Cervical Cancer

Introduction

Cervical cancer originates in the cells of the cervix, the lower, narrow end of the uterus that connects to the vagina. It typically develops slowly, beginning with dysplasia—a precancerous condition involving abnormal cell growth. If untreated, these cells may progress to invasive cancer. The cervix comprises two main regions: the ectocervix, lined with squamous cells, and the endocervix, lined with mucus-secreting glandular cells. The squamocolumnar junction (transformation zone), where these regions meet, is the most common site of malignant transformation.

The primary histological types of cervical cancer include:

- **Squamous Cell Carcinoma (~90%):** Arises from ectocervical squamous cells.
- **Adenocarcinoma:** Originates in endocervical glandular cells; includes rare subtypes like clear cell carcinoma.
- **Adenosquamous (Mixed) Carcinoma:** Exhibits features of both major types.
- Rarely, other cell types may give rise to cervical malignancies. Understanding the cellular origin aids in diagnosis, screening, and treatment planning [1].

Incidence, Mortality and Prevalence

Category	Female
Incidence	662,301 cases
Mortality	348,874 deaths
5-Year Prevalence	1,708,000 cases

Source [2]

Diagnosis

The diagnosis of cervical cancer involves a comprehensive, multimodal approach aimed at detecting early lesions, confirming malignancy, and evaluating disease extent. Initial screening typically includes the Papanicolaou (Pap) smear and high-risk human papillomavirus (HPV) testing to identify precancerous changes and viral oncogenic drivers. Abnormal results are followed by colposcopy, which allows magnified visualization of the cervix after acetic acid application to highlight atypical epithelium. Targeted cervical biopsies—such as punch biopsy, colposcopy-guided biopsy, loop electrosurgical excision procedure (LEEP), cone biopsy, and endocervical curettage (ECC)—are performed to histologically assess cervical intraepithelial neoplasia (CIN) or invasive carcinoma. Imaging plays a crucial role in staging: MRI provides high-resolution detail of local invasion into parametrial tissues, bladder, and rectum, whereas CT is preferred for assessing lymph node involvement and distant metastasis. Advanced imaging with PET/CT can evaluate tumor metabolism and spread, with metrics such as SUVmax and metabolic tumor volume (MTV) serving as prognostic indicators. Histopathological analysis of biopsy specimens remains the definitive method for confirming diagnosis and guiding treatment [3].

Biomarkers of Cervical Cancer

Several biomarkers have shown diagnostic and prognostic value in cervical cancer. Squamous Cell Carcinoma Antigen (SCC Ag), typically under 37 U/mL, is elevated in 24–90% of patients, with higher levels indicating advanced squamous cell carcinoma. CA19-9, although non-specific, may also rise above 37 U/mL in cervical malignancy and reflects tumor burden, aiding in monitoring treatment response. CYFRA 21-1, normally <3.3 ng/mL, shows strong association with squamous histology and disease progression; its decline during therapy suggests treatment efficacy. In recent years, microRNAs such as miR-29a, miR-25, and miR-486-5p have emerged as promising non-invasive biomarkers, particularly for early-stage detection. While baseline values for these miRNAs vary, their elevated expression contributes to high sensitivity and specificity when used in multi-marker panels. These biomarkers collectively enhance early diagnosis, therapeutic monitoring, and prognostic assessment in cervical cancer [4-9].

Cytogenetics

Cytogenetic studies in cervical cancer have revealed recurrent chromosomal abnormalities that are intimately linked to HPV-driven oncogenesis. Classical and molecular techniques, such as fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH), have identified nonrandom gains and losses of chromosomal regions. Common chromosomal gains include 3q (housing TERC and PIK3CA), 5p, 8q (MYC), 11q22 (YAP1, BIRC2/3), and 7p11.2 (EGFR), which promote oncogenic signaling and proliferation. Conversely, frequent losses are seen at 3p, 4q35.2 (FAT1), 10q23.31 (PTEN), 11q, and 18q21.2 (SMAD4), suggesting the inactivation of tumor suppressor genes. FISH patterns vary with HPV subtype, showing diffuse, punctate, or mixed signals depending on the viral genotype (e.g., HPV 16 or 58), reflecting integration status and genomic instability. These chromosomal alterations not only provide insight into disease mechanisms but also offer potential targets for molecular diagnosis and therapy [10].

