Genetic mutations and molecular alterations may explain racial differences in head and neck cancers

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A team of scientists at Johns Hopkins and in Texas has identified a handful of genetic mutations in black Americans, in addition to some chemical alterations affecting gene activity, which may help explain why the death rate among African-Americans from the most common form of head and neck cancer continues to hover some 18 percent higher above the death rate of whites with the same cancer.

The so-called survival gap persists, the team says, despite decades of steep declines in deaths from head and neck squamous cell carcinomas among Americans of all races, which is largely attributed to the sharp drop in smoking since the mid-1970s.

The team's latest analysis of tumor tissue and blood samples from 60 black and 168 white men and women with the disease is believed to be the first and most in-depth analysis of the genetic and epigenetic origins of such common cancers of the lip, mouth, tongue and throat based on race.

Researchers plan to present the study findings on Dec. 7 in Atlanta at the Sixth American Association for Cancer Research Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved. More than 30,000 Americans die annually from some form of head and neck squamous cell carcinoma.

According to lead study investigator and genomics epidemiologist Rafael Guerrero-Preston, Dr.P.H., his team's research findings represent what could be the final piece in the survival-gap mystery, adding to such well-studied and well-known contributing factors such as poor education, poverty, limited access to health care and untimely access to treatments.

"Our study results are essential to understanding and eventually remedying head and neck cancer survival disparities between races," says Guerrero-Preston, an assistant professor in otolaryngology – head and neck surgery at the Johns Hopkins University School of Medicine and its Sidney Kimmel Comprehensive Cancer Center. "The genetic and epigenetic changes we identified can be used for improved risk assessment, early detection, targeted therapy and patient follow-up for people of all races."

Among the study's key findings were some 317 epigenetic modifications significantly more prevalent in people with head and neck cancers and the four most common that were more prevalent in blacks and whites, primarily in a half-dozen biological pathways.

One pathway, called TP53, was linked by earlier research from the same Johns Hopkins team to increased rates of head and neck cancers in people of all races. Another, NOTCH1, has only recently been tied to squamous cell carcinomas.

Researchers also found several related epigenetic alterations – molecular modifications of nuclear DNA—in the PAX pathway, primarily at PAX1 and PAX5, where a chemical process called methylation blocks tumor-suppressing gene activity, silencing the gene.

In their study, survival outcomes for all head and neck cancers were worse for blacks, with some 20 percent fewer blacks surviving past five years than whites.

Three out of 10 people of either race with head and neck cancer and both a TP53 mutation and PAX5 methylation do not live as long as people who have had head and neck cancer and just a TP53 mutation.

Survival outcomes after five years were two and a half times worse for blacks with PAX5 methylation than whites. Indeed, people of either race with PAX5 methylation did not live as long as those without.

Moreover, the team's analysis showed that these related molecular changes were dependent on where the original tumor arose.

For cancers originating at the back of the mouth, or oropharynx, blacks had significantly more NOTCH1 mutations than whites, at 67 percent and 14 percent, respectively. Outside the oropharynx, however, the reverse occurred, with no blacks and 18 percent of whites having a NOTCH1 mutation. PAX1 and PAX5 epigenetic alterations were similarly reversed depending on tumor location, with PAX1 methylation in 52 percent of blacks and in 62 percent of whites in the oropharynx, compared to 70 percent and 60 percent, respectively, for tumors originating elsewhere in the head and neck.

TP53 mutations, on the other hand, were significantly higher in blacks than in whites, regardless of tumor site.

As part of the team's analysis, which took three years to complete, researchers decoded and then validated the cancer genetic profiles of all study participants, mostly from the Baltimore region, and then compared the results with genetic information obtained from 279 squamous cell carcinoma tissue samples in The Cancer Genome Atlas, a national database.

Guerrero-Preston says that further examination of the genetic and epigenetic modifications will be required before precise survival

numbers, measured in months or years, can be ascribed to any particular genetic mutation or combination of changes. Such detailed findings, he says, will require some 200 additional study volunteers in order for the study to be scientifically accurate.

Guerrero-Preston plans to not only continue his genetic analyses in blacks, but also to study head and neck cancer disparities in Latinos, another ethnic group in which a survival disadvantage, although smaller, persists versus whites.

"Our research goal is to figure out how all of these ethnically predisposing genetic markers interact; how they turn off and on in response to environmental stimuli such as inflammation and lifestyle factors including smoking and nutrition, and how they trigger cancers of the head and neck," says Guerrero-Preston.

More information: Abstract Number: PR06

Presenter: Rafael Guerrero-Preston, Dr.P.H.

Title: Integrated genomic and epigenomic deep sequencing analyses reveal head and neck cancer survival disparities associated to alterations in the PAX, NOTCH1 and TP53 pathways

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Black and Puerto Rican men have a higher head and neck cancer (HNSCC) burden than Non-Latino White (NLW) men in the United States, but the biological basis for these health disparities are poorly understood. The disparity in overall HNSCC survival rates between NLW and Black patients in the United States has remained at 18% for

more than 30 years. This survival disparity in HNSCC may be due, among other factors, to a different profile of genetic and epigenetic alterations among Black patients. However, there is a lack of molecular or genomic studies that examine health disparities in HNSCC.

We performed an integrated molecular analysis using methylation sequencing, exome sequencing, mRNA expression and qPCR platforms in 107 head and neck squamous cell carcinoma (HNSCC) samples. Our findings were validated in 279 samples from The Cancer Genome Atlas (TCGA) project.

We uncovered 316 genes harboring cancer specific promoter methylation and identified 10 tumor suppressor genes with concurrent promoter methylation and somatic mutations. We found clustering of genetic and epigenetic events that distinguished smokers from non-smokers, HPV positive from HPV negative tumors, and Blacks from NLW HNSCC patients.

We observed disparities in the frequency of mutated and methylated events in the PAX, NOTCH1 and TP53 pathways. Black HNSCC patients have higher frequencies of TP53 (B-50% vs 39%), FBXW7 (B-13% vs 7%), and NOTCH1 (B-25% vs 16%) mutations and no differences in PAX1 (B-63% vs 65%) or PAX5 (B-86% vs 88%) greater promoter methylation across all tumor sites combined. Interestingly, these patterns differed when we stratified on tumor site. Blacks have higher ZIC4 (B-100% vs 70%), PLCB1 (B-60% vs 50%), and PAX5 (B-80% vs 73%) greater promoter methylation and p53 (B-60% vs 48%) mutations than NLW, and no NOTCH1 (B-0% vs 18%) mutations, outside the oropharynx. Conversely, NLW have a higher frequency of PAX5 (B-67% vs 86%) greater promoter methylation in the oropharynx when compared with Blacks. In the oropharynx NLW also had a higher frequency of combined p53mut or PAX5met (B-14% vs 33%), while Blacks had a higher frequency of combined NOTCH1mut or PAX1met (B-33% vs 10%). We found that for all HNSCC patients combined, PAX5 greater promoter methylation and p53 mutations had worse overall survival than patients with p53 mutations. Survival analyses

revealed that overall HNSCC survival disparities were associated to age and PAX5 greater promoter methylation.
Co-localization analyses uncovered genomic and epigenomic alterations in the PAX gene family, which selectively impact canonical NOTCH and TP53 pathways to determine cell fate, cell survival, and genome maintenance. Our results highlight the differential genomic and epigenomic alterations between PAX, NOTCH, and p53 pathways in Black and NLW HNSCC patients, which underlie the complex biology of morphologically similar tumors and explain HNSCC survival disparities.

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