



Diagnostic Value of Pap Smear and Colposcopy in Non-benign Cervical Lesions

Manizheh Sayyah-Melli¹, Vahideh Rahmani^{1*}, Elaheh Ouladsahebmadarek¹, Mehri Jafari-Shobeiri¹, Parvin Mostafa Gharabaghi¹, Maryam Nooshin Vahidi¹

Abstract

Objectives: Cervical cancer is a very common and lethal condition; however, owing to longstanding premalignant lesions, it is possible to prevent morbidity and mortality by screening tests. Pap smear, colposcopy, and biopsy are among the main modalities in this regard, however there is no consensus on the diagnostic utility of the first 2 methods. This study sought to examine the diagnostic utility of Pap smear, colposcopy, and cytology in evaluating the non-benign cervical lesions.

Materials and Methods: A cross-sectional study was carried out between 2014 and 2016 in an out-patient setting at Alzahra teaching hospital of Tabriz University of Medical Sciences. After obtaining informed consent, all 315 participants with abnormal Pap test underwent colposcopy and biopsy from the abnormal areas. Cervical biopsy was considered as a gold standard and the diagnostic values of Pap smear and colposcopy were individually compared by calculating sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio.

Results: The mean age of patients was 38.49±10.31 years (17-68 years). On the basis of biopsy findings, non-benign cervical lesions were present in 31 cases (9.8%). Accordingly, the sensitivity, specificity, positive predictive value, negative predictive value, and positive likelihood ratio of Pap smear in revealing non-benign cervical lesions were 77.4%, 69.7%, 21.8%, 95.6%, 70.7%, and 2.55%, and for colposcopy, were 90.3%, 90.9%, 51.9%, 98.9%, 90.8%, and 99.2%, respectively.

Conclusions: Based on our results, the colposcopy is a sensitive and specific method in differentiating benign cervical lesions from non-benign cervical lesions. The accuracy of Pap smear is intermediate in this regard, and the utility is limited. Therefore, this method should not be considered as the main criterion for decision making.

Keywords: Pap smear; Colposcopy; Biopsy; Cervix

Introduction

Cervical cancer is one of the most frequent malignancies of the female genital system and health problems of women around the world. This cancer is the fourth most common cancer in women and the seventh frequent cause of cancer-related mortality. The World Health Organization (WHO) estimates that yearly, about 530 000 women worldwide are identified with cervical cancer and 275 000 women die from the disease (1). However, cervical cancer is a treatable condition, and there is a good chance of cure if the cancer is found and treated in the early stages. Devising and carrying out correct and regular screening plans such as Pap smear and colposcopy and the confirmation of their findings with biopsy and definite histopathological examinations can reduce related morbidity and mortality (2-4).

A critical issue in this regard is that cervical premalignant lesions usually appear for a long time before a full-fledged cancer, providing enough time for screening and preventive measures to be fulfilled (1).

However, there is still no consensus on the diagnostic efficacy of Pap smear and colposcopy in such cases, and

the diagnostic accuracy of these two methods varies significantly in different settings. This heterogeneity is more evident for the Pap smear, and false negative findings, in particular, have been reported to be substantially high in many studies. In contrast, available reports provide a more positive attitude toward colposcopy, suggesting it as a more efficient screening test as compared to Pap smear. The supporting data, however, are still conflicting (5-9).

For instance, despite the presence of a consensus on the necessity of doing colposcopy in the patients with high-grade squamous intraepithelial lesion (HSIL) in Pap smear, in other cases with abnormal Pap smear findings, a required colposcopy has not been confirmed (10).

On the other hand, some investigators have proposed colposcopy and biopsy in suspected cases for constructing a therapeutic plan. However, agreement between cytological findings, colposcopic findings, and histopathological diagnosis remains to be elucidated (11).

New technologies for cervical cancer screening continue to evolve. American Society for Clinical Pathology (ASCP) and the Society of Gynecologic Oncology (SGO) provide a review of the best available evidence regarding



the prevention and early detection of cervical cancer (12).

