



## Low-Fat Diet Helps Genetically Predisposed Animals Avoid Liver Cancer

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In a study comparing two strains of mice, one susceptible to developing cancer and the other not, researchers found that a high-fat diet predisposed the cancer-susceptible strain to liver cancer, and that by switching to a low-fat diet early in the experiment, the same high-risk mice avoided the malignancy. The switched mice were lean rather than obese and had healthy livers at the end of the study.

The findings, from a joint University of Pennsylvania School of Medicine and Case Western Reserve University study, appear online this month in *Human Molecular Genetics*.

The investigators studied hepatocellular carcinoma (HCC), a type of liver cancer that is one of the leading causes of cancer death worldwide. Thirty percent of cases of this type of liver cancer are associated with obesity, type 2 diabetes, and related metabolic diseases, although a direct link between these and liver cell cancer has not been completely established. "The connection between obesity and cancer is not well understood at this point," says senior co-author John Lambris, PhD, the Dr. Ralph and Sallie Weaver Professor of Research Medicine at Penn. The researchers hope the results will lead to the development of blood tests that can detect precancerous conditions related to diet.

The remaining seventy percent of HCC cases result from hepatitis B and C viral infections, exposure to the fungal toxin aflatoxin, chronic alcohol use, or genetic liver diseases.

The usual outcome of hepatocellular carcinoma is poor, because only 10 to 20 percent of these tumors can be surgically removed. If the cancer cannot be completely removed, the disease is usually deadly within 3 to 6 months. Hepatocellular carcinoma causes close to 700,000 deaths worldwide per year, mostly outside the US.

The researchers tested the long-term effects of high-fat and low-fat diets on males of two inbred strains of mice and discovered that one strain, named C57BL/6J, was susceptible to non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma on a high-fat, but not a low-fat diet. The other strain, called A/J, was not susceptible to disease on a high-fat diet. The mice were fed their respective diets for close to 500 days, weighed periodically, and then analyzed for the presence of disease.

RNA profiles of hepatocellular carcinoma versus tumor-free liver tissue at the end of the experiment showed that two signaling networks one centered on Myc and the other on NF-kappa B were involved. This result is similar to findings obtained from studies on the two major classes of hepatocellular carcinoma in humans.

At the end of the experiment, mice susceptible to cancer showed characteristics of NASH such as inflammation and fibrosis, and, in some cases, cirrhosis as well as hepatocellular carcinoma, in their livers. A switch from a high-fat to a low-fat diet reversed these outcomes in groups of C57BL/6J mice that were fed a high-fat diet early in the experiment. The switched C57BL/6J mice were lean rather than obese and had healthy livers at the end of the study. All mice kept on a high-fat diet for the duration of the experiment had liver tumors at the end of 500 days.

A similar change in diet may have important implications for preventing liver cancers in humans, suggest the researchers. "The reason these findings are so provocative is that it relates to diet and we now have a unique model we know will develop cancer," says Lambris.

"By waiting for evidence of disease before terminating the study, instead of using an arbitrary endpoint as is done in most experimental studies, we were able to discover an important new experimental model for a common cancer in humans," says senior co-author Joseph Nadeau, Professor and Chair of the Department of Genetics at Case Western Reserve University School of Medicine.

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Co-authors, in addition to Lambris and Nadeau are Maciej M. Markiewski from Penn, Annie E. Hill-Baskin, David A. Buchner, Haifeng Shao, David DeSantis, Nathan A. Berger, and Colleen Croniger from Case Western, and Gene Hsiao, and Shankar Subramaniam from University of California, San Diego.

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