THE ROLE OF PAP SMEAR, HPV TYPES AND PUNCH BIOPSY IN EVALUATION OF CERVICAL PATHOLOGIES

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Abstract

Aim of study: Aim of our study is to determine the relation between high risk HPV(16,18,31,33) types, Pap smear and punch biopsy results.

Material and methods: We used for our study patients which referred with abnormal cervical lesions and pathological cytology findings, from 2010-2017 years in Derince Training and Research Hospital.

The data of the patients who underwent colposcopy were examined retrospectively. 151 patients were included in the study.

Results: As a result of study-high risk lesions (CIN2-3) were observed in 18,18% (n=8/44) of NORMAL,10% (n=2/20) of ASCUS,27,27% (n=6/22) of LSIL,50% (n=5/10) of HSIL smear result reported patients.

The result was reported as cervical squamous cell carcinoma in 1 patient with HSIL and 1 patient with LSIL.

As a result, high–risk lesions (CIN2 and CIN3) were found 30,18% (n=16/53) in pathologic evaluation in HPV type 16 and 18 positive patients. In one patient with HPV18 was detected cervical squamous cell carcinoma.

In our study was high risk lesions in 40% (4/10) of HPV other type patients.

Pap smear result was reported as normal in 56,81% (n=25/44) of HPV type 16 and 18 patients,13,63% (n=6/44) of these patients were smear LSIL and HSIL.50% (n=3/6) of other positive HPV types Pap smear result reported as LSIL.

Conclusions: Combined evaluation of Pap smear, colposcopy and punch biopsy while examining cervical pathologies is more convenient, than using these methods separately and more reliable approach to diagnosis of precancerous lesions.

Keywords: Colposcopy, Pap smear, Punch biopsy, uterine cervical neoplasm's

Introduction:

Thanks to early diagnosis and treatment of cervical lesions a marked decrease in the incidence of cervical carcinoma was observed. At the same time, mortality rates a significant decrease was detected. Various cervical screening methods have been established for early diagnosis (1-2). Conventional cervical smears , fluid-based techniques, visual methods, acetic acid test, spectroscopy, cervicography, colposcopy, HPV typing, punch biopsy are some types of cervical screening techniques (3). Cervical screening for cervical carcinoma is of great importance, especially for high risk groups(1). The cytological examination of the cervix was first performed by George Papanicolaou in 1940. The sensitivity of this screening test, which has great importance in the early recognition of cervical neoplasm's, has been proven in various investigations.

The recent incorporation of DNA-HPV as primary test in a cervical cancer screening setting has increased the finding rate for CIN2+ as compared with the traditional Pap smear(4).

The finding of cytological pathology through screening has resulted in a fall in the incidence of cervical cancer because of treatment of these precancerous lesions (5).

Colposcopic inspection of the cervix let assessment of the pathology before it is

treated, either by excision or ablation (6-7). In the management of CIN2+ the punch biopsy is mainly used to approve the diagnosis of a high-grade pathology, thereby decrease the number of needless treatments and the associated morbidity (8-9). The punch biopsy also plays a main role in the management of women undergoing ablative treatment for CIN because pretreatment biopsies are necessary to except invasive disease (10-11). In clinical trials, multiple-biopsy protocols have been used to maximize disease finding (11-12). It is more appropriate of taking multiple lesion-directed biopsies and an additional biopsy of normal-appearing cervix in a colposcopy.

Aim of our study is to determine the relation between high risk HPV (16, 18, 31, 33) types, Pap smear and punch biopsy results.

Material and method

We used for our study patients which referred with abnormal cervical lesions and pathological cytology findings, from 2010-2017 years in Derince Training and Research Hospital.

The data of the patients who underwent colposcopy were examined retrospectively. 151 patients were included in the study.

As a result of cervical Pap smear-ASC-US, AGUS, ASG-H, LSIL, HSIL reported patients were referred to colposcopy. Also, patients with macroscopically lesions directed to colposcopy.

Inclusion criteria

1. Cervix bleed on touch
2. Post coital / intermenstrual / perimenopausal / post menopausal bleeding
3. Cervical hypertrophy
4. Persistent vaginal discharge
5. Cervical erosion / ulceration/ growth surface
6. Unexplained occasional foul smelling discharge per vaginum.
7. Cervix flushed with petechiae spot

The cervix was cleaned with saline and then scanned with green filtrate for atypical vascularization, pathological findings are noted.

