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Predictive factors for invasive cervical cancer in patients referred for colposcopy after abnormal cervical smear screening

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ABSTRACT

Aims: To evaluate the clinical and pathological factors associated with invasive cervical cancer in patients referred for colposcopy after abnormal cervical smear screening.

Methods: This retrospective cohort study included 5,033 patients aged 18 years and older who underwent colposcopic evaluation between September 2019 and December 2025 at a tertiary gynecologic oncology center after an abnormal cervical smear result. Patients were classified according to the presence or absence of histopathologically documented invasive cervical cancer based on the highest-grade diagnosis available during follow-up. Age, smear category, human papillomavirus (HPV) status, colposcopic biopsy findings, endocervical curettage (ECC) findings, and final pathology results were analyzed. Logistic regression analysis was performed to identify variables independently associated with invasive cervical cancer.

Results: Invasive cervical cancer was identified in 32 of 5,033 patients (0.64%). Patients with invasive cancer were significantly older than those without invasive disease (49.8±11.0 vs 41.8±11.3 years, p=0.00026). High-risk smear findings were more common in the invasive cancer group than in the non-invasive group (46.9% vs 6.1%, p<0.001). Invasive cancer was detected in 4.34% of patients with high-grade squamous intraepithelial lesion or worse (HSIL+) on colposcopic biopsy versus 0.07% of those with non-HSIL biopsy findings (OR 65.99, 95% CI 20.04-217.25, p<0.001). Similarly, invasive cancer was identified in 11.6% of patients with HSIL+ on ECC compared with 0.31% of those with non-HSIL ECC results (OR 42.47, 95% CI 20.76-86.88, p<0.001). In multivariable analysis, older age, high-risk smear findings, HSIL+ on colposcopic biopsy, and HSIL+ on ECC remained significantly associated with invasive cervical cancer. Some invasive cancers were identified only in final pathology specimens, suggesting that preoperative assessment may underestimate invasive disease in a subset of patients.

Conclusion: Invasive cervical cancer was uncommon but clinically relevant in patients referred for colposcopy after abnormal cervical smear screening. Older age, high-risk smear findings, HSIL+ on colposcopic biopsy, and HSIL+ on ECC were the variables most strongly associated with invasive disease. An integrated interpretation of cytology, HPV status, biopsy, ECC, and clinical context may improve recognition of patients at increased risk for invasive cervical cancer.

Keywords: Cervical cancer, colposcopy, cytology, HPV, endocervical curettage, invasive disease

INTRODUCTION

Cervical cancer continues to impose a substantial global disease burden despite major advances in screening, human papillomavirus (HPV) vaccination, and early detection strategies.[1,2] It remains one of the most common gynecologic malignancies in women worldwide, particularly in settings where screening coverage, follow-up, and access to preventive care remain suboptimal.[3] Because the natural history of cervical carcinogenesis usually includes a prolonged precancerous phase, screening programs create an opportunity to detect clinically significant lesions before invasive disease develops.[4]

Cervical cytology has long served as one of the main tools in screening practice and still plays an important role in identifying patients who require further diagnostic evaluation.[5] Abnormal smear results often reflect an underlying spectrum of disease ranging from transient HPV-related changes to high-grade squamous intraepithelial lesions and, in some cases, invasive cervical cancer.[6] For this reason, clinicians routinely refer patients with abnormal cytology for colposcopic examination, which allows direct assessment of the cervix and targeted tissue sampling when necessary.[7] In daily practice, colposcopy-directed biopsy and endocervical curettage (ECC) provide tissue-based

information that helps distinguish preinvasive disease from more advanced pathology and guides subsequent management. Even so, the relationship between screening abnormalities and invasive cancer is not straightforward. High-risk cytologic findings clearly increase the probability of clinically significant cervical pathology, but invasive disease does not arise exclusively within those categories.[8] Some patients with markedly abnormal cytology have no invasive disease on further evaluation, whereas others with less alarming smear results may still harbor invasive cancer. This discrepancy suggests that cytology alone cannot fully capture the biological and anatomical complexity of cervical disease at the time of colposcopic assessment.

