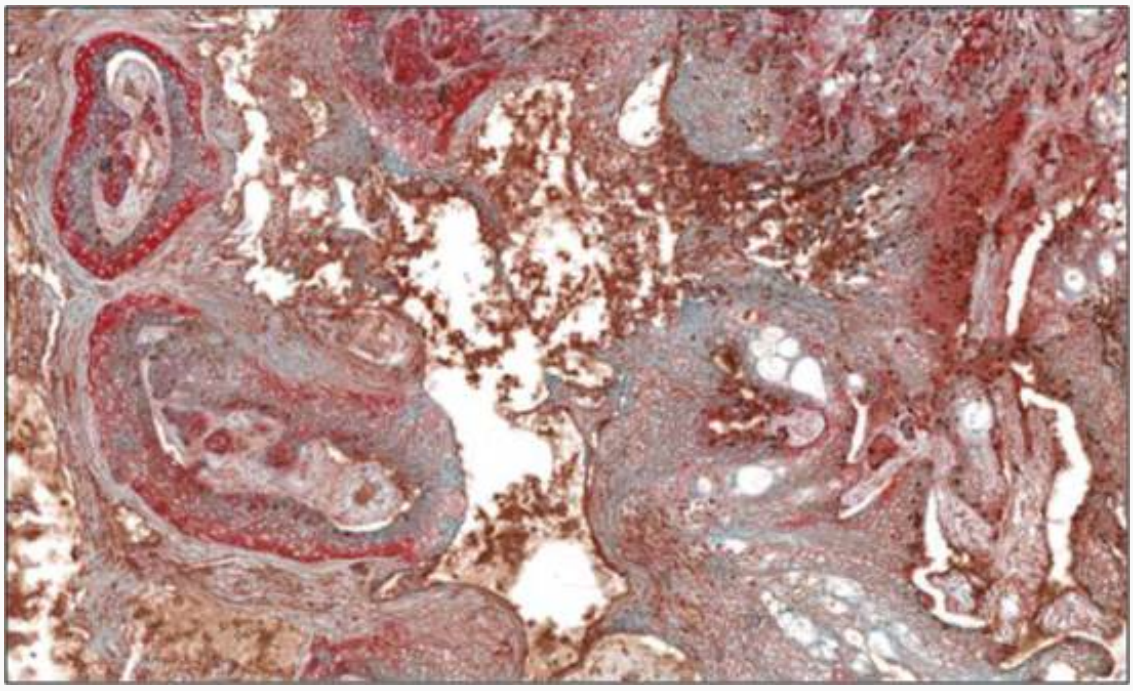
Head and Neck Cancer: Building the Evidence Base for Precision Oncology

directorsblog.nih.gov/2015/02/10/head-and-neck-cancer-building-the-evidence-base-for-precision-oncology/

by Dr. Francis Collins



Caption: Triple immunohistochemical stained oral squamous cell carcinoma: nuclei in brown, cytoplasm in red, and cytoplasmic membranes in blue green.
Credit: Alfredo A. Molinolo, Oral and Pharyngeal Cancer Branch, National Institute of Dental and Craniofacial Research, NIH

An exciting new era in cancer research is emerging, called precision oncology. It builds on decades of research establishing that cancers start with glitches in the genome, the cell's instruction book. Researchers have now identified numerous ways that mutations in susceptible genes can drive the cancer process. Knowing where and how to look for them brings greater precision to diagnosing cancers and gives doctors key clues about which treatments might work and which ones won't.

To build a firmer evidence base for precision oncology, more and more cancer genomes, from many different body sites, must be analyzed for clues about the drivers of the malignant process. That's why it's always exciting to see a new genomic analysis that adds substantially to our understanding of a common tumor. The latest to appear, published online at the journal *Nature*, comes from an NIH-supported study on the most common type of head and neck cancer, called squamous cell carcinoma. The technologically advanced analysis confirms that many previously suspected genes do indeed play a role in head and neck cancer. But that's not all. The new data also identify several previously unknown subtypes of this cancer. The first descriptions of the abnormal molecular wiring in these subtypes are outlined, suggesting possible strategies to neutralize or destroy the cancer cells. That's potentially good news to help guide and inform the treatment of the estimated 55,000 Americans who are diagnosed with a head and neck cancer each year.

