

Risk Factors Associated with Abnormal Smear and Histology Result

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Objective: To identify risk factors linked with high-grade histology, including human papillomavirus (HPV) changes found in Pap smears.

Setting: Department of Obstetrics and Gynecology, Bahrain Defense Force Hospital.

Design: A Retrospective Study.

Result: One hundred forty-two females had colposcopy and cervical biopsy. Four (2.8%) females with risk factors had high-grade histology compared to 37 (26%) who had low-grade histology, P value = 0.2163.

Seven (4.9%) of the LEEP group (23) had high-grade histology (Cervical Intraepithelial Neoplasia CIN 2 and worse), and 16 (11.3%) had low-grade histology.

HPV changes in Pap smear test is a poor indicator for high-grade histology. HPV group was associated with low-grade histology, 82 (57.7%) and not high-grade histology, 17 (11.9%) only.

Conclusion: The study was unable to predict the progression to high-grade histology by the available data. HPV changes found in Pap test is a poor indicator for high-grade histology. Nevertheless, it is related to low-grade histology.

High-grade smear (moderate/severe dyskaryosis) is a good indicator for high-grade histology (CIN 2 or worse). Only 7 (4.9%) of patients that underwent LEEP had high-grade histology.

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Cervical cancer is the 11th most common cancer among females in the UK and the most common cancer in females under the age of 35 years. Between 2008 and 2009, incidence rates increased by more than 20% in the age group of 25 to 34 (22% for females aged 25-29 and 21% for females aged 30-34)¹. Cervical screening saves approximately 4,500 lives per year in England and prevents up to 3,900 cases of cervical cancer per year in the UK¹.

The first stage in cervical screening is taking a sample using liquid-based cytology (LBC). The second stage is referral to the colposcopy service that delineates the extent of the lesion on the cervix and thus, aids in selecting the best area for biopsy. Therefore, the colposcope could not replace the microscope for two main reasons: invasion and micro-invasion could not be excluded by cytology and colposcopy; colposcopy picture could produce different histological changes, each of which may have different biologic significance².

Ablation, loop electrosurgical procedure (LEEP) and cold knife conization are all treatment options provided for abnormal cytology/histology. Pain, sexual dysfunction, poor obstetric outcomes and increased cost have been associated with those cervical surgeries³.

Atypical squamous cells of undetermined significance (ASC), persistent or incident low-grade squamous intraepithelial lesion

(LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells (AGC), presence of high-risk human papillomavirus (HR-HPV) and Pap smears that suggest squamous or glandular carcinoma should be referred to colposcopy⁴.

The aim of this study is to identify risk factors linked with high-grade histology, including human papillomavirus (HPV) changes found in Pap smears.

METHOD

The abnormal Pap smear registry of the Pathology Department was reviewed from 2009 to 2012. In addition, the patients' records referred from Gynecological Outpatient Department (GOPD) to colposcopy were reviewed from 2009 to 2013.

The reasons for referral were Pap smear result, HPV changes were present in the cytology report, the presence of erosion/cervicitis and symptoms such as post-coital bleeding or inter-menstrual bleeding. Use of Oral Contraceptive Pills (OCP), parity, female's age, tobacco use, the number of sexual partners, Sexually Transmitted Diseases and immune state were documented. The data was collected through patient's electronic file, colposcopy operative notes and interviewing the patient through phone. The procedure documented were punch biopsy, cauterization or LEEP.

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RESULT

One-hundred forty-two females were categorized: those with risk factors causing abnormal smear and those with no risk factors had colposcopy and biopsy. Forty-one (28.9%) females had abnormal smear due to the following risk factors: intermenstrual bleeding, post-coital bleeding, previous abnormal smear, cervical erosion, tobacco use, OCP use, parity and age. Four (2.8%) females had high-grade histology compared to 37 (26%) who had low-grade histology. One hundred and one females had no risk factors, 81 (57%) of them had low-grade histology, see table 1.