HPV-related information adds another important layer to risk stratification. Persistent infection with high-risk HPV genotypes, especially HPV16 and HPV18, drives the development of most cervical cancers and their precursor lesions.[9] Accordingly, HPV testing has become a central component of modern screening and triage algorithms.[10] Colposcopic biopsy and ECC may help answer that question more directly because they reflect tissue-level abnormalities rather than screening risk alone.[11] In particular, high-grade lesions identified on biopsy or ECC may indicate not only severe intraepithelial disease but also a greater likelihood of occult invasion, especially in patients with endocervical extension or limited lesion visibility.[12] However, in patients referred after abnormal smear screening, it remains unclear which combination of clinical and histopathological findings is most informative for identifying the subgroup already harboring invasive cervical cancer.

In the present study, we evaluated a large cohort of patients referred for colposcopy after abnormal cervical smear screening and examined the clinical and pathological factors associated with invasive cervical cancer. Specifically, we analyzed age, smear category, HPV status, colposcopic biopsy findings, and ECC findings to determine which variables were most strongly associated with invasive disease.

METHODS

This study was approved by the No. 1 Scientific and Ethical Review Board for Medical Researches of Ankara Bilkent City Hospital (Date: 22.04.2026, Decision No: TABED: 1-26-2515) and was conducted in accordance with institutional ethical standards and the principles of the Declaration of Helsinki.

This retrospective cohort study was conducted at the Department of Gynecologic Oncology Surgery, Ankara Bilkent City Hospital, Obstetrics and Gynecology Hospital. Patients aged 18 years and older who were referred for colposcopic evaluation because of an abnormal cervical smear result and who underwent colposcopy between September 2019 and December 2025 were considered eligible for inclusion. Patients were included if HPV test results and genotyping data were available and if sufficient follow-up and/or treatment data were present to allow histopathological confirmation of the final diagnosis. Patients with missing HPV data, absent histopathological outcome data, or insufficient follow-up to verify the final diagnosis were excluded. Clinical and pathological data were retrieved retrospectively from the institutional electronic medical record system and colposcopy database. Recorded variables included age at presentation, cervical smear result, HPV test result and genotype, adequacy of colposcopic examination, colposcopic biopsy result, ECC result, and final histopathological diagnosis.

Smear results were categorized according to cytologic risk status and, for the purpose of analysis, were grouped as high-risk smear and non-high-risk smear. For the purpose of analysis, high-risk smear was defined as HSIL, ASC-H, AGC, and AIS, whereas non-high-risk smear included ASC-US, LSIL, negative for intraepithelial lesion or malignancy, and insufficient smear. HPV status was classified as HPV16/18-related positivity, other HPV-positive or genotype-unspecified status, HPV negativity, or unknown HPV status. Unknown HPV status was retained as a separate category in all analyses, including the multivariable model. All patients underwent colposcopic examination according to routine institutional practice following an abnormal smear result. Directed cervical biopsy and ECC were performed when clinically indicated based on colposcopic findings and transformation zone characteristics. The primary study outcome was the presence of invasive cervical cancer. Invasive cancer was defined as the histopathological detection of squamous cell carcinoma, microinvasive squamous cell carcinoma, or adenocarcinoma in any of the diagnostic or therapeutic specimens, including colposcopic biopsy, ECC, or final pathology obtained after an excisional or surgical procedure. Adenocarcinoma in situ was not classified as invasive cancer. For analytical purposes, colposcopic biopsy and ECC findings were further classified as high-grade squamous intraepithelial lesion (HSIL) + and non-HSIL, with the HSIL+ category including high-grade squamous intraepithelial lesions and more advanced pathological findings. Final diagnosis was established on the basis of the highest-grade histopathological finding documented during follow-up. Final pathology referred to the definitive histopathological result obtained from excisional or surgical specimens during follow-up, including conization, LEEP, or hysterectomy when such procedures were performed.

