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Differential Expression of HPV16/18 E6 in Gynecological Cancers and its Association with MMP-2 Expression

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ABSTRACT

Background. Human Papillomavirus (HPV) is the most common sexually transmitted infection, worldwide. High-risk HPV 16 and 18 remain significant factors in the development of HPV-related malignancies. In Pakistan, where HPV screening and vaccination programs are not yet widespread, exploring HPV prevalence in gynecological cancers is essential. Matrix metalloproteinase-2 (MMP-2) is an enzyme responsible for extracellular matrix degradation and contributes to tumor invasion and metastasis. This study aimed to investigate the prevalence of HPV16/18's oncoprotein E6 expression in gynecological malignancies and its relationship with MMP-2.

Methods. The study cohort included formalin-fixed paraffin embedded (FFPE) tissue biopsies from patients with cervical cancer (n= 29), ovarian cancer (n= 16), and endometrial cancer (n= 16). Immunohistochemistry was performed to evaluate the expression levels of HPV16/18 E6 and MMP-2. Protein-protein interaction was investigated using PEPPI and INTAct tools.

Results. The study found HPV16/18 E6 expression in 93% of cervical cancer cases, as compared to 12% ovarian and 18% endometrial cancer cases. This difference in expression across tissues is highly significant *($p<0.0001$),* emphasizing the strong association of E6 expression with cervical cancer. A strong correlation was also observed between E6 and MMP-2 *($p=0.001$*). When analyzed separately, only MMP-2 expression significantly predicted malignancy ($p=0.025$); however, their co-expression demonstrated a stronger association with malignant phenotype *($p=0.008$*). Interestingly, protein-protein interaction analysis suggested that E6 does not directly bind to MMP-2 but may instead act through a broader interaction network, indirectly driving disease progression.

Conclusion. HPV E6 expression has a strong association with MMP-2 and their co-expression serves as a significant predictor of malignancy.

Keywords: Human papillomavirus 16 (HPV16), endometrial and ovarian cancers, Matrix Metalloproteinase 2 (MMP2), uterine cervical neoplasms

Highlights

- Cervical cancer tissues exhibited significantly higher E6 expression as compared to both endometrial and ovarian tissues.

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- HPV16/18 E6 expression was found to be associated with MMP-2 in the majority of cervical, ovarian, and endometrial cancers.
- No evidence of direct interaction was found between HPV16/18 E6 and MMP-2 using bioinformatics approaches.

1. INTRODUCTION

The Human Papillomavirus (HPV) is a significant contributor to cervical cancer, with high risk HPV 16 and 18 being major determinants in the progression of HPV-related malignancies [1]. In Pakistan, approximately twenty (20) women are diagnosed with cervical cancer on a daily basis, placing the country among the top 10 nations with the highest female mortality rates from this disease [2]. In fact, 80% of cervical cancer cases are due to HPV high-risk serotypes 16 and 18 [3]. HPV is associated with proliferative epithelial lesions in the skin and mucosa of the lower vaginal tract, as well as many oropharyngeal and upper aerodigestive tract sites. However, its role in the upper genital tract cancers, including endometrial and ovarian cancer remains controversial [4]. Pakistan, a lower-middle-income country with a high incidence of cervical cancer, lacks a comprehensive nationwide HPV screening and vaccination program. The effectiveness of a vaccine in reducing disease burden depends on its acceptance and uptake within the community. Lack of routine testing and large-scale HPV screening hinder the implementation of an effective vaccination program. Therefore, in the context of Pakistan, where HPV screening and vaccination programs are not yet widespread, the exploration of its etiological role in gynecological cancers remains essential.

The pathogenesis of HPV-induced malignancies is intricately connected to the expression of the HPV E6 protein, which is pivotal in disease onset and progression. Matrix Metalloproteinases (MMPs) have been linked to patient prognosis in HPV associated cancers and are key mediators of extracellular matrix degradation [5]. HPV E6 and E7 promote their activity and contribute towards cell migration [6, 7]. MMPs are proteases involved in degrading extracellular matrix (ECM), a crucial process for cancer cell migration and metastasis [8].