Based on the WHO guidelines updated in 2013 and American Society for Colposcopy and Cervical Pathology (ASCCP) guideline updated in 2014, management policies may vary in developing countries if all women have not access to perform all modalities. It is worth to notice that guidelines should never be a substitute for clinical judgment (13).

Accordingly and noting the importance of the issue, the present study sought to examine the performance of Pap smear and colposcopy independently in diagnosing cervical non-benign lesions, compared to definite results from biopsy.

Materials and Methods

This study was carried out on married women aged between 16-70 years who had referred to Tabriz Alzahra teaching hospital from December 2014 to January 2016, with abnormal gynecologic complaints other than uterine and ovarian problems. A total of 315 participants were evaluated for cervical pathology. Informed written consents were obtained from the participants. Exclusion criteria were: patients with previous abnormal Pap smear results ($n = 44$), those with a history of cervical colposcopy/biopsy ($n = 12$), pregnant subjects ($n = 6$), and those with a positive history of cervical malignancy and receiving related therapies ($n = 2$).

For this purpose, liquid-based Pap smear technique using a broom device was used for obtaining the samples. The results were interpreted according to the Bethesda protocol.

The need for performing a colposcopy was decided by the attending specialist according to abnormal cervical and Pap test findings. Colposcopy was carried out after using 5% acetic acid on the cervical region by a skilled gynecologist, and all the specifications of the transformation zone were documented. If the full squamous-columnar junction could have been seen, the colposcopy was deemed satisfactory (14).

Biopsies were performed under direct visualization, and histopathologic examinations were done by a skilled pathologist, and reported as malignant and nonmalignant. The result of histopathologic examination was regarded as the golden standard, and Pap smear and colposcopy findings were compared accordingly.

Statistical analyses were performed using SPSS software version 18.0. Kolmogorov-Smirnov test was used to show the normal distribution of data. Sensitivity, specificity, likelihood ratio, and accuracy of Pap smear and colposcopy were determined and reported independently. P value less than 0.05 was considered as the significance level.

Results

A total of 315 patients were examined. The characteristics of the study population are summarized in Table 1 and the results of Pap smear are shown in Table 2.

False positive results in Pap smear were: ASCUS in 40 cases, LSIL in 31 cases, AGUS in 12 cases, and HSIL in 3 cases. The results of colposcopy are shown in Table 3.

Pathologic examinations showed nonmalignant and malignant results in 284 (90.2%) and 31(9.8%) patients, respectively.

Variables indicating diagnostic performance of Pap smear and colposcopy versus pathology results in detecting malignant lesions are set out in Table 4.

Discussion

In this study, the diagnostic values of Pap smear and colposcopy in detecting non-benign cervical lesions were determined employing definite results from histopathologic examinations. Accordingly, variables in association with the diagnostic accuracy of colposcopy indicated its high performance in detecting non-benign cervical lesions; whereas the accuracy of Pap smear was only intermediate. The results showed that positive likelihood ratio of colposcopy [99.2 (96.7-99.8)] increases post-test probability of cervical abnormality and diagnostic accuracy of the colposcopy compared to Pap smear [2.55(1.4 -3.1)] (Table 4).

The importance of such studies relies on a longstanding existence of cervical premalignant lesions prior to

Table 1. The Characteristics of the Studied Patients

Variable	Number of Participants (n=315)	Data
Age (y)		38.49±10.31 (17-68)
Marital status	Married	310 (98.4)
	Widowed/divorced	5 (1.6)
	Housewife	267 (84.9)
	Clerk	17 (5.4)
Occupation	Teacher	9 (2.9)
	Student	8 (2.5)
	Self-employed	6 (1.9)
	Retired	5 (1.6)
	Doctor/pharmacist	3 (1)
	Withdrawal	114 (36.2)
	Condom	53 (16.8)
Contraceptive method	Infertile/no contraception	43 (13.7)
	Oral contraceptives	35 (11.1)
	Female tube ligation	28 (8.9)
	Intrauterine device	22 (7)
	Vasectomy	15 (4.8)
Hysterectomy	5 (1.6)	