Statistical Analysis

For data analyses, the cohort was divided into 2 groups according to the presence or absence of histopathologically documented invasive cervical cancer. Patients with invasive cervical cancer were compared with all remaining patients without histopathologically documented invasive disease based on the highest-grade diagnosis available during follow-up. Continuous variables were expressed as mean±standard deviation, whereas categorical variables were presented as number and percentage. Continuous variables were compared using the independent-samples t test. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the association of colposcopic biopsy and ECC findings with invasive cervical cancer. To identify independent predictors of invasive cervical cancer, a 2-step logistic regression analysis was performed. The first model included age, smear category, and HPV16/18-related positivity. In the second model, colposcopic biopsy findings and ECC findings were added to these variables. Results were reported as ORs, 95% CIs, and p values. A 2-sided p value of <0.05 was considered statistically significant.

RESULTS

A total of 5,033 patients were included in the study cohort, and invasive cervical cancer was identified in 32 patients (0.64%). A simplified flow diagram of the final analytic cohort is presented in **Figure 1**. Invasive cancer was defined as the presence of squamous cell carcinoma, microinvasive squamous cell carcinoma, or adenocarcinoma in any of the diagnostic steps, including colposcopic biopsy, ECC, or final pathology. Among the 32 invasive cancer cases, 22 were squamous cell carcinoma, 1 was microinvasive squamous cell carcinoma, and 9 were adenocarcinoma. Patients with invasive cancer were significantly older than those without invasive disease (49.8±11.0 years vs 41.8±11.3 years, p=0.00026). High-risk smear findings were also markedly more common in the invasive cancer group than in the non-invasive group (46.9% vs 6.1%, p<0.001). Although HPV16/18-related positivity was frequent among patients with invasive cancer, its distribution was less distinct than that of age and smear category. Baseline demographic and clinical characteristics of the study population are summarized in **Table 1**.

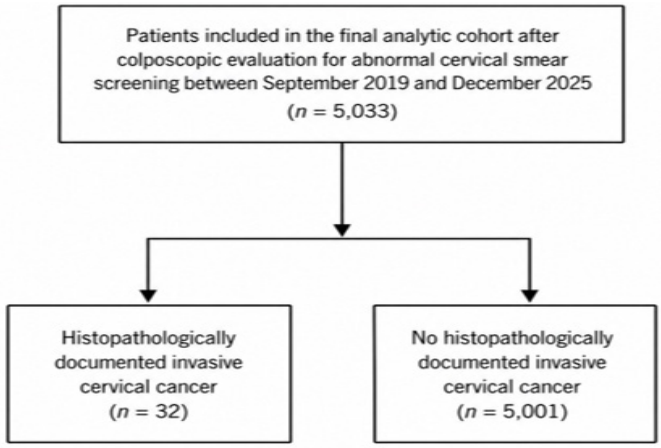

Figure 1. Simplified flow diagram of the final analytic cohort

Table 1. Baseline characteristics of patients with and without invasive cervical cancer

Variable	Invasive cancer (n=32)	Non-invasive disease (n=5001)	p value
Age (years), mean±SD	49.8±11.0	41.8±11.3	<0.001
High-risk smear, n (%)	15 (46.9)	307 (6.1)	<0.001
Non-high-risk smear, n (%)	17 (53.1)	4678 (93.9)	
HPV16/18-related positivity, n (%)	17 (53.1)	2523 (50.5)	
Other HPV-positive/ genotype unspecified, n (%)	4 (12.5)	1002 (20.0)	0.031*
HPV negative, n (%)	3 (9.4)	923 (18.5)	
HPV status unknown, n (%)	8 (25.0)	553 (11.1)	
Adequate colposcopy, n (%)	32 (100)	4860 (97.2)	0.63
Inadequate colposcopy, n (%)	0 (0)	136 (2.7)	

SD: Standard deviation, HPV: Human papillomavirus, *p value represents the overall comparison across HPV status categories

Notably, invasive disease was not limited to patients with the traditional high-risk smear categories. Among the 32 patients diagnosed with invasive cervical cancer, only 15 (46.9%) had high-risk smear findings, whereas 17 patients (53.1%) were in the non-high-risk smear category. When the rates were calculated within smear groups, invasive cancer was detected in 4.66% of patients with high-risk smear findings and in 0.36% of those without high-risk smear findings. These findings suggest that although high-risk cytology is strongly associated with invasive disease, invasive cervical cancer may also be encountered in patients outside the traditionally high-risk smear categories.

