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Rethinking the Risk: Evalution of the Malignant Potential of Non-16 and 18 HPV Types VIA Colposcopic Results

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Abstract

Introduction: The malignancy risks of high-risk HPV types like 16 and 18 are well-known. The oncogenic potential of other HPV types, however, remains unclear. This study reevaluates malignancy risks across HPV types, stressing comprehensive colposcopic evaluations in cervical cancer screening.

Materials and Methods: Conducted at a tertiary care center (January 2021 - July 2023), this retrospective study included 138 women divided into two groups: those infected with HPV 16/18 and those with other HPV types. We analyzed and compared colposcopic and histopathological outcomes, correlating colposcopic results with biopsy outcomes to assess cervical neoplasia.
Statistical analysis was performed using GraphPad Prism 10 (GraphPad Software Inc.; San Diego, CA, USA). Descriptive statistics, including means and standard deviations for continuous variables and frequencies and percentages for categorical variables, were calculated. The chi-square test was used to compare categorical variables between the two groups, and an independent t-test was employed to compare continuous variables. A p-value of less than 0.05 was considered statistically significant.

Results: Significant differences were noted between groups. While HPV 16 and 18 are linked to higher cervical neoplasia incidences, non-16/18 HPV types were also frequently associated with smear abnormalities. The average age of first sexual intercourse was 20.49 ± 4.2 years. Forty-nine percent of the women were smokers, 8% had only primary school education, and 78% were homemakers. High rates of known risk factors like low educational and socioeconomic status, and smoking were also significant.

Conclusion: Our findings suggest that non-16/18 HPV types might have a higher malignancy potential than HPV 16-18, highlighting their importance in cervical cancer screenings and colposcopic evaluations. The study's small sample size limits its conclusions, pointing to the need for larger studies to refine cervical cancer screening strategies globally.

Key words: Human papillomavirus; pap smear; colposcopy; cervical cancer.

Introduction

The predominance of certain human papillomavirus (HPV) types, particularly HPV 16 and 18, in the etiology of cervical cancer is well-established. These types are recognized for their high oncogenic potential and are the primary targets of existing HPV vaccines and screening programs. However, emerging evidence suggests that the oncogenic potential of non-16/18 HPV types may have been underestimated in the past. As the global prevalence of HPV 16 and 18 declines due to successful vaccination programs, the relative importance of other HPV types in cervical cancer pathogenesis is becoming more apparent. Recent studies have indicated that non-16/18 HPV types, while traditionally classified as lower risk, can also contribute significantly to the burden of cervical cancer. For instance, a comprehensive review by Kohli et al. (2007) discussed the broader implications of prophylactic HPV vaccines and highlighted the necessity to consider protection against a wider array of oncogenic HPV types, beyond just HPV 16 and 18 (1). Similarly, research by Checchi et al. (2023) documented a shift in the type-specific prevalence of HPV among young females in England, revealing a decrease in HPV 16 and 18 prevalence but a persistent presence of other high-risk types (2). Moreover, Wu et al. (2022) have emphasized the different oncogenic potentials of HPV genotypes, suggesting that the risk associated with non-16/18 HPV types could be similar to that of the more well-known high-risk types (3). This shift in the landscape calls for a reevaluation of current screening and prevention strategies to include a broader spectrum of HPV types,

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ensuring that prevention efforts remain effective as the epidemiology of HPV evolves. The objective of this study is to meticulously evaluate the malignant potential of these non-high-risk HPV types using colposcopic examination results as a key investigative tool. By integrating colposcopic findings with histopathological outcomes, this research endeavors to provide a comprehensive view of the oncogenic capacity of a broader range of HPV types. The goal is to expand the existing paradigm of HPV-related malignancies, encouraging a more inclusive screening protocol that could lead to improved detection rates and outcomes in cervical health management.

Materials and Methods

This retrospective analysis, conducted from January 2021 to July 2023 at a tertiary care center, involved 138 female patients who underwent colposcopic examinations at our clinic. Patients who had undergone hysterectomy, trachelectomy, or conization were excluded from the study. Demographic data (age, age at first sexual intercourse, smoking status, educational level, employment status) were collected for all participants. Additionally, smear results, HPV test outcomes, colposcopic findings, and histopathological results were recorded. Cervical samples were collected using the Female Swab Specimen Collection Kit (Hybribio, Hong Kong). DNA isolation was performed in our hospital's Medical Microbiology Laboratory using the HPV GenoArray Test Kit (Hybribio, Hong Kong). Amplification was conducted using Hybribio PCR kits, and the analysis was completed on the Automated HybriMax device (Hybribio, Hong Kong) utilizing HybrbioMemHPV21 membrane strips. Colposcopic examinations were performed using a binocular colposcope (Olympus-OCSS-BA). Demographic data of patients presenting for colposcopy were also documented. Conventional cervical smear cytology evaluation of these patients was performed according to the Bethesda system by an expert pathologist using a light microscope. Atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells where HSIL cannot be excluded (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), squamous cell carcinoma (SCC), glandular cell abnormalities (AGC) are divided into categories (4). Histopathological evaluation of the colposcopic biopsy was performed by an expert pathologist using a light microscope, according to the 2020 World Health Organization (WHO) Female Genital Tumors book. It is divided into diagnostic categories of low-grade squamous intraepithelial lesion (LSIL/CIN I), high grade squamous intraepithelial lesion (HSIL/CIN II - CIN III), squamous cell carcinoma, adenocarcinoma in situ, adenocarcinoma (5). In compliance with the Declaration of Helsinki, written consent was obtained from all participants involved in our study. The University Medical Faculty Clinical Research Ethics Committee granted clearance for the study, with the decision number 2023-09/22, on 21.09.2023.

