

Cytological, Histological Correlations and Human Papillomavirus Testing in the Diagnosis of Cervical Intraepithelial Neoplasia

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Introduction: Persistent infection with high risk Papillomavirus (HR HPV) is the main risk factor for cervical cancer. Usually there is a period of approximately 10 years since someone gets infected with HPV till the incidence of an invasive cancer. The slow evolution of precancerous lesions allows their detection before the invasive stage. The objective of this study is to evaluate correlations among cytology, colposcopically guided biopsy and HPV testing, HR HPV prevalence and the reliability of cervical-uterine smears as screening method.

Material and method: The study comprises a number of 64 patients who underwent colposcopy, cytodiagnosis and biopsy examinations during January 2010 – December 2011 at Saint Die Hospital (France). Testing for HR HPV was performed especially in case of ASCUS Pap smears.

Results: ASCUS results of cervical-uterine smears corresponded to histological diagnosis of normal aspect and benign lesions in 60% of the cases, in 26.66% of cases with low grade malignant lesions and in 13.33% of the cases with high grade malignant lesions. HR HPV testing was positive especially in patients younger than 30 years (93.33% of patients who performed the HR HPV test), for patients between 30 and 50 years HR HPV was present in 80% of tested patients and for patients over 50 years was present only in 20% of the cases. Neither of the patients who tested negative for HR HPV presented high grade malignant lesions as a result of the biopsy test.

Conclusions: There is a direct correlation between the presence of HPV and grade of malignancy, thus all patients presenting high grade malignant lesions tested positive for HR HPV. HPV testing should not be performed in patients with LSIL results when sampling cervical-uterine smears, because the HPV prevalence is highly increased and a positive HR HPV test result would only create panic in young patients.

Keywords: cervical intraepithelial neoplasia, infection, high-risk Papillomavirus, Pap smears, biopsy

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Introduction

Persistent infection with high-risk Papillomavirus (HR HPV) is the main risk factor in malignant cervical lesions. Usually there is a period of approximately 10 years since someone gets infected with HPV till the incidence of an invasive cancer. The slow evolution of precancerous lesions allows their detection before the invasive stage. Sampling cervical-uterine smears (CUS) allows the detection of precancerous lesions (the results are assessed according to the Bethesda 2001 classification) [1].

The CUS results are atypical in 5–6% of the cases, inconclusive smears with unidentified significance (ASCUS) represent 2–3% of the cases, low grade lesions (LSIL) are present in 1.5–1.8% and high grade lesions (HSIL) in approximately 1% of the cases, invasive cancer being present in 0.04–0.06 % of CUS [2–3].

Approximately 60–65% of invasive cancers are diagnosed in women who did not perform the CUS test or performed it at over three years intervals, quite the opposite, 30% of invasive cancers are diagnosed in women who had regular CUS (within less than three years interval) [4]. This fact demonstrates that CUS with 20–45% false-negative results is not accurate enough [5].

Smear is preferred in liquid medium because this way

it has a higher sensitivity compared to conventional smears [6]. Liquid based smear cytology also improves the quality of the collected sample, reduces the number of smears which can not be interpreted and can also be used to detect HPV [7–10].

After obtaining an abnormal CUS, detecting HR HPV is closely correlated with high-grade CIN (98% sensitivity). Negative predictive value of the test (close to 100%) allows patients with LSIL or ASCUS cytology results to avoid unnecessary colposcopy-biopsy and too frequently performed cytological screening [11,12].

HPV testing is useful in case of discrepancies among colposcopy, cytodiagnosis and biopsy examinations for monitoring purposes too after the treatment (conization) of CIN 2 or CIN 3 type lesions [13].

The objective of this study was to evaluate correlations among cytology, colposcopically guided biopsy and HPV testing, HR HPV prevalence and the reliability of cervical-uterine smear as screening method.

Material and method

The study comprises a number of 64 patients who underwent Colposcopy, cytodiagnosis and biopsy examinations during January 2010 – December 2011 at Saint Die Hospital (France).