When histopathological findings were evaluated, the strongest associations with invasive cervical cancer were observed for HSIL+ findings on colposcopic biopsy and ECC. Among patients with HSIL+ on colposcopic biopsy, the rate of invasive cancer was 4.34%, whereas this rate was only 0.07% in those with non-HSIL biopsy findings (OR 65.99, 95% CI 20.04–217.25, p<0.001). Similarly, invasive cancer was identified in 11.6% of patients with HSIL+ findings on ECC, compared with 0.31% of patients with non-HSIL ECC results (OR 42.47, 95% CI 20.76–86.88, p<0.001). Detailed associations between biopsy, ECC findings, and invasive cancer are presented in **Table 2**. A visual summary of the independent predictors identified in the multivariable model is presented in **Figure 2**.

In the logistic regression analysis, older age and a high-risk smear result remained significantly associated with invasive cervical cancer in the clinical/pretest model, whereas HPV16/18-related positivity was not independently associated with invasive disease. In model 1, age increased the odds of invasive cancer by 6% per year (OR 1.06, 95% CI 1.02-1.09, p<0.001), and high-risk smear findings were associated with a markedly increased risk (OR 12.39, 95% CI 6.07-25.28, p<0.001). After the addition of colposcopic biopsy and ECC findings in the expanded model, age remained independently associated with invasive cancer (OR 1.10, 95% CI 1.06-1.14, p<0.001), as did high-risk smear findings (OR 3.23, 95% CI 1.45-7.21, p=0.004), HSIL+ on colposcopic biopsy (OR 54.43, 95% CI 14.65-202.27, p<0.001), and HSIL+ on ECC (OR 6.43, 95% CI 2.82-14.62, p<0.001). HPV16/18-related positivity did not retain statistical significance in the expanded model (OR 0.67, 95% CI 0.30-1.49, p=0.328). The results of both regression models are shown in **Table 3**.

The diagnostic pathway of invasive disease was also examined in detail. Invasive cancer was detected in 22 patients at colposcopic biopsy, in 13 patients at ECC, and in 18 patients in the final pathology specimen. When the detection patterns were analyzed, invasive disease was found only in the final pathology specimen in 9 patients, only in colposcopic biopsy in 6 patients, and only in ECC in 1 patient. In some cases, invasive disease was identified at more than one diagnostic step, including biopsy plus ECC, biopsy plus final pathology, or biopsy plus ECC plus final pathology. These findings indicate that invasive cervical cancer may become evident at different stages of the diagnostic process and that preoperative assessment may not fully capture the presence of invasive disease in all patients. The distribution of these diagnostic patterns is presented in **Table 4**.

DISCUSSION

In this large colposcopy cohort, invasive cervical cancer was uncommon; however, several variables were strongly associated with invasive disease. The main findings of this

Table 2. Association of colposcopic biopsy and ECC findings with invasive cervical cancer

Variable	Invasive cancer (n=32)	Non-invasive disease (n=5001)	Odds ratio (95% CI)	p value
HSIL+ on colposcopic biopsy	29	639	65.99 (20.04–217.25)	<0.001
Non-HSIL on colposcopic biopsy	3	4362	1.00 (reference)	
HSIL+ on ECC	17	130	42.47 (20.76–86.88)	<0.001
Non-HSIL on ECC	15	4871	1.00 (reference)	