Ethical approval: Ethics Committee permission (without specifying the institution from which it was obtained) was obtained from an Sivas Cumhuriyet University Medical Faculty Clinical Research Ethics Committee with the decision number 2023-09/22 on 21.09.2023.

Statistical analysis: The statistical analysis for this study was performed using GraphPad Prism 10 (GraphPad Software Inc.; San Diego, CA, USA). Continuous variables, such as age and age at first sexual intercourse, were expressed as means and standard deviations (SD). Categorical variables, such as educational level, employment status, and smoking status, were summarized as frequencies and percentages. Comparative analyses were conducted to evaluate the differences between patients with HPV 16/18 and those with other HPV types regarding demographic and clinical characteristics. A p-value of less than 0.05 was considered statistically significant for all analyses. Data were presented using appropriate tables and graphs to illustrate key findings.

Results

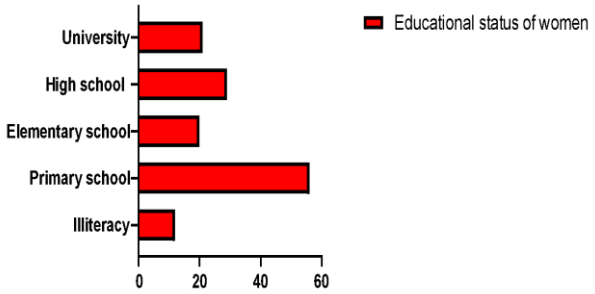
The demographic characteristics of the participants were analyzed by age groups and age at first sexual intercourse as depicted in Table 1. The mean age of the patients was 43.22 ± 8.63, and the average age at first sexual intercourse was 20.49 ± 4.2. Additionally, patients were categorized and assessed based on smoking status, educational level, and employment status.

Table 1: Distribution of demographic characteristics in patients undergoing colposcopy

	Mean ± SD
Age	43.22 ± 8.63
Age at First sexual experience	20.49 ± 4.2

SD: Standard deviation

Table 2: Educational status of women undergoing colposcopy



Notably, 36% of the patients (n=49) were smokers. Approximately 8% of the patients were illiterate. The largest group was primary school graduates, comprising 41% of the participants (Table 2). When examining the employment status of women undergoing colposcopy, it was observed that 78% were homemakers (Table 3). This may indicate a lower socioeconomic level. Along with cytology results, the HPV types of the participants were also examined. When analyzing the distribution of HPV types, 34% were found to be HPV 16-18, while 66% were other HPV types. Although HSIL was the most commonly observed cytological abnormality among those positive for HPV 16-18, the most frequently observed HPV type in cases with HSIL was other types. Except for adenocarcinoma in situ, other HPV types were more commonly associated with all cytological abnormalities (Table 4). The relationship between cytology results and smear outcomes was also examined. The most common cytological

Table 3: Employment status of women undergoing colposcopy

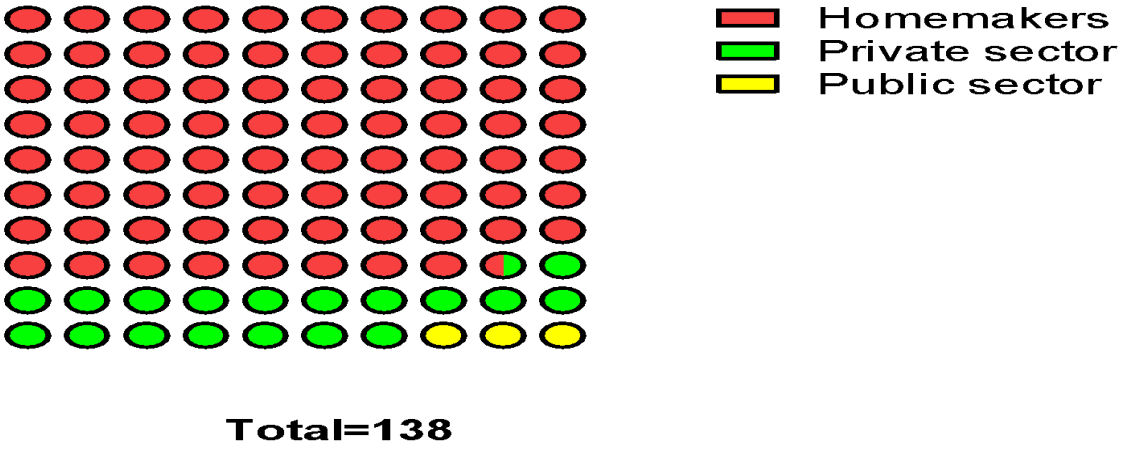


Table 4. Distribution of HPV and pathological results according to cytology results

