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Integrative Molecular Profiling of Cervical Cancer Subtypes: Biomarkers, Molecular Pathways, and Precision Oncology Implications

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ABSTRACT

Cervical cancer remains one of the most prevalent malignancies affecting women globally, with a disproportionate burden in low-resource settings where screening and vaccination programs are limited. Persistent infection with high-risk human papillomavirus (HPV) strains is the primary etiological factor, leading to the expression of E6 and E7 oncoproteins that disrupt tumor suppressor pathways, including p53 and retinoblastoma protein, thereby promoting uncontrolled cell proliferation and genomic instability. Histologically, cervical cancer is classified into squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and neuroendocrine carcinoma, each exhibiting distinct molecular alterations. Squamous cell carcinoma, the most common subtype, is frequently associated with PIK3CA mutations, while adenocarcinomas demonstrate ERBB2 amplification and KRAS mutations. Rare subtypes such as adenosquamous and neuroendocrine carcinomas show mixed or aggressive molecular profiles. Key signaling pathways—including PI3K/AKT/mTOR, RAS/MAPK, Wnt/β-catenin, and JAK/STAT—contribute to tumor initiation, progression, and metastasis. Molecular biomarkers have become pivotal in clinical management: diagnostic markers such as p16^INK4a, HPV DNA, and E6/E7 mRNA facilitate early detection; prognostic markers, including TP53 mutations and Ki-67 proliferation index, inform disease outcome; and predictive markers like PD-L1 expression guide immunotherapy decisions. The integration of multi-omics approaches, encompassing genomics, transcriptomics, proteomics, and epigenomics, has enhanced tumor profiling, enabling the identification of novel therapeutic targets. These advances underpin precision medicine strategies, including PI3K inhibitors, immune checkpoint blockade, and anti-angiogenic therapies, aiming to improve treatment efficacy and minimize toxicity. Overall, cervical cancer is a molecularly heterogeneous disease, and combining histopathological classification with molecular characterization is critical for accurate diagnosis, risk stratification, and personalized therapy. Continued research into the molecular landscape of cervical cancer promises to advance targeted interventions and improve patient outcomes globally.

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Introduction

One of the most prevalent cancers affecting women, cervical cancer is a significant global public health issue, especially in poorer nations where screening programs and immunization rates are still low. The condition is mostly linked to oncogenic human papillomavirus (HPV) infections that are persistent and cause a series of molecular changes that result in malignant transformation [1,2].

Cervical intraepithelial neoplasia, invasive carcinoma, and persistent HPV infection are the first steps in the multistep process of cervical carcinogenesis. The overexpression of the E6 and E7 oncoproteins caused by viral integration into the host genome disrupts important tumor suppressor mechanisms and encourages unchecked cell cycle progression [3,4].

Cervical cancer has historically been divided into squamous cell carcinoma, adenocarcinoma, and other less prevalent variations according to histological characteristics. However, significant variation within these histological subtypes has been discovered thanks to developments in molecular biology and high-throughput sequencing. Our knowledge of the pathophysiology of cervical cancer has been revolutionized by the incorporation of molecular profiling into tumor categorization, which has also created new opportunities for targeted treatment [5,6].

Histopathological Subtypes of Cervical Cancer

Squamous Cell Carcinoma

The squamous epithelium of the ectocervix is the source of squamous cell carcinoma, which makes up 70–80% of instances of cervical cancer. This subtype is closely linked to high-risk HPV infection, especially HPV-16. Mutations in PIK3CA and other genes implicated in the PI3K/AKT signaling pathway have been often found in molecular research.