Head and neck cancer is a diverse group of tumors that arise in the mouth, nose, throat, and larynx (voice box). Most squamous cell carcinomas, which account for 90 percent of all head and neck cancers, are

associated with heavy smoking and alcohol use. Over the last decade, researchers have reached a consensus on a second type caused by certain strains of the human papillomavirus virus, typically HPV 16, which also is associated with cervical cancer.

In head and neck cancer, HPV-positive tumors typically form in the middle of the throat behind the mouth, an area called the oropharynx. What's interesting—and highlights the tremendous value of precision oncology approaches—is that people diagnosed with an HPV-associated oropharyngeal cancer tend to have tumors that are different in their molecular wiring than non-HPV head and neck cancers, and often respond better to treatment. In fact, people with an HPV-positive head and neck cancer have a far better survival rate than those who don't.

In the current paper, the authors present their analysis of 279 head and neck squamous cell carcinomas. They were primarily oral (62 percent), with other tumors from the larynx (26 percent) and oropharynx (12 percent). There were 243 non-HPV tumors, most linked to heavy smoking, and 36 HPV-positive tumors largely from the oropharynx. Importantly, rather than just focusing on a single type of genetic mutation, the researchers examined the tumors for various types of DNA alterations that can trigger or drive cancer growth.

For the cancers linked to smoking, almost all had lost the normal function of TP53, a much-studied gene that many other cancers frequently inactivate. Unfortunately, the gene's protein, p53, is thus far not a good therapeutic target, for a variety of reasons. More interesting were the distinct subsets of smoking-related tumors, each exploiting a different growth-activating signaling pathway. These variations will help to distinguish between tumors and provide a better idea of the molecular landscape and where to use targeted drugs to stop their growth.

For the cancers attributed to HPV, almost all had working TP53 genes. Many had alterations in a gene called TRAF3, which is important for fighting viral infections. That suggests that HPV cleverly disables one of the body's antiviral defense genes, which then allows it to proliferate. Some HPV-tumors carried mutations that boosted the activity of the growth-promoting PIK3CA gene. PIK3CA mutations are also common in HPV-cervical cancer, which suggests a common mechanism.

The confirmation that a substantial fraction of head and neck cancers are attributable to HPV is yet another reason to be grateful that two highly-effective HPV vaccines have been developed (with major leadership by NIH's Douglas Lowy and John Schiller [2]). The Centers for Disease Control and Prevention recommends that all children, male and female, receive the HPV vaccine at age 11 or 12 to help prevent cervical cancer. These vaccines also may thwart oral HPV and cancer, but this remains to be established.

As we roll out President Obama's Precision Medicine Initiative in the coming months, expect a lot more genomic analyses of cancer to be included. This initiative will greatly expand the evidence base to enhance our capability to diagnose, prevent, and treat cancer.

References:

[1] Comprehensive genomic characterization of head and neck squamous cell carcinomas . Cancer Genome Atlas Network. *Nature*. 2015 Jan 29;517(7536):576-82.

[2] Understanding and learning from the success of prophylactic human papillomavirus vaccines. Schiller JT, Lowy DR. *Nature Rev Microb*. 2012 Oct;10(10):681-692.

Links:

Head and Neck Cancers (National Cancer Institute (NCI)/NIH)

HPV and Cancer (NCI/NIH)

The Cancer Genome Atlas (NIH-supported research network that authored the article in *Nature*)

Precision Medicine Initiative (NIH)

NIH support: National Cancer Institute; National Human Genome Research Institute; National Institute on Deafness and Other Communication Disorders