Table 2. Pap Smear Results for Study Population

Finding	No. (%)
Normal	205 (65.1)
ASCUS	52 (16.5)
LSIL	33 (10.5)
AGUS	15 (4.8)
HSIL	10 (3.2)

HSIL, High-grade squamous intraepithelial lesion; AGUS, Atypical glandular cells of undetermined significance; LSIL, Low-grade squamous intraepithelial lesion; ASCUS, Atypical cells of undetermined significance

changing into an evident cancerous status which gives sufficient time to enhance the prognosis of such cases considerably by correct and on-time diagnoses. Previous studies have shown that although Pap smear is the most commonly recognized and practical method in detecting cervical lesions, it cannot be used as a reliable guide in clinical decision-making and planning therapeutic approaches (14,15).

In a study by Lonky et al (16) in California, only 17% of cases with high grade dysplasia and 38% of patients with invasive malignancy were recognized using Pap smear and the abnormality was found trivial in 77% of Pap smear results. This study emphasized a poor correlation between Pap smear and cytology findings when a low grade lesion was reported in Pap smear. Accordingly, they proposed that treatments should not be planned on the basis of Pap smear findings only and in suspicious cases, colposcopy is required.

In a study by Cuzick et al (17), the sensitivity and specificity of Pap smear in detecting cervical intraepithelial neoplasia or higher grade lesions were 49%-57% and 96%-97%, respectively.

In a study by Farzaneh et al (18), the sensitivity, specificity, positive predictive value, and negative predictive value of Pap smear in detecting non-benign cervical lesions were 34%, 85%, 76%, and 35%, respectively. In this study, the investigators emphasized that the sensitivity and specificity of Pap smear in Iran is clearly lower than that in more developed countries, and this discrepancy was

related to the exerted inadequate qualitative controls on the process of Pap smear testing including sampling, preparation, and final reporting in this country.

In contrast, in a study by Moy et al (19) in China, the sensitivity and specificity of Pap smear in detecting non-benign cervical lesions were 85% and 91%, respectively, which were considerably higher than that in relevant reports.

Maybe a higher sensitivity of Pap smear in the present work compared to similar reports is the scarcity of menopause cases, because it has been shown that menopause induces atrophic changes in the cervix, reducing the sensitivity of Pap smear testing.

Studies have shown that in many patients with apparently normal Pap smear findings, histopathologic findings indicate normal to intraepithelial lesions (21,22).

The inability of patients in repeating Pap smear every 4-6 months is another disadvantage for this test (18).

The sensitivity, specificity, positive predictive value, and negative predictive value of colposcopy in detecting non-benign cervical lesions was reported 45%-97%, 19%-90%, 50%-90%, and 70%-92%, respectively, in the study of Massad et al (14).

As it is apparent, our results barring the positive predictive value were in the top limits of the reported ranges (Table 4).

In a study by Karimi Zarchi et al (22), the diagnostic accuracy of colposcopy in early diagnosis of cervical cancer in females with ASCUS was determined. In this study on 213 patients, the sensitivity and specificity of Pap smear were 15% and 93%, respectively; and the sensitivity and specificity of colposcopy was reported 80% for both. Finally, in accordance with our results, it was suggested that noting a lower accuracy of Pap smear in this regard, colposcopy and biopsy are better to be employed instead.

Similarly, Ghaem Maghami et al (23) in a similar study suggested that in females with ASCUS in Pap smear, colposcopy and biopsy should be used without wasting time, because Pap smear is not sufficiently accurate and colposcopy is a better surrogate.

It has been suggested that bowing to a high prevalence of papilloma virus infection among young females with cervical cancer and the long-lasting premalignant condition related to this infection, all females older than 20 years be screened for human papilloma virus infection in a primary screening for cervical cancer by cytology (19).