Testing for HPV HR was performed especially in case of ASCUS Pap smears (the only one recommended test,

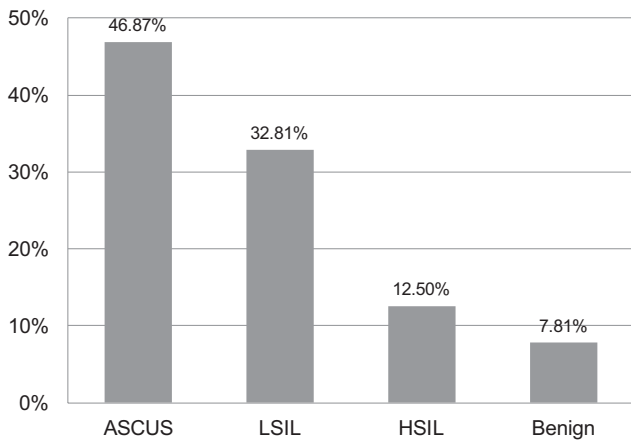


Fig. 1. The results of cervical uterine smears (CUS)

which is compensated in France, and patients' medical education makes difficult to perform other analyses which are not free of charge). The used method (Hybrid Capture II) allows DNA identification for 13 high risk HPV genotypes (genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68).

Results

Patients' average age was 33.5 years, ranging from 19 to 65 years. CUS results were mostly ASCUS (46.87%), followed by LSIL (32.81%), HSIL (12.5%). In 7.81% of the cases were benign alterations (inflammation).

Histological diagnosis consisted of 4 groups:

- ▶ Group 1 included low grade squamous intraepithelial lesions (warts and CIN 1) (34.37%)
- ▶ Group 2 comprised high grade squamous intraepithelial lesions (CIN2, CIN3 and carcinoma in situ) (25%)
- ▶ Group 3 included benign lesions and normal aspect lesions (40.62%)
- ▶ Group 4 comprised microinvasive or invasive carcinomas (0%)

Colposcopy was unsatisfactory in 9.37% of the cases (the squamous cylindrical junction could not be visualized).

HR HPV testing was performed in 46.85% of the cases (Fig. 3); in case of ASCUS smears was performed in 80% of the cases, in case of LSIL smears was performed

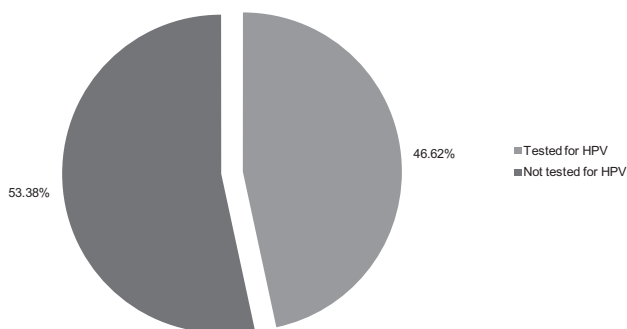


Fig. 3. HPV testing in the studied group of patients

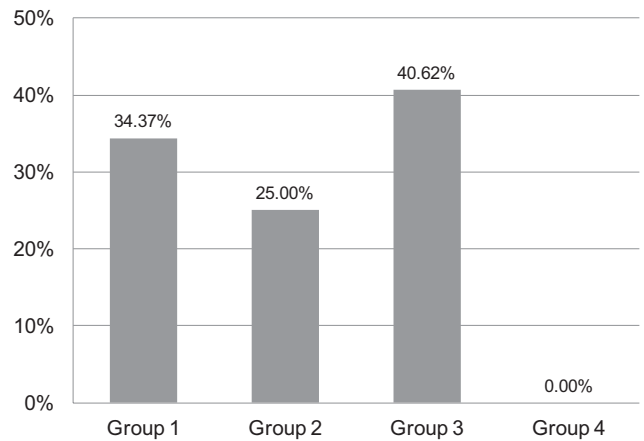


Fig. 2. Classification of the studied group according to the histological group

in 23.8% of the cases, HPV testing was not performed for HSIL smears. In case of smears with inflammatory alterations testing was performed in one case (20%).

In case of ASCUS smears HR HPV was detected in 56.6% of the cases, the HR HPV test was negative in 23.33% of the cases and in 20% of cases the HR HPV testing was not performed.

An ASCUS result for CUS corresponded with a histological diagnosis of normal expression and benign lesions (60% of the cases), in 26.66% of the cases with low grade malignancy lesion and in 13.33% of the cases with high grade malignancy lesion.