Followed, we applicated 3% concentration of asetic asid to the cervix. After one minute of application, the cervix was scanned for aseto-white appearance and pathological findings are noted.

Punch biopsies taken from aseto-white, atypical vascular, punctuation areas and sent to pathology. Highest grade lesion in biopsy results was evaluated as a result.

ABBREVIATIOUS

• ASCUS- atypical cells of undetermined significance

• LSIL- low–grade squamous intraepithelial lesion

• ASC-H- changes in cervical cells have been seen, cannot rule out HSIL

• HSIL- high–grade intraepithelial lesion

• AGUS- atypical glandular cells of undetermined significance

• Usually endometrial biopsy done with this too

• AIS- adenocarcinoma in situ (a cancer limited to the surface which has not invaded); rarest diagnosis

• CIN1-3- mild dysplasia to severe dysplasia

•HPV-human papillomavirus

Result

As a result of study-high risk lesions (CIN2-3) were observed in 18,18% (n=8/44) of NORMAL, 10% (n=2/20) of ASCUS, 27,27% (n=6/22) of LSIL,50% (n=5/10) of HSIL smear result reported patients.The result was reported as carcinoma in 1 patient with HSIL and 1 patient with LSIL.

Table 1:

The cytology and histology diagnoses of patients who underwent biopsy.

HISTOLOGY DIAGNOSIS							
PAP SMEAR	NORMAL	CHRONIC CERVICITIS	CIN1	CIN2	CIN3	CA	TOTAL
NORMAL	-	17	6	3	2	-	28
INFLAMATION	-	9	4	3	-	-	16
ASCUS	2	13	3	2	-	-	20
LSIL	-	9	6	6	-	1	22
HSIL	-	3	1	3	2	1	10
TOTAL	2	51	20	17	4	2	96

As a result, high –risk lesions (CIN2 and CIN3) were found 30,18% (n=16/53) in pathologic evaluation in HPV type 16 and 18 positive patients. In one patient with HPV18 cervical squamous cell carcinoma was detected.

In our study was detected high risk lesions in 40% (4/10) HPV other type .

Table 2:

The results of HPV types and histology diagnoses.

HISTOLOGY DIAGNOSIS							
HPV TYPE	NORMAL	CHRONIC CERVICITIS	CIN1	CIN2	CIN3	CA	TOTAL
HPV 16	2	19	6	11	5	-	43
HPV 18	-	6	3		-	1	10
HPV 31	-	1	-	1	-	-	2
HPV 33	-	1	-	-	-		1
HPV OTHER	-	4	2	4	-	-	10
TOTAL	2	31	11	16	5	1	66

Pap smear result was reported as normal in 56,81% (n=25/44) of HPV type 16 and 18 patients, 13,63% (n=6/44) of these patients were smear LSIL and HSIL. 50% (n=3/6) of other positive HPV types smear result reported as LSIL.

Table3:

The results of HPV types and cytology.

PAP SMEAR						
HPV	NORMAL	ENFLAMATION	ASCUS	LSIL	HSIL	TOTAL
HPV 16	20	7	3	3	3	36
HPV 18	5	2	1	-	-	8
HPV 31	1	-	-	-	-	1
HPV 33	-	-	-	-	-	-
HPV OTHER	1	-	1	3	-	5
TOTAL	27	9	5	6	3	50

Discussion: A community-based screening program is very important in preventing cervical cancer. Diagnosis of asymptomatic preinvasive lesions led to a significant decrease in mortality and morbidity of the

disease due to early intervention (13). Since screening programs cannot be implemented in underdeveloped countries, cervical cancer remains a major health problem. 85% of deaths due to cervical cancer occur in these countries (14). When cervical smear is used alone, it is recommended to be repeated every 3 years (15). Spontaneous regression of the low-grade dysplasia's is likely, whereas high-grade ones may progress to a higher rate in cervical cancer. The main objective of the screening program is to identify CIN 3 cases (15). According to statistics in Turkey abnormal smear results (ASCUS, ASC-H, LSIL, HSIL, AGC, squamous carcinoma, and adenocarcinoma) ratio is 1.76% (14). Management of these pathological findings is important for the purpose of the screening program. Moreover, the sensitivity of Pap smear can be up down to 30% (16, 17). Therefore, the pathological findings obtained by Pap smear should be evaluated with biopsies taken with colposcopy. HPV DNA screening is an important tool for the evaluation of cervical pathologies.In addition to cervical cytology, the use of HPV DNA (co-test) useful to management patients after positive cervical cytology (15).