Similar to our study, previous reports also agreed upon the high accuracy of colposcopy in detecting non-benign cervical lesions (4,22-24).

In addition, it has been shown that the results of colposcopy in examining cervical lesions are highly concordant with biopsy findings (25-31).

Various factors may affect the accuracy of colposcopy in diagnosing premalignant and malignant cervical lesions, including the quality of performing colposcopy and result interpretation, operator skill, and classifications of results.

Table 3. Colposcopy Results for Study Population

Finding	No. (%)
Normal	258 (81.9)
Acetowhite	30 (9.5)
Malignant	12 (3.8)
Punctuation	5 (1.6)
Abnormal vessel	4 (1.3)
Abnormal vessel and acetowhite	3 (1)
Punctuation and acetowhite	1 (0.3)
Mosaic pattern and acetowhite	1 (0.3)
Mosaic pattern and punctuation	1 (0.3)

Table 4. Variables Indicating Diagnostic Performance of Pap Smear and Colposcopy Versus Pathology Results in Detecting Malignant Lesions

Variable	Pap Smear	Colposcopy
True positive	24 (7.6)	28 (8.9)
True negative	198 (62.9)	258 (81.9)
False positive	86 (27.3)	26 (8.3)
False negative	7 (2.2)	3 (1)
Sensitivity (%)	77.4 [58.9-90.4]	90.3 [74.3-97.9]
Specificity (%)	69.7 [64.0-75.0]	90.9 [86.9-94.9]
Positive predictive value (%)	21.8 [14.5-30.7]	51.9 [37.8-65.7]
Negative predictive value (%)	95.6 [93.1-98.6]	98.9 [96.7-99.8]
Positive likelihood ratio	2.55 [1.4-3.1]	99.2 [96.7-99.8]
Negative likelihood ratio	0.32 [0.18-0.56]	0.01 [0.002-0.03]
Accuracy (%)	70.5	90.8

The low positive predictive value of colposcopy in the present work is in line with that of the previous study (32).

This finding means that a considerable proportion of cases with malignant colposcopy are actually benign and this problem may be explained by using different classification boundaries. This was also true in the present study in a way that the majority of false positive results in colposcopy were actually LSIL (33).

Limitations and Strengths

This study is an important study because it concomitantly examined the diagnostic performance of Pap smear and colposcopy considering biopsy as the method of choice in a rather large number of patients. However, this work bears some limitations that should be acknowledged here. Although cost-effectiveness was out of the primary objectives of the present work, colposcopy was more cost-effective (34). To reach a definite conclusion in this regard, however, further studies are needed.

Another limitation of this work was confining patients to symptomatic cases. Although there are ethical issues in relation with performing similar studies of asymptomatic cases, a kind of selective bias may compromise the results of study, making difficulty in generalizing findings to all females.

Reports in our study were made by a single observer. Although reaching more accurate results compared to other studies is an indicator of high expertise of the observer in this study, to examine inter-observer agreements and repeatability, studies with more than an observer are required.

Finally, a single-center nature of the present work is also another limitation. Further multi-center studies are recommended to be carried out in this regard.

Conclusions

In conclusion, the present study showed that the diagnostic accuracy of colposcopy in diagnosing non-benign cervical lesions is considerable. At the same time, Pap smear was found with intermediate accuracy and possibly it is an unreliable option in this regard. Therefore, colposcopy is recommended in all suspected cases. In order to reduce spectrum bias and overestimation of the accuracy of the test, studies on a wider range of patients are recommended.

Ethical Issues

Informed written consents were obtained from the participants.

Conflict of Interests

The authors declare that they have no conflict of interests.

Financial Support

This study was funded by Women's Reproductive Health Research Centre, Tabriz University of Medical Sciences.

Acknowledgements

We sincerely thank all the participants in this study. We are also thankful to our colleagues who provided expertise that greatly assisted the research.

