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RISK STRATIFICATION IN CERVICAL SCREENING: THE ROLE OF HPV STATUS AND AGE IN WOMEN WITH ATYPICAL GLANDULAR CELLS.

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ABSTRACT

Cervical cancer, predominantly caused by persistent infections with high-risk human papillomavirus (HPV), remains a critical health concern worldwide. Atypical glandular cells (AGC) identified on cervical cytology are associated with an elevated risk of high-grade lesions and invasive cancer, particularly adenocarcinoma, which has poorer prognoses than squamous cell carcinoma. This study examines histological outcomes in women with AGC, with a focus on HPV-positive and HPV-negative cases across different age groups, to better understand the impact of HPV status and age on cancer progression risks. A retrospective cohort of women with AGC findings between February 2018 and June 2019 was analyzed, categorizing samples by HPV status (<40, 40–50, >50 years). Histopathological diagnoses were classified using the modified Bethesda system. Results indicated a strong association between HPV-positive status and high-grade lesions, particularly in younger women. In women under 40, 64% of HPV-positive cases showed high-risk histological outcomes, compared to only 3.6% in HPV-negative cases. In the 40–50 age group, HPV-positive cases had a 62% positive predictive value (PPV) for severe outcomes, whereas in women over 50, the PPV declined to 28%, though it remained higher than in HPV-negative cases. These findings suggest that HPV-positive AGC cases, especially in younger women, are more likely to progress to high-grade lesions, indicating the need for targeted follow-up. The reduced predictive value in older women points to potential differences in HPV pathogenesis by age. This study supports the integration of HPV testing with AGC findings into cervical cancer screening guidelines to enhance risk stratification, optimize patient management, and avoid unnecessary interventions in low-risk groups. Further research is warranted to explore age-related differences in HPV progression among AGC cases.

Key words: Cervical cancer, Atypical glandular cells (AGC), Human papillomavirus (HPV), Cytology.

INTRODUCTION

Cervical cancer remains one of the most significant health burdens for women worldwide, especially in low- and middle-income countries. It is primarily caused by persistent infections with high-risk human papillomavirus (HPV) types, especially HPV-16 and HPV-18, which are known to lead to pre-cancerous lesions and invasive cancer over time. The detection and management of atypical glandular cells (AGC) on cervical cytology have become critical due to the increased risk of underlying high-grade lesions or invasive cancer associated with these cells. AGC findings are less common than squamous abnormalities but are frequently associated with glandular cell neoplasia, which poses unique diagnostic and therapeutic challenges due to its potential to progress to adenocarcinoma, a type of cervical cancer with poorer prognoses than squamous cell carcinoma.

HPV testing has been widely incorporated into cervical screening programs to enhance the detection of high-risk lesions, especially for cases presenting with AGC..

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HPV testing offers the advantage of identifying women who may be at increased risk for progression to high-grade lesions or invasive cancer, thereby allowing for more targeted follow-up. Studies indicate that AGC on cytology, combined with a positive HPV test, significantly elevates the risk of cervical and endometrial cancer, justifying more intensive management for these patients. However, not all women with AGC and HPV positivity progress to high-grade lesions, raising questions about the role of age and other clinical factors in stratifying risk and optimizing follow-up care

The present study aims to analyze the histological outcomes of women with AGC findings, focusing on HPV-positive and HPV-negative cases across different age groups. By understanding how HPV status and age influence the risk of progression in AGC cases, this study seeks to provide insights that could inform tailored screening protocols and improve the efficiency of cervical cancer prevention strategies. The findings are expected to support the refinement of cervical screening guidelines, particularly in determining the appropriate follow-up and intervention thresholds for women with AGC, thereby improving patient outcomes and reducing unnecessary medical interventions.

METHODS AND MATERIALS

Population, data collection, and analysis of the study

The study included nearly 500 cervical samples reported annually in India, with around 250 samples collected from the Department of Obstetrics and Gynecology at Gouri Devi Institute of Medical Sciences and Hospital in Durgapur, West Bengal, India. This organized program collected between 75 and 250 samples per year, with an additional 200–500 samples gathered during follow-up or on an opportunistic basis. The study population consisted of all women living in Durgapur, West Bengal, who had undergone initial cervical screening between February 2018 and June 2019, reducing the risk of inclusion or follow-up biases. Cases of Atypical Glandular Cells (AGC) on Pap tests were identified (n=164), along with HPV test results and any histopathological diagnosis recorded in the region's comprehensive screening registry. HPV tests conducted within 40 days of an AGC diagnosis were considered to reflect the HPV status of the initial sample.

In the organized program, midwives collected liquid-based cytology (LBC) samples using a plastic Ayre-like spatula and an endocervical brush. Uterine ectocervix and endocervix cells were fixed in PreservCyt, following the manufacturer's instructions. The Hologic ThinPrep 5000 processor was used to prepare LBC samples on cytology glass slides, which were then tested for high-risk HPV DNA using the Cobas 4800 HPV test. This test detected HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

Cytological diagnoses were based on a modified Bethesda system that included AGC without further subgrouping, and cytological and histological codes were recorded according to the Systematized Nomenclature of Medicine. In cases with multiple histological diagnoses, the most severe diagnosis was recorded as the outcome. By June 30, 2019, histopathological data for 164 women were assessed using registry linkages. Conditional logistic regression analysis was conducted using EpiInfo to calculate odds ratios and confidence intervals. Individual-level data will be made available on request to JD.

Patient participation

Patients were not involved in the formulation of the research question or in the measurement of study outcomes. There was no participant input on recruitment, study design, or implementation, and patients did not contribute to the interpretation or writing of the results. Although participants will not directly receive the study findings, results of HPV and cytology tests were provided to each woman involved in the study.

