

January 13, 2020 | By Yadira Galindo

How Marijuana Accelerates Growth of HPV-related Head and Neck Cancer Identified

University of California San Diego School of Medicine researchers have identified the molecular mechanism activated by the presence of tetrahydrocannabinol (THC) — the ingredient that causes people to feel the euphoria or “high” associated with cannabis — in the bloodstream that accelerates cancer growth in patients with human papillomavirus (HPV)-positive head and neck squamous cell carcinoma.

“HPV-related head and neck cancer is one of the fastest growing cancers in the United States. While at the same time, exposure to marijuana is accelerating.

This is a huge public health problem,” said Joseph A. Califano III, MD, senior author and professor and vice chief of the Division of Otolaryngology in the Department of Surgery at UC San Diego School of Medicine.

Head and neck squamous cell carcinoma is the sixth most common cancer worldwide. These cancers begin in the cells that line the mucous membranes inside the mouth, nose and throat. Approximately 30 percent of cases of this disease are related to HPV infection, and it is these cases, in particular that are on the rise. Califano suggested increased marijuana use may be a driving factor.

Previous studies have linked daily marijuana exposure to an increased prevalence of HPV-related throat cancer. However, a mechanism linking cannabis exposure to increased growth of the cancer was unknown.

Reporting in the January 13, 2020 online edition of *Clinical Cancer Research*, a journal of the American Association for Cancer Research, researchers outline how the presence of THC in the bloodstream activates the p38 MAPK pathway, which controls programmed cell death called



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apoptosis. When activated, p38 MAPK prevents apoptosis from occurring, thus allowing cancer cells to grow uncontrollably.

Working with Chao Liu, MD, visiting scientist at UC San Diego and a physician at China's Central South University, and other colleagues, Califano and team used animal and human cell lines to show that THC turns p38 MAPK on and were able to stop the growth of HPV-positive head and neck cancer by turning off the pathway.

The team then analyzed blood samples from patients with HPV-related throat cancer who had their genomes comprehensively mapped to define activated gene pathways. Similar to the cell lines, the blood samples showed p38 MAPK activation and loss of apoptosis in tumors from patients with THC in their blood.

The authors said studies and public opinion suggestions that THC and other cannabis products have cancer-fighting properties need additional, more critical evaluation. Past studies showing anticancer effects of THC and other cannabinoids often used levels of THC higher than those found with recreational use, but doses used recreationally clearly activate a cancer-causing pathway, said Califano.

"We now have convincing scientific evidence that daily marijuana use can drive tumor growth in HPV-related head and neck cancer," said Califano. "Marijuana and other cannabis products are often considered benign, but it is important to note that all drugs that have benefits can also have drawbacks. This is a cautionary tale."

According to the Centers for Disease Control and Prevention (CDC), HPV infections are responsible for approximately 35,000 new cancer diagnoses each year in the United States. Infection is so common that nearly all men and women will get at least one type of HPV at some point in their lives. Most clear up on their own, without the person ever knowing they've had it.

Several vaccines are available that can prevent the majority of HPV-related cancers. The vaccines work best when they are given before a person is exposed to the virus. The CDC recommends vaccinating boys and girls age 11 to 12 years old but it can be administered as early as age 9.

According to the National Institute on Drug Abuse, 15 percent of youth 12 to 17 years old and 47 percent of adults age 26 and older have used or tried marijuana.

Together, a low HPV vaccination rate and an increase in marijuana use among youth has the makings of a storm, said Califano, physician-in-chief and director of the Head and Neck Cancer Center at Moores Cancer Center at UC San Diego Health.

Moores Cancer Center is one of only 51 National Cancer Institute-designated Comprehensive Cancer Centers in the country and the only such center in San Diego County.

Treatment options for patients with early- or late-stage head and neck cancers include minimally invasive surgery, reconstruction and rehabilitation, proton therapy and other radiation therapy, innovative clinical trials and targeted therapy, including immunotherapy.

The Head and Neck Cancer Center provides comprehensive care that includes counseling, education and support groups, nutrition, dental rehabilitation, speech and language therapy and social workers to help patients through every step of the process beginning with diagnosis to support lifelong wellness.

Califano and team are now looking at whether cannabidiol, or CBD, has a similar effect to THC. CBD is another major chemical compound found in marijuana, but does not produce the “high” and is now commonly used in various over-the-counter products, such as lotions, ointments and edibles.

In addition, the team is investigating whether p38 MAPK can be targeted with drugs to stop HPV-related head and neck cancer from growing.

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Funding for this research came, in part, from the National Institute of Dental and Craniofacial Research and National Institute of Health (R01 DE023347, U01CA217885, R01HG009285, R01CA121941 and P30CA023100).

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