ECC: Endocervical curettage, CI: Confidence interval, HSIL: High-grade squamous intraepithelial lesion

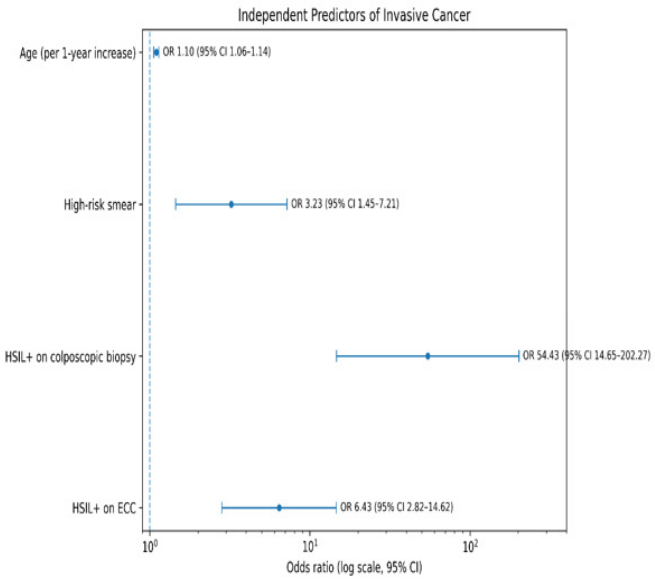

Figure 2. Forest plot of independent predictors of invasive cervical cancer identified in the multivariable logistic regression model

ECC: Endocervical curettage, CI: Confidence interval, HSIL: High-grade squamous intraepithelial lesion, OR: Odds ratio

Table 3. Logistic regression analysis for invasive cervical cancer

Model 1. Clinical/pretest model			
Variable	**OR**	**95% CI**	**p value**
Age (per 1-year increase)	1.06	1.02–1.09	<0.001
High-risk smear	12.39	6.07–25.28	<0.001
HPV16/18-related positivity	1.51	0.74–3.11	0.258
Model 2. Expanded model			
Age (per 1-year increase)	1.10	1.06–1.14	<0.001
High-risk smear	3.23	1.45–7.21	0.004
HPV16/18-related positivity	0.67	0.30–1.49	0.328
HSIL+ on colposcopic biopsy	54.43	14.65–202.27	<0.001
HSIL+ on ECC	6.43	2.82–14.62	<0.001

OR: Odds ratio, CI: Confidence interval, HPV: Human papillomavirus, HSIL: High-grade squamous intraepithelial lesion, ECC: Endocervical curettage

Table 4. Diagnostic steps at which invasive cancer was identified

Pattern of detection	Number of patients
Final pathology only	9
Colposcopic biopsy only	6
ECC only	1
Biopsy + ECC	7
Biopsy + final pathology	4
Biopsy + ECC + final pathology	5
Total	32

ECC: Endocervical curettage

study were that older age, high-risk smear findings, HSIL+ on colposcopic biopsy, and HSIL+ on ECC were the variables most strongly associated with invasive cervical cancer, with these factors remaining significant in multivariable analysis. These results suggest that although invasive cancer is rare among patients referred after abnormal cervical smear screening, a subgroup of patients carries a distinctly higher risk and may require more careful diagnostic assessment and treatment planning.

One of the most relevant findings was the independent effect of age. Patients with invasive cervical cancer were significantly older than those without invasive disease, and age remained significant in both regression models. This finding is clinically plausible, as increasing age is associated with reduced visibility of the transformation zone and a greater likelihood of endocervical localization, which may decrease the diagnostic yield of surface-directed sampling.[13] Our results therefore suggest that age should be considered a clinically meaningful factor when estimating the likelihood of invasive disease in patients referred for colposcopy.

High-risk smear findings were also strongly associated with invasive cervical cancer. This is consistent with the established relationship between increasing cytologic severity and the probability of clinically significant cervical pathology.[14] However, an important observation in our cohort was that invasive cancer was not limited to the traditional high-risk smear categories. More than half of the invasive cases occurred in patients outside the high-risk smear group. This finding suggests that cytology alone may underestimate invasive disease in a subset of patients.