Table 1: Risk Factors and Cervical Histology

Histology/Risk	Low-Grade Histology	High-Grade Histology	Total Patients
No Risk	81 (57%)	20 (14%)	101 (71.1%)
Risk	37 (26%)	4 (2.8%)	41 (28.9%)
Total	118 (83%)	24 (16.9%)	142

Fisher-Freeman-Halton exact P value=0.2163

One-hundred forty-two females referred to colposcopy were classified into two groups: see and treat with LEEP and random biopsy. Twenty-three 23 (16.1%) had colposcopy and LEEP, the result of histology was as follows: 7 (4.9%) had high-grade histology, and 16 (11.3%) had low-grade histology. One-hundred nineteen (83.8%) females underwent random biopsy; 17 (11.9%) were high-grade histology, see table 2.

Table 2: LEEP and Random Biopsy

Histology/LEEP	Low-Grade Histology	High-Grade Histology	Total Patients
No LEEP	102	17	119
LEEP	16	7	23
Total	118	24	142

Chi-square=3.579026 DF=1 P value= 0.0585

Women were referred to the colposcopy, based on their smear result. Ninety-five (66.9%) had low-grade smear and only 7 (4.9%) of them had high-grade histology. Forty (28.1%) females had high-grade smear; 17 (11.9%) of them had high-grade histology, the result was statistically significant.

Table 3: Pap-Smear and Histology

Histology/Smear	Low-Grade Smear	High-Grade Smear	Repeat Smear	Total Patients
Low Grade Histology	88 (61.9%)	23 (16.1%)	7 (4.9%)	118 (83%)
High Grade Histology	7 (4.9%)	17 (11.9%)	0 (0%)	24 (16.9%)
Total	95 (66.9%)	40 (28.1%)	7 (4.9%)	142

Fisher-Freeman-Halton exact P value < 0.0001

Ninety-nine (69.7%) specimen showed human papilloma virus (HPV) changes, 38 (26.8%) had no HPV changes, 5 (3.5%) patients were excluded because HPV status was not checked. One hundred thirty-seven were referred to colposcopy, and cervical biopsy was taken. The HPV group was associated to low-grade histology, 82 (57.7%) and not high-grade histology 17 (12%), P value = 0.8633.

Table 4: HPV Changes and Histology

Histology/HPV	Low-Grade Histology	High-Grade Smear	Total Patients
No HPV	31 (21.8%)	7 (4.9%)	38 (26.8%)
HPV Changes	82 (57.7%)	17 (11.9%)	99 (69.7%)
Not Checked			5 (3.5%)
	113	24	142

Chi-square = 0.029663 DF = 1 P value = 0.8633

DISCUSSION

Human papillomavirus infection and abnormal pap smears are common; though not necessarily would progress to cervical cancer. It is crucial to establish "a risk prediction model" to fulfill the criteria for referral for colposcopy⁵.

In this study, 40 females with high-grade cytology (moderate/severe dyskaryosis) are at higher risk of developing cancer, and it is appropriate to refer those patients to colposcopy with cervical biopsy; 17 of those were linked to high-grade histology, P value < 0.0001. In the low-grade smear group, only 7 (5%) were high-grade histology, which was similar to another study³.

Females with abnormal cytology are at risk of developing cervical cancer; appropriate triage and treatment would reduce this risk⁵. Our study has supported the trend of performing colposcopy. The evidence suggests that conservative management and observation for CIN1 is recommended^{5,6,7}.

HPV infection cofactors could be classified into three groups: (i) exogenous factors, including OCP use, tobacco use, diet, STD; (ii) host factors such as the immune response; and (iii) viral factors, HPV type and variant, viral load and viral integration⁸. In this study, HPV typing and variant was not performed.

Nevertheless, the presence of HPV changes detected during Pap test has proven to be a poor indicator for high-grade histology (CIN II and worse) and is related to low-grade histology, our findings were similar to another study⁵.

It is better to standardize the referral pattern to colposcopy by establishing risk prediction model that identifies females most likely to develop precancerous lesions (CIN2/3–adenocarcinoma in situ), modify our management protocols, particularly to LEEP at the first colposcopic visit and improve the colposcopy care provided for females⁹.

CONCLUSION

Referral to colposcopy should be made for females with a high-grade smear (moderate/severe dyskaryosis) as those females were associated with high-grade histology. In an initial visit to colposcopy, it is not necessary to undergo LEEP compared to random biopsy. It is not necessary to refer those females with HPV changes in normal cytology to colposcopy.

Potential Conflicts of Interest: None.

Competing Interest: None. **Sponsorship:** None.

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