Although several MMPs have been observed in invasive cervical cancer, only MMP-2 [9] and MMP-9 [10] have been successfully associated with poor disease outcome in patients. MMP-2 has a verified role in cancer pathogenesis. Its expression in cervical cancers has been linked to HPV infection, with high-risk HPV16/18 E6 associated with upregulated MMP-2 expression [11, 12]. Enhanced MMP-2 expression has been observed in HPV 16/18–positive cell lines [13]. High MMP-2 expressions have been observed in high-grade cervical lesions, but not in normal cervix or low-grade lesions, suggesting MMP-2 as a potential biomarker for cervical cancer and advanced pre-malignant lesions [14-16]. Data from The Cancer Genome Atlas (TCGA) indicated that MMPs 2 and 9 are expressed in HPV positive and HPV negative lesions. However, MMP overexpression was correlated with poor 5-year survival in HPV positive patients only, suggesting different roles for these proteins in HPV positive and negative lesions [17]. Herbster *et al.,* demonstrated that the expression of MMP-2 and its regulator TIMP-2 plays a crucial role in the invasive capacity of cervical tumor and their metastatic potential [16]. These findings indicate that MMPs are regulated through specific mechanisms in HPV-induced cancers and contribute uniquely to cancer aggressiveness.

The detection and prognostic potential of HPV E6 stem from its exclusive expression in transformed human cells, where it serves as a crucial factor in driving malignancy [18, 19]. Identifying the correlation between E6 expression and MMPs in gynecological cancers could serve as a promising prognostic indicator, shedding light on the potential role of HPV E6 in predicting disease outcome.

Previously, immunohistochemical detection of E6 was demonstrated to provide more conclusive evidence regarding the etiological involvement of HPV subtypes in cervical cancer [20]. This technique allows us to detect the actual expression of E6 which reflects its functional activity in tumor cells, rather than just the presence of viral DNA. Since this study is aimed to explore the association between E6 and MMP-2, measuring protein expression was more relevant to understanding the biological role of HPV in cancer progression. Hence, the current study aims to extend the detection of HPV16/18 E6 to ovarian and endometrial cancers, thereby broadening our understanding of its role in gynecological malignancies.

2. MATERIALS AND METHODS

2.1. Patient Group

The study included formalin-fixed paraffin embedded (FFPE) tissue biopsies of cervical cancer (n= 29), ovarian cancer (n= 16), and endometrial cancer (n= 16) from Kulsum International Hospital (Islamabad) and the Pakistan Institute of Medical Sciences (PIMS), Islamabad. Tissue samples were obtained from these hospitals after approval from the ethical committee, while ensuring that their personal information remained confidential. The age of the study participants ranged from 25 to 86 years. Of the 61 participants, 11 (18%) were younger than 45 years, while 50 (82%) were 45 years or older. In the cervical cancer cohort, there were 21 cases of squamous carcinoma, 5 cases of adenocarcinoma, and 3 cases of carcinoma-in-situ. Among the ovarian cancer samples, 11 cases were classified as serous, 1 as squamous carcinoma, and 4 as adenocarcinoma. For endometrial cancer, the cohort included 13 cases of endometrioid adenocarcinoma, 1 case of inflamed endocervical polyp with squamous metaplasia, and 2 cases of serous carcinoma. Male genital cancers were excluded from the study.

2.2. Immunohistochemical Analysis of Samples

Immunohistochemistry (IHC) was performed on the collected slides comprising FFPE biopsies and tissue sections of 4µm thickness to evaluate the expression of HPV16/18 E6 protein in cervical, ovarian, and endometrial cancers by using the protocol described previously in our study (20). The tissue sections were incubated separately with primary antibody mouse monoclonal anti-HPV16/18 E6 antibody (ab70; Abcam, UK) and anti-MMP-2 antibody (ab86607) overnight. HRP labeled goat anti-mouse secondary antibody (ab47827; Abcam, UK) incubation was done at room temperature for 1 hour. DAB staining kit (Abcam Cat: ab64238, UK) was used for detection. Counterstaining of tissue sections was carried out through hematoxylin. For negative control, 1% BSA solution was used.

2.3. Staining Evaluation

Visualization of the slides and staining assessment was carried out by using IRMECO Biological Laboratory Microscope (UK) at ×100 and Scope Image 9.0 software for each section. Positive staining was defined as brown color staining observed in the epithelial cells. It was measured by counting positive cells at 100X in 3

representative high-power fields for each section. The scoring of the expression was conducted according to the staining observed as follows: 0 for negative staining, 1 for positive staining.