In ASCUS patients who underwent HR HPV testing, the result was positive in case of all (100%) patients tested histologically with high grade malignant lesion, in 66.66% of patients with low-grade malignant lesions and similarly 66.66% of patients with normal histology and benign lesions.

HR HPV testing was positive especially in patients younger than 30 years (93.33% of patients with HPV HR test performed), for patients between 30 and 50 HR HPV was present in 80% of patients tested and for patients over 50 was present only in 20% of cases.

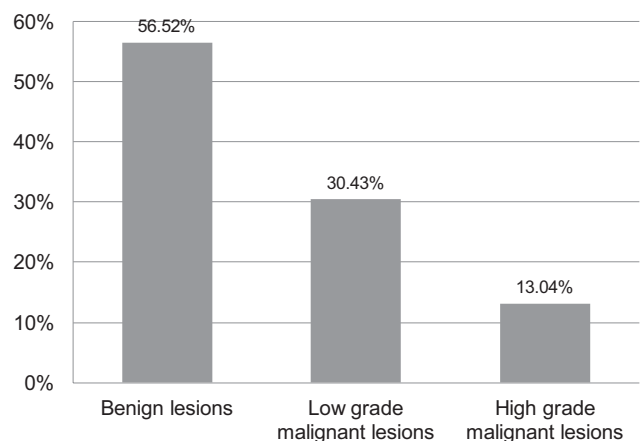


Fig. 4. Graphic representation of patients who tested positive for HR HPV

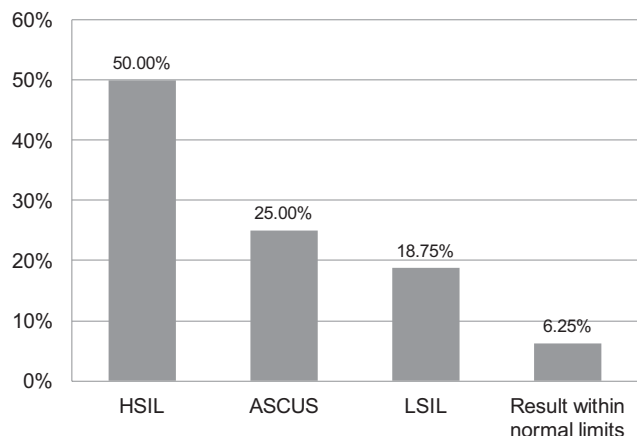


Fig. 5. Distribution of patients with high malignant potential tumors

The 23 patients who tested positive for HR HPV, on biopsy presented results within the normal limits and benign alterations (LB) in 56.52% of the cases, low grade malignancy lesions (GSM) in 30.43% of the cases and high grade malignancy lesions (GCM) in 13.04% of the cases.

The group of 7 patients with negative HR HPV testing showed normal results on biopsy and benign modifications in 71.42% of the cases, low grade malignancy lesions in 28.57% of the cases, on biopsy neither of the patients with negative HR HPV testing results showed high grade malignancy lesions.

The 16 histologically diagnosed patients with high malignant lesions presented for CUS: HSIL in 50% of cases, ASCUS in 25% of cases, LSIL in 18.75% and in one case (6.25%) CUS within normal limits.

HR HPV was present in all 3 patients who underwent HPV testing. Most cases of high grade malignancy lesions were in patients in the age group of 30 - 40 years old patients (62.5% of the cases), we found no case of HR HPV in the age group of over 40 years old patients.

The 22 patients tested on CUS with low grade malignancy lesions presented: LSIL in 59.09% of cases, ASCUS in 36.36% and one case (4.54%) was within normal limits for CUS. Out of the total number of patients who performed HPV testing HR HPV was present in 77.77% of them.

The 5 patients with benign modifications (inflammatory) on CUS presented on biopsy benign lesions in 60% of the cases, low grade malignancy lesions in 20% of the cases and high grade malignant lesions in 20% of the cases.

