The number of head and neck cancers (HNC) associated with the human papillomavirus (HPV) is rising to “almost epidemic proportions,” said Wendell Yarbrough, MD, MMHC, FACS, Professor of Surgery and of Pathology, Co-Director of the Virus and Other Infection-associated Cancers Research Program, and Director of Sidney Cancer Hospital’s Head & Neck Cancers Program. HPV was first discovered as a factor causing HNC in the 1990s, and is now more frequently diagnosed than uterine cervical cancer, making it the most common cancer caused by HPV in the United States. “It’s a big public health issue, and it affects males three times more frequently than females.” This upswing is happening despite the availability of an effective vaccine against HPV, which 40 percent of U.S. adolescents have not received.

There are two types of head and neck cancer - the first is associated with HPV, the other is associated with smoking tobacco. To track how these HNCs develop and progress, Dr. Yarbrough and his lab turned to The Cancer Genome Atlas (TCGA), a national database that contains maps of genomic changes in 33 types of cancer. The scientists were looking for genetic mutations in HPV-associated HNCs.

They found two defective genes that appeared only in HPV+ HNCs among all solid cancers. Both genes—TRAF3 and CYLD—help cells activate immunity against viral or bacterial infection. When the genes mutate, this protection disappears. Equally important, the TCGA data revealed that patients who carried either mutation responded better to therapy and had a significantly better rate of survival. Also good news about 30 percent of patients with HPV+ HNCs had one of the mutations.

“Patients who are diagnosed with HPV+head and neck cancer could be easily tested for these two biomarkers with relatively inexpensive, commercially available kits,” said Natalia Issaeva, PhD, Assistant Professor of Surgery and member of Dr. Yarbrough’s lab. “If they have one of the mutations, they have a good prognosis and may not require the very aggressive therapy currently used, which involves high doses of radiation and chemotherapy.”

The standard aggressive therapies were developed for head and neck cancers caused by tobacco, and as HPV+HNC was recognized this therapy was also used for these tumors. “At first we didn’t know we were treating HPV+ cancers,” said Dr. Yarbrough. “We thought they were all the same, but they’re very different, and they should be treated differently.”

Drs. Yarbrough and Issaeva are now validating the two biomarkers on biopsies from another cohort of patients. If their previous findings are confirmed, a clinical trial will soon begin to test less aggressive treatment for this subset of HNC patients.

The TCGA data also showed that HPV+ HNCs have a distinct methylation profile. Methylation is a DNA modification that regulates gene expression, and so, flaws within this modification can lead to cancer. The scientists noticed that the genomes of HPV+ HNCs were hypermethylated, a condition known to silence some tumor suppressors. What would happen to the tumors if the HPV+ genome was demethylated, which reactivate the silenced genes? The scientists treated both HPV+ and HPV- cancer cells with an FDA approved demethylating agent called 5-azacytidine (5-aza).

“The HPV+ cancer cells died instantly,” said Dr. Issaeva. The drug reduced the expression of HPV genes and boosted a tumor suppressor called p53, which begins killing cancer cells. There was more good news—5-aza also repressed proteins called matrix metalloproteinases (MMPs), which tumor cells secrete before invading the blood or lymphatic systems.

“That means that demethylating drugs can prevent tumor cells from spreading and can prevent metastasis,” said Dr. Issaeva.

The researchers tested their findings in a window clinical trial led by Dr. Hari Deshpande, Associate Professor of Medicine (Medical Oncology), on a small group of patients with HPV+ HNCs. They were biopsied, given 5-aza for five days, then had surgery to remove their tumors. Tumor samples before and after 5-aza treatment were used to compare molecular changes.

“The results corroborated what we saw before,” said Dr. Yarbrough. “The tumors were responding dramatically to demethylation even after just five days, with few side effects.” Dr. Yarbrough hopes to expand this clinical trial to give more patients longer treatment and has included the trial in a planned Specialized Program of Research Excellence (SPORE) in Head & Neck Cancers application, along with co-Principal Investigator Dr. Barbara Burtness.