Another notable result was the limited independent contribution of HPV16/18-related positivity in the expanded multivariable model. Although HPV16 and HPV18 are central to cervical carcinogenesis and remain highly relevant in screening and triage algorithms,[15,16] their predictive contribution appeared to decrease after tissue-based findings from biopsy and ECC were incorporated into the analysis. This likely reflects the fact that HPV status is most informative at the screening stage, whereas histopathological findings provide more direct information about already established invasive disease.

The strongest associations in this study were observed for HSIL+ findings on colposcopic biopsy and ECC. Biopsy and ECC findings should therefore be interpreted as tissue-based findings obtained during diagnostic evaluation, rather than as baseline screening predictors. In particular, the very high OR for HSIL+ on colposcopic biopsy suggests that advanced histopathological abnormalities detected during colposcopic assessment may serve as a major warning sign

for underlying invasion. A similar, although less pronounced, association was also observed for ECC. This is clinically important because ECC may detect lesions extending into the endocervical canal, particularly in cases where lesion visibility is limited.[17] Our findings therefore support the continued value of ECC in selected patients.

An additional clinically relevant finding was that invasive disease was not identified at the same diagnostic step in all patients. In some cases, invasion was detected on colposcopic biopsy or ECC, whereas in others it became evident only in the final pathology specimen. This pattern suggests that preoperative assessment may underestimate invasive disease in a subset of patients, even when biopsy and ECC are performed. The invasive cancers detected only in excisional or surgical specimens highlight that initial colposcopic biopsy and ECC may not completely exclude invasive disease in selected patients. Therefore, clinical, cytologic, and pathologic findings should be interpreted together. Similar observations have been reported in studies addressing pathologic upgrade to invasive carcinoma after preoperative diagnosis of high-grade cervical disease.[18] From a practical perspective, this finding supports a cautious approach in patients with older age and concerning cytologic or histopathological findings, even if definite invasion is not demonstrated at the initial sampling stage.

Limitations

This study has several strengths, including a large real-world cohort and the simultaneous evaluation of age, cytology, HPV status, biopsy findings, ECC findings, and final pathology within the same analytical framework. However, some limitations should also be acknowledged. The retrospective design may have introduced selection and information bias. Because unknown HPV status was more frequent among invasive cases than among non-invasive cases, the possibility of informative missingness should also be considered. However, no imputation procedure was applied, and unknown HPV status was analyzed as a distinct category. HPV vaccination status was not available in the dataset and could not be evaluated, which should be considered when interpreting the findings, particularly given the study period. In addition, although the overall cohort was large, the number of invasive cervical cancer cases was relatively small, which may have limited the precision and stability of the multivariable estimates. Therefore, these findings should be interpreted with caution and should not be considered a definitive risk prediction model. Operator- and observer-related variability in colposcopic and histopathological assessment should also be considered.

CONCLUSION

Overall, our findings indicate that invasive cervical cancer is uncommon but clinically relevant among patients referred for colposcopy after abnormal cervical smear screening. Older age, high-risk smear findings, HSIL+ on colposcopic biopsy, and HSIL+ on ECC were the variables most strongly associated with invasive disease. A more integrated interpretation of cytology, HPV status, biopsy, ECC, and clinical context may improve recognition of patients at increased risk for invasive cervical cancer.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the No. 1 Scientific and Ethical Review Board for Medical Researches of Ankara Bilkent City Hospital (Date: 22.04.2026, Decision No: TABED: 1-26-2515).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: YÖU, OA; Design: YÖU, TT; Control/Supervision: MÜ, FK; Data Collection and/or Processing: YÖU, AEK, NTŞ; Analysis and/or Interpretation: YÖU, TT, OA; Literature Review: YÖU, MÜ, AAT; Manuscript Writing: YÖU, FK, AAT, TT; Critical Review: All Authors.

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