Pharmacogenomics

Pharmacogenomic profiling has revealed significant gene–drug interactions influencing the efficacy of cisplatin-based chemoradiation in cervical cancer. Variants in CYP2E1 (rs6413432) affect drug metabolism, with the TA/AA genotypes linked to poorer responses to cisplatin, particularly when administered concurrently with 5-FU and radiation at 40 mg/m² weekly or 75 mg/m² every 21 days. Similarly, polymorphisms in DNA repair genes such as RAD51 (rs1801320) and XRCC1 (rs25487) modulate treatment outcomes. Patients with the GC/CC genotypes of RAD51 exhibit better therapeutic responses, while those with the GG genotype of XRCC1 are associated with poorer survival. These genetic markers underscore the importance of integrating pharmacogenomic data into personalized treatment planning to optimize therapeutic outcomes in cervical cancer [11].

Treatment

Cervical cancer management involves a multidisciplinary approach encompassing surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, tailored to cancer stage, location, and patient health. Surgical interventions range from conservative procedures like cone biopsy and radical trachelectomy for early-stage disease to extensive operations such as hysterectomy and pelvic exenteration for advanced cases. Chemotherapy, especially with agents like cisplatin, carboplatin, and paclitaxel, is pivotal for locally advanced or metastatic disease, often used with radiotherapy or targeted drugs such as bevacizumab. Radiotherapy includes external beam radiation and brachytherapy, frequently used in combination to maximize local control. Targeted therapies such as bevacizumab (anti-VEGF), PARP inhibitors (e.g., olaparib), HER2-targeted agents, and immune checkpoint inhibitors like pembrolizumab have shown promise, particularly in recurrent or metastatic settings. Immunotherapy strategies ranging from checkpoint inhibitors and therapeutic vaccines to adoptive cell therapy are rapidly evolving, offering hope for durable responses, especially in HPV-driven tumors. Emerging combination regimens continue to redefine the landscape of personalized cervical cancer care [12].

Drugs for Cervical Cancer

Cervical cancer treatment leverages a spectrum of systemic agents, each with defined mechanisms and toxicity profiles. Cisplatin, a platinum-based chemotherapeutic, induces DNA cross-linking and is widely used in chemoradiation for locally advanced cases, though nephrotoxicity and ototoxicity are notable concerns. Carboplatin, another platinum analog forming DNA adducts, is preferred in recurrent/metastatic settings due to its relatively milder toxicity, with Oxaliplatin as an alternative for platinum-allergic patients. Paclitaxel, a microtubule-stabilizing taxane, is employed in combination regimens for metastatic disease but is limited by neuropathy and alopecia; Docetaxel may serve as an alternative. Bevacizumab, an anti-VEGF monoclonal antibody, is indicated for persistent or metastatic disease, though associated with hypertension and thromboembolic events. Pembrolizumab, a PD-1 inhibitor, is used in PD-L1-positive recurrent/metastatic disease, with Cemiplimab as an emerging alternative. Tisotumab vedotin, an antibody-drug conjugate targeting tissue factor, is approved for post-chemotherapy recurrence, though ocular toxicity and neuropathy warrant caution. Ifosfamide, an alkylating agent, is used second-line with mesna for bladder protection, and Topotecan, a topoisomerase I inhibitor, offers additional second-line options, with Irinotecan as an alternative under limited use [13-14].