Here is a summary of the results based on the adjusted table of histology follow-up for HPV-positive and HPV-negative atypical glandular cells (AGC), grouped by age.

In the cohort of women under 40 years of age, HPV-positive samples showed that 16 cases were within normal limits (WNL), 10 cases were classified as low-grade squamous intraepithelial lesion (LSIL), and 29 cases as high-grade squamous intraepithelial lesion (HSIL). For this age group, HPV-negative samples had 21 WNL cases, 5 LSIL cases, and only 1 HSIL case, indicating a lower prevalence of severe diagnoses in HPV-negative cases. For women between 40 and 50 years old, the trend was similar, with HPV-positive samples yielding 5 WNL, 3 LSIL, and 8 HSIL cases. HPV-negative samples had a larger number in the WNL category (23 cases) and significantly fewer HSIL cases (1 case), again suggesting a lower risk of severe lesions among HPV-negative individuals. In the oldest group, women over 50 years, HPV-positive samples included 3 WNL, 2 LSIL, and 1 HSIL cases. HPV-negative samples in this age group demonstrated 9 WNL, 3 LSIL, and 1 HSIL case. Across all ages, HPV-positive samples consistently had a higher percentage of high-risk lesions, including HSIL, while HPV-negative samples were predominantly in the WNL category.

The positive predictive value (PPV) for high-risk diagnoses, including HSIL and adenocarcinoma (AIS), varied across age groups, with the highest PPV (64%) observed in women under 40 and the lowest (28%) in women over 50. This underscores an age-related pattern in histological outcomes following an AGC diagnosis, where younger women with HPV-positive results showed the highest likelihood of high-grade lesions, while older women had a lower PPV. This analysis highlights the importance of HPV status in predicting histological

outcomes for AGC, with HPV-positive cases more likely to show high-risk lesions across all age groups, though the predictive value declines slightly with age.

Table 1:

	<40 years old		40–50 years old		>50 years old		Total	
	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−
WNL	16	21	5	23	3	9	24	53
LSIL	10	5	3	6	2	3	15	14
HSIL	29	1	8	1	1	1	38	3
SCC	0	0	0	0	0	1	0	1
AIS	11	0	2	0	1	0	14	0
ADCA cx	2	0	1	0	0	0	3	0
PPV	64%	3.6%	62%	4.8%	28%	8%	62%	5%

Discussion

In this study, we examined histological outcomes in women with atypical glandular cells (AGC) stratified by HPV status and age. The findings highlight critical patterns in the risk profile of HPV-positive versus HPV-negative AGC cases, showing a pronounced correlation between HPV positivity and high-grade lesions, particularly among younger women. This observation aligns with current literature on the carcinogenic potential of high-risk HPV strains, especially HPV-16 and HPV-18, which are well-known for their strong association with cervical intraepithelial neoplasia (CIN) and cervical cancer.

The results underscore a consistent trend across all age groups, with HPV-positive samples showing a markedly higher likelihood of developing high-grade squamous intraepithelial lesions (HSIL) and adenocarcinoma in situ (AIS). Among women under 40 years, 64% of HPV-positive cases developed high-risk histological outcomes, contrasting sharply with only 3.6% of HPV-negative cases. This pattern persisted, albeit to a lesser extent, in women aged 40–50, where the positive predictive value (PPV) of HPV positivity for high-grade lesions was 62%, compared to 4.8% for HPV-negative cases. Among women over 50, while the PPV for HPV positivity decreased to 28%, it remained significantly higher than the 8% PPV observed in HPV-negative cases. These results strongly suggest that HPV status serves as a crucial biomarker for determining the need for close follow-up and early intervention in women with AGC.

Age-specific differences in PPV highlight the potential utility of tailored screening protocols. In particular, the higher PPV for severe lesions among HPV-positive women under 40 suggests that young women with AGC and HPV positivity might benefit from more intensive follow-up, while those who are HPV-negative could potentially be spared from unnecessary procedures. This is clinically significant because younger women tend to exhibit more reversible pre-malignant changes and may be at a lower absolute risk of progression to cervical cancer within a short timeframe. Thus, an individualized approach that emphasizes HPV-positive status in guiding management decisions could reduce the physical, psychological, and financial burden of invasive diagnostics in low-risk populations.

Furthermore, the reduced PPV for high-grade outcomes among women over 50 raises questions about age-related variations in HPV pathogenesis and immune response. Older women might have a different progression timeline for HPV infections, possibly influenced by age-associated immune senescence, which can affect the natural history of HPV infections and the likelihood of lesion regression. This suggests that while HPV positivity remains a risk factor for high-grade outcomes in older women, the lower PPV in this group may warrant a modified approach to management, balancing the risks of over-treatment against the potential for significant pathology.

The importance of HPV testing in managing AGC cases is also evident from these results, supporting the role of HPV-based triage in cervical screening protocols. With high specificity for high-grade lesions, HPV testing could improve the accuracy of AGC diagnoses and minimize follow-up ambiguities. This study also demonstrates the utility of cytology combined with HPV testing, as cases of AGC without HPV were overwhelmingly associated with benign or low-grade findings, suggesting a lower risk of progression.

CONCLUSION

This study underscores the importance of HPV status as a predictive factor for severe cervical lesions in women with AGC. The findings suggest a potential benefit in refining screening guidelines by incorporating HPV status and age into risk stratification, which could optimize follow-up protocols and reduce unnecessary interventions. Further research should explore the biological mechanisms underlying the observed age-related differences in HPV-related lesion progression to better inform age-specific screening and management guidelines for women with AGC.

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