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Original Contributions

Screening properties of human papillomavirus testing for predicting cervical intraepithelial neoplasia in atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesion smears: a prospective study

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Abstract The aim of the present study was to determine the usefulness of human papillomavirus (HPV) testing for predicting cervical intraepithelial neoplasia (CIN) 1 and 2 to 3 on cervical biopsies in women who had atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL) on Papanicolaou tests. In this prospective cohort, 167 women with abnormal cytologic examination (ASCUS and LSIL) were evaluated by colposcopy-directed biopsy and endocervical curettage. Colposcopy was performed on all study participants to obtain cervical tissue for histologic examination for detection of underlying CIN in patients with an initial cytologic test result of ASCUS and LSIL. A sample for HPV DNA detection by polymerase chain reaction was obtained. The HPV type 16 was positive in 35.4% of the 167 women with abnormal cytologic examination result in our gynecologic outpatient's clinic. Histologic diagnosis of CIN 1 was found in 45 of 135 women with ASCUS and in 17 of 32 women with LSIL. According to the cytologic findings, the frequency of CIN grade 2 or 3 in patients classified as ASCUS and LSIL was 12.5% (17/135) and 18.7% (6/32), respectively. Of the ASCUS smears, 9.6% were positive for HPV type 16. The sensitivity of the HPV type 16 using polymerase chain reaction technique threshold in detecting CIN 1 and CIN 2 to 3 was 57% and 46% in ASCUS-LSIL cytologic examination, respectively. The positive predictive value of HPV type 16 ranged from 60% in patients with CIN 1 and 42% in CIN 2 to 3 in ASCUS-LSIL. By contrast, negative predictive value was 58% in patients with CIN 1 and 80% in CIN 2 to 3. The low positive predictive value of HPV testing with ASCUS smears suggests that HPV positivity could be not used for predicting the presence of CIN 2 to 3.

Keywords: Cervical intraepithelial neoplasia; Colposcopy; Human papillomavirus typing; ASCUS; LSIL

1. Introduction

Atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSILs) are detected in 5% to 10% of women undergoing cervical cytologic screening [1,2].

Their management is controversial [3]. About 30% of these women have low-grade cervical intraepithelial neoplasia (CIN 1); although many of these lesions will spontaneously regress, about 15%, and perhaps up to 40%, will progress to CIN 2 or 3 [4].

According to the American Society for Colposcopy and Cervical Pathology 2001 Consensus Guidelines for the Management of Women with Cervical Cytologic Abnormalities, women with ASCUS should be managed using a program of 2 repeated cytologic tests, immediate colposcopy, or HPV DNA testing for high-risk human papillomavirus (HPV) types [5].

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Table 1
Cytologic abnormalities and HPV DNA detection rates related to biopsy results

Cytologic abnormalities	HPV testing	Histologic diagnosis							
		Normal		CIN 1		CIN 2-3		Total	
		n	%	n	%	n	%	n	%
ASCUS + LSIL	HPV−	59	51	42	36	14	12	115	100
ASCUS + LSIL	HPV+	16	30	24	46	12	23	52	100
ASCUS	HPV−	33	37	40	45	15	17	88	100
ASCUS	HPV+	40	83	5	10	2	4	47	100
LSIL	HPV−	2	9	15	68	5	22	22	100
LSIL	HPV+	7	70	2	20	1	10	10	100

Oncogenic types of HPV are present in more than 90% of women with cervical cancer and high-grade CIN [6,7]. The HPV testing may be useful in identifying high-grade CIN in women with ASCUS or LSIL on cervical cytologic screening [8,9].

The HPV testing for routine clinical management of ASCUS and LSIL is not yet warranted and continues to be an investigational tool. Previous studies have demonstrated the usefulness of adjunctive HPV DNA testing as a complement to cytologic examination in primary screening [10,11].

The HPV DNA testing may reduce costs by triaging patients into appropriate management strategies and reducing unnecessary colposcopy and less frequent screening in low-risk patients. Most HPV-induced cervical cell changes are transient, and 90% regress spontaneously within 12 to 36 months as the immune system eliminates the virus [12].

The aim of the current study was to determine whether HPV testing by polymerase chain reaction could discriminate between the presence and absence of high-grade squamous intraepithelial lesions in patients with ASCUS or LSIL smears.

2. Material and method

The sample of the study included a series of 167 women referred to the Colposcopy Unit, Haseki Training and Research Hospital, Istanbul, Turkey, between February 2006 and November 2007 due to an abnormal Papanicolaou test (ASCUS and LSIL). Women were excluded from the study if (*a*) they had a history of CIN or cervical, vaginal, or vulvar cancer; (*b*) they were referred because of an high-grade squamous intraepithelial lesion (HSIL) cervical smear; (*c*) they had immunosuppression; or (*d*) they were pregnant. All women were subjected to colposcopy and HPV testing. The study was approved by the ethical committee of the hospital, and all women gave an informed consent to participate.

Cervical smear was taken with a cervex-cytobrush, smeared onto a microscope slide, fixed with 96% alcohol, and stained according to the Papanicolaou method. An HPV DNA sample was obtained with cervex-brush and fixed with 24% alcohol and transferred for HPV DNA testing.

In all patients, colposcopy was performed after application of 3% acetic acid. Colposcopically targeted biopsies were taken from the most abnormal area of the cervix. An endocervical curettage was performed if the transformation zone was not entirely visible. The material was fixed in formaldehyde.

2.1. Statistical analysis

The correlation between variables was tested with χ^2 test. We calculated sensitivity, specificity, and positive and negative predictive values of the HPV screening test to detect CIN grade 2 or 3 in the colposcopy-directed specimens. The 95% confidence intervals were computed based on the binomial distribution.

3. Results

The 167 women recruited for this study had the following cytologic abnormalities: ASCUS in 135 cases and LSIL in 32 cases. The mean ages of the patients were 41 ± 8.19 (range, 17-65) years for the study group. When stratified by age group; the proportion was detected (12.6%, 9.4%) in the 17 to 30 years, (46.9%, 48.9%) in 31 to 45 years, and (43.8%, 38.5%) in older than 45 years in ASCUS group and in LSIL group, respectively.

Of 167 women with ASCUS/LSIL who underwent histologic sampling, we found 75 without CIN (44%), 66

Table 2
Performance of cytologic examination, colposcopy, and HPV DNA testing in identification of biopsy-confirmed CIN 1

Diagnostic method	Sensitivity		Specificity		PPV		NPV	
	%	95% confidence interval	%	95% confidence interval	%	95% confidence interval	%	95% confidence interval
ASCUS + LSIL HPV DNA testing	57	51-63	78	72-85	60	53-65	58	52-64
ASCUS-HPV DNA testing	7	3-11	44	39-48	11	8-14	45	41-49
LSIL-HPV DNA testing	11	7-15	22	18-26	22	17-27	11	5-17