Nutrigenomics in Cervical Cancer Prevention and Management

Nutrigenomic interventions offer promising strategies for reducing cervical cancer risk by modulating host gene expression and molecular pathways associated with HPV persistence and carcinogenesis. Compounds from plant sources such as cactus fruit, banana flower, and fig support DNA methylation and repair through folate metabolism, reducing the risk of HPV-induced malignancy. Antioxidant-rich foods like muskmelon, chayote squash, and neem fruit enhance p53 and NF-κB stabilization, mitigating DNA damage and cancer progression. Bioactive flavonoids and polyphenols, sourced from peanuts, passiflora, and green tea, modulate apoptosis and PI3K/AKT signaling, suppressing tumor growth and enhancing therapeutic sensitivity. Carotenoids, present in carrots and tomatoes, influence APOBEC activity, counteracting mutation-driven oncogenesis. Sulforaphane from cruciferous vegetables activates NRF2-mediated detoxification, while isoflavones from soy mitigate ER-driven proliferation in HPV-integrated cells. Moreover, dietary fiber and omega-3 fatty acids from flaxseed and fatty fish modulate inflammation and COX-2 expression, reducing tumor-promoting conditions. Adherence to a Mediterranean diet, rich in polyphenols and fiber, further supports anti-inflammatory and epigenetic regulation, offering a holistic dietary approach to cervical cancer prevention [15-16].

Dietary Nutrients and Food Sources in Cervical Cancer Prevention

Nutritional components such as Vitamin C, Vitamin A, Vitamin D, Vitamin E, Flavonoids, Polyphenols, Sulforaphane, Omega-3 Fatty Acids, and Folate play a significant role in reducing cervical cancer risk, especially in HPV-positive individuals. Food sources like guava, bell peppers, citrus fruits, muskmelon, and chayote squash are rich in Vitamin C, while sweet potatoes, carrots, spinach, and neem fruit provide ample Vitamin A. Additionally, salmon, flaxseeds, walnuts, and UV-treated mushrooms are excellent sources of Omega-3 fatty acids and Vitamin D. Broccoli, Brussels sprouts, and green tea contribute to anti-inflammatory and antioxidant effects, helping prevent cancer progression. Regular intake of these nutrients can potentially lower cervical cancer risk by modulating inflammation, oxidative stress, and DNA repair pathways. Monitoring these dietary components may serve as a useful adjunct in the prevention and management of cervical cancer [17].

Genes associated in Cervical Cancer

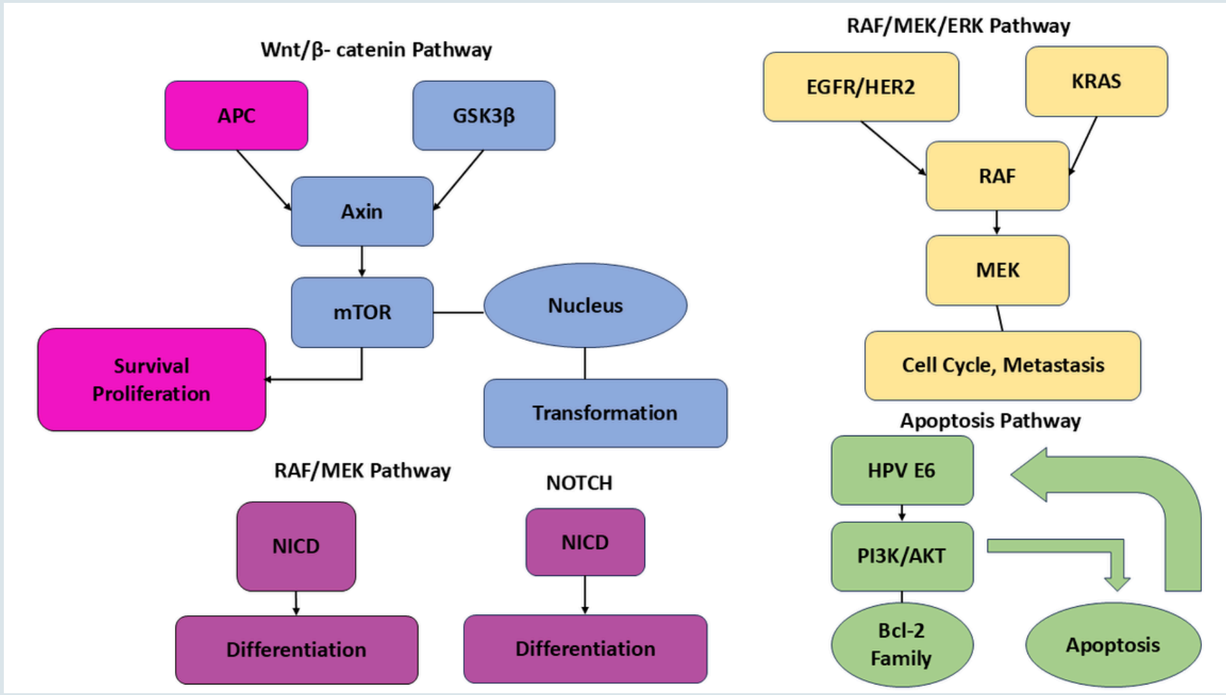
Key genetic alterations in cervical cancer include oncogenes like PIK3CA, which regulates PI3K-AKT-mTOR signaling and harbors activating mutations (E542K, E545K) driving tumor growth and resistance. Mutations in TP53 disrupt apoptosis, promoting genomic instability, while FAT1 deletions (36%) affect cell adhesion and growth regulation. BRCA1/2 mutations impair DNA repair, increasing genomic instability. ERBB3 mutations drive proliferation, making it a therapeutic target. CD274 (PD-L1) amplifications allow immune evasion, and mutations in HLA-A/B and TGFBR2 alter immune responses to HPV-infected cells. TTK overexpression correlates with poor prognosis, while FOXM1 upregulation in tumors promotes metastasis and recurrence. PAX8 and FGFR mutations contribute to tumorigenesis and therapy resistance, respectively. Epigenetic disruption by KMT2C/D mutations also plays a role in oncogenesis. Additionally, GSDMB has been GWAS-linked to cervical cancer risk, influencing inflammation. These genetic alterations are central to understanding the molecular mechanisms underlying cervical cancer progression and therapeutic resistance [18-24].

Polymorphism

Several genetic polymorphisms influence cervical cancer risk by modulating key biological pathways. Polymorphisms in the CYP1A1 gene (MspI, Ile462Val), involved in xenobiotic metabolism and activation of procarcinogens, are associated with increased cancer susceptibility. Variants in XRCC1 (Arg194Trp, Arg280His, Arg399Gln), a DNA repair gene, compromise genomic stability and are significantly linked to elevated cervical cancer risk, especially in individuals with the TT genotype. The MTHFR rs1801133 variant, crucial in folate metabolism and DNA synthesis, appears protective against cervical cancer. A polymorphism in COX-2 (+8473CC), involved in inflammatory signaling, is also linked to reduced risk. Meanwhile, the CXCL12 rs266085 polymorphism, which affects immune response, shows conflicting associations across populations. Lastly, the GSTM1 deletion (Del2), affecting detoxification of carcinogens, is correlated with heightened cervical cancer susceptibility. These polymorphic variants underscore the interplay of metabolic, DNA repair, immune, and inflammatory pathways in cervical carcinogenesis [25-28].

Cervical cancer development is closely linked to persistent high-risk HPV infection, particularly through the actions of viral oncoproteins E5, E6, and E7, which disrupt host cell signaling. The PI3K/AKT/mTOR pathway, frequently activated by E6/E7, promotes cell survival, proliferation, migration, and resistance to apoptosis, while also enabling epithelial-mesenchymal transition (EMT). Wnt/β-catenin signaling is enhanced via E6/E6AP-mediated degradation of NHERF1, leading to oncogene transcription (e.g., c-Myc, cyclin D1). The MAPK/ERK cascade is upregulated by E5-stabilized EGFR, stimulating proliferation and therapy resistance. Notch signaling is disrupted by E6-MAML1 interaction, impairing epithelial differentiation and sustaining viral persistence. The Hedgehog (Hh) pathway, upregulated in squamous cell carcinoma (SCC), contributes to tumor stemness and growth. NF-κB signaling, modulated by HPV and inflammatory cytokines, fosters immune evasion and chronic inflammation. Lastly, the JAK/STAT pathway, often upregulated via IL-6 or interferons, enhances immune suppression and tumor cell survival. Collectively, these dysregulated pathways underpin cervical carcinogenesis and therapeutic resistance [29-32].

Signalling Pathways



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Thank you