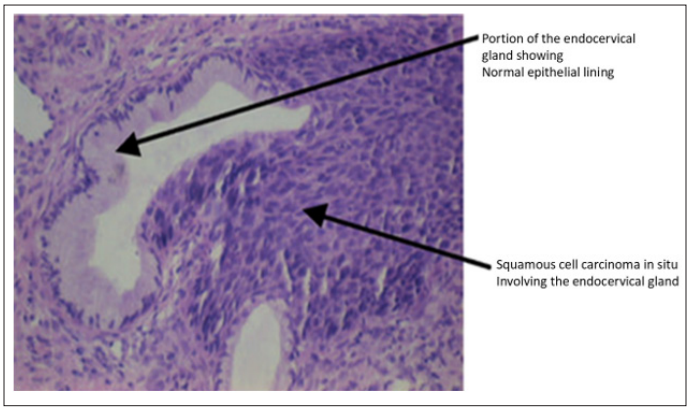

Figure 1: Showing Squamous Cell Carcinoma in Situ in an Endocervical Tissue Section(Adapted From Google Picture)

Adenocarcinoma

About 15–20% of cervical malignancies are adenocarcinomas, which originate from the glandular epithelium of the endocervix. In recent decades, adenocarcinoma has become more common. When compared to squamous cell carcinoma, molecular profiling shows unique genetic changes, such as ERBB2 amplification and KRAS mutations [7].

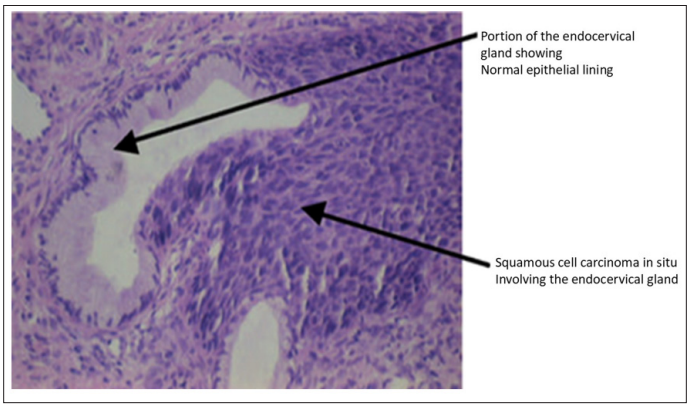

Figure 2: Shows Adenocarcinoma of the Cervix with Papillary Projections (Picture Adapted from the Google)

Adenosquamous Carcinoma

Adenosquamous carcinoma is a rare subtype characterized by the presence of both glandular and squamous differentiation. This tumor type tends to exhibit aggressive clinical behavior and demonstrates mixed molecular characteristics derived from both epithelial components.

Neuroendocrine Cervical Carcinoma

Cervical neuroendocrine carcinoma is an uncommon but extremely aggressive cancer with a dismal prognosis. Tumor suppressor genes and signaling pathways involved in cell cycle regulation are frequently altered, according to molecular research.

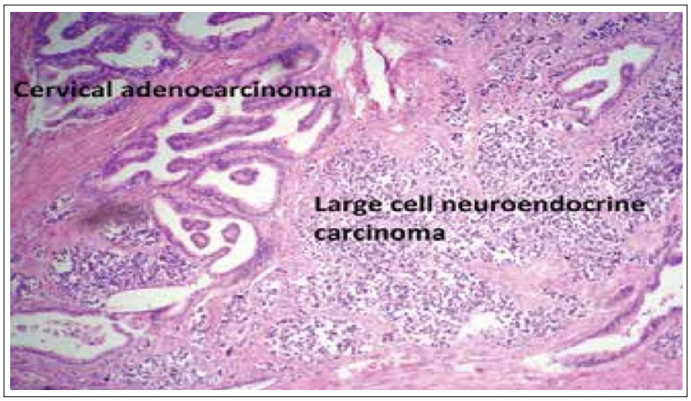

Figure 3: Shows Concomitant Existence of Cervical Adenocarcinoma and Neuroendocrine Carcinoma in A Section of the Endocervical Tissue Section (Picture Adapted from the Google)

Molecular Pathogenesis of Cervical Cancer

• Role of HPV Infection

Cervical carcinogenesis is mostly initiated by persistent infection with high-risk HPV strains. The E6 and E7 oncogenes are continuously expressed when viral DNA is integrated into the host genome [8].

• E6 Oncoprotein

Through ubiquitin-mediated proteasomal processes, the E6 protein facilitates the tumor suppressor p53's destruction. Genetically unstable cells can survive when p53 function is lost because it hinders DNA damage response systems and stops apoptosis. E6 also stimulates telomerase activation and promotes cellular immortalization by upregulating human telomerase reverse transcriptase [9].