2.4. Statistical Analysis

The association between HPV16/18 E6, MMP-2 expression, and clinicopathological features was determined using the Chi-square test. Binary logistic regression was conducted to evaluate the predictive contribution of E6 and MMP-2. Due to limited sample size and distribution constraints within certain categories, the analysis was performed using a univariate model. Confounders such as age and tumor grade were not included as covariates to avoid model overfitting. The dependent variable was the binary outcome of malignancy (malignant vs non-malignant). The primary independent variable (E6 and MMP-2 co-expression) was treated as a categorical predictor with four levels, where null expression was used as the reference group.

When comparing expressions across different cancers or tissue types, the study started with Kruskal-Wallis H test to detect overall difference. For more detailed pairwise comparisons, the test was followed by Mann-Whitney U tests. The Statistical Package for Social Sciences (version 21.0) was used to conduct statistical tests (SPSS Inc., Chicago, IL, USA) and *p*-value less than 0.05 was considered as statistically significant.

2.5. Protein-Protein Interaction analysis

To predict the interaction between MMP-2 and E6, protein-protein interaction prediction tool (PEPPI) was used. Based upon the amino acid sequence, PEPPI predicts the likelihood of a direct physical interaction by making use of several independent prediction methods, such as structural modeling, sequence homology, and machine learning based classification [21]. To determine the experimentally proven interactions of MMP-2 and E6 with other proteins, protein-protein interaction data visualization tool INTAct was used [22].

3. RESULTS

The study sample included a total of 61 tissue biopsies from patients aged 25 to 86. Among these samples, 29 were cases of cervical cancer, 16 of ovarian cancer, and 16 of endometrial cancer. Clinicopathological features including age, tumor grades, and malignancy status were recorded from clinical reports. Among 61 samples tested for HPV16/18 E6, the expression was observed in all three types of gynecological cancers: 93% (27/29) in cervical, 12.5% (2/16) in ovarian, and 18.7% (3/16) in endometrial cancers (Figure 1). The overall HPV16/18 E6 positivity was 52% across the combined cases. Among the tumors examined, 67% of the tumors were found to be positive for MMP-2 expression (Figure 2). Various factors, including age, grade, and malignancy were examined in connection with HPV16/18 E6 and MMP-2.

3.1. Significant Expression of HPV16/18 E6 in Cervical Cancer Only

The Kruskal-Wallis test revealed a significant difference in E6 expression among tissue types ($H = 18.54$, $p < 0.0001$) (Table. 1 and Figure 3). Subsequent pairwise Mann-Whitney U tests (Bonferroni-adjusted) demonstrated that cervical tissues exhibited significantly higher E6 expression, as compared to both endometrial and ovarian tissues. On the contrary, MMP-2 expression showed no significant variation across tissue types, although cervical samples showed a higher expression.

