Researchers Explore Mechanisms That May Link Obesity and Cancer

By Susan Jenks

A s obesity’s ties to multiple cancers strengthen, a new study suggests that inflammation may be the primary culprit in at least one malignancy: liver cancer. The Cell study, published January 22, found that high levels of interleukin 6 and tumor necrosis factor, which are associated with obesity, turned healthy cells into malignant ones through chronic low-grade inflammation of the liver.

Using knockout mice to unravel the mechanism, Michael Karin, Ph.D., and his team at the University of California, San Diego, concluded that enhanced production of these signaling molecules during obesity leads to persistent inflammation, which activates STAT3, a tumor-promoting transcription factor. That, in turn, causes proliferation of aberrant hepatic cells and leads to hepatocellular carcinoma.

Similar mechanisms may underlie, and perhaps markedly increase, the risk for pancreatic, gastrointestinal, and kidney cancers as well, according to Karin. Epidemiological studies show associations with obesity and at least five different cancers: colon, postmenopausal breast, endometrial, kidney, and esophageal. Excessive weight plays a suspected role in other cancers and recently has been implicated as a risk factor for poor survival in several of them, including prostate, breast, and colon.

**Alternative Pathways**

However, inflammation is just one possible link between obesity and cancer now under study. The Cell study allows for the focus on one pathway, but that information must “be pulled back together in humans,” according to Susan Gapstur, Ph.D., vice president of epidemiology for the American Cancer Society. She argued that inflammation interacts with other factors linked to both obesity and cancer.

“The biology underlying obesity’s relationship to cancer might vary a little site by site,” she said, “but the pathways to malignancy are clearly intertwined.” For example, sex hormones are important to certain cancers, and insulin and insulin-like growth factors (IGFs), which stimulate estrogen production, also play substantial roles.

“There’s an independent effect and also an intertwined one,” Gapstur said. And on top of that, there’s inflammation.”

“The overlap is evident,” agreed Edward L. Giovannucci, M.D., Sc.D., at Harvard’s School of Public Health in Cambridge, Mass. He said that high levels of circulating insulin, which increase the risk for developing some cancers, especially colon and pancreatic cancers, is “at least correlated and probably integrated” with other factors. In human populations with liver cancer, he said, alcohol, hepatitis viruses, and many other factors exist that probably affect these cells, besides inflammation.

Among the various mechanisms that may link obesity and cancer, those related to diabetes are of special interest to many experts. Epidemiologic studies have shown that people with cancer and diabetes who take diabetes drugs have better cancer outcomes.

“We still don’t know why,” said Rachel Ballard-Barbash, M.D., associate director of the applied research program at the National Cancer Institute. However, a large, randomized clinical trial now under way with the common diabetes drug metformin hopes to answer that question in breast cancer survival. The trial is looking at insulin resistance and whether metformin can reduce cell proliferation in tumor tissue to improve survival, said Ballard-Barbash. Sponsored by the NCI and the National Cancer Institute of Canada, the trial began recruiting participants last year.

One link between cancer and diabetes is thought to be insulin and IGF. Cancer cells can have more IGF receptors on their surface, which heightens their sensitivity to circulating insulin and IGF-1.

“And that’s not good if you have preneoplastic cells with extra receptors,” said Giovannucci. “It’s not yet proven, but we suspect there’s a highly proliferative effect and the prevention of normal apoptosis.”

Recently, researchers at the Prostate Center at Vancouver General Hospital in British Columbia found more IGF-1 and insulin receptors on malignant prostate epithelial cells than on benign cells. The Canadian investigators, reporting in the journal Prostate in January, concluded that their findings support ongoing clinical trials of targeted drug therapies to these sites. Also, they said, the results show that obesity-associated hyperinsulinemia carries a poor prognosis for prostate cancer survival.

An earlier study, published in Cancer Research in December 2008, tied poorer survival in breast cancer to phosphorylation of the IGF-1 and/or insulin receptors. Researchers from the University of British Columbia’s Child and Family Research Institute examined tissue arrays representing 438 cases of invasive breast cancer. Where molecular evidence showed a higher activation of the IGF-1/insulin receptor, they said, it accurately predicted a worse outcome in this cancer.

Insulin-related mechanisms are not the only ones under study. Recently, Peter T. Campbell, Ph.D., and his colleagues in the American Cancer Society’s epidemiology research program in Atlanta looked at body mass index and colorectal cancer risk in relation to the microsatellite instability status of patients’ tumors (see J. Natl. Cancer Inst. 2010;102:391–400). The case–control study found that obese patients diagnosed with tumors that are microsatellite stable, or have low microsatellite instability, have poorer 5-year survival rates than do patients whose tumors have high microsatellite instability.

Another possible tumor-promoting mechanism “meriting further and dedicated studies,” in Karin’s opinion, is mammalian target of rapamycin (mTOR). mTOR is an
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important regulator of cell metabolism and tumor growth whose abnormal activation is thought to give cancer cells a competitive growth advantage over normal cells. Its activity is elevated in the obese liver, Karin said, and metformin inhibits mTOR. The mouse model is suitable for looking at this “relevant player,” he said.

Karin also noted that research is needed on the correlation between cancer risk and degree of overweight. “We still don’t know the difference between being a little chubby and a lot chubby,” he said.