References

1. McGraw SL, Ferrante JM. Update on prevention and screening of cervical cancer. *World J Clin Oncol.* 2014;5(4):744-752. doi:10.5306/wjco.v5.i4.744
2. Koh WJ, Greer BE, Abu-Rustum NR, et al. Cervical Cancer, Version 2.2015. *J Natl Compr Canc Netw.* 2015;13(4):395-404; quiz 404.
3. Barut MU, Kale A, Kuyumcuoglu U, et al. Analysis of Sensitivity, Specificity, and Positive and Negative Predictive Values of Smear and Colposcopy in Diagnosis of Premalignant and Malignant Cervical Lesions. *Med Sci Monit.* 2015;21:3860-3867.
4. Arbyn M, Castellsague X, de Sanjose S, et al. Worldwide burden of cervical cancer in 2008. *Ann Oncol.* 2011;22(12):2675-2686. doi:10.1093/annonc/mdr015
5. Gullotta G, Margariti PA, Rabitti C, et al. Cytology, histology, and colposcopy in the diagnosis of neoplastic non-invasive epithelial lesions of the cervix. *Eur J Gynaecol Oncol.* 1997;18(1):36-38.
6. Pandey K, Bhagoliwal A, Jain S. Optical Imaging: Future Tool in Detection of Pre-cancerous and Cancerous Lesions of Cervix and Its Comparison to Colposcopy. *J Obstet Gynaecol India.* 2015;65(3):176-180. doi:10.1007/s13224-014-0511-x
7. Atanassova D, Zlatkov V, Borisov S, Veleva G. [Diagnostic value of TruScreen, cytology and colposcopy]. *Akush Ginekol (Sofia).* 2013;52(3):7-18.
8. Giannella L. The clinical problem of colposcopy is represented by false-negatives. *Arch Gynecol Obstet.* 2015;291(4):711-712. doi:10.1007/s00404-015-3619-z
9. Sakano CR, Ribalta JC, Zucchi P. Tracking of cervical cancer in 7,519 patients: a study of the prevalence of altered cytologies. *Eur J Gynaecol Oncol.* 2015;36(4):437-441.
10. Mayeaux EJ Jr, Harper MB, Abreo F, Pope JB, Phillips GS. A comparison of the reliability of repeat cervical smears and colposcopy in patients with abnormal cervical cytology. *J Fam Pract.* 1995;40(1):57-62.
11. Akhter S, Bari A, Hayat Z. Variability study between Pap smear, Colposcopy and Cervical Histopathology findings. *J Pak Med Assoc.* 2015;65(12):1295-1299.
12. Practice Bulletin No. 157: Cervical Cancer Screening and Prevention. *Obstet Gynecol.* 2016;127(1):e1-e20. doi:10.1097/aog.0000000000001263
13. American Society for Colposcopy and Cervical Pathology (ASCCP). WHO guidelines updated in 2013 and ASCCP guideline updated in 2014.
14. Massad LS, Collins YC, Meyer PM. Biopsy correlates of abnormal cervical cytology classified using the Bethesda system. *Gynecol Oncol.* 2001;82(3):516-522. doi:10.1006/gyno.2001.6323
15. McKee MD, Lurio J, Marantz P, Burton W, Mulvihill M. Barriers to follow-up of abnormal Papanicolaou smears in an urban community health center. *Arch Fam Med.* 1999;8(2):129-134.
16. Lonky NM, Sadeghi M, Tsadik GW, Petitti D. The clinical