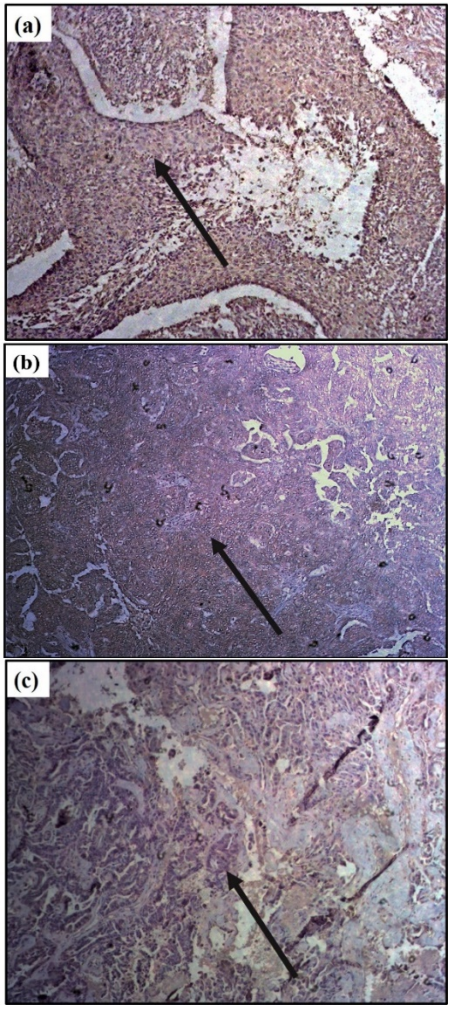

Figure 1. Immunohistochemical Staining of Gynecological Cancer Tissue with HPV16/18 E6. (a–c) HPV16/18E6 Expression in a) Cervical Cancer; b) Ovarian Cancer; c) Endometrial Cancer. Black Arrows Heads Indicate Tumor Cells; Positive Staining Was Defined as Brown Color Staining Observed in The Epithelial Cells and It Was Measured by Counting the Positive Cells At 100X In 3 Representative High-Power Fields for Each Section (Original Magnification 100X).

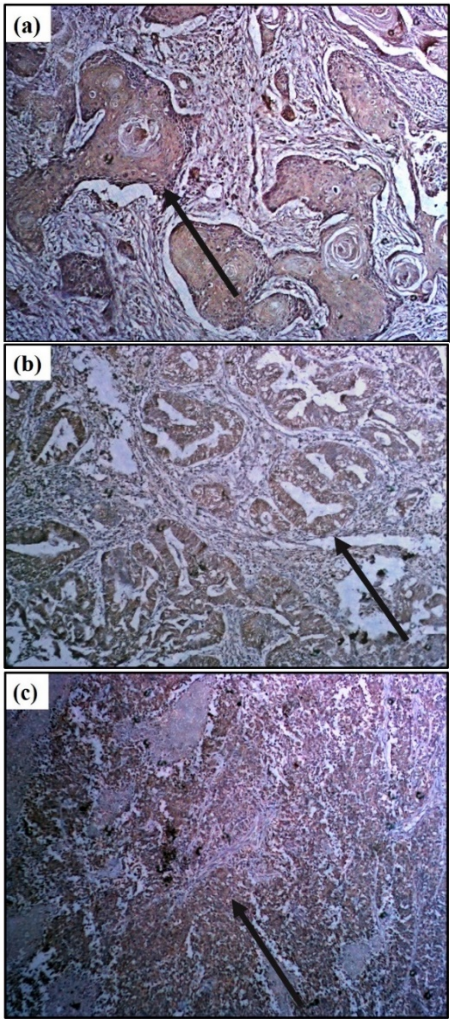

Figure. 2. Immunohistochemical Staining of Gynecological Cancer Tissue with MMP-2. (a–c) MMP-2 Expression in a) Cervical Cancer; b) Ovarian Cancer; c) Endometrial Cancer. Black Arrows Heads Indicate Tumor Cells; Positive Staining Was Defined as Brown Color Staining Observed in The Epithelial Cells and It Was Measured by Counting the Positive Cells At 100X In 3 Representative High-Power Fields for Each Section (Original Magnification 100X).

Table 1. Comparison of HPV E6 and MMP-2 Expression across Cervical, Endometrial and Ovarian Cancers

Marker	Cancer Type	Kruskal–Wallis H	*p*-value
E6 Exp	Cervical Cancer Endometrial Cancer Ovarian Cancer	H = 18.54	< 0.0001
MMP-2	Cervical Cancer Endometrial Cancer Ovarian Cancer	H = 5.09	0.082