It has been reported in the literature that ASCUSs can be followed by HPV DNA, followed by cytology repetition with 6 months intervals or by colposcopy (18). However, it recommended in the final guideline that smear repetition or HPV DNA assessment be preferred to colposcopy (15).

In our study-high risk lesions (CIN2-3) were observed in 18, 18% (n=8/44) of NORMAL, 10% (n=2/20) of ASCUS, 27, 27% (n=6/22) of LSIL, 50% (n=5/10) of HSIL smear result reported patients. The result was reported as carcinoma in 1 patient with HSIL and 1 patient with LSIL.

HPV DNA positivity rates vary in various countries, even in various regions of our country. HPV DNA positivity was investigated in a study conducted on patients with normal cervical cytology in Iran , HPV DNA positivity rate was found 13% (19). Two studies reported 23.6-27.2% of the screening group as HPV positive (20, 21). HPV DNA positivity in the HSIL group was reported higher than in the LSIL and / or ASCUS group. Abalı et al. (22) found HPV DNA positivity in the HSIL group 100%, in the LSIL group 14.2% and in the ASCUS group 13.5%.Park et al. (23) reported the high-risk HPV DNA positivity rate as 17.6% in women with normal cervical cytology, 73.5% in the LSIL group, 92.2% in the HSIL group and 95.2% in the invasive cervical cancer cases.

Pap smear result was reported in our study as normal in 56, 81% (n=25/44) of HPV type 16 and 18 patients, 13,63 % (n=6/44) of these patients were smear LSIL and HSIL. 50% (n=3/6) of other positive HPV types smear result reported as LSIL.

HPV infections are frequently asympto-matic in 70% of infected women , the virus is completely cleared and eliminated in 90% of the infected patients in two years (24). HPV infections become persistent in 10% of women infected with HPV (25). The development of cervical cancer shows a progressive course. Cervical intraepithelial neoplasia (CIN) is characterized initially by mild dysplastic changes. These lesions may progress to CIN-2 / CIN-3 characterized by severe dysplasia. Invasive squamous cell carcinoma may develop if the lesions are not detected and treated early. HPV infections may turned cervical cancer an average of 10 years, but this may be during a year (26).

As a result, high –risk lesions (CIN2 and CIN3) were found 30, 18% (n=16/53) in pathologic evaluation in HPV type 16 and 18 positive patients. In one patient with HPV18 cervical squamous cell carcinoma was detected.

In our study was detected high risk lesions in 40% (4/10) HPV other types.

The novelty our study was detection of high grade (CIN2-CIN3) lesions in HPV other types which is thinks more innocent in cervical lesions, and it consider as be more careful in investigating cervical lesions.

Our study showed that it is misleading approach to refer patients to colposcopy according to only abnormal Pap smear or HPV high-risk variant. This approach may lead to escape precancerous lesion. Another important point is that HPV other type observed patients have the possibility of high risk lesion (CIN2 and CIN3).

Combined evaluation of Pap smear, colposcopy and punch biopsy while examining cervical pathologies is more convenient, than using these methods separately and more reliable approach to diagnosis of precancerous lesions.

LITERATURE:

1. Kuzu I. [Diagnostic methods in cervical carcinomas].Turkish ulletin of Pathology 1993;10 (1):11-9.
2. Zekioğlu O, Özdemir N. [Pathology of cervical carcinoma]. Turkiye Klinikleri J Med Oncol-Special Topics 2011;4 (1):14-9.
3. Duraisamy K, Jaganathan KS, Bose JC. Methods of detecting cervical cancer. Adv Bio Res 2011;5 (4):226-32.
4. Zorzi M., Del Mistro A., Farruggio A., et al: Use of a high-risk human papillomavirus DNA test as the primary test in a cervical cancer screening programme: a population-based cohort study. BJOG 2013; 120: pp. 1260-1267
5. Sasieni P, Adams J. Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age period cohort model. BMJ 1999;318: 1244–5.
6. NHSCSP. Colposcopy and Programme Management: Guidelines for the NHS Cervical Screening Programme, 2nd edn. London: NHSCSP, 2010.
7. Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al. European guidelines for quality assurance in cervical cancer screening. Second edition – summary document. Ann Oncol 2010;21: 448–58.
8. Arbyn M, Kyrgiou M, Simoens C, Raifu AO, Koliopoulos G, MartinHirsch P, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. BMJ 2008; 337:a1284.
9. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet 2006; 367:489–98.
10. Anderson MC. Invasive carcinoma of the cervix following local destructive treatment for cervical intraepithelial neoplasia. Br J Obstet Gynaecol 1993; 100: 657–63.
11. Shumsky AG, Stuart GC, Nation J. Carcinoma of the cervix following conservative management of cervical intraepithelial neoplasia. Gynecol Oncol 1994; 53: 50–4.
12. Stoler MH, Vichnin MD, Ferenczy A, et al. The accuracy of colposcopic biopsy: Analyses from the placebo arm of the Gardasil clinical trials. Int J Cancer. 2011; 128:1354–1362. [PubMed]
13. Valdespino V M , Valdespino V E. Cervical cancer screening: state of the art. Curr Opin Obstet Gynecol 2006;18(1):35-40.
14. Turkish Cervical Cancer and Cervical Cytology Research Group., Prevalence of cervical cytological abnormalities in Turkey. Int J Gynaecol Obstet 2009;106(Issue):206-9.
15. Saslow D, Solomon D, Lawson H W, Killackey M, Kulasingam S L, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin 2012;62(3):147-72.
16. Keskin H L, Secen E I, Tas E E, Kaya S , Avsar A F. Servikal smear sitolojisi ile kolposkopi eşliğinde servikal biyopsi korelasyonu. Türk Jinekolojik Onkoloji Dergisi 2011;3:71-5.
17. Nanda K, McCrory D C, Myers E R, Bastian L A, Hasselblad V, Hickey J D, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann Intern Med 2000;132(10):810-9.
18. Wright T C, Jr., Massad L S, Dunton C J, Spitzer M, Wilkinson E J, Solomon D, et al. 2006 consensus guidelines for the management of women with abnormal cervical screening tests. J Low Genit Tract Dis 2007;11(4):201-22.

19. Ghaffari SR, Sabokhar T, Mollahajian H, Dastan J, Ramezanzadeh F, Ensani F, et al. Prevalence of human papillomaviruse genotypes in womwn with normal and abnormal cervical cytology in İran. Asian Pac J Cancer Prev 2006; 7(4):529- 532.

20. Kulmala SM, Shabalova IP, Petrovitchev N, Syrjänen KJ, Gyllensten UB, Syrjänen SM. Prevalence of the most common high-risk HPV genotypes among women in three new independent states of the former Soviet Union. J Med Virol 2007; 79(6):771-781.

21. Kroupis C, Thomopoulou G, Papathomas TG, Vourlidis N, Lazaris AC. Population-based study of human papillomavirus infection and cervical neoplasia in Athens, Greece. Epidemiol Infect 2007; 135(6):943-950.

22. Abalı R, Bozkurt S, Arıkan İ, Şahin A, Erdener O, Özkılıç T ve ark. Serviksin Prekanseröz Lezyonlarının Değerlendirilmesinde Sitoloji, Kolposkopi, Histoloji ve Human Papillomavirusün Yeri. Jinekoloji ve Obstetrik Dergisi 2006; 20:38-45.

23. Park TC, Kim CJ, Koh YM, Lee KH, Yoon JH, Kim JH, et al. Human papillomavirus genotyping by the DNA chip in the cervical neoplasia. DNA Cell Biol 2004; 23(2):119-125

24.Pagliusi SR, Aguado TM: Efficacy and other milestones for human papillomavirus vaccine introduction, Vaccine 2004;23(5):569-78.

25.Munoz N, Bosch FX, de Sanjosé et al: Epidemiologic classification of human papillomavirus types associated with cervical cancer, N Eng J Med 2003;348(6):518-27

26. 16.Miller AB: Failures of cervical cancer screening, Am J Public Health 1995; 85 (6): 761-2.

Declarations:

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