Cancer is widely considered to be a disease of the genome and the contribution of mutations and other genetic rearrangements are well established. However, there are other contributions that need to be considered as well. According to a recent survey, for instance, one in six cancers is caused by infection and epimutations (e.g. changes in DNA methylation) increasingly outnumber mutations in many types of cancers. To determine the possible involvement of epigenetic mechanisms in virus-induced cancers, we conducted an epigenome-wide association study (EWAS) of head and neck squamous cell carcinomas (HNSCC) that were either positive or negative for human papillomavirus (HPV). Using array- and sequencing-based methylome analysis, we identified an HPV-mediated hypermethylation signature and discuss its use for the development of biomarkers and therapeutic targets.