
Jade Cabello*, Marcella Ras*, Katelyn Tran*, Athit Voytas*, Mary Coolbaugh-Murphy, Ph.D., MB(ASCP)CM;
Denise J. Murosky Short, Ph.D., MB(ASCP)CM

Undergraduate Program in Molecular Genetics Technology, School of Health Professions, UT MD Anderson Cancer Center

*Authors contributed equally & are listed in alphabetical order

Guiding Research Question

How do the genes E1 and E2 influence the epigenetic mechanisms—DNA methylation and histone modifications—of Human Papillomavirus (HPV) in the context of all stages of affected uterine cervical cancer in female patients between the ages of 30-60, with consideration to the patient’s HPV genotype?

Background Information

Cancer of the cervix starts when cervical cells undergo abnormal changes. However, this dysplasia is not yet malignant but can progress to a more severe and more advanced form of the disease. This cell change usually occurs “at the junction of the columnar cells with the squamous epithelial cells of the external os” (the transformation zone). The majority of cervical carcinomas arise from squamous cells” (Hubert & Vannmeter, 2022). Cervical cancer is usually asymptomatic in the beginning stages, causing severe and more severe symptoms that sometimes take almost a decade to manifest. Due to this, it is fortunate that changes in these tissues can be caught quite early with routine screenings. Human Papillomavirus (HPV), a sexually transmitted disease (STD), is strongly linked to cervical cancer, with strains HPV-16 and HPV-18 accounting for 66% of all cervical cancer cases (Johnson et al., 2019). Fortunately, an HPV vaccine that protects against strains 6,11,16, and 18 was developed in 2006 (Hubert & Vannmeter, 2022) and has decreased cervical cancer occurrence by 1-2% each year (Johnson et al., 2019). 99.7% of patients with cervical cancer have some form of a “high-risk HPV genotype” as their causative agent in developing cervical cancer, meaning that the development of the vaccine greatly increased the preventative chances of highly susceptible individuals (Johnson et al., 2019). HPV does not cause changes in the DNA sequence however, genomic stability and gene expression are affected “in both the viral DNA and the genome of the infected cells: DNA methylation, histone modification and gene silencing by non-coding RNAs” (Du Silva et al., 2021).

Figure 1: HPV 16 versus HPV 18

Significance of the Study

Uterine cervical cancer is the fourth most common type of cancer in women (Du Silva et al., 2021), making conduuctive research on the role of epigenetics in cervical cancer caused by HPV vital for a myriad of reasons. Initially, delving into the epigenetic roots and mechanisms of the disease can lead to early detection and prevention, minimizing the severity of the disease and augmenting preventative knowledge.

Identification of the epigenetic specifics of HPV affecting uterine cervical cancer can progress to more specialized treatments for patients, leading to the favorable outcome of elimination of this challenge. Extensive research on this topic can largely impact patients globally; these advances can help to bring awareness and help the nation.

Methodology

To conduct this review, Google Scholar and the MD Anderson Research Library’s databases were accessed: PubMed and Web of Science. The research focused on articles published within the last 5 years (2019-2024), with ongoing updates. Initially, the study considered only research conducted in the United States, but this restriction was removed to broaden perspectives. Search terms included “Human Papillomavirus,” “cervical cancer,” “E1 and E2,” “Epigenetics in HPV for Cervical Cancer,” “HPV causing cancers,” “Epigenetics of HPV,” “Epigenetic variations of HPV causing cancers,” and “HPV cancer.” The search aimed to minimize research bias by omitting conjunctions and defining words.