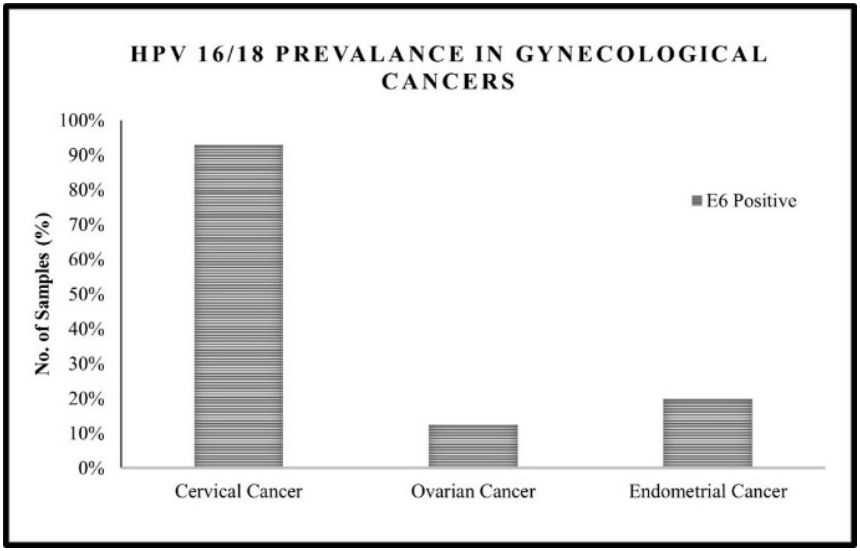

Figure 3: Detection of Positive HPV16/18 E6 Expression across Different Types of Gynecological Cancers (Cervical, Ovarian, and Endometrial) in The Twin Cities Of Rawalpindi and Islamabad

3.2. Strong Association of HPV16/18 E6 Expression with MMP-2

HPV16/18 E6 expression was found to be associated with MMP-2 in majority of the samples examined. Among the 32 samples positive for E6 expression, 28 (88%) also showed MMP-2 expression. A statistically significant moderate positive correlation was found between both proteins (χ^2=17.736, p=0.001, n =61) (Table.2 and Figure 4).

Table 2. Association of HPV16/18 E6 Expression with MMP-2 Expression

Marker	Expression Status	E6 Positive (n=32)	χ^2	*p*-value
MMP-2	Positive (n=28)	88%	17.736	*0.001*
	Negative (n=4)	13%		

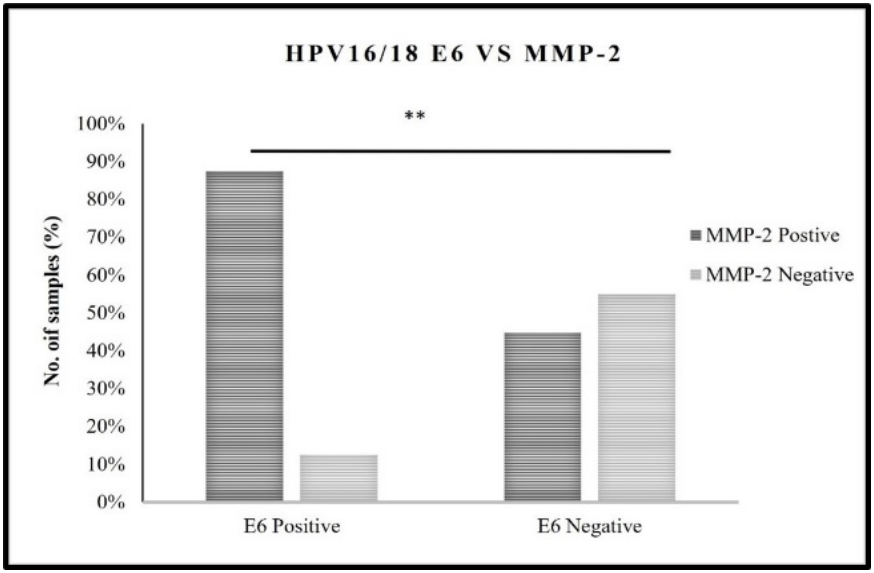

Figure 4. Association of E6 and MMP-2 Expression in Gynecological Cancer Tissue Sections

3.3. Co-expression of HPV16/18 E6 and MMP-2 is Associated with Malignancy

Malignancy was reported in 39 cases. Tissue classification as malignant or non-malignant was based on histopathological evaluation by trained pathologists according to WHO criteria, considering features such as cellular atypia, mitotic activity, and stromal invasion. Immunohistochemical analysis revealed a variable expression of HPV E6 and MMP-2 proteins among all 3 cancers. Both proteins showed a higher expression in malignant tissues as compared to non-malignant samples, although only MMP-2 showed a significant positive association with malignant phenotype (χ^2= 7.923, *p=0.015*). However, when their combined expression was analyzed, a stronger association was observed with malignant phenotype (χ^2= 13.692, *p=0.008*). A higher proportion of malignant cases was observed among samples exhibiting co-expression, as compared to those with no expression (Table 3).

