New clues may link hereditary cancer genes to increased risk of cancer from alcohol

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In laboratory experiments conducted on human cell lines at the Johns Hopkins Kimmel Cancer Center, scientists have shown that people carrying certain mutations in two hereditary cancer genes, BRCA2 and PALB2, may have a higher than usual susceptibility to DNA damage caused by a byproduct of alcohol, called acetaldehyde.

The scientists say they suspect that the two genes in their normal forms evolved to protect cells against the damaging effects of acetaldehyde, which can lead to cancer.

While the scientists caution that the research is preliminary, they say their findings suggest that studies on disease risk factors should take into account these particular genetic variations and the use of alcohol.

"We need to identify which behaviors in certain populations increase disease risk, and keep in mind that our genetic susceptibility plays a large role in cancer risk," says Scott Kern, M.D ., the Everett and Marjorie Kovler Professor in Pancreas Cancer Research at Johns Hopkins.

Acetaldehyde (pronounced ah-set-AL-deh-hide) is produced during the metabolism of alcohol and is known to cause DNA damage. Scientists say the chemical is ubiquitous in nature, found in many sources, including apples and gut bacteria, and is responsible for the "hangovers" people experience after heavy alcohol use. Alcohol use has long been linked to cancers of the upper aerodigestive tract, breast, pancreas, and

stomach.

After reading reports linking acetaldehyde and a related chemical, formaldehyde, to a rare cancer-susceptibility disease called Fanconi anemia (which is characterized by mutations in BRCA2 and other genes), Kern and his team took a closer look at the growth response of cells exposed to acetaldehyde and other compounds. The team created human cell lines that lacked BRCA2 and PALB2 genes.

"You can add any chemical to a cell culture and growth of the cells will go down, so the significant responses are ones that differ by 10-fold or larger," says Kern.

The scientists found that BRCA2 and PALB2-mutant cell lines exposed to acetaldehyde had up to 25 times more growth reduction when compared with related cells lacking these mutations. The significant reduction in cell growth indicates that these cell lines, which lack the two genes, are more susceptible to the DNA damage caused by acetaldehyde, say the scientists. They suggest that the DNA-damaging effects of acetaldehyde exposure in people lacking these genes may accelerate cancer growth.

Kern and his team estimated that the BRCA2 and PALB2 genes, when they function normally, protect cells against up to 96 percent of the toxicity associated with acetaldehyde. Results of the experiments are published in the January 2014 issue of the *American Journal of Pathology*.

Kern says that the acetaldehyde model could, theoretically, be used to develop drugs that kill cancer cells, as well as to alter cancer risk. They found that cell lines with mutations in PALB2 were up to 20 percent more sensitive to chemotherapy agents, such as cisplatin, that work by breaking down DNA, compared with anticancer drugs that work in other

ways.

When the genes function correctly, BRCA2 and PALB2 bind to each other to repair DNA damage. Mutations in the genes disable their DNA–repairing capability and make carriers more susceptible to cancer, the researchers say.

"BRCA2 and PALB2 may have evolved over time to repair or protect us from acetaldehyde damage," says Kern. "In most people, the genes function well and we're equipped to handle most of our exposure to acetaldehyde, but patients or carriers with mutations in these genes could face a higher risk of cancers with high exposure to alcohol or acetaldehyde-containing foods."

Kerns says that there is a possibility acetaldehyde leaves a signature of damage in cells. He adds that scientists may have been overlooking the role of acetaldehyde in disease and aging.

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