Table I. Distribution of patients according to age groups in patients with high malignant potential tumors

Age group	No. of patients
21–30	6
31–40	10
41–50	0

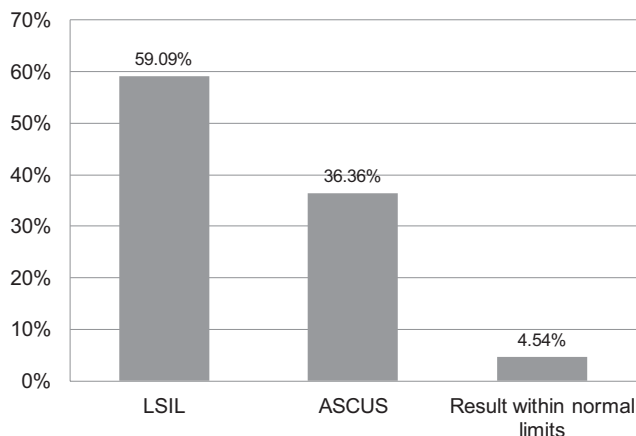


Fig. 6. Distribution of patients with low malignancy potential tumors

Discussions

It is known that high-risk HPV are responsible for pre-cancerous lesions and cervical cancers. HPV infection is common (about 7 of 10 women are exposed to HPV infection during their lifetime). The prevalence of the infection in subjects younger than 30 years is estimated to about 30%, 10% between the ages of 30 and 50 years and 5% in subjects older than 50 years. The majority of HPV infected women successfully eliminate the virus by immune mechanisms within 12–18 months (in 60–80% of the cases) [5].

There are specialists who believe that HR HPV testing has no importance, but among those who propose the replacement of classical CUS with HPV testing, there are many who recommend HPV testing in specific circumstances (eg. for selecting atypical squamous cells of undetermined significance (ASCUS)) or combination of CSU with HR HPV testing [14].

HPV testing is more sensitive than CUS and would allow patients to avoid colposcopy in about 50% of the cases, colposcopy being performed only in HR HPV positive patients. Colposcopy with biopsy is unnecessary and induces stress in ASCUS patients who tested negative for HR HPV. Colposcopic guided cervical biopsy allows the improvement of colposcopy results and provides histological results. Cervical biopsy results depend on the localization of the biopsy area [15].

The introduction of HPV testing combined with CUS would provide safety for patients with negative HPV test results [2].

The presence of HR HPV in patients with ASCUS Pap smear is observed in 30–59% of the cases [16] and 93.3% of cases correspond to CIN 2–3. Testing is especially interesting in adult women [17] where the prevalence of HPV infection is much lower than in adolescents [18].

In our study 56.6% of patients with ASCUS results tested positive for HPV HR.

HR HPV testing in ASCUS patients was positive in all cases, with reported histological result as high grade malignancy lesion.

An ASCUS result corresponds in 5–10% of the cases with a histological diagnosis of CIN 2–3 or exceptionally invasive carcinoma [1,19].

In our study patients with ASCUS results on CUS, presented biopsy results that showed the presence of high grade malignancy lesion in 13.33% of the cases.

HPV testing should not be performed in patients with LSIL results on CUS because HPV prevalence is extremely high (80–95% of the cases).

In our study 77.77% of LSIL patients who underwent HPV testing were detected HR HPV positive.

In Europe, a group of experts (EUROGIN) [20] suggested three cytological screening methods by evaluating the sensitivity and detection range of the screening method:

- ▶ one conventional CUS/ year, because its sensitivity is not optimal
- ▶ one liquid based CUS every two year, because its sensitivity is high
- ▶ one CUS combined with HPV HR testing every three year, because its sensitivity is almost 100%

Almost 100% negative predictive test results for HR HPV may allow the increase of screening interval up to 5 years [13].

Conclusions

There is a direct correlation between the presence of HPV and grade of malignancy, thus all patients presenting high grade malignant lesions tested positive for HR HPV.

Negative HR HPV testing offers long term protection that cannot be provided only by sampling cervical-uterine smears. In our study neither of the patients who tested negative for HR HPV presented high grade malignancy lesions at the histology test.

Negative testing for HR HPV may allow the increase of screening interval (up to 5 years).

HPV testing should not be performed in patients with LSIL results when sampling cervical-uterine smears, because the HPV prevalence is highly increased and a positive HR HPV test result would only create panic in young Romanian patients.

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