Table 3. Association of Marker Expression with Malignancy

Marker	Expression Status	Malignant cases (*n*=39)	χ^2	*p*-value
MMP-2	Positive (n=29)	74%	7.923	0.015
	Negative (n=10)	26%		
E6–MMP-2 Co-expression	Positive (n=23)	82%	13.692	0.008
	Negative (n=6)	18%		

A binary logistic regression test was also performed to evaluate the predictive effects of E6 and MMP-2 on malignancy. Among both proteins, MMP-2 expression was the only significant predictor of malignancy (OR= 4.17, 95% CI: 1.19-14.54, *p= 0.025*) in cervical, endometrial, and ovarian cancers.

3.4. No Direct Interaction between HPV16/18 E6 and MMP-2 Detected

Once it became evident that a correlation does exist between the expressions of E6 and MMP-2, we sought to predict a direct physical interaction between these two proteins. The prediction of such an interaction would enhance the current understanding of their role in the development and progression of HPV induced gynecological cancers. To achieve this, protein-protein interaction prediction tool (PEPPI) was used. Based on the amino acids sequence comparison, PEPPI predicts the likelihood of a direct physical interaction by making use of several independent prediction methods. The PEPPI analysis ruled out any direct interaction between HPV16/18 E6 and MMP-2 proteins (Figure 5 and 6). Similarly, INTAct was used to find the experimentally proven interactions of MMP-2 and E6 with other proteins [22]. This suggests that the observed association between E6 and MMP-2 expression is indirect, possibly mediated through intermediate regulatory factors, such as transcriptional controls and signaling cascades.

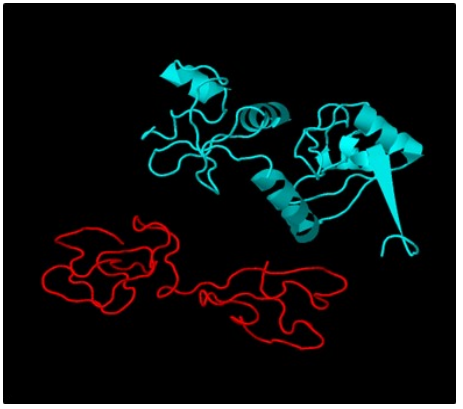

Figure 5. Physical Interaction Prediction by PEPPI. MMP-2 (Blue) and HPV16 E6 (Red) Shows No Direct Physical Interaction.

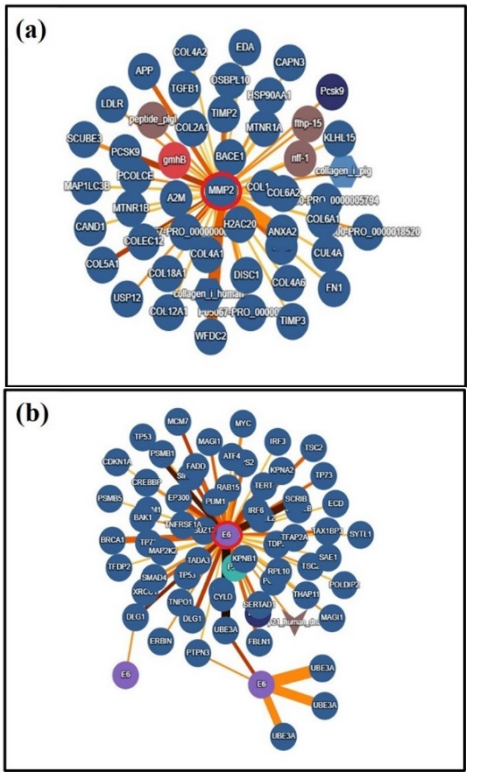

Figure 6. Protein-protein Interaction Using Data Visualization Tool INTAct. Proteins Which Have Been Shown Experimentally to Be Interacting with a) Human MMP-2 and b) HPV16 E6

4. DISCUSSION

The expression levels of HPV oncoproteins E6 and E7 provide critical insights into the course of infections and the prognosis of HPV associated diseases [23]. While HPV's involvement in cervical cancer is well-established, reports on its prevalence in endometrial and ovarian cancer vary considerably [24-27].

The upregulation of MMPs has been observed in various human carcinoma. It correlates with increased invasiveness, metastasis, and poor prognostic outcomes (8, 28-30). MMPs are involved in remodeling

the extracellular matrix (ECM) and releasing growth factors during early tumorigenesis, creating a microenvironment conducive to primary tumor establishment [31]. HPV-induced cancers progress through a complex series of stages, starting from precursor intraepithelial lesions. The transition from these intraepithelial lesions to invasive cancers is heavily influenced by the altered expression and distribution of MMPs [32].

