening is not widely available, cervical cancer is still common.<sup>4</sup> In 2007, there were 87,466 cases of cervical cancer in the developed world, as opposed to 473,430 cases in the developing world.<sup>5</sup>

Cervical cancer is preventable because it has a premalignant lesion which can be picked up by various screening methods. Treatment of the premalignant lesions may prevent the progression to cervical cancer. Hence, an effective screening method is very

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important. A screening test is not intended to be a diagnostic test but it is only meant as an initial examination. The main purpose of screening is to find those who are likely to have a disease from a large group of apparently healthy people. Screening can be carried out firstly, by mass screening, whereby a whole population is screened irrespective of their risk of contracting a disease. Secondly, selective screening will be done for those in high risk groups based on epidemiological research. Lastly, multiphasic screening will be done, whereby a combination of two or more screening tests will be used on a large number of people at one time.<sup>6</sup>

In Malaysia, screening tests used for cervical cancer include conventional Pap smear, liquid-based cervical cytology, HPV-DNA

test and visual inspection with acetic acid.<sup>7</sup> The Pap smear is also known as the Papanicolaou test. Regular Pap screenings reduce cervical cancer rates and mortality by up to 80%.<sup>8</sup> It is a simple, quick and painless screening tool used to detect cancerous and precancerous cells in the cervix. By detecting cancerous cells earlier, it is possible to treat the problem at early stages and to avoid complications arising from the disease.<sup>9</sup>

The American Cancer Society has recommended that all women should undergo Pap smear testing at least every 3 years starting from age 21 to 65 years old.<sup>10</sup> A human papilloma virus (HPV) testing is done when a woman reaches the age of 30. If both the Pap smear and HPV test are negative, a regular Pap smear screening will be done every 5 years. For women above 65 years age who have had adequate prior screening and are not otherwise at high risk for cervical cancer, Pap smear testing can be avoided.<sup>11</sup>

After the interpretation of the results according to the Bethesda system the patient will be notified about the condition and the treatment option available.<sup>12</sup> In Malaysia, all women with suspicious looking cervix must be referred for colposcopy regardless of their Pap smear results.<sup>13</sup> Colposcopy is used more as a guide in diagnostic biopsy, rather than used as a screening tool.<sup>14</sup> In a study by Cantor, it was found that colposcopy used alone fared poorly in the screening setting, but performed well in the diagnostic setting.<sup>15</sup> A study by Massad on the evaluation of 939 images by multiple experienced colposcopy revealed that disagreements arise in 99% of the time when a high-grade lesion was used, and that real-time colposcopy had poor interobserver variability.<sup>16</sup>

There had been a broad range of sensitivity reported for Pap test, with a range from 30–87% sensitivity for dysplasia in conventional cytology. A different study reported 68% sensitivity for conventional cytology, and 76% sensitivity for LBC, with 79% specificity for conventional cytology and 86% specificity for LBC.<sup>17</sup> Due to these limitations, some cervical cancers may go undiagnosed in the earlier stage which has a better prognosis.

Thus, this study was conducted to increase our understanding of Pap smear, as well as to contribute to the amount of data available on the accuracy of Pap smear.

## MATERIALS AND METHODS

A descriptive cross-sectional study was carried out using a purposive sampling method which encompassed patients from January 2015 to June 2017 which involved 125 patients and was randomly selected. The study was conducted in the Department of Obstetrics and Gynaecology in Pantai Hospital, Sungai Petani, Kedah, Malaysia. Data were collected from the medical records database of the obstetrics and gynaecology department. The data were taken only if both Pap smear and colposcopy-guided biopsy followed by histopathology was done. Patients who did not meet the criteria were excluded. Since the numbers of respondents were limited, patient symptomology was not included in the study. For each patient, the following information was extracted: age, marital

status, parity, and indication for latest Pap smear, Pap smear results, indication for cervical biopsy and the histopathology report of cervical biopsy.

## Sample Size Determination

Random sampling was done to obtain the study sample. The formula that was used for calculation of the required sample size is:  $n = Z^2 P(1 - P)/d^2$ ,  $n$  = sample size  $Z$  = Z statistic for a level of confidence (1.96 for level confidence of 95%)  $P$  = expected prevalence or proportion (0.2),  $d$  = precision (0.05). Using population correction formula and adding 10% nonresponse rate the sample size was 125. After collection of data, they were checked for completeness and exported to SPSS 22.0 version for further analysis.

## RESULTS

During the two and a half years study period, from January 2015 to June 2017, 125 patients ranging from 23 years old to 70 years old, mean age of 44 year underwent Pap smear and colposcopy guided biopsy.

In this study, Pap smear result showed that among 125 patients, 100 (true positive for intraepithelial lesion or malignancy = 38, false-negative for intraepithelial lesion or malignancy = 62) were biopsy positive for precancerous lesion, 25 (false-positive for intraepithelial lesion or malignancy = 9, true negative for intraepithelial lesion or malignancy = 16) patient were biopsy negative for intraepithelial lesion or malignancy and prior probability was 80% (4.0). The positive test result for intraepithelial lesion or malignancy showed that positive likelihood ratio = 1.06, 95% confidence interval = [0.59, 1.88]; posterior probability (odds) = 81% (4.2), 95% confident interval = [70%, 88%] and (~1 in 1.2 with positive test are biopsy positive). The negative test result for intraepithelial lesion or malignancy showed that negative likelihood ratio: 0.97, 95% confidence interval = [0.70, 1.35]; posterior probability (odds) = 80% (3.0), 95% confident interval: [74%, 84%] and (~1 in 4.9 with negative test are biopsy negative for intraepithelial lesion or malignancy).