	HPV 16-18 n (%)	O HPV n (%)	n	Normal	Chronic cervicitis	LSIL (CIN I)	HSIL (CIN II)	HSIL (CIN III)	AIS
Normal	31 (47)	35 (53)	66	2	43	7	9	5	0
Chronic inflammation	7 (37)	12 (63)	19	2	9	3	3	2	0
ASC-US	2 (11)	17 (89)	19	0	8	4	4	2	1
LSIL	1 (20)	4 (80)	5	0	3	0	0	1	1
HSIL	3 (30)	7 (70)	10	0	2	1	2	4	1
AGC	2 (25)	6 (75)	8	0	8	0	0	0	0
AIS	1 (100)	0	1	0	1	0	0	0	0
Atrophy	0	1 (100)	1	0	0	1	0	0	0
Unsatisfactory	0	1 (100)	1	0	1	0	0	0	0
ASC-H	0	8 (100)	8	0	5	0	2	1	0
Total	47 (34)	91 (66)	138	4	71	25	20	15	3

abnormality was ASC-US, which was most frequently reported as chronic cervicitis following colposcopic biopsy. The highest incidence of premalignant lesions was identified in smears reported as HSIL. Among the three cases of AIS, one smear result was HSIL, one was LSIL, and one was ASC-US (Table 4).

Discussion

Although traditionally considered less oncogenic, our findings suggest that non-16/18 HPV types may possess a notable malignancy potential, warranting further investigation to fully understand their role in cervical cancer pathogenesis. While HPV 16 and 18 are established as the primary high-risk types associated with cervical cancer, our findings, along with recent literature, indicate that the risk from other types is not negligible. The prevalence of cervical lesions associated with non-16/18 HPV types observed in our cohort is consistent with findings from Sung et al. (2016), who highlighted significant risk stratification among non-16/18 high-risk HPV genotypes. These authors emphasize the variability in oncogenic potential among these types, suggesting a more nuanced approach in risk assessment and management strategies (6). Xiao et al. (2022) identified specific risk factors for cervical cytological abnormalities among women infected with non-16/18 high-risk HPV. Their cross-sectional study underlines similar trends noted in our research, where demographic factors such as low educational attainment and high prevalence of smoking significantly correlate with increased cervical disease risk among these HPV types (7). Robadi et al. (2018) further support our argument by demonstrating the clinical importance of these other high-risk HPV types in the development of cervical neoplasia. Their research advocates for expanded screening protocols that encompass a wider range of high-risk HPV types to effectively mitigate the risk of cervical cancer (8). Moreover, the study by Wang et al. (2021) on the risks for cervical abnormalities in a South Shanghai cohort underscores the geographic variability in HPV type distribution and its implications for local screening strategies. This reinforces the need for region-specific public health interventions that consider local epidemiological data on HPV prevalence and type distribution (9). The study by Wang et al. conducted a large cross-sectional study of 25,173 women in Tibet to evaluate HPV genotype distribution and its correlation with cervical lesions. They found a diverse distribution of HPV genotypes with a notable presence of non-16/18 types (10). Both Bai et al. (11) and Tang et al. (12) emphasized the significance of non-16/18 HPV types in cervical cancer pathology, similar to findings in Wang et al. Bai et al. pointed out the diagnostic value of these types in high-grade cervical lesions among cytology-negative women, suggesting a need for their inclusion in screening protocols. Tang et al. provided extensive data on the genotype distribution, supporting the idea that a wider range of HPV types contributes to cervical cancer risks. Similar to the study by Wang et al. (10), our research considers geographical and demographic factors that can influence the prevalence of HPV types. However, it's important to note that our sample size and scope are significantly smaller, which limits direct comparisons. Despite these differences, our findings also support the need for tailored screening strategies that consider local demographic and environmental factors.

Study limitations: While our study contributes valuable insights, the limitations include a relatively small sample size and a retrospective design that may impact the generalizability of the findings. Future research should aim to include larger, prospective cohorts to validate these results and potentially influence changes in current screening recommendations.

Conclusion

Considering the substantial role of non-16/18 HPV types in cervical carcinogenesis, as highlighted by this study and supported by recent literature, future research should focus on longitudinal studies to track the progression of cervical abnormalities in women infected with these types. Such studies could help refine the risk models and screening guidelines, ensuring they are inclusive of all high-risk HPV types to better prevent cervical cancer globally.

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