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Researchers find genetic variants associated with susceptibility to mouth and throat cancer

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A number of genetic variants associated with susceptibility to oral cavity and pharyngeal cancer have been described in an international study published in the journal *Nature Genetics*. The most noteworthy finding was an association between cancer of the oropharynx and certain polymorphisms (alternative versions of a given DNA sequence) found in the human leukocyte antigen (HLA) genomic region. HLAs, proteins found on the surfaces of most cells in the body, play an important role in recognizing potential threats and triggering the immune response to foreign substances.

According to Eloiza Helena Tajara, a professor at the São José do Rio Preto Medical School (FAMERP) in São Paulo State, Brazil, and co-author of the article, a specific group of variants in this region, located on chromosome 6, is associated with enhanced protection against oropharyngeal cancer caused by human papilloma virus (HPV).

"Previous research showed that these same variants confer protection against cancer of the uterine cervix, which is known to be associated with HPV," Tajara said. "Our findings suggest that the genes that control the immune system play a key role in predisposition to HPV-related tumors. This discovery points to the possibility of clarifying the mechanisms whereby such tumors develop and of designing methods for monitoring risk groups."

The study was coordinated by the International Agency for Research on Cancer (IARC) and involved 40 research groups in Europe, the United States, and South America. The Brazilian participants are members of the Head & Neck Genome Project (GENCAPO), a consortium of scientists affiliated with several institutions.

In a recent study, GENCAPO evaluated more than 7 million genetic variants in samples from 6,034 patients with head and neck cancer. The cases comprised 2,990 oral cavity tumors, 2,641 oropharyngeal tumors, 305 tumors in the hypopharynx (the bottom part of the pharynx near the esophagus), and 168 tumors in other regions or more than one region concurrently. The study population also included samples from 6,585 people without cancer as controls.

The researchers detected eight loci (genomic sites) associated with susceptibility to these types of tumor. Seven had not previously been linked to mouth or throat cancer.

According to Tajara, the IARC focused on analyzing oral cavity and oropharynx tumors because there are no genome-wide association studies of these two tumor types. Although these cancers are predominantly caused by tobacco and alcohol use, the importance of HPV, particularly HPV16, as a cause of oropharyngeal cancer has become more evident in recent years.

"The throat is the most affected area among head and neck cancer subsites, likely because its tissue is more receptive to the virus," Tajara said.

In the article, the researchers note that the proportion of HPV-related oropharyngeal cancer cases is estimated to be approximately 60 percent in the US and 30 percent in Europe, but lower in South America.

"One finding that was expected to some extent was the absence of HLA associations with oropharyngeal cancer, which may be due to the fact that the frequency of HPV-positive oropharyngeal cancer is less than 10 percent in South America," Tajara said. "The same factor appears to account for the weak association between the variants identified and HPV-positive oral cavity cancer, which is also far less frequent than HPV-negative oral cavity cancer."

In her view, the strong rise in cases linked to HPV in the U.S. could be partly due to a change in sexual habits, especially regarding the practice of oral sex. "It's possible that Brazil is still in a transition stage and that the habits that favor infection are only starting to become more common. If so, the effects will appear in a few years' time," she said.

Previous studies have already shown that HPV-associated head and neck cancers affect younger people and develop rapidly. By contrast, cases associated with tobacco and alcohol use, as well as poor oral hygiene, are more prevalent in those over 50 years old and progress more slowly, but are harder to treat.

In addition to DNA in tissue samples taken from participants of the study, data were also collected on environmental and clinical factors possibly associated with the development of this type of cancer, such as smoking, alcohol consumption and age.

According to Tajara, thanks to the joint efforts of 40 research groups, it was possible to obtain data on a significant number of patients, thus enhancing the impact and reliability of the results. The GENCAPO team contributed some 1,000 samples from tumors for analysis.

"Based on these results, we can try to understand from a molecular standpoint how the observed polymorphisms interfere with the response to HPV infection," Tajara said. "This may give us clues as to how to

protect people and how to reduce the incidence of this type of tumor."

More information: Corina Lesseur et al, Genome-wide association analyses identify new susceptibility loci for oral cavity and pharyngeal cancer, *Nature Genetics* (2016). DOI: 10.1038/ng.3685

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