The sensitivity of Pap smear was found to be 0.380 (38%), specificity = 0.640 (64%), percentage of false-negative for intraepithelial lesion or malignancy was 62%. Based on the results of Pap smear, 62% of the patients with cervical dysplasia would have been falsely told that their cervix is normal and healthy. Percentage of false-positive for intraepithelial lesion or malignancy was 36% which showed 36% of patients who did not have precancerous cervical lesion tested positive for intraepithelial lesion or malignancy by Pap smear. The positive predictive value was (0.8085) 80.85%. This showed that the probability of the patients who tested positive for intraepithelial lesion or malignancy by Pap smear has 80.85% chance of having precancerous cervical lesion. negative predictive value was (0.2051) 20.51% which showed that the probability of the patients who tested negative for intraepithelial lesion or malignancy by Pap smear did not have precancerous cervical lesion was 20.51% (Table 1).

**Table 1:** Results of Pap smear tests and colposcopically directed cervical biopsies

		Colposcopy guided biopsy result		Total
		Positive ILM	Negative ILM	
Pap smear result	Positive ILM	38	9	47
	Negative ILM	62	16	78
	Total	100	25	125

Positive ILM, positive for intraepithelial lesion or malignancy; negative ILM, negative for intraepithelial lesion or malignancy

**Table 2:** Pap smear results against histopathology results

		HPE results		Total
		Low risk	High risk	
Pap smear results	Positive ILM	15	32	47
	Negative ILM	15	63	78
	Total	30	95	125

Positive ILM, positive for intraepithelial lesion or malignancy; negative ILM, negative for intraepithelial lesion or malignancy

**Table 3:** Results of cervical biopsy against indication for cervical biopsy

Result of cervical biopsy	Indication for cervical biopsy		Total
	Abnormal Pap smear	Clinical suspicion	
Positive ILM	38	62	100
Negative ILM	9	16	25
Total	47	78	125

Histopathology (colposcopy-guided cervical biopsy) results showed that among 125 patients 30 patients (true positive for intraepithelial lesion or malignancy = 15, false-negative for intraepithelial lesion or malignancy = 15) were high risk, 95 (false-positive for intraepithelial lesion or malignancy = 32, true-negative = 63) were low risk. Among 38 Pap smear positive for intraepithelial lesion or malignancy and biopsy positive for intraepithelial lesion or malignancy were only 15 patients were as high risk (CIN 2, CIN 3) and rest 32 patients were low risk (normal and CIN 1) on histopathology results. Whereas of 62 patients as Pap smear negative for intraepithelial lesion or malignancy and biopsy positive for intraepithelial lesion or malignancy only 15 patients were found to be high risk on histopathology results and rest 63 was low risk (Table 2).

Of the total 125 patients studied, 62.4% were indicated to have a cervical biopsy due to clinical suspicion and among them biopsy report was positive for intraepithelial lesion or malignancy in 79.5%. This shows the importance for having a high index of clinical suspicion and not relying alone on abnormal Pap smear results for further management (Table 3).

## DISCUSSION

Multiple researches were done to determine the specificity and sensitivity of different methods of screening when compared to the result of cervical biopsy. One research by Karimi-Zarchi showed that liquid based cytology (LBC) Pap smear was better than conventional Pap smear for early diagnosis of premalignant lesions or cervical cancer in women with abnormal conventional Pap smear. The research also compared conventional Pap smear, LBC Pap smear, and colposcopy to identify any cervical lesions, which gave the following results. First, the sensitivity of colposcopy is superior compared to conventional and LBC Pap smear. Second, specificity of these three procedures revealed no correlation.<sup>18</sup>

A study by Karimi-Zarchi on the three screening methods (conventional Pap smear, LBC and colposcopy) revealed that colposcopy has the highest sensitivity (70.9%), compared to conventional Pap smear (51%) and LBC (55.3%).<sup>18</sup> Another research revealed that colposcopy results were more consistent to the biopsy result.<sup>19</sup>

Another study in Latin America by Syrjänen, which compared conventional Pap smear and LBC in detecting squamous

intraepithelial lesion (SIL), suggested that LBC was superior to conventional Pap smear for detecting intraepithelial lesions.<sup>20</sup>

Based on the analytic findings, it shows that the sensitivity and specificity of Pap smear alone is lower compared to similar studies which have been done before. In comparison to the study which reported 68% sensitivity and 79% specificity for conventional cytology,<sup>17</sup> results from this study are very low which can also be attributed to the small sample size.

The results also showed that most of the precancerous cervical lesions were picked up by indication of clinical suspicion and not by abnormal Pap smear. This clearly shows how important is the role of the doctor having a high index of clinical suspicion, in carrying out the examination.

We must acknowledge several limitations in our study. First of all, the sample size of 125 patients is too small a sample size to be considered significant. Therefore, results from this study may not be applicable to the general population. All of the patient data were taken from the patient's files hence certain pieces of information that would have affected the depth and accuracy of our study were not available. These include the total number of Pap smear done prior to colposcopy guided cervical biopsy and past sexually transmitted diseases.

## CONCLUSION

In conclusion, the sensitivity and specificity of Pap smear as a screening tool for precancerous cervical lesions is low. It is therefore inadequate to be used alone as a screening tool. The study also shows that having a high index of clinical suspicion even when the Pap smear results were normal was important in order not to miss a precancerous cervical lesion as early detection can prevent progression to cervical cancer. Hence, a more experienced doctor with a high index of clinical suspicion is vital.

## DECLARATION

The work reported is the outcome of original research without fabrication, fraud, or plagiarism. Wherever appropriate, I have referred to the sources from where we reviewed literature, as well as images or any other material.

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