Cervical cancer represents one of the most common malignancies in women worldwide and predominantly affects women of poor socioeconomic status. Persistent infection with high-risk human papillomavirus (HPV) is an essential factor for development of cervical cancer. HPV infection is also associated with cancers of the vulva, vagina, anus, and oropharynx. Globally, an estimated 610,000 (4.8%) of the 12.7 million new cancer cases that occurred in 2008 could be attributed to HPV infection, and >500,000 of those cases represent cancers of the cervix alone (1). Within the last 2 decades, research has culminated in major advances in techniques for cervical cancer screening using HPV DNA and has led to a vaccine to prevent HPV infection. Yet, our strategies for the care and treatment of today’s patients already infected with HPV need urgent attention. Women diagnosed with invasive and metastatic cervical cancer are in critical need of more-sophisticated prognostic markers, targeted therapeutic options, and more-accurate surveillance strategies.

**Viral Integration and Oncoprotein Targets**

There are about 120 HPV types, and types 16 and 18 are associated with 70% of the cases of cervical cancer worldwide. Many studies have shown that HPV-18-associated cervical cancer is a strong independent prognostic factor for poorer disease-free survival for women undergoing surgery or radiation for early-stage invasive cervical cancer (2). The biology behind the poorer outcomes is unknown, but studies have suggested that sequence variation in HPV genes produces differences in their oncogenic potential. For example, HPV-18 E6 (E6 transforming protein) oncogene variants differentially regulate members of the Akt/P13K pathway and show increased expression of genes involved in cancer cell extravasation and metastasis (3, 4).

HPV integration into the host genome is a critical step in cervical carcinogenesis and is found in almost all invasive cervical cancers. Integration frequently disrupts HPV E2 (E2 regulatory protein) gene expression, leading to increases in E6 and E7 viral oncoproteins, which in turn promote cellular immortalization and transformation. E6 and E7 (E7 transforming protein) gene overexpression contribute to marked genomic instability, accumulation of secondary mutations, and malignant transformation (5). In addition, the virus integrates into host genes and regulatory elements, which may cause structural alteration of the host genome and transcriptional deregulation of gene expression (6). The sites of integration occur frequently at common fragile sites in the genome, but these sites may be less random than originally appreciated. Further evaluation of HPV integration sites by the various HPV types could shed light on additional cancer-causing genes.

The 8-kb HPV genomes have CpGs scattered throughout their genes. With advancing disease, these CpGs are increasingly methylated by the host cell’s DNA methyltransferases. This methylation may alter the expression patterns of viral genes that are relevant to transformation. DNA hypermethylation of the HPV genome is greater in invasive cervical carcinomas than in cervical dysplasias. Snellenberg et al. showed that methylation of several HPV-16 E2 binding sites is significantly higher in invasive cervical cancer than in situ cervical lesions (7). The reasons for such observations are still under investigation. Larger epidemiologic studies are needed to confirm these findings.
Host Immune and Genome Targets

Studies of immunosuppressed individuals and immune system manipulation with animal models indicate that a defective immune response is an important factor in the progression of HPV-associated disease. The innate immune system detects damage due to HPV infection, activates secretion of interferons, and promotes cytokine secretion, which activates antigen-presenting Langerhans cells in the cervix. Signals from the innate immune system will promote activation of the adaptive immune system, which generates specific CD4+ T-helper 1 cells, which in turn support the development of effector and memory CD8+ cytotoxic T cells. HPV-induced diseases are associated with a lack of an adequate HPV-specific CD4+ and CD8+ T-cell response, leading to immune tolerance rather than clearance. The ratio between tumor-infiltrating CD8+ T cells and Foxp3+ T-regulatory (Treg) cells appears to be a significant independent prognostic factor in cervical carcinoma (8). Together, low CD8+/Treg cell ratios and decreased HLA gene expression is associated with reduced survival in invasive cervical cancer (8). These pathways of immune response provide many novel opportunities for biomarker development and targeted immune therapies.

Inherited susceptibility to invasive cervical cancer is also of major clinical interest. The pattern of decreasing familial relative risk with decreasing degree of genetic relationship indicates that a strong relationship exists between genetics and familial aggregation (5). Inherited germline variants have been identified in several of the genes important in virus–host interactions and immune function (5, 9, 10). Genes under long-term investigation include HLA class I genes, HLA class II genes, and TP53 (tumor protein p53) (5). More recently, Wang et al., using single-nucleotide polymorphism analysis, identified the IFNG (interferon, gamma), TMC6 (transmembrane channel-like 6; previously known as EVER1), and TMC8 (transmembrane channel-like 8; previously known as EVER2) genes to be associated with progression to cervical cancer (10). Further work in host and viral genetics would help identify important host-susceptibility factors linked to invasive and metastatic cervical cancer.