- significance of the poor correlation of cervical dysplasia and cervical malignancy with referral cytologic results. *Am J Obstet Gynecol.* 1999;181(3):560-566.
17. Cuzick J, Clavel C, Petry KU, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer.* 2006;119(5):1095-1101. doi:10.1002/ijc.21955
 18. Farzaneh F, Tamimi M, Amiri Z, Alizadeh K. The value of Pap smear in detecting cervical neoplasia compared with histopathologic findings in patients referred to Taleghani Hospital, Tehran 2007-2009. *Pajoohandeh.* 2011;16(2):92-97.
 19. Moy LM, Zhao FH, Li LY, et al. Human papillomavirus testing and cervical cytology in primary screening for cervical cancer among women in rural China: comparison of sensitivity, specificity, and frequency of referral. *Int J Cancer.* 2010;127(3):646-656. doi:10.1002/ijc.25071
 20. Sasieni P, Castanon A, Cuzick J. Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data. *BMJ.* 2009;339:b2968. doi:10.1136/bmj.b2968
 21. Prussia PR, Gay GH, Bruce A. Analysis of cervico-vaginal (Papanicolaou) smears, in girls 18 years and under. *West Indian Med J.* 2002;51(1):37-39.
 22. Karimi Zarchi M, Binesh F, Kazemi Z, Teimoori S, Soltani HR, Chiti Z. Value of colposcopy in the early diagnosis of cervical cancer in patients with abnormal pap smears at Shahid Sadoughi hospital, Yazd. *Asian Pac J Cancer Prev.* 2011;12(12):3439-3441.
 23. Ghaemmaghami F, Ensani F, Behtash N, Hosseinijad SE. Histologic findings of uterine cervix among women with cytologic diagnosis of ASCUS (atypical squamous cells of undetermined significance). *Tehran University Medical Journal.* 2004;62(4):326-331.
 24. Matsuura Y, Kawagoe T, Toki N, Sugihara K, Kashimura M. Early cervical neoplasia confirmed by conization: diagnostic accuracy of cytology, colposcopy and punch biopsy. *Acta Cytol.* 1996;40(2):241-246. doi:10.1159/000333745
 25. Pete I, Toth V, Bosze P. The value of colposcopy in screening cervical carcinoma. *Eur J Gynaecol Oncol.* 1998;19(2):120-122.
 26. Tuon FF, Bittencourt MS, Panichi MA, Pinto AP. [Sensitivity and specificity of cytology and colposcopy exams with the histological evaluation of cervical intraepithelial lesions]. *Rev Assoc Med Bras (1992).* 2002;48(2):140-144.
 27. Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol.* 1998;91(4):626-631.
 28. Teixeira LA, Lowy I. Im perfect tools for a difficult job: colposcopy, 'colpocytology' and screening for cervical cancer in Brazil. *Soc Stud Sci.* 2011;41(4):585-608. doi:10.1177/0306312711408380
 29. Wojciech R. [The diagnostic value of cytology and colposcopy in women with cervical intraepithelial neoplasia]. *Ginekol Pol.* 2011;82(8):607-611.
 30. al-Nafussi A, Rebello G, al-Yusif R, McGoogan E. The borderline cervical smear: colposcopic and biopsy outcome. *J Clin Pathol.* 2000;53(6):439-444.
 31. Belinson JL, Pretorius RG, Zhang WH, Wu LY, Qiao YL, Elson P. Cervical cancer screening by simple visual inspection after acetic acid. *Obstet Gynecol.* 2001;98(3):441-444.
 32. Hegde D, Shetty H, Shetty PK, Rai S. Diagnostic value of acetic acid comparing with conventional Pap smear in the detection of colposcopic biopsy-proved CIN. *J Cancer Res Ther.* 2011;7(4):454-458. doi:10.4103/0973-1482.92019
 33. Carta G, Di Stefano L, Catellani Perelli A, Toro G, Moscarini M. Colposcopy, cytology and histology in the diagnosis of squamous intraepithelial lesions of the cervix. *Clin Exp Obstet Gynecol.* 1999;26(2):60-66.
 34. Zamani M, Torabian S. Evaluation the colposcopic and histologic findings in oncology ward of Fatemeh hospital, Hamadan, Iran. *The Iranian Journal of Obstetrics, Gynecology and Infertility.* 2013;16(78):1-6.

© 2019 The Author (s); This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.