The expression of MMP-2 and its tissue inhibitor regulating type 2 metalloproteinases (TIMP-2) was observed to be fundamental to the invasive behavior and metastatic potential of cervical tumors (16). In cervical cancer, the HPV oncoproteins E6/E7 have been shown to promote MT1-MMP, MMP-2, and MMP-9 (6). Enhanced MMP-2 expression has been observed as well in HPV 16/18–positive cell lines [13]. Consistent with these findings, the current results demonstrate that E6 expression is associated with MMP-2 expression which, in turn, impacts disease prognosis. Most samples co-expressing higher E6 and MMP-2 were strongly correlated with malignancy. Previous studies confirmed higher levels of E6 and E7 mRNA in malignant cervical cancers, as compared to pre-malignant lesions [33]. The current analysis demonstrates that HPV E6 and MMP-2 expression pattern are interrelated and contribute to the malignant phenotype. Studies examining the interplay between HPV E6 and MMP-2 consistently indicate that their relationship is non-linear and driven by multiple regulatory layers, rather than a simple dose dependent effect. Since the interaction is not direct, E6 may modulate its effect through a regulatory mechanism, possibly through pathways involving p53 suppression or epithelial to mesenchymal transition.

The lack of routine screening for HPV oncoproteins at early disease stages continues to negatively influence prognosis and clinical outcomes. Many studies have established the usefulness of oncoprotein detection as an etiological marker for HPV. Simple PCR detection of HPV DNA does not show the etiological involvement of HPV in any cancer, as many infections resolve on their own. In a previous study, we established the importance of detecting E6 as an etiological marker in cervical cancer [20]. The findings reinforce the established etiological role of HPV in cervical cancer by highlighting the significant expression of E6 exclusively in cervical cancer and not in endometrial or ovarian cancers.

To the best of our knowledge, this is the first study from Pakistan to examine HPV etiology and association with MMP-2 across 3 gynecological cancers. However, these were preliminary findings and to establish HPV's role in endometrial and ovarian cancers requires further studies with larger cohorts. Nonetheless, the strong correlation observed between E6 and MMP-2 expression emphasizes the functional interplay between these proteins in driving cervical malignancy. Their heightened co-expression enhances their invasive potential, while contributing to poor disease prognosis. The bioinformatics analysis, which revealed no direct interaction between E6 and MMP-2, implied an indirect interaction, possibly through other molecules. E6 may affect MMP-2 expression by interacting with other proteins, suggesting that both are part of a larger protein interaction network in HPV induced cancers (Figure 5). However, more studies are required to elucidate it mechanistically.

4.1. Conclusion

- The current research has strived to extend the focus beyond cervical cancer to include ovarian and endometrial

cancers, thereby broadening the understanding of HPV's oncogenic potential.

- While establishing a foundation for subsequent studies, the current work holds promise for improving clinical outcomes and enhances awareness of HPV in Pakistan.
- A key limitation is the retrospective design of the study which results in the generation of incomplete data; thus prospective studies with larger samples sizes are recommended.

4.2. Prospects for further research.

Future research should evaluate these findings in larger cohorts to confirm the association of E6 with MMP-2 in gynecological malignancies. Investigating additional predictors and conducting longitudinal studies would also be valuable to understand temporal changes in E6 expression and disease development.

Author Contribution

Sabreen Abdul Qayyum: Investigation, Methodology, Visualization. **Shagufta Maroof:** Investigation, Methodology, Visualization. **Sobia Tabassum:** Project administration, Funding acquisition, Resources. **Aamna Dilshad:** Data curation, Methodology, Visualization. **Huma Saifullah:** Data curation, Formal analysis. **Ammad Aslam Khan:** Methodology, Writing – review & editing, Software. **Naureen Ehsan Ilahi:** Conceptualization, Supervision, Funding Acquisition, Formal Analysis, Software, Writing – original draft

Conflict of Interest

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

Data Availability Statement

Data supporting the findings of this study will be made available by the corresponding author upon request.

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Generative AI Disclosure Statement

The authors did not use any type of generative artificial intelligence software for this research.

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