Figure 2: Results – Flow Diagram

Table 1. Key Findings - Strengths and Limitations

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<thead>
<tr>
<th>STRENGTHS</th>
<th>LIMITATIONS</th>
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<td>The research studies included valid processes in selecting cases and controls to produce good results.</td>
<td>The limitations were that there were no diverse population groups for the studies and a limited number of participants.</td>
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<td>A good sample was utilized due to the population containing the highest incidences of genetic variations of HPV-associated cervical cancer.</td>
<td>Compared to articles not included in the research project, some studies needed more current information for accuracy.</td>
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Results – Key Findings

- Bioinformatic analysis determined over 367 nucleotide substitutions across the viral genome, with variations ranging from
  - E1, E2, and L2 regions showed extremely high variability in both
  - ICC and NLM samples.
- HPV-16 genomes exhibited over 350 nucleotide variations, with
  - E1, E2, and L2 showing higher frequencies of variations,
- Multimomics analysis identified two HPV-16 integration hotspots affected by altered DNA methylation, potentially aiding
  - chemotherapy and “HPV cancer.” The search aimed to minimize research bias by omitting conjunctions and defining words.

Figure 3: Discussion – Summary Image

Discussion Summary Findings

The gene E1 is known to be most involved in the process of initiation of DNA replication, a vital first step in which a cell replicates itself and ensures that the daughter cells have an identical match. “Nucleotide variation of HPVB16 E1 occurred in 109 samples with 48 variation sites, and the amino acids of 19 samples were changed. (“Johnson et al., 2019.”) This is consistent with the research question that E1 is one factor affecting the epigenetic mechanisms of Human Papillomavirus-associated cervical cancer.

The most common nucleotide variation sites in the HPV16 E1 include A189C being changed to T363D, T75 to 116T8, A978G to B1361M, and G1473A to M1491. For HPV 16 E2, the nucleotide variations were less common in 91 samples with 25 variation sites, 20 of which caused amino acid changes. Namely G1964A to D255N, C2298A to T135K, G2385A to R165Q, C2548T to L380, and C2564A to R2189T respectively. (Wang et al., 2020). These overall findings of the women with cervical cancer patients of all stages from the ages 30-60 relate to the research question by noting the specific nucleotide variations that affect and exist in both HPV E1 and E2.

Researchers found it possible to determine the magnitude of the link between cervical precancer and cancer by more than a chain of species. Lineages, sublineages, and nucleotide variations can be also defined. Their study contributed to understanding the oncogenic features of HPV52 connected with genetic variation and epigenetic modifications. Their results supported other findings, which elevated levels of methylation that were connected with high-grade cervical neoplasia and cancer that increased methylation could be a barrier to provide a more in-depth understanding of HPVB52 sublineage with the increased risk of cervical cancer.

Figure 4: Cervical Intraepithelial Neoplasia

Conclusions and Recommendations

According to the articles reviewed, DNA methylation and histone modifications are key factors in all stages of uterine cancer in women between the ages of 30 and 60. More specifically, E1 and E2 participate in these actions due to their nucleotide variations. E1 is a vital first step in cell replication and has 48 variation sites. The E2 gene has only 25 variation sites. They study articles support the conclusion that both genes play a factor and role in HPV uterine cancer.

References


Vanmeter, J. (2022). Cervical cancer is usually asymptomatic in the beginning stages, causing severe and more severe symptoms that sometimes take almost a decade to manifest. Due to this, it is fortunate that changes in these tissues can be caught quite early with routine screenings. Human Papillomavirus (HPV), a sexually transmitted disease (STD), is strongly linked to cervical cancer, with strains HPV-16 and HPV-18 accounting for 66% of all cervical cancer cases (Johnson et al., 2019). Fortunately, an HPV vaccine that protects against strains 6,11,16, and 18 was developed in 2006 (Hubert & Vannmeter, 2022) and has decreased cervical cancer occurrence by 1-2% each year (Johnson et al., 2019). 99.7% of patients with cervical cancer have some form of a “high-risk HPV genotype” as their causative agent in developing cervical cancer, meaning that the development of the vaccine greatly increased the preventative chances of highly susceptible individuals (Johnson et al., 2019). HPV does not cause changes in the DNA sequence however, genomic stability and gene expression are affected “in both the viral DNA and the genome of the infected cells: DNA methylation, histone modification and gene silencing by non-coding RNAs” (Du Silva et al., 2021).