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The effect of HPV analysis on the ASC/SIL ratio which is one of the quality control criteria for PAP smears

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ABSTRACT

Objective: The high number of smear tests has a workload on pathologists/cytopathologists, which raises the concern for the quality of diagnoses. The application of high-risk human papillomavirus (hr-HPV) analyses with the PAP smear has begun to contribute to the clinical practice. In this study, we aimed to show the effect of hr-HPV analysis on the results of PAP smear via atypical squamous cell/squamous intraepithelial lesion (ASC/SIL) ratio on the quality standards.

Materials and Methods: A total of 12799 cervical cytology reports, between 2014-2016, from the Pathology Department of Marmara University Hospital, were included. Between November 2014 and May 2016, hr-HPV analysis was performed on a total of 4307 cases with Hologic Aptima HPV™, USA. Smear diagnoses before and after the start of the HPV test application were recorded.

Results: The cytology diagnoses, during when hr-HPV screening was not performed, were: negative for intraepithelial lesion or malignancy (NILM) 99.4%, atypical squamous cells of undetermined significance (ASCUS) 0.6%, low-grade squamous intraepithelial lesion (LSIL) 0.2%, ASC-H 0.04%, and high-grade squamous intraepithelial lesion (HSIL) 0.13%. The cytology diagnoses that were evaluated with HPV test were as follows: NILM 93.67%, ASCUS 2.31%, LSIL 2.82%, ASC-H 0.3%, and HSIL 0.91%. ASC/SIL ratio has been dropped from 1.9 to 0.7 after the initiation of hr-HPV use.

Conclusion: During the period without hr-HPV analysis, the ASC/SIL ratio was 1.9. Later with the initiation of hr-HPV screening this ratio decreased to 0.7. This shows that knowing HPV test results affects and improves the quality of the laboratory diagnoses.

Keywords: ASC/SIL ratio, Quality, PAP smear, HPV analysis

1. INTRODUCTION

The widespread adaptation of cervical smear (PAP smear) screening programs led to the diagnosis and treatment of squamous intraepithelial lesions (SIL). It has been used since the 1950s and this caused a dramatic decrease in cervical cancer incidence. The PAP smear has not lost its reputation even after the introduction of the human papillomavirus (HPV) vaccine, due to its population-wide effect and affordable cost in comparison to HPV vaccines. The high number of smear tests, on the other hand, has a workload burden on pathologists/cytopathologists, which raises the concern for the quality of diagnoses. In recent years, the application of high-risk HPV (hr-HPV) analyses (HPV DNA and/or mRNA) reflexively or simultaneously with the PAP smear has begun to contribute to the clinical practice [1,2].

Atypical squamous cells of undetermined significance (ASCUS] and atypical squamous cells, cannot exclude a high-grade lesion (ASC-H) categories of Bethesda Classification are sometimes overused by those who sign-out a high number of smears. Some quality control measures have been developed to overcome this bias, such as the ASC/SIL ratio [3-6].

In this study, we aimed to show the effect of hr-HPV analysis on the results of PAP smear assessment in general and via ASC / SIL ratio on the quality standards.

2. MATERIALS and METHODS

A total of 12799 cervical cytology reports, between 2014-2016, from the Pathology Department of Marmara University Hospital, were included. Between November 2014 and May 2016, hr-HPV analysis was performed on a total of 4307 cases with Hologic Aptima HPV (Hologic Panther, USA™). Smear

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diagnoses before and after the start of the HPV test application were recorded.

The study protocol was approved by the Institutional Ethics Committee of Marmara University, School of Medicine.

Statistical Analysis

The distribution of cases according to Bethesda Classification and HPV test usage were compared using Chi-square test. For statistical analysis "The jamovi project (2020). jamovi. (Version 1.6) [Computer Software]. Retrieved from https://www.jamovi.org. " was used.

These distributions were significantly different ($\chi^2 = 321.1944$, df = 4, $p<0.001$), where the ratios of non-negative for intraepithelial lesion or malignancy (NILM) diagnoses (atypical epithelial cells) were more common in the cases with known hr-HPV results.

3. RESULTS

The mean age of the patients were 40.4 ± 12.2 years (min: 16, max: 94). The cytology diagnoses, during when hr-HPV screening was not performed, were: NILM 99.4% (n=8422), ASCUS 0.6% (n=51), low grade squamous intraepithelial lesion (LSIL) 0.2% (n=17), ASC-H 0.04% (n=3), and high grade squamous intraepithelial lesion (HSIL) 0.13% (n=11). The distribution of cytology diagnoses that were evaluated with HPV test were as follows: NILM 93.67% (n=4023), ASCUS 2.31% (n=99), LSIL 2.82% (n=121), ASC-H 0.3% (n=13), and HSIL 0.91% (n=39).

These distributions were significantly different ($p<0.0001$), where the ratios of non-NILM diagnoses were more common in the cases with known hr-HPV results.

ASC/SIL ratio has been dropped from 1.9 to 0.7 after the initiation of hr-HPV use.

4. DISCUSSION

Human papillomavirus (HPV) PCR technique continues to be one of the most popular topics of the recent cytology literature. Its use in cervix cancer screening, both alone and together with cytology, is widely studied [7,8]. HPV test has been included in the American Society for Colposcopy and Cervical Pathology guidelines to refer positive patients to colposcopy [9].

The PAP smear and the hr-HPV results should not be considered as separate diagnoses. Currently, PAP smear and HPV analysis are performed and reported simultaneously (co-test) in many centers. In the co-test, the pathologist/cytopathologist has the chance to evaluate the smear by knowing the HPV result. Whether this affects the pathologist's final decision in the diagnosis of PAP smear is also a matter of debate [3,10]. In our department, after the initiation of hr-HPV tests, we detected a significantly higher number of cellular anomalies (non-NILM) ($p<0.0001$). However, how the increase in non-NILM diagnoses changes the diagnostic quality of the laboratory is also important.

The Bethesda Classification classifies ASC as cells showing cytologic changes suggestive of the SIL but not enough for a definitive diagnosis of SIL [5]. ASC is a diagnosis of uncertainty and many laboratories monitor their ASC rates to ensure that it is not overused. The ASC categories (ASCUS and ASC-H) should be less than 5% of cases to ensure avoiding their misuse [5]. For interlaboratory comparisons and comparing cervical dysplasia ratios in different populations, ASC/SIL ratio is used, which is calculated as the number (or percentage) of ASCUS and ASC-H cases divided by LSIL, HSIL, and malignant cases. If this ratio is over 3, then it is regarded as the overuse and potential misuse of ASC categories [3,5,6,11,12].

In our laboratory, during the period without hr-HPV analysis, the ASC/SIL ratio was 1.9. Later with the initiation of hr-HPV screening this ratio decreased to 0.7. This shows that knowing HPV test results affects and improves the quality of the laboratory diagnoses. Our ASC/SIL ratio was lower than recommended standard in both periods. These results lead us to think whether the recommended ASC/SIL ratio in co-test performing laboratories remain as 3 or should it be lowered. Further studies comparing ASC/SIL ratios in different co-test performing laboratories are required.

Compliance with Ethical Standards

Ethical Approval: The study protocol was approved by the Institutional Ethics Committee of Marmara University, School of Medicine.

Financial Support: The author has no relevant financial information to disclose.

Conflict of Interest: The author has no potential conflicts to declare.

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