• E7 Oncoprotein

The retinoblastoma protein (RB) is bound and degraded by the E7 protein, which interferes with cell cycle regulation. The E2F transcription factor, which promotes the transcription of genes necessary for S-phase entry and DNA replication, is released by this interaction. E6 also stimulates telomerase activation and promotes cellular immortalization by upregulating human telomerase reverse transcriptase.

• E7 Oncoprotein

The retinoblastoma protein (RB) is bound and targeted for degradation by the E7 protein, thereby disrupting normal cell cycle regulation. This interaction leads to the release of the E2F transcription factor, which subsequently activates the transcription of genes required for S-phase entry and DNA replication. Together, the combined actions of E6 and E7 create a cellular environment characterized by uncontrolled proliferation, genomic instability, and increased susceptibility to oncogenic transformation [10,11].

Molecular Signaling Pathways in Cervical Cancer

Multiple signaling pathways contribute to cervical cancer development and progression.

• PI3K/AKT/mTOR Pathway

In cervical cancer, the PI3K/AKT pathway is one of the most often dysregulated signaling cascades. Increased AKT activation brought on by PIK3CA mutation or amplification promotes cell migration, proliferation, and survival [12,13]

• RAS/MAPK Pathway

Mutations in KRAS and other components of the MAPK signaling pathway have been reported particularly in adenocarcinoma subtypes.

• Wnt/β-catenin Pathway
Aberrant activation of Wnt signaling contributes to tumor progression by promoting epithelial-mesenchymal transition and cellular invasion.
• JAK/STAT Pathway
The JAK/STAT pathway mediates inflammatory signaling and immune regulation and has been implicated in cervical tumor progression.

Molecular Biomarkers in Cervical Cancer
The molecular biomarkers in cervical malignancy studies can be categorized into three as follows:

• Diagnostic Biomarkers
Basically, this includes p16^INK4a expression, HPV DNA detection and HPV e6/e7 testing. The overexpressed p16^INK4a in cervical cells is indicative of high-risk HPV presence and used for detection of precancerous lesions; HPV DNA identifies the presence of high-risk HPV strains that drive cervical carcinogenesis. HPV E6/E7 mRNA testing detects transcriptionally active viral oncogenes, indicating ongoing viral -mediated transformation [14].
• Prognostic Biomarkers
TP53 mutation status is one the major prognostic markers in cervical cancer. It is a tumor suppressor whose alterations in tumor is indicative of poor prognosis and higher risk of disease progression. Next, is Ki-67 – a proliferation index measuring cell proliferation and higher levels correlate with aggressive tumor behavior and worse outcomes [15]
• Predictive Biomarkers
PD-L1 expression- a predictive marker in cervical tumors, guides immunotherapy decisions; tumors with high PD-L1 may respond better to checkpoint inhibitors [16].

These biomarkers help in early detection, risk stratification, and treatment personalization, ultimately improving patient management.

Multi-Omics Approaches in Cervical Cancer
Cancer research has been transformed by contemporary molecular technologies. To provide a thorough understanding of tumor biology, multi-omics techniques combine data from genomes, transcriptomics, proteomics, and epigenomics. These methods make it possible to find new biomarkers and treatment targets, which supports precision oncology techniques for the treatment of cervical cancer [17,18].

Precision Medicine and Targeted Therapy
Advances in molecular profiling have paved the way for targeted therapies in cervical cancer.
Examples include:
a. PI3K inhibitors targeting PI3K pathway mutations
b. Immune checkpoint inhibitors targeting PD-1/PD-L1
c. Anti-angiogenic therapies targeting VEGF signaling

The implementation of precision medicine approaches has the potential to improve treatment outcomes and reduce therapy-related toxicity [19,20].

Conclusion
Cervical cancer is a molecularly heterogeneous disease driven by complex interactions between viral oncogenes and host cellular pathways. Advances in genomic technologies have significantly improved our understanding of the molecular mechanisms underlying cervical cancer development and progression. Integrating histopathological classification with molecular profiling will enhance diagnostic accuracy, facilitate risk stratification, and guide personalized treatment strategies. Continued research into the molecular landscape of cervical cancer will be essential for the development of novel targeted therapies and improved clinical outcomes.

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