Several studies have demonstrated abnormal promoter hypermethylation leads to silencing or diminished expression of tumor suppressor genes in cervical carcinoma (11). These epigenetic alterations are thought to be reversible and to occur early in cervical carcinogenesis. Such characteristics make them very attractive potential targets for pharmacologic manipulation. The most promising candidate genes are associated with such functions as cell cycle control, apoptosis, cell signaling, and DNA repair. These candidate genes include DAPK (death-associated protein kinase 1), CDH1 [cadherin 1, type 1, E-cadherin (epithelial)], RASSF1 [Ras association (RalGDS/AF-6) domain family member 1], CDKN2A (cyclin-dependent kinase inhibitor 2A), FHIT (fragile histidine triad), MGMT (O-6-methylguanine-DNA methyltransferase), and RARB (retinoic acid receptor, beta). The cancer cell genome shows global hypomethylation in addition to regional promoter hypermethylation. Progressive hypomethylation has been shown to occur with increasing progression of dysplasia to invasive cervical cancer (11). Hypomethylation, which is believed to contribute to chromosome instability, may play an important role in the development of invasive disease. Additional studies are needed to discover new candidates that can be correlated with patient outcomes, be validated in larger populations, and be used to standardize technology to improve reliability.

Molecular Imaging

Imaging with [18F]fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT) is central to planning treatment for and surveillance of invasive cervical cancer. The concentration of FDG imaged indicates tissue metabolic activity from regional glucose uptake. In a study using pretreatment FDG-PET imaging, Kidd et al. showed that within a clinical stage, patients with FDG-PET–positive lymph nodes had significantly worse disease-specific survival prospects than those with FDG-PET–negative nodes (12). FDG-PET imaging provides a noninvasive whole-body assessment for planning treatment, and the combination of pretreatment FDG-PET lymph node status, cervical tumor SUVmax (maximum standardized uptake value), and tumor volume provided a model for predicting recurrence-free survival, disease-specific survival, and overall survival in cervical cancer patients. Posttreatment FDG–PET has also been shown to be predictive of progression-free and overall survival outcomes (12). A study by Zighelboim et al. (13) evaluated the FDG-PET/CT response to topotecan, cisplatin, and bevacizumab in women with recurrent cervical cancer. Although the patient sample was too small to identify a definitive trend for predicting response, the study found that 50% of patients with disease progression had increases in SUVmax, compared with increases of 11% for the patients with stable disease. Those with the greatest ΔSUVmax were associated with an increased likelihood of deriving clinical benefit. A study by Schwartz et al. (14) used gene expression profiling to identify signaling pathways associated with FDG-PET response in women undergoing primary chemotherapy and radiation for cervical cancer. The investigators identified altered gene expression in the
PI3K/Akt pathway to be correlated with a poor response to treatment, suggesting that targeted inhibition of the PI3K/Akt pathway may provide a means to improve clinical outcomes for patients with cervical cancer by improving chemoradiation response. In another study by Schwartz et al., p16 immunohistochemistry, performed on tissue microarrays from biopsies of patients undergoing advanced cervical cancer, was found to have prognostic significance. Patients with p16 positive tumors were found to have a greater likelihood of having complete metabolic response at 3 months on assessment with FDG-PET/CT than those patients with p16 negative tumors (15). FDG-PET is a powerful surrogate biomarker for response to therapy that should be used to further explore the interaction of genomic and metabolic changes in cervical cancer.

**Future Directions**

The global prevalence of HPV infection in women is approximately 11%–12%, underscoring the urgent need for more research (1). Much progress has been made in understanding the life cycle of HPV and its role in cervical cancer, but much more progress is needed if we are going to eradicate cancers in patients already infected with the virus. Research is needed to further characterize the cellular and viral changes at HPV integration sites, increase our understanding of the significance of HPV subtypes/variants, and define the genomic aberrations of the virus and host in invasive cervical cancer. Positive results from such efforts would provide new targets for creating patient-tailored strategies for treating women with locally invasive or metastatic cervical cancer, and they would provide more-meaningful prognostic indicators of clinical outcomes. In addition, tackling the relationship of the virus and host in cervical cancer could lead to a better understanding of